Application of a Constant Indicator Dilution Method to the Measurement of Local Venous Flow

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Many investigations of the cardiovascular system require estimations of regional or single vessel blood flow. Although direct methods have been devised for this purpose, most have a limited application in man because they involve exposure of the appropriate blood vessel. When multiple and frequent flow estimations over a long period are desired in experimental animals, repeated exposures of the same vessel or region may present difficulties. Hence, a technique that would eliminate this procedure would be of value.

Although indicator dilution methods have been used to estimate regional or single vessel blood flow in man and experimental animals, certain problems in their application have emerged. Andres et al. measured human brachial artery flow, Peterson et al. left ventricular output, and Grace et al. thoracic aortic flow by injecting Evans blue dye at a constant rate into the artery distal to the injection site. The production of uniform mixing of indicator and blood across the segment of vessel or vascular bed proximal to the sampling site without damaging the blood or altering its flow proved a major problem.

Using a thermodilution method, Fegler measured blood flow in the central veins and with Hill in the portal vein. They injected cold Ringer's solution and recorded thermodilution curves with distally placed thermocouples. Good results were obtained in vivo and in the perfused vena cava of dog carcasses, but poor results in model experiments due to rapid heat exchange. Linzell, using exteriorized veins, found a systematic overestimation of flow with this method, indicating the trouble with rapid heat exchange, especially at low flow rates. Katsura et al. placed on a catheter tip a tiny thermistor which controlled both heating and temperature sensing elements and applied it to the measurement of single vessel blood flow. They regarded the device as unsuitable for quantitating flow in that movements of the catheter produced erroneous deflections. Fronek and Ganz developed a more generalized method using local thermodilution. They injected a bolus of cool saline into the vessel and with a thermistor mounted on the injection catheter recorded...
a dilution curve from the change in temperature in the immediate neighbourhood of the injection. Blood flow could be measured in any vessel in which the tip of the catheter could be introduced. It was observed that for adequate mixing to occur throughout the cross section of large vessels, suitable spatial orientation of the indicator jet had to be insured.

Recently, Shillingford et al.\textsuperscript{17} described a dilution technique for the measurement of segmental venous flow in man. They devised a double lumen catheter and injected an indicator substance under pressure at a constant rate through fine holes in its tip, and simultaneously sampled the diluted blood downstream through the other lumen. In in vitro experiments, good correlation between predicted and actual flow was obtained. Estimations of venous flow in external iliac veins, inferior cava and renal veins in man gave consistent and reasonable results. This paper describes an extension of this work and especially the application of the technique to the serial measurement of regional venous flow in animals.

**Methods**

**INJECTION SYRINGE, RECORDING AND SAMPLING SYSTEMS**

To achieve uniform mixing of indicator and blood throughout the cross section of the vessel over a short distance, the special syringe and injection system as described by Shillingford et al. has been used with the addition of an automatic sampling system (fig. 1). The syringe barrel is made of precision-bore stainless steel with an internal diameter of 1.0 cm and a length of 54 cm. The piston is attached to a sliding carriage which runs along two guide rails and is connected by

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**FIGURE 1**

Overall view of the injection syringe, recording and sampling systems. Weight which provides force necessary for injection is seen in descent in center of trolley. Arrow shows the proportioning pipette used for sampling during injection.

**FIGURE 2**

Designs of nylon double lumen catheters. A, B, C, and D are forward-spray catheters; E and F are retrograde-spray catheters. Below are shown the connecting head and introducer needle.
two nylon cords, running over pulleys, to weights which may be varied. The sliding carriage is provided with a brake, and upon release, allows the weights to fall, forcing the piston along the barrel. The forward end of the syringe is fitted with a lucite collar through which one may see if any air bubbles have gained entrance into the syringe; this in turn is connected to the catheter by two three-way taps for filling the syringe with indicator solution and flushing the catheter.

Adjacent to the guide rails is a recording drum which revolves at one revolution per minute. The writing pen is attached to the sliding mechanism that operates the syringe piston. Thus, volume and time of injection may be accurately measured and constancy of injection continuously monitored.

The trolley table holding the syringe mechanism is provided with a stand for three drip bottles. One bottle holds the indicator solution and the other two contain flushing solutions. A small bracket near the end of the table holds another three-way tap to which the collection lumen of the catheter is attached for flushing and sampling. Adjacent to the syringe tip is a proportioning pipette* which automatically transfers integral numbers of equal volumes of 0.2 or 0.3 ml per delivery. The number of "volumes" transferred may be preselected by means of an automatic selector system. The collection lumen of the catheter is attached to the pipette during injection for sampling.

CATHETERS AND INJECTION HEADS

Double lumen catheters were made from nylon tubing and had a length of 100 to 125 cm. The smallest practical sizes were chosen. The dead space of the sampling lumens varied from 1.8 to 2.6 ml. Six designs were investigated. Four had the injecting lumens upstream from the sampling lumens and two the injecting lumens downstream from the sampling lumens (fig. 2). In three designs the nylon tubes were fixed side by side with a nylon cement. In the other three, a smaller nylon tube was placed within a larger tube. They were connected at one end, keeping their lumens separated by placing the inner tube over an appropriate size needle and securing it with a 10:1 mixture of epoxy resins AY105 and araldite hardener HY951. The outer tube was secured also with the fixative mixture over a larger needle that had been inserted over and fixed to the smaller needle at its upper end and opened from its side (fig. 2). In three designs the nylon tubes were fixed side by side with a nylon cement. In the other three, a smaller nylon tube was placed within a larger tube. They were connected at one end, keeping their lumens separated by placing the inner tube over an appropriate size needle and securing it with a 10:1 mixture of epoxy resins AY105 and araldite hardener HY951. The outer tube was secured also with the fixative mixture over a larger needle that had been inserted over and fixed to the smaller needle at its upper end and opened from its side (fig. 2). The sampling and injecting lumens were separated by distances of 5, 7, and 10 mm.

Since inadequate mixing of indicator and water occurred around the tip of open-end catheters 0.5

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* Manufactured by Baird & Tatlock Ltd., Freshwater Road, Chadwell Heath, Essex, England.
‡ Manufactured by Ciba Ltd., Cambridge, England.
to 0.7 mm inner diameter at high flow rates in glass tubes greater than 10 mm inner diameter, stainless steel heads were placed on the injecting and sampling lumens in two designs (fig. 3). In the forward-spray design, the stainless steel head had three equally spaced holes facing outward at 45 degrees to the long axis of the catheter. Both lumens screwed over portions of the injecting head and were secured with the epoxy-resins-araldite fixative mixture. In the retrograde-spray design, the inner tube was pulled through a centrally placed hole in the stainless steel head and the other lumen screwed over and bevelled down to the head, both being secured with the epoxy-resins-araldite fixative mixture. Three equally spaced holes were placed around the periphery of the outer tube, pointing retrograde at 45 degrees to the long axis of the catheter. In a side-by-side retrograde-spray design, the tip of the injecting lumen was closed and three equally spaced holes placed around the periphery, pointing retrograde at 45 degrees to the long axis of the catheter.

CHOICE OF INDICATOR

Normal saline with its effect on hematocrit dilution, dyes such as Evans blue, cardiogreen or Coomassie blue and radioactive tracers may be used. Although dilution of the blood with saline is an attractive idea, its accuracy declines at high flow rates due to difficulty in reading very small changes in the hematocrit and to the magnification of these errors in the flow calculation. Dyes are disadvantageous because plasma extractions are time consuming and prone to inaccuracies. The better indicator so far has been radioactive I131 albumin, which requires very small amounts and allows rapid determinations on whole blood samples.

CALCULATIONS

In the constant-rate injection technique of Stew- art, volume flow is determined by dividing the quantity of indicator injected per unit time by the concentration of the indicator in the sampled blood at equilibrium. Since the volume of injectate must also be accounted for, the following formula applies:

\[ F = \left( \frac{C}{c} \times f \right) - f \] or \[ F = f \left( \frac{C}{c} - 1 \right) \]

where \( C \) is the concentration of the indicator injected, \( c \) is the concentration of the indicator in the sample, and \( f \) is the rate of indicator injection. The rate of indicator injection (\( f \)) is determined by the formula \( f = \frac{K}{L} \), where \( K \) is a constant for the particular sized syringe, drum and an arbi-

trary distance the piston of the syringe travelled during constant injection. The distance \( L \) is the height the recording pen travelled above the base line over distance \( D \) for any single injection (fig. 4). Once \( K \) is determined, \( f \) can be rapidly calculated for each injection.

MODEL EXPERIMENTS

Glass tubes with side arms (fig. 4) were connected to a constant level reservoir containing water. A steady flow could be obtained through the tubes over a range of 20 to 6,000 ml/min. Indicator solution was prepared by adding 10 \( \mu \)c of KI to 1,000 ml of iodinated water. The extra KI prevents the radioactive KI from sticking to the syringe and catheter. Inner diameters of the tubes were 5, 8, 10, and 13 mm. Catheters were introduced through the side arms against (for forward-spray catheters) or with (for retrograde-spray catheters) the flow of water. Flow through each tube was progressively increased, the catheters removed and replaced, until their presence affected the rate of flow. The indicator was injected at various constant known rates. Samples of the resulting mixtures were simultaneously withdrawn from the collecting lumens of the catheters and from the ends of the tubes. Flow in the glass tube was measured by collection in a graduated cylinder for 60 seconds before injection and for 10 seconds during injection. If the concentration of the two samples was the same, it was assumed that mixing had been complete and that the sample obtained from the catheter lumen was representative of the final mixture. Estimated flow was then compared with actual flow. To see if the position of the catheter tip in relation to the side of the tube affected mixing, the tips were placed along the side, midstream, and diagonally across the stream and the experiments repeated.

EXPERIMENTS IN ANIMALS

Measurements of local venous flow were performed on healthy greyhound dogs lightly anaesthetized with sodium pentobarbital. Of the six catheter designs tested in vitro, only two, the tube-within-a-tube forward-spray and retrograde-spray catheters were used in these experiments. The sampling lumens were 7 or 10 mm from the injecting lumens. The side-by-side catheters resulted in leakage at the site of entrance into the vein and results from model experiments indicated that open-end catheters may result in inadequate mixing in large vessels at slow injection rates. Catheters were introduced into the appropriate vein via the femoral or external jugular vein percutaneously. When the external jugular vein was used, the catheters were made radio-opaque with 45% hypaque and under fluoroscopic guidance.
passed through the heart into the inferior vena cava. The abdomen was opened through a midline incision and the catheters appropriately placed. The retrograde-spray catheter was introduced into the portal vein either via a small tributary of the superior mesenteric vein or directly, being secured with a purse-string suture. Indicator was prepared by placing 10 ml of I mg albumin in 500 ml saline to which 10 ml dog plasma was added to prevent sticking of the I mg to the syringe and catheter. Flows were measured in the portal vein, renal veins, inferior vena cava, iliac, and femoral veins. In chronic experiments, metal clips were placed in the muscles opposite the inferior vena cava and iliac veins at the first operation and flows repeated several days or weeks later at these sites. The catheters were introduced into the femoral vein through a needle, which was withdrawn after the catheter was in the vein, and appropriately placed using the fluoroscope for guidance.

To compare this method with direct measurements of flow, kidneys were transplanted to the neck as autografts or homografts. The renal artery was anastomosed end-to-end with the common carotid artery, the renal vein end-to-end with the external jugular vein and the ureter brought out to the skin. After blood flow was well established, the retrograde-spray catheter was introduced through a needle (which was withdrawn after the catheter was in the vein) into the transplanted renal vein. Indicator was injected at a constant rate (50 to 80 ml/min) and simultaneous samples taken. The catheter was removed and the vein immediately cut; the flow was measured directly for 15 seconds.

Results

EXPERIMENTS IN VITRO

It was technically possible to develop a double lumen tube-within-a-tube forward-spray catheter slightly smaller than the retrograde-spray catheter, the outer diameters being 2.45 and 2.75 mm respectively. The limiting factor was the size of the sampling lumen, which had to be large enough in its inner diameter to deliver 0.3 ml per revolution through the automatic pipette without formation of air bubbles from suction. The side-by-side catheters with spray injections had the same accu-
racy as the tube-within-a-tube catheters with stainless steel heads of similar size. The accuracy of the open-end catheters fell off rapidly in tubes greater than 10 mm inner diameter, especially at slow injection rates. In tubes 10 mm inner diameter and larger the position of the catheter tip also influenced mixing, which was not observed with the spray-injection catheters. In the 5 mm inner diameter tube, catheter size, injection rate, and separation distance of sampling and injecting lumens were critical factors, injection rate being the least important. Using the larger tube-within-a-tube retrograde-spray catheter, good mixing was more dependent on the separation distance of sampling and injection lumens than with the smaller forward-spray catheter. The minimal distance for good mixing was 10 mm at any rate of injection (fig. 5). With the smaller forward-spray catheter, good mixing occurred with the sampling lumen 7 mm from the injection lumen, but inadequate mixing if they were separated by 5 mm. However, at high flows, the accuracy was better if the injection rate was increased (fig. 6). In the 5 mm inner diameter tube, using open-end catheters the separation distance of sampling and injecting lumens was not critical, 5 mm being adequate for good mixing. The presence of the larger retrograde-spray catheter in the 5 mm inner diameter tube began to affect the flow at about 310 ml/min and the smaller forward-spray catheter at about 360 ml/min.

In larger tubes, the separation distance of sampling and spray-injecting lumens became less important than the injection rate and catheter size. Figure 7 shows the results of the retrograde-spray tube-within-a-tube catheter in a 10 mm inner diameter tube at various injection rates, the sampling and injecting lumens being separated by 7 mm. By increasing the injection rate, adequate mixing and accurate estimated flows extend over faster flow rates. However, if the injection rate is too fast, flow may be reduced. This is true for any size tube. When rapid injection alone changed the flow, good mixing occurred and estimated flow was the same as actual flow during the injection up to the point where the presence of the catheter in the tube began to affect the flow.

When the optimal injection rate and separa-
VENOUS FLOW BY INDICATOR DILUTION

**FIGURE 7**

Estimated flow rates of water in a 10 mm inner diameter glass tube plotted against actual flow rates, using the tube-within-a-tube retrograde-spray catheter with sampling and injecting lumens separated by 7 mm. KI151 used as indicator with injection rates varying from 74 to 189 ml/min.

MEASUREMENTS OF LOCAL VENOUS FLOW IN DOGS

Table 1 presents normal values of venous flow in the portal vein, inferior vena cava above and below the renal veins, renal, iliac, and femoral veins in four dogs. Two problems were encountered during these measurements. If the injection rate was too fast (greater than 90 ml/min) in the renal veins, flow was frequently reduced. In the central and peripheral veins, injecting the indicator at a rate of 120 ml/min or greater frequently produced hemolysis and vasodilatation. However, repeated flow measurements in the renals, portal, central, and peripheral veins, under stable conditions, at an injection rate of 60 to 90 ml/min gave small variations. Figure 10 shows a portal phlebogram made with the retrograde-spray catheter.

The correlation between estimated and direct measurements of venous flow in kidneys transplanted to the neck is shown in figure 11. During injection no visual distortion of the vein was noted. An injection lasted from seven to ten seconds, which was long enough to clear the sampling lumen and collect a sample.

Attempts were made to leave these catheters in veins during chronic experiments. Several problems were encountered: (1) inability to secure them in place as they were usually out or dislodged by the fourth day; (2) nylon...
irritated the veins and resulted in fibrous stricture especially in the renal veins; (3) if the catheter was made from inert materials like Teflon, it became too soft after a few hours and the lumen collapsed on suction, preventing sampling.

These problems led to the development of an introducer needle, which obviated the necessity of leaving the catheters in veins for chronic experiments. At the first operation, a radio-opaque marker was placed in the muscle opposite the site in the vein where repeat flow estimations were desired and under fluoroscopic guidance the catheter tip was placed there, introducing it via the external jugular or femoral vein percutaneously. Through the sampling lumen venous pressure may also be measured. Although the introducer needle for the tube-within-a-tube retrograde-spray catheter was 3.65 mm in its outer diameter, severe damage to the vein was usually avoided. These nylon catheters had one disadvantage in that they did not withstand repeated usage.

**Discussion**

The basic assumption on which the application of this constant indicator dilution method to the measurement of local venous flow is based, is that uniform mixing of the indicator and blood occurs throughout the segment of vessel before sampling. Mixing occurs when the critical Reynolds number is exceeded, the

![FIGURE 9](http://circres.ahajournals.org/content/14/5/384.full.jpg)

*High speed flash photographs of mixing of Coomassie blue dye and water at different rates of flow in a 10 mm inner diameter tube using the retrograde-spray tube-within-a-tube catheter. Injection rate 120 ml/min.*

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point at which laminar is converted to turbulent flow. Injecting against the stream and through fine holes in the catheter tip makes this possible. In model experiments, several factors were found necessary to achieve adequate mixing in any given size glass tube: (1) flow rate in the tube, (2) catheter size, (3) separation distance of sampling and injecting lumens, and (4) rate of indicator injection.

Although the spray-head injection catheters are better in large tubes, in very small tubes a minimum separation distance of sampling and injecting lumens is necessary, and open-end catheters are more satisfactory.

Although the optimal conditions necessary to achieve adequate mixing over a short segment of glass tube have been established, several points must be considered in the application of this method to flow estimations in vivo. If the sampling lumen is opposite a tributary vessel, a true sample of mixed blood may not be obtained resulting in overestimations of flow. This can be overcome by making several estimations over short segments of the vein.

It is for this reason that the sampling and injecting lumens should be as close as possible. The injection rate should be the lowest that will give adequate mixing for the maximum flow in the vessel under study, usually 60 to 90 ml/min. The volume of flow above which complete mixing does not occur is much higher in any given size tube with these catheters than is ever likely to be encountered under physiological conditions. The spray injection as described does not seem to affect the veins, but hemolysis has been noted at rapid injection rates. This is presumably the result of the liberation of adenosine triphosphate from the damaged red cells, resulting in the vasopressor response.

The method probably has one disadvantage in that it measures only mean flows and phasic changes cannot be observed. The advantages probably overshadow this, for it is accurate, calculations are simple, operation is easy, and estimations are not dependent on catheter position in the vessel or factors affecting the blood or surrounding tissues. It offers a unique way of estimating portal venous flow independent of hepatic artery flow under surgical conditions. Chronic experiments are possible without repeated vessel exposure, permitting venous flow estimations under virtually normal physiological conditions.
Summary

A method for measuring local venous flow by a constant indicator dilution technique is described. The optimal conditions have been outlined and the accuracy tested in vitro and found to be within ± 3%. When compared with direct measurements of venous flow in dogs, its accuracy was within ± 5%. The method is safe, easy to perform and, with the catheters described, flow can be measured over ranges of 20 to 5,700 ml/min in any vein greater than 4 mm inner diameter in which the catheter tips can be introduced.

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References

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