Radiologic Technic for Qualitative and Quantitative Study of Blood Flow

By Charles T. Dotter, M.D., and Louis H. Frische, M.D.

Radiology is the only practical means for directly visualizing the motion of blood within the cardiovascular system of intact subjects. It not only makes possible the direct determination of the instantaneous velocity and volume of blood flow, but also allows the demonstration and localization of abnormal intravascular turbulence generally accepted as the source of heart murmurs. In radiologic visualization, a direct and highly informative approach to hemodynamics appears to have been overlooked in favor of more elaborate but less direct, reliable or productive techniques such as ballistocardiography, phonocardiography and vectorcardiography. Does the aeronautical engineer confine his attention to listening to the outside of the wind tunnel? The question is purely rhetorical.

Laminar and Turbulent Flow—Basic Considerations

Fluids in motion may be said to exhibit laminar or streamline flow when all component motion is unidirectional. Disregarding static factors, the energy loss in laminar flow is mainly determined by friction, which in turn is related to the viscosity of the fluid and the characteristics of the system through which it moves. Frictional energy-loss occurs mainly between layers of fluid near the periphery of the stream since the layer in contact with the containing wall is theoretically stationary. The velocity contour of such a stream is parabolic in shape. Maximum velocity occurs in midstream and amounts to twice the mean velocity.

Turbulent flow, on the other hand, involves multidirectional movement at different points within the stream. The net effect of factors which determine the character of flow is conventionally represented by Reynolds numbers—a dimensionless expression—the value of which varies directly with the size of conduit, the density and mean velocity of the fluid, and indirectly with the viscosity. Turbulent flow usually occurs when the Reynolds number exceeds 2,000.

In the cardiovascular system, turbulent flow favors efficient mixing; laminar flow favors the transportation of blood. Although perhaps all murmurs are due to turbulence, the converse is not true, judging from the combined evidence of contrast visualization and intracardiac phonocardiography. Theoretically, the murmur implies inefficiency since the production of sound wastes a finite though small amount of the heart’s labor.

Unlike a glass circulatory model, the cardiovascular system does not lend itself to mathematical analysis of isolated factors governing fluids in motion. Though basic hydrodynamic principles certainly apply to the circulatory system, the modifying influence of elasticity, compliance and contractility of blood vessels is difficult to assess and even harder to control. Additional complications are introduced by the fact that blood flow is neither steady nor uniform. Indeed, the cyclic variation in the intensity of a murmur is but the audible manifestation of a continuously rising and falling Reynolds number!

The approach described in this report suggests that it is feasible to obtain fairly accurate cyclic curves expressing the velocity of blood and the caliber of the vessels through
which it flows. Since the density and viscosity of blood would not be likely to change during the period of observation, it follows that in various locations Reynolds numbers might be derived as a nearly continuous function of the heart beat.

MULTIPLE EXPOSURE TECHNICS FOR RADIOLOGIC STUDY OF INTRAVASCULAR MOTION

Multiple exposure photographic technics have been used successfully for tracking satellites, advertising girdles and determining blood velocity. However, the cardiovascular application is unavoidably limited, being confined to photographically accessible structures (superficial capillaries) or highly artificial experimental situations (circulation models, bubble flowmeters, etc.). Radiology overcomes the limitations through its ability to record pictorially the changes in position—and thereby the velocity, acceleration, deceleration and path of motion—of objects deep within the intact circulatory system.

The basic principle is exceedingly simple. When two x-ray exposures of a moving object are cast on the same film and the intervening time is known, the distance between the resultant double-image permits calculation of the object's velocity. Controlled experiments using objects moving at known velocities and rates of acceleration or deceleration have shown the reliability and limitations of this method of study (fig. 1).

Each year literally thousands of chance-begotten motion studies slip unnoticed past the sharpest eyes in clinical medicine, those of radiologists (!). Seemingly single, the routine x-ray exposure actually consists of a series of evenly-spaced bursts which are ordinarily superimposed to cause only one image on the film. Since the time interval between these impulses is exactly 1/120 second, it is possible to determine velocity of an object during an x-ray exposure by observing the distance between successive images. Typical examples of fortuitous velocity determinations are shown in figure 2.

Since one radiograph provides a two-dimen- 

sional record of three-dimensional objects, it follows that velocity cannot be measured without making allowances for movement toward or away from the x-ray tube. Simultaneous filming in two different planes is desirable in order to obtain empirical data concerning this variable.

In addition to facts about velocity, pictures can give information concerning the direction or path of motion. Night, "time-exposure" photography provides familiar illustrations of the basic principle (for example, in the streaks caused by moving headlights or the pattern of bursting fireworks). In a similar manner, radiographs can be used to study turbulent motion. The streaked images of moving radiopaque objects demonstrate the paths of their movement. Where high velocities are involved, the images of test objects will tend to be "over-extended" or blurred and thus harder to see. In order that the radiographic appraisal of velocity as well as direction of flow be made at the same time and with maximum precision, it is desirable to employ very short, pulsed, multiple exposures of known duration and frequency. The shorter these exposures, the sharper the resultant images; the briefer the pulse-to-pulse
interval, the faster the motion which can be studied. It seems unlikely that movement "in depth" will prevent the study of flow-patterns, though it complicates the task.

In short, it is clear that radiology offers promising means for the study of the two major hemodynamic parameters, velocity and direction of flow. There is no doubt that radiologic study of these parameters may be applied to blood in motion, since we have done so repeatedly. Over three thousand radiographs were exposed in studying motion and evaluating various contrast agents for this purpose. The comments which follow are based on experimental data and practical experience.

Special Contrast Agents

Conventional methods of angiocardiography have proved highly useful in the delineation of gross anatomic structures and have been helpful in determining mean circulation times. Unfortunately, however, the contrast agents now in general use are far from satisfactory. Because of them, angiocardiography is an unpleasant experience to the patient and is not without risk. Heretofore, the procedure has involved the exclusive use of organic iodine-containing molecules in water solutions, several of which are commercially available. Due to their high miscibility, particularly in the presence of motion, these preparations fail to provide an adequate interface with sur-
Fig. 3. Various contrast media in right-heart of dog during angiocardiography. A. Urokon Sodium 70 per cent, aqueous solution. Intra-atrial turbulence is evident. B. Lipiodol droplets. C. Mallinckrodt MIV-311BL (high-viscosity Urokon preparation). Laminar flow in pulmonary arteries clearly demonstrated. D. Mallinckrodt MM-27 (2 mm. solid pellets of Urokon 80 per cent and Dextrin 20 per cent, suspended in aqueous solution of 20 per cent Urokon).

rounding blood. They consequently cannot serve as reference points for the radiographic study of blood velocity, a problem best solved through the use of contrast media producing multiple small, discrete, punctate or particulate areas of intravascular radiopacity.

When high-viscosity solutions are employed as an alternate approach, useful information can be obtained about flow patterns within the right atrium and its tributaries. Thereafter, turbulent mixing during right ventricular filling defeats the purpose. Striking exceptions were noted in the Mallinckrodt MIV series (high viscosity preparations of Urokon Sodium), some of which were clearly capable of demonstrating laminar flow in the pulmonary arteries of the dog. Contrast agents, the properties of which we have studied in dogs, are presented in table 1. Figure 3 shows the appearance of several types of media.

It is not within the scope of this discussion to cover fully the many problems which re-
TABLE 1.—Partial List of Contrast Media Tested for Applicability to Motion Studies In Dogs

<table>
<thead>
<tr>
<th>Agents</th>
<th>Remarks</th>
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<tbody>
<tr>
<td>Commerically available</td>
<td></td>
</tr>
<tr>
<td>Diodrast, Hypaque, Miokon,</td>
<td>Watery, organic iodine-containing intravascular agents used in various concentrations.</td>
</tr>
<tr>
<td>Renografin, Urokon Sodium</td>
<td></td>
</tr>
<tr>
<td>Ethiodol</td>
<td>Viscid, bronchographic agent.</td>
</tr>
<tr>
<td>Lipiodol</td>
<td>Oily, bronchographic agent.</td>
</tr>
<tr>
<td>Iodoehloral</td>
<td>Oily, bronchographic agent.</td>
</tr>
<tr>
<td>Salpix</td>
<td>Viscid, Urokon Sodium preparation for hystero-therapy.</td>
</tr>
<tr>
<td>Dionosil, aqueous</td>
<td>Watery, bronchographic agent.</td>
</tr>
<tr>
<td>Dionosil, oily</td>
<td>Oily, bronchographic agent.</td>
</tr>
<tr>
<td>Thorotrace</td>
<td>Watery, thorium dioxide (26%).</td>
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For investigational use only

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<thead>
<tr>
<th>Agents</th>
<th>Remarks</th>
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<tbody>
<tr>
<td>MIV-302, MIV-308BL, MIV-309BL, MIV-310-311BL</td>
<td>High viscosity, Urokon Sodium preparations.</td>
</tr>
<tr>
<td>MIS-224</td>
<td>Diethyl ether, Urokon Sodium suspension.</td>
</tr>
<tr>
<td>MM-26</td>
<td>1 mm. pellets, Urokon Sodium and Dextrase.</td>
</tr>
<tr>
<td>MM-27</td>
<td>2 mm. pellets, Urokon Sodium and Dextrase.</td>
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Miscellaneous

<table>
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<th>Agents</th>
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<tr>
<td>Air</td>
<td></td>
</tr>
<tr>
<td>Carbon dioxide</td>
<td></td>
</tr>
<tr>
<td>Lead EDTA</td>
<td></td>
</tr>
<tr>
<td>Sugar pellets in Urokon Sodium</td>
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Main to be solved before the ideal agent becomes available. However, certain desirable characteristics can be stated. A particulate contrast agent should, when injected into the blood stream, produce small (0.25 to 1.0 mm.) discrete spots of radiopacity on an appropriately exposed x-ray film. These spots must be sufficiently radiopaque to be perceptible on multiple-impulse radiographs made while the particles are moving at a rate equal to peak arterial velocities. Intravenously injected in useful amounts, a satisfactory agent should be at least as safe as the conventional media (actually there is reason to believe they might be considerably safer).

Theoretically, the desired particles could be bubbles of gas, drops of fluid or small solid masses. Our experience indicates that bubbles of gas are unsuitable, even when surrounded by a bolus of radiopaque fluid, due to insufficient radiographic contrast. Unusually high kilovoltage x-rays might improve this, but more proximate possibilities exist. It has been said that nongaseous agents capable of producing punctate opacification would probably produce death due to embolization. That this is not true has been repeatedly demonstrated in connection with the use of the most promising of the substances tested to date, small solid cyndroid pellets composed of Urokon Sodium (80 per cent) and Dextrin (20 per cent) (fig. 4).

The Mallinckrodt Chemical Works has provided a number of contrast substances for testing, and has also generously given advice on chemical subjects. The solid particles discussed here are designated products MM-26 and MM-27 of the Mallinckrodt Research Laboratories. Inasmuch as these particles have provided a useful approach to experimental hemodynamics, improved versions are being sought. The principal objectionable feature of the present pellets is not, as one might first assume, their embolic potential. Several hundred have been injected (up to 100 at once) into each of several medium-sized dogs without observed acute or chronic effects. These
particles have been so contrived as to dissolve in blood within a few seconds' time. Serial angiocardiographic studies reveal that some of the injected pellets immediately pass through the heart, are arrested in medium sized pulmonary arteries and become invisible in from 10 seconds to 2 minutes. Other injected pellets appear to become trapped in the right auricular appendage, while surprisingly, some appear to adhere to the walls of veins leading to the right atrium. In any event, all have disappeared completely, promptly and without ill effect. Their apparent tendency to adhere to vascular walls is an interesting phenomenon as well as a technical problem. Figure 5, consisting of views selected from a dog study, illustrates pellet adhesiveness and dissolution-time, as well as the determination of velocity in the inferior vena cava (a) at one time in two places and, (b) at a later time and a third place.

Another promising approach to the prob-
Fig. 6. Radiographic study of turbulence in lucite model. Particles of barium carbonate suspended in SAE-10W motor oil, forced through cavity with syringe and interconnecting rubber tubing.

Problem of spot-opacification lies in the use of suspensions or solutions of radiopaque agents in droplets of relatively immiscible fluids. Initially it was hoped that diethyl ether would provide an ideal solvent for this purpose. Cinefluorographic studies were done during the first trial injection of such a suspension (MIS-224, Mallinckrodt). The dog died immediately since, as the movies later showed, the ether had promptly turned into a gas as it left the catheter. To our embarrassment, we learned that the boiling point of ether is 34.5° C. Methyl-propyl ether has been tested for toxicity in the experimental animal and may offer a satisfactory substitute since its boiling point is higher than normal body temperature. However, many problems must be overcome before the achievement of a satisfactory suspension of radiopaque agent within a safe but relatively immiscible fluid.

With respect to the work under discussion, it is necessary to comment upon an important aspect of radiographic technic. Utilizing conventional x-ray circuitry and dogs as experi-
mental animals, we have been able to make satisfactory double-impulse observations of 1 to 2 mm. pellets moving in the inferior vena cava at velocities of approximately 75 to 100 cm. per second. Unfortunately, the image has usually been "blurred" due to long pulse-duration. To help solve this problem a Machlett Dynapulse high-tension switching system was developed.* This unit provides exposures of from 1 to 5 msec. duration at up to 1000 ma. tube current and 100 KV. Circuitry is being added to provide multiple pulses separated by known intervals in the order of 1 msec.

Available knowledge concerning velocity of arterial blood flow plus practical experience have aided in establishing the requisite duration of exposure and the necessary interval between impulses. The maximum blood velocity to be found is probably that which occurs in pure valvular pulmonary stenosis. In this condition, despite the usual prolongation of systole, blood must pass through the narrowed

*This prototype Dynapulse unit now in operation at the University of Oregon Medical School was made available to the Minthorn Laboratory for Cardiovascular Research through the generosity of the Machlett Laboratories, Inc., Mr. John Stevenson, President.
DIVERSIFICATION OF VENOUS ANATOMY IN RELATION TO BLOOD FLOW

orifice at truly remarkable velocities in order to maintain a cardiac output consistent with life. That such velocities exceed 500 cm per second is indicated by simple calculations based upon known orifices and outputs in this condition. Published experimental observations appear to confirm the calculations.5 Since 1/120 second exposure-duration has been shown to be sufficient for determination of a velocity close to 100 cm per second, a 1 msec exposure should suffice for the highest blood velocity likely to be encountered.

Discussion

It is hoped that further development of the basic approach described here will result in a new tool for research and teaching in cardiovascular physiology. Clinical applications have not been explored completely, nor could they be for a matter of years. Even though the determination of absolute blood velocity and flow-volume were to fall short of present expectations, relative observations would be clinically useful. For example, knowledge of the proportionate amount of blood flowing to the various lobes of both lungs could aid in determining the need for and scope of resectional surgery. Relative pulmonary arterial velocities may provide a means for the differential diagnosis of a number of conditions affecting the pulmonary vascular tree—and there are many of these. The determination of the curve of myocardial power output, a possible outcome of this work, would have considerable impact on clinical cardiology. One of this work's more dramatic applications would lie in the clinical appraisal of turbulence. For all practical purposes, murmurs are the audible manifestations of turbulent blood flow. Our own experiments with models, such as that shown in figures 6 and 7, indicate that radiologically recognizable changes in flow-pattern occur with or before an audible murmur whenever factors favoring turbulence are increased. It is possible, therefore, that the proposed approach could significantly expand the information provided by auscultation. Unlike the stethoscope, the radiograph would provide a permanent record of the site of origin of murmurs as well as the direct cause. Clinical terms, such as 'functional murmurs,' could happily be discarded in favor of precise knowledge as to the genesis of the sound in question.

Summary

This preliminary report deals with the direct radiographic study of discrete, relatively small spots of artificial radiopacity during their passage through the cardiovascular structures and offers a new and promising technique for studying the motion of blood. As used here, motion refers to movement of and within the blood stream. So defined, it is fundamental to the subject-matter of hemodynamics. Continuing studies are focused upon two major hemodynamic parameters: 1. The velocity, acceleration and deceleration of circulating blood. Through appropriate specialized radiographic techniques, it is possible to measure the movement of blood as a function of time. Observations may be completed in 1 msec, repeated in rapid sequence and made simultaneously at many different points within the cardiovascular system. 2. Flow characteristics of circulating blood. The graphic study of flow patterns at multiple points within the blood stream can be carried out simultaneously with blood velocity observations. By analogy, in this technic the blood vessels and chambers of the heart serve as wind tunnels; the blood is the wind, the spots of opacity are smoke tracers and the myocardium is the source of power.

The results of extensive experimental studies indicate that the above goals are achievable and warrant the considerable effort and costs involved. It is hoped that this preliminary report will encourage others to explore the possibilities of the method and thereby hasten its perfection.

 Summario in Interlingua

Isto es un reporto preliminari que tracta del directe studio radiographic de discrete e comparativamente miere areas de radio-opacitate artificial durante lor passage a transverso le structuras cardiovascular. Te reporto pre-
sentato un nove e prominente methodo pro le studio del motion del sanguine. Le termino ‘motion’ es usate hie pro designar un movimento del sanguine e intra le sanguine. In iste senso, le termino es de importantia fundamental pro le thematica del studio hemodynamic. Studios nunc in progresso se occupa de duo complexos major del hemodynamic. (1) Le velocitate, acceleration, e deceleration del sanguine circulante. per le uso de appropriate technique radiographic specialiste, il es possibile mesure le movimento del sanguine como function del tempore. Le observationes pote esser completate in 1 msec, repetite in un sequentia rapide, e facite simultaneamente a multe differente punctos intra le systema cardiovascular. (2) Caratteristicas del fluxo del sanguine circulante. Le studio graphic del conditiones de fluxo a multiple punctos intra le currente de sanguine pote esser effectuate simultaneamente con observationes del velocitate del sanguine. A parlar analogicamente, in iste methodologia le vasos de sanguine e le cameras del corde es un tunnel aerodynamic: le sanguine es le aere (i.e. le vento), le areas de radio-opacitate es traciateores-fumo, e le myocardio es le fonte de energia.

Le resultatos de extense studios experimental indica que le supra-signalate objectivos pote esser attingite e que le costo e le effortio (le quales es considerabile) non es guastate. Es exprimite le spero que le presente reporto preliminari va incoragiar alteros e explorar le possibilitates del methodo e a accelerar assi su perfection.

REFERENCES
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