Evaluation of Roentgen Cinedensitometry for Flow Measurement in Models and in the Intact Circulation

By Wilhelm Rutishauser, M.D., Hansjörg Simon, M.D., Jean Paul Stucky, M.D., Niklaus Schad, M.D., Giorgio Noseda, M.D., and Josef Wellauer, M.D.

SUMMARY

The flow of blood in vitro and in the carotid artery of the dog was calculated by a new cinedensitometric technique and compared with the flow as measured simultaneously by graduated cylinder and stopwatch. Cineangiographic films were projected onto a frosted screen and the light intensity was measured at two neighboring cross sections of the vessel in question. The passage of the contrast medium yielded a pair of indicator-dilution curves of which the difference in mean transit time was calculated. The distance between the cross sections and the diameter of the vessel was measured with the aid of x-ray-dense scales. The flow through the vessel was calculated as the product of cross-sectional area and mean velocity.

The correlation coefficient between the volumetric flow and the flow as found by cinedensitometry was 0.976 in vitro and 0.946 in the intact dog with no systematic deviation from the line of identity. The method enables the blood flow in the intact circulation to be calculated in milliliters per second in any vessel that can be clearly visualized by cineangiocardiography.

Additional Indexing Words:
Indicator-dilution method  Mean circulation time  Blood velocity
Blood flow pattern  Carotid flow  Contrast medium for blood flow determination

Angiocardiography has been studied widely from the point of view of its morphological applications. Until recently, however, only a few attempts had been made to utilize the injection of contrast media for quantitative flow studies of the circulation.1-5

To the knowledge of the present writers, Wood and his group were the first to recognize the functional potential of angiocardiography as an indicator-dilution method. They worked first with the film and subsequently with the television technique.6-9

The experiments described in the present paper were designed to study the reliability of blood flow measurements using a cinedensitometric technique. Angiographic films were projected, and the light intensity was recorded at selected sites during the passage of the contrast medium. The envelope of the observed light intensity versus time curve corresponds to an indicator-dilution curve. The flow was calculated as the product of mean velocity (that is, the distance between two cross sections divided by the mean transit time) and the cross-sectional area of the vessel. The rates of flow thus determined were compared with those found with the aid of a calibrated cylinder and stopwatch in both the vitro and the in vivo experiments.

Methods

The flow was measured in Teflon tubes and in the carotid artery of dogs. The methods applica-
Mg-methrizoate, the a onto with a cm, 25 mg

This pump has an extremely fast pressure rise (90% in 25 msec) and either delivers a pre-selected volume of contrast medium, triggered by hand or by the ECG, or provides a time-controlled diastolic injection triggered by the ECG according to the intermittent-injection technique.10

The passage of the contrast medium was recorded on 35-mm Kodak + X film by means of an x-ray source (generally unpulsed), using a Phillips 9-inch image intensifier and an Arriflex camera2 at a speed of 48 to 53 frames/sec. The injection period and the ECG were recorded on an Elema type, EM 8 direct writer** and sometimes by means of a cinetrace system on the film. A half-second signal was projected onto the film to record the exact number of frames per second during the exposure.

A contrast wedge, that is, a series of known concentrations of Isopaque (c, c/2, c/4, c/8, c/16, c/32, c/64, and c/128) in plane parallel plexiglass cuvettes with a depth of 0.5, 1, and 2 cm, was used for relative calibration of the contrast medium (fig. 1). The cuvettes whose depth approached most closely to the diameter of the tube or vessel to be measured were moved over the area under examination just before the injection of contrast medium. During the actual injection and passage of the contrast medium a layer of water of the same depth as the cuvettes was left over the area.

The films were processed by hand as uniformly as possible at 20 C for 10-minute periods with the aid of Kodak D 76 developer. They were projected in a specially designed Askania projector†† with a DC light source (12-volt, 100-watt lamp) onto a frosted glass screen whose distance from the objective could be varied between 50 and 110 cm (fig. 2). The light intensity was simultaneously measured with two Siemens TP 60 sili-

can photoelectric cells† selected because they have roughly the same sensitivity and a logarithmic relationship between voltage and light intensity. The photoelectric cells could be adjusted on a coordinate system to any point of interest on the frosted glass screen. Different apertures of the photoelectric cells (slits of 1, 2, 3, or 4 mm) and the variable distance of the frosted glass from the objective made for optimum adaptation of the light-sensitive area to the structure under examination. The output of the photoelectric cells was recorded on an Electronics for Medicine recorder.‡ The speed of film transport in the Askania projector could be infinitely varied during projection between 3 and 36 pictures/sec. During the recording of the indicator-dilution curves the film was transported at exactly one tenth of the speed used during exposure.

†Siemens Reiniger, Erlangen, Germany.
‡Electronics for Medicine, Inc., White Plains, New York, U.S.A.

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*Na-methrizoate, 660 mg; Ca-methrizoate, 28 mg; Mg-methrizoate, 25 mg; and Methylglucamine-methrizoate, 37 mg per ml; Nyegaard & Co., Oslo, Norway (Ronpacon 440, Citag-Chemie, Schaffhausen, Switzerland).
†Oedmann, Kifa, Sweden.
‡Siemens A. G., Dept. SRW, Zurich, Switzerland.
§Arnold & Richter, Munich, Germany.
**Elema Schöneider, Stockholm, Sweden.
††Kinotechnik A. G., Zurich, Switzerland.

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Figure 1

X-rays of contrast wedges in plexiglass plates (17.5 by 28 cm) used for relative calibration of the concentration of contrast medium. The layer thickness of the cuvettes on the left is 1 cm and of those on the right 2 cm. Eight cuvettes, filled with a geometric series of dilutions of Isopaque with water (pure Isopaque = c, c/2, c/4, c/8 ... c/128), are followed by a large cuvette containing water only. It will be noted that the x-ray absorption of, for example, the 1-cm cuvette containing c/4 is approximately the same as that of the 2-cm cuvette containing c/8. After the various concentrations have been moved over the object (so that changes in deflection due to a known change of concentration are known at any point), the large water-filled cuvette covering the whole x-ray field is left over the object during injection and passage of contrast medium.
For continuous projection, the films were mounted as endless loops. During the transport phase of each frame the diaphragm was closed so that no light fell on the photoelectric cells, with the result that the signal fell to the base line (fig. 4). In some recordings a cone blind with two slits was used to reduce flickering; it closed a second time during the standstill phase of each frame. In these cases the signal reached the same height twice and dropped to the base line once during the projection of each frame (fig. 3). The envelope of the output of the photoelectric cells during illumination corresponds to an indicator-dilution curve.

The flow $Q$ was calculated by means of the following formula:

$$ Q = \left( \frac{d}{2} \right)^2 \pi \frac{\Delta s}{\Delta t} $$  \hspace{1cm} (1)

In this formula $d$ is the diameter of the vessel or tube. In the in vitro experiments this diameter was measured directly, and in the experiments with dogs it was calculated on the basis of the projected image of the vessel corrected to the real value by means of a known scale. In case of different diameters their squares were averaged.

The symbol $\Delta s$ represents the distance between the two photoelectric cells A and B, which were set to take readings over two cross sections of the vessel, measured from center to center of each aperture and similarly corrected to the real value by means of the scale.

The symbol $\Delta t$ represents the difference in mean transit time between the pair of indicator-dilution curves recorded with the photoelectric cells A and B. It was found (in some curves after extrapolation of the tail) by means of the following formula:

$$ \Delta t = \frac{\int c_B (t) \cdot t \, dt}{\int c_B (t) \, dt} - \frac{\int c_A (t) \cdot t \, dt}{\int c_A (t) \, dt} \hspace{1cm} (2) $$

where $c_A$ and $c_B$ are the concentrations at the two measuring sites.

When the relationship between the concentration and the deflection due to transmitted light, as found by means of the contrast wedge, was linear (fig. 3) or nearly so, the envelopes of the curve were copied onto thick paper and cut out. The line perpendicular to the time axis running through the center of gravity was found by balancing each curve on the edge of a knife. Where the relationship between concentration and deflection was not linear, the curve was linearized.
In theory, Lambert-Beer's law is valid only for monochromatic x-rays. The low-energy x-rays were therefore filtered out with copper and aluminium in some experiments to obtain monochromatic x-rays.

**In vitro Experiments**

The system of cinedensitometric in vitro flow measurement is shown schematically in figure 5. Human blood was pumped by a roller pump from a reservoir through a closed circuit. The roller pump produced an almost steady flow that could be varied at will and led by means of clamps through Teflon tubes of internal diameter 6.1, 9.0, 10.5, or 12.0 mm. An x-ray-dense scale was placed just outside the tubes. Films were exposed with 90 to 100 kv and 5 ma, with the soft x-rays being filtered out by 1.2 mm of copper and 6 mm of aluminium. By this means it was attempted to obtain a linear relationship between deflection and concentration (fig. 3).

Before the contrast medium was introduced by the high speed injector, the contrast wedge was passed over the field so that the increase in light due to a known increase in iodine concentration could be measured at any point. A volume of 4 to 6 ml of Isopaque 75% was then injected in 0.10 to 0.15 sec. Before each injection the blood flow was directed into a calibrated cylinder and the volume was collected for a given period of time, usually 10 to 30 sec.

**In vivo Experiments (Dog)**

The flow through the left carotid artery was measured in five dogs cinedensitometrically and at the same time volumetrically as shown in the schematic diagram in figure 6. After premedication with approximately 1 mg of morphine sulfate per kilogram of body weight, the animals were anes-
thetised with 90 mg/kg of alpha-chloralose, intubated, and connected to an Engström respirator Model 200* for positive pressure respiration with a frequency of 20/min and a ventilation of 6 to 9 L/min. The following catheters were inserted. A grey Oedmann catheter with tapered end and six side holes (length, 60 cm) was advanced from the right carotid artery into the ascending aorta for the injection of Isopaque. A 7 F Teflon catheter was advanced from the right femoral artery to the descending aorta for pressure measurements. A no. 6 Goetz bipolar electrode catheter† was inserted in dogs 2, 3, and 4 via the left femoral vein and advanced into the upper part of the right atrium or the outflow tract of the right ventricle for pacing the heart at constant frequency. A 10 F Lehmann catheter‡ was inserted into the right femoral vein for reinjection of blood and chloralose. The left carotid artery was dissected near the base of the skull and in the lower part of the neck. After anticoagulation with 300 IU of heparin per kilogram of body weight, a piece of metal guide exactly 5 cm in length and 0.06 cm in diameter was introduced through the cranial thyroid artery so that it lay within the lumen of the carotid artery. The guide was used as a scale for accurate dimensional measurements. Care was also taken to tie off other intervening side branches of the carotid artery. A three-way valve with an inner diameter of 4.5


†United States Catheter and Instrument Company, Glens Falls, New York, U.S.A.
Isopaque was injected for the exact period of one diastole (usually 7 to 10 ml), or in some cases a predetermined volume (up to 18 ml) was injected from the beginning of the diastole. A few seconds before the injection of the contrast medium the three-way valve was turned and the blood collected in a calibrated cylinder before and during the passage of the contrast medium. The collection time varied between 2.2 and 12.8 sec.

Results

In vitro Experiments

In the model circulation the measurement of the blood flow through the tubes by cinedensitometry is very accurate. The experimental values found are plotted in figure 7. There was no systematic deviation between the values obtained by cylinder and stopwatch and those found densitometrically. The correlation coefficient of the two methods was 0.976.

In vivo Experiments

The detailed results of the volumetric and cinedensitometric flow measurements in five

mm was inserted into the carotid artery at the base of the skull so that the blood flow to the head could be diverted instantaneously. The wound at the neck was then closed by sutures.

For the flow measurements the dogs were in the left lateral decubitus position and the neck was turned so that the x-ray projection of the left carotid artery was free from other underlying arteries. For dog no. 1 the films were exposed with the same x-ray data and filtering as in the model experiments, and in dogs 2 to 5 with 70 to 82 kv and 5 to 10 ma. A linear relationship between iodine concentration and deflection was found only over a certain range of concentrations.

The flow through the carotid arteries was controlled by altering the depth of anesthesia or by ventilating the dog with a concentration of 7% CO₂ in oxygen. Decrease in flow during the period of measurement could be obtained by increasing the outflow resistance by means of a clamp. The flow always slowed down spontaneously toward the end of the experiment. Because of pronounced sinus arrhythmia in dogs 2, 3, and 4, the heart was paced from the right atrium or right ventricle at a constant rate.

Comparison of cinedensitometric and volumetric measurement of blood flow in carotid artery of dog. A three-way valve (S) is built into the left carotid artery near the base of the skull so that the blood flowing through the artery can be collected. With the aid of an x-ray tube (X), an image intensifier (II), and a cinecamera (FC), a film is exposed while the contrast medium injected into the ascending aorta (A) by the injection pump (I) passes through the artery. At the same time blood is collected in the cylinder (C) and the rate of flow is calculated with the aid of the stopwatch (W). The contrast wedge (CW) is passed over the field under examination prior to the injection. The artery is measured with the help of the scale (M).
dogs are given in table 1. The distance between the two photoelectric cells varied from 4.50 to 7.44 cm, and the mean diameter of the carotid artery from 3.64 to 5.25 mm. Changes in diameter between systole and diastole were usually smaller than 5%. In many experiments no change was visible. The difference in mean circulation time varied between 0.052 and 0.174 seconds. The experimental flow values found in five dogs are plotted in figure 8. There was no systematic deviation between the flow as measured by graduated cylinder and stopwatch and that found by cinedensitometry. The correlation coefficient was 0.946. Out of 47 measurements five deviated more than 20% from the line of identity.

Discussion

Many methods for measuring the blood flow in single vessels are currently available. All those that measure the flow in absolute units (that is, milliliters per second) entail the insertion of a sensing device into or around the vessel in question. For this reason measurements in absolute units of the flow through individual vessels in the intact circulation, and particularly in conscious man, have not been widely possible. The method described here makes it possible to measure the flow in any unbranched vessel outlined clearly by angiocardiography in intact conscious man without the insertion of a sensing device.
Table 1
Comparison of Volumetrically and Densitometrically Determined Flow of Blood in Left Carotid Artery of Five Dogs

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<th>t (sec)</th>
<th>Qv (ml/sec)</th>
<th>d (cm)</th>
<th>Δs (cm)</th>
<th>Δt (sec)</th>
<th>Qd (ml/sec)</th>
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<td>5.98</td>
<td>0.111</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>8.8</td>
<td>4.5</td>
<td>0.372</td>
<td>5.98</td>
<td>0.119</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Abbreviations: V = collected volume; t = collection period; Qv = volumetric flow; d = mean diameter of artery; Δs = distance between photoelectric cells; Δt = difference in mean circulation time; Qd = densitometric flow.
Figure 8

Comparison of rate of blood flow through left carotid arteries of five dogs as measured volumetrically and densitometrically at the same time. The y-axis gives the flow rate calculated with the aid of the cylinder and stopwatch, and the x-axis, the rate calculated by means of formula 1 from the indicator-dilution curves. The correlation coefficient is 0.946 and there is no systematic deviation between the two methods. The best equation through all individual points and the origin is \( y = 0.98x \). The line of identity \( y = x \) is indicated.

Indicator-dilution methods have proved to be very valuable for flow measurements. The indicator-dilution principle commonly used, however, can be applied to single vessels only if all the injected indicator or a known quantity of it passes through the vessel in question and if the absolute concentration (that is, mg/ml) of the indicator after mixing is known. For the technique described in this paper it is necessary to know neither the quantity of indicator passing through the vessel nor the concentration in absolute units since these two values do not appear in formula 1. It is accordingly possible to inject the indicator somewhere upstream in the central circulation for arterial flow measurements or in the peripheral circulation for venous measurements, while calibration of the relative concentration of the indicator can be done easily with the aid of a contrast wedge.

The flow measurement outlined here is independent of flow pattern. It is irrelevant whether the flow in the vessel is turbulent or laminar. In contrast to other indicator-dilution methods in which measurements are made at a point or a circumscribed area (conventional and fiber optic-dye dilution, thermodilution), the indicator is detected as an integrated
sample, since the photoelectric cells are arranged in such a manner that they observe the entire cross section of the vessel. All particles of the indicator passing cross section A will eventually pass cross section B.

With the technique described it is possible to record as many indicator-dilution curves at multiple sites as are required by using several photoelectric cells or replaying the film or both.

The method has a high dynamic response depending on the number of frames of the camera.

Factors Influencing Accuracy of Flow Measurement

1. In vitro Experiments

In the circulation model the accuracy of the flow measurement was referable in part to the constant diameter of the tubes, which could be measured with great precision. In addition the background of the model was of uniform x-ray absorption, and there was a linear relationship between the concentration of the contrast medium and the deflection of the curve since the low-energy x-rays had been filtered out by copper. Thirdly, there was for practical purposes no pulsatile flow since a roller pump was used. Thus, the velocity of the indicator could be regarded as constant, and the distance between the photoelectric cells could not become a critical factor. This part of the study was no more than an experimental confirmation of Meier and Zierler’s neat mathematical proof for the measurement of blood volume from mean transit time and output under the simplest conditions (cylindrical vessel, steady flow) with the aid of a radiopaque indicator.

2. In vivo Experiments

Diameter of the Vessel

For the measurement of flow in the intact circulation the roentgenopaque picture must be of good quality, mainly because accurate measurement of the diameter of the vessel, which is squared in the formula, is essential. The observed changes in the diameter of the carotid artery during systole and diastole were small, less than 5% and often not perceptible. Inconstant diameter of the artery may be a source of error. Such errors were minimized by averaging the diameters measured at different points and at different times between the two cross sections where the photoelectric cells were located.

X-ray Absorption and Measurement of Indicator Concentration

Differences in background (that is, differences in the x-ray absorption at the two measuring sites) might also interfere with the accuracy of in vivo measurements. The same change in concentration and layer thickness of the contrast medium may lead to different changes in light intensity if the measurements are made over more or less dense areas (bone, trachea, and so forth). To eliminate this potential error, the change in deflection caused by the passage of a known step of the contrast wedge was made equal for both photoelectric cells in a given position by adjusting the gain on the recorder. A relative concentration scale with reference to zero contrast medium in the blood is sufficient for calculation of the mean circulation time. Background effects of tissue will affect calculation of the mean transit time only if contrast medium is detected passing through superposed structures as a function of time. It is, of course, essential that x-ray projection be done in such a manner that no other large artery underlies the measurement site. Since the flow in the arteries is faster than in the branching adjacent small vessels and capillaries, it is probable that these background changes are not a very important factor for measurement of arterial flow. If necessary they could be compensated for by simultaneously sensing the concentration immediately beside the artery and as close as possible to the two photoelectric cells A and B and subtracting the value found. In the experiments described, this was not necessary.

It is desirable that the relationship between the concentration of the contrast medium and the deflection of the recording apparatus should be linear. This is a difficult requirement to satisfy and sometimes is possible only over a certain range of concentrations. Too
many interfering factors are involved: even if nearly monochromatic x-rays are used (so that Lambert-Beer's law applies), the function of the image intensifier, the quality of the film and the development process, and the sensitivity of the photoelectric cells will all affect linearity. Since the sequence of processes involved in the recordings cannot be assumed to be completely unchanging from one experiment to another, it is necessary to provide for individual calibration of relative concentration by means of the contrast wedge at any point and in each experiment. By means of this procedure linearization of the concentrations at any area of measurement is possible. For the determination of the mean circulation time by the equilibrium method, however, it must be conceded that linearity of concentration calibration is not very critical since only the difference in mean circulation time figures in the formula: if non-linearity had been about equal at both cross sections and had not been taken into account, both apparent mean circulation times would have been shifted in the same direction and to a roughly equal extent.

**Nonstationary Flow Conditions**

The effect of time-average versus flow-proportional sampling in conventional indicator-dilution methods may lead to an error in all unstationary conditions of flow.\(^\text{16}\) The distance between the two photoelectric cells may become critical in nonstationary flow conditions of the type obtaining in the animal and human circulation: If the mean distance traveled by the indicator during one cycle is longer than the distance between the two cross sections at which measurement is carried out, an appreciable error in the densitometric flow calculations might result. This would be the case, however, only if the spatial dispersion of the bolus of indicator were small compared with the distance between the two cells, and this could be compensated for by injecting the indicator at an upstream site more distant from the cross sections. Since in the experiment described the contrast medium was injected not into the carotid artery but into the ascending aorta, this error was of no importance. The heart cycle length was always much shorter than the passage time of the indicator bolus. In the event of transient back flow in a vessel, the error could become more important. Variations in the heart rate and stroke volume during the period of blood collection may also act as an apparent source of error and increase the scatter. Since the sampling of the blood was usually done over a period of time much longer than that required for passage of the indicator bolus past the points of measurement, individual differences between the calculated flow and the flow as measured by cylinder and stopwatch could be expected to arise. Cinedensitometry determines the flow over the short period of passage, while volumetric sampling gives an average over a longer period during which the rate of flow may fluctuate. This conclusion is supported by the observation that the scatter of the values was greater in the presence of marked arrhythmia whereas it tended to be smaller when the heart was paced electrically at a constant rate.

**Hemodynamic Effects of Contrast Media and Mode of Injection**

An essential requirement for any indicator is that it should behave like blood and that it should possess no pharmacological action of its own. Changes in hemodynamics resulting from the injection of contrast medium into the heart or the vessels have been reported by many researchers.\(^\text{17-23}\) Hemodynamic changes are clearly dependent on the dosage and the nature of the hyperosmotic substances introduced. In the experiments described the amount of contrast medium injected into the circulation for a single measurement was small, usually 0.2 to 0.3 ml/kg of body weight, that is, about one fifth of the dosages generally reported. Decreases in the peripheral resistance, one of the most marked changes induced by contrast media, probably occur when the hyperosmotic agent reaches the arterioles and capillaries. If the contrast medium is injected into the ascending aorta,
about 2 sec pass before it reaches the periphery. A procedure for flow measurement that does not take longer than 2 sec from the beginning of the injection until the moment when measurement is complete should therefore not be greatly affected by any pharmacological action on the part of the contrast medium.

The method described really measures plasma flow, since the contrast medium is restricted to the plasma phase of the blood, while the erythrocyte volume shrinks due to the hyperosmolarity. Under the experimental conditions employed, however, any difference between plasma flow and erythrocyte flow is clearly negligible.

Low-viscosity contrast medium and a quick injection are also important. An injection pump with a slow pressure rise will not deliver a short bolus thoroughly mixed with the blood that can be observed completely before its front reaches the capillaries. The possibility that high velocity injection may destroy erythrocytes cannot be excluded. It is known that hemolyzed blood has a vasodilative property due to adenosine triphosphate and possibly other substances released from the erythrocytes. Again, however, this effect can occur only if the hemolyzed blood reaches the periphery, which probably does not happen during the time required for measurement.

The further development of contrast media will, it is hoped, produce agents whose pharmacological effects at the doses required are entirely negligible. The development of high-speed cinematographic equipment (200 or more frames/sec) may lead to greater accuracy in the measurement of differences in the mean transit time over shorter distances.

The injection of radiopaque media is a routine procedure in every vascular diagnostic unit. If cine-equipment can also be made available, the method described in the foregoing will make possible not only morphological assessment but also measurement of the most important functional parameter, namely, the flow of blood through the vessels in absolute units.

Cinedensitometry has been used up to July 1967 in 187 patients. Flow was measured through the carotid, renal, splenic, hepatic and even coronary arteries as well as the caval veins.

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