Detection and Assessment of Mitral Regurgitation by Left Atrial Indicator-Dilution Curves

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In the continuing search for an accurate method of assessing mitral regurgitation, an indicator has been injected into the left ventricle, and the subsequent dilution curves have been recorded from both the left atrium and a peripheral artery. With increasing mitral regurgitation, an increasing concentration of early appearing dye can be detected in the left atrium, when normally there is little or none. Because it is based on the detection of an indicator at a time when the normal concentration of such a substance is virtually zero, this technique has a high potential sensitivity. However, early experience in man and in dogs with open thorax showed false results, both positive and negative, compared with findings at operation. In order to make a systematic assessment of the technique and to examine factors that might produce false results, investigations have been made on dogs with graded degrees of surgically created chronic mitral regurgitation, under conditions that did not require thoracotomy. It has been demonstrated that in this situation the presence of mitral regurgitation and its degree of severity can be estimated with satisfactory accuracy.

Methods

Two methods were used for rendering the mitral valve incompetent. In the first method some chordae tendineae were tied against the ventricular wall, as described by Kuykendall and co-workers. In the second method an approximately circular hole was made in the center of the anterior leaflet of the mitral valve (fig. 1) with a punch and cutters of varying size, as described elsewhere. The holes ranged in size from 4 to 24 sq. mm. The dogs were studied 3 to 13 weeks postoperatively, and at the conclusion of the experiment the mitral valve was inspected at necropsy. The holes in the cusp were found to have firm, raised, fibrous edges so that their areas could be measured accurately and with reasonable assurance that the dimensions of the hole determined at necropsy were closely related to its dimensions during life. One animal had a small atrial septal defect, which might have been traumatic or congenital in origin.

The animals were anesthetized with combinations of morphine sulfate (5 to 10 mg./Kg. intramuscularly) plus chloralose (100 mg./Kg.), and pentobarbital sodium (125 to 375 mg. intravenously). Morphine sulfate with chloralose produced bradycardia, sinus arrhythmia, and, occasionally, atrial fibrillation. Supplements of pentobarbital sodium or atropine sulfate in a total dose of 0.2 to 0.3 mg. produced more regular heart rates, usually of 60 to 90 beats per minute. The dogs were positioned on the left side and were given oxygen via an endotracheal tube. All catheters were introduced via peripheral vessels, and the thorax was not opened. A Rodriguez-type catheter (size 5 F.) with a blind tip and multiple side holes (spray tip) was introduced into a femoral artery. It was passed along the aorta and through the aortic valve into the left ventricle.

A modification of Ross's technique was used to place the catheter in the left atrium. A 22-cm. long, 13-gauge needle with a curved tip was introduced into the right jugular vein, and through it was passed a close-fitting Lehman catheter (size 6 F.) until it protruded 1 to 2 cm. beyond the tip of the needle. Both catheter and needle were then advanced to the right atrium and into the orifice of the inferior vena cava, where the tip of the catheter was withdrawn into the needle. The tip of the needle was withdrawn 2 to 3 cm. and advanced through the floor of the fossa ovalis into the left atrium, and then the catheter was advanced into the left atrium. Care was necessary...
to avoid placing the tip of the left atrial catheter into a pulmonary vein; the normal procedure was to loop the catheter so that its tip passed into the left ventricle and then to withdraw it to the desired position in the left atrium. In animals with slow heart rates, these manipulations occasionally induced atrial fibrillation, which was reversed by changing the position of the catheter, by increasing the heart rate with intravenously administered pentobarbital sodium or atropine sulfate, or by applying external electroshock, for which the same apparatus and technique were used as are employed for resuscitation from ventricular fibrillation.

A venous catheter was placed with its tip in the right ventricle, and occasionally another was placed with its tip in the superior vena cava. A short nylon catheter was introduced into a femoral artery for sampling. Manipulations of the catheters were performed under fluoroscopic control, and the positions of the tips of the catheters were recorded by two-plane roentgenography (fig. 2). Pressures at all sites were recorded by strain-gauge manometers.

Injections of dye into the left ventricle were made either from a manually operated hypodermic-syringe assembly such as is routinely used for sudden single injections of dye or from a pneumatically activated syringe. In the pneumatic method the opening and closing of the solenoid control valve located in the line connecting the pneumatic syringe to the left ventricular catheter was synchronized with the cardiac cycle by means of an electronic variable delay-and-hold circuit, which was activated by the R wave of the electrocardiogram. The electrocardiogram was recorded simultaneously with the left ventricular pressure pulse so that the duration of injection and the time of its onset could be varied and the period of injection made to coincide with the systolic or diastolic portion of the cardiac cycle. Alternatively, injections of short duration (0.04 second) could...
Figure 2
Lateral view of thorax, showing catheters in situ. Advanced up the aorta from below is the injecting catheter with its tip near the apex of the left ventricle. Advanced from above, through a needle that perforates the interatrial septum, is the sampling catheter, which is looped in the left atrium. Additional catheters are placed with their tips in the superior vena cava and pulmonary artery.

be made at any desired phase of the cycle. The time, duration, and volume of the synchronized injections were derived from a recording of the position of the syringe piston obtained by means of a linear potentiometer. The volume of the stainless-steel syringe was 8.5 ml. Manual injections were made into the right ventricle at spaced intervals throughout the experiment for measurement of cardiac output. When rates of respiration were slow, injections were made immediately after the expiratory phase.

Dye-dilution curves were recorded simultaneously from the left atrium and from the femoral artery by withdrawing blood at uniform rates through cuvette oximeters.8 Sampling from the left atrium was at a rate of 25 to 35 ml. per minute through a system having a dead space of 1.2 ml. Arterial sampling was at a rate of 35 to 50 ml. per minute through a dead space of 0.3 ml. The blood withdrawn for each set of dilution curves was reinfused into the animal immediately after inscription of the curves. No anticoagulant was added. The 90-per cent response times of these systems to stepwise changes in concentration of indicator were 3.8 to 5.0 seconds for the left atrial system and 2.1 to 2.5 seconds for the femoral artery system. For experiments with a system of fast response, left atrial blood was sampled at 90 ml. per minute through an interference filter densitometer,10 total dead space being 1.1 ml. This system gave a 90-per cent response in 1.4 seconds.

Analysis of Records
The area of the dye-dilution curve representing regurgitant flow into the left atrium was calculated as a per cent of the area of the femoral-artery curve. This ratio, the "regurgitant fraction,"11 theoretically expresses the fraction of left ventricular stroke volume that flows backward, i.e., the ratio of backward flow to backward plus forward flow (see Theoretical Considerations).

Areas were routinely measured by the "triangle" method of Warner and Wood.12 In 39 curves recorded from the left atrium the ratio of the areas measured this way and by the standard Hamilton method of logarithmic extrapolation was 0.88, with a standard deviation of ±0.06; in 45 curves recorded from the femoral artery the ratio was 0.95, with a standard deviation of ±0.05. The triangle method gives a proportionally smaller estimate of the area of the left atrial curve than of that of the femoral curve; thus, the regurgitant fraction measured in this way will be slightly less than the value that would be obtained if the Hamilton method were used throughout. In 92 pairs of replicate curves obtained in this way, the mean difference between two estimates of the regurgitant fraction was 2.6 per cent, with a standard deviation of ±2.5 per cent.

The cardiac output was estimated by the Stewart-Hamilton method from dye-dilution curves recorded at the femoral artery after injection into the right ventricle. Regurgitant flow was calculated as follows:

\[
\text{Regurgitant flow} = \frac{\text{Cardiac output} \times R.F.}{100 - R.F.}
\]

where R.F. = regurgitant fraction expressed as per cent.

Regurgitant flow was calculated entirely independently of dye-dilution curves from the hydraulic formula of Gorlin and Dexter:13

\[
\text{Regurgitant flow} = \frac{\text{Area of defect} \times \text{duration of systole per minute} \times 0.7 \times 44.5 \times \sqrt{L.V. \text{ systolic pressure} - L.A. \text{ systolic pressure}}}{\sqrt{L.V. \text{ systolic pressure} - L.A. \text{ systolic pressure}}}
\]

The area of the regurgitant orifice, the duration of systole per minute, and the systolic pressures in the left ventricle and left atrium were recorded or measured, and the constants were assumed to have the values given by Gorlin and Dexter.13

Studies were made on 24 dogs weighing 13 to 25 Kg.; 6 were normal, 6 had chordae tendineae tied back to the left ventricular wall, and 12 had the punch-type lesion in the anterior cusp of the mitral valve.

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Figure 3
Dye-dilution curves recorded simultaneously from the left atrium and femoral artery after injection of dye into the left ventricle of a dog with severe mitral regurgitation. Atrial sampling was from region near the mitral valve; a recording system of rapid dynamic response was used. Curve shows peaks of high concentration of dye after each systole. Time of injection, right ventricular pressure, electrocardiogram, and flow rates of sampling systems are shown.

Results
In normal dogs the regurgitant fraction was less than 1 per cent when the cardiac rhythm was normal. During severe sinus arrhythmia at slow rates, occasional values of 2 to 10 per cent were recorded, especially when either the injection site or the sampling site was adjacent to the mitral valve and when the injection was made during a long diastole (two to three seconds).

In abnormal dogs the regurgitant fractions ranged from 15 to 73 per cent. It should be noted that values of more than 50 per cent indicate that regurgitant flow is greater than forward flow. Figure 3 shows an example of the photokinographic recordings of dilution curves obtained by rapid sampling from the left atrium in an animal with severe mitral regurgitation. Sampling from systems of rapid and slow dynamic response produced left atrial curves of similar area. The slower system was commonly used.

Comparison Between Estimates of Regurgitant Flow Made by Dye Technique and by Hydraulic Formula
A representative value for the regurgitant fraction in each animal was taken as the mean of all values obtained by sampling near the mitral valve, irrespective of the site or timing of the left ventricular injection. Estimates made during arrhythmias were excluded. In figure 4 these values for the regurgitant fraction are shown to have a close relationship to the area of the defect in the valvular cusp as measured at necropsy. The relationship is clearer when the area is expressed in terms of the body weight of the animal, thus allowing for expected changes in cardiac output with body size. The flattening of the graph at higher values results from the expression of backflow as a fraction of backward plus forward flow, so that with increasing degrees of regurgitation the regurgitant fraction approaches the value of 100 per cent asymptotically.

These values for the regurgitant fraction were used for the calculation of regurgitant flow in absolute volumes; for this purpose, the most closely proximate estimates of cardiac output were taken. Pressure recordings made at the same time as estimates of cardiac output were used in conjunction with the area of the valvular defect for the calculations of the regurgitant flow on a hydraulic basis. The

Figure 4
Comparison between estimates of regurgitant fraction and area of defect at necropsy in 11 dogs. Values of the regurgitant fraction were usually the mean of two measurements made by sampling near the mitral valve, irrespective of timing or site of injection into the left ventricle. In animal with amended value, shown as an open circle, there was an atrial septal defect, the ratio of pulmonary arterial to systemic arterial flow being 1.3:1, as estimated from dye-dilution curves. In the presence of such inequality, the regurgitant fraction gives a proportionately low index of regurgitation; correction for this error gives higher of the two values shown. Note that, as might be expected, correlation was improved when the area of defect was corrected for body size (left panel).
Comparison between independent estimates of mitral regurgitation made by a hydraulic formula and by dye-dilution technique. Hydraulic estimate, $R_H$, uses measured values for defect; duration of systole per minute, $T_{sys}$; a constant, $K$; and systolic pressures in left ventricle and left atrium, $P_{LV}$ and $P_{LA}$. Dye estimate, $R_D$, is calculated from cardiac output and regurgitant fraction. See text for detail.

Comparison between the independently determined estimates of regurgitant flow made by the hydraulic formula and by the dye-dilution technique in 11 animals is shown in figure 5. There is a close linear relationship, the coefficient of correlation being 0.96. Although this high degree of correlation may have resulted partly fortuitously from a cancellation of opposing errors, it is certain that a reasonable agreement exists between the separate estimates. Thus the dye technique can be accepted as accurate under the particular conditions selected for these measurements. These conditions were chosen as the result of the following experiments.

**Effect of Changing Position of Injecting Catheter Within Left Ventricle**

Injections into the left ventricle were made at four different sites, where they could be repeated with reasonable accuracy. The sites were designated as the inflow tract, apex, mid-cavity, and outflow tract. These positions were described as such, first, on the basis of the position of the mitral and aortic valves, as determined by fluoroscopy during manipulation of the tip of the catheter across the valves; the pressures at the tip were monitored continuously. Second, they were described from the apparent position of the tip of the catheter, as determined from lateral roentgenograms taken at each position studied. Replicate injections were made at each position, and the series of injections at the various positions were carried out as rapidly as possible during periods when the animals appeared to be in a stable condition.

The findings in 11 animals are shown in figure 6. No consistent difference was noted between the regurgitant fractions determined after injections at any of the various sites. In one animal (fig. 6, no. 11), when the left ventricular catheter was in the “inflow” position, injection was clearly made preferentially into the left atrium; values for the regurgitant fraction were 61 per cent and 95 per cent, compared with values of 29 to 43 per cent from other sites in the left ventricle. Sometimes the tip of the injecting catheter could be passed through the mitral valve into the left atrium and pulmonary veins, where, as would be expected, injections produced regurgitant fractions of about 100 per cent.
the regurgitant fraction was obtained, even when the injection was timed to coincide with ventricular systole and the catheter was placed within 1 cm. of the aortic valve (fig. 6, no. 13). Injections made when the tip of the catheter was within the aortic valve, as indicated by erratic levels of diastolic pressure on the pressure tracing, resulted in a fall of about 50 per cent in the concentration of dye regurgitating to the left atrium. With injection into the aorta just beyond the valve, no early appearing dye was detected in the atrium.

Effect of Changing Position of Sampling Catheter in Left Atrium

Studies were made with the tip of the sampling catheter in five distinguishable regions of the left atrium: cephalad, dorsal, left lateral, septal, and near the valve. These positions were determined on the basis of the anteroposterior and lateral roentgenograms taken at the time of sampling. The findings in 11 animals are shown diagrammatically in figure 7. The values are the mean of replicate estimates.

Sampling from positions near the mitral valve produced the most consistent values for the regurgitant fraction. When dilution curves were recorded from three or more atrial sites, the results obtained from the position near the valve always agreed with those from at least one other site. When dilution curves were recorded from only two atrial sites and the results disagreed (fig. 7, nos. 3, 4, and 6), measurements at other stages of the experiment always confirmed the estimates made by sampling near the valve rather than those made from sampling elsewhere.

In five instances (fig. 7, nos. 2, 4, 6, 10, and 13), values well below the average were obtained in the cephalad region of the left atrium near the entry of the pulmonary veins. In three instances (fig. 7, nos. 3, 10, and 11), values clearly above the average were obtained in the cephalad and left lateral regions.

The atrial catheter was often passed into a pulmonary vein, where sampling occasionally showed no early appearing dye but often showed a surprising amount of dye. An example is seen in figure 8. First, the catheter was in the septal position in the left atrium just beyond the tip of the needle; analysis of the dye-dilution curves gave a value of 37 per cent for the regurgitant fraction. The catheter was then advanced by stages into a pulmonary vein. Dye-dilution curves continued to show early appearing dye, and the regurgitant fraction was still 19 per cent, even at the point of impaction of the catheter about 4 cm. outside the atrial shadow.

Effect of Repositioning of Catheters

When the injecting catheter was moved from a given position in the left ventricle and then replaced in this position and the injections were repeated, even after considerable intervals, estimates of the regurgitant fraction were similar to those made previously (fig. 9a). Similar results were obtained with replicate sampling after movement and repositioning of the left atrial catheter in various positions (fig. 9b).

Effect of Time of Injection in Relation to Cardiac Cycle

Estimates of regurgitant fractions were compared after left ventricular injections were made that were timed to coincide accurately with systole, diastole, or the full cardiac

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cycle. The positions of the catheter appeared stable and were not knowingly altered throughout such a series. In 30 comparisons the mean difference between regurgitant fractions obtained with systolic and diastolic injections was 0.03 per cent, with a standard deviation of \( \pm 5.2 \) per cent. Good agreement was also obtained between these values for the regurgitant fraction and those obtained after full-cycle injections and after unsynchronized manual injections of approximately 0.5 to 1.0 second's duration. Figure 10 illustrates typical findings in a dog with a regurgitant fraction of 15 per cent.

Injections of short duration (0.04 second) into the left ventricle were made at different phases in the cardiac cycle in six series of experiments, each involving 10 to 22 injections of dye in a total of three animals. The left ventricular injection sites were mid-cavity, apex, low outflow, and extreme outflow, the latter being within 1 cm. of the aortic valve. The timing of these short-duration injections in relation to the cardiac cycle did not systematically affect the amount of early appearing dye detected in the left atrium.

**Effect of Extrasystoles, Atrial Fibrillation, and Tachycardia**

When injections into the left ventricle induced extrasystoles, the associated dye-dilution curves showed a fall in the regurgitant fraction by as much as half or two thirds of
the usual value. During transient atrial fibrillation at slow heart rates, estimates of the regurgitant fraction became erratic. High values were associated with long periods of diastole. During tachycardia, whether spontaneous or induced, the regurgitant fraction increased. For example, in one animal it varied from 50 per cent during an atrial tachycardia (rate 160 per minute) to 20 per cent during sinus rhythm (70 per minute) and back to 50 per cent after the administration of atropine sulfate (160 per minute).

**Discussion**

This study was undertaken to elucidate factors other than the degree of mitral regurgitation that may affect the amount of early appearing dye detected in the left atrium after injection of dye into the left ventricle. The results were expected to show whether a reliable estimate of the degree of regurgitation could be made by the use of established equipment and methods, or whether more specialized procedures were necessary.

The technique satisfactorily permitted detection of mitral regurgitation in every animal in which the function of the valve had been impaired operatively, even when the abnormality was slight. Thus, a regurgitant fraction of 15 per cent was obtained in the animal in which the area of the punch hole in the valvular cusp was only 4 sq. mm. Reproducible values were obtained even after long intervals of experimentation. On the other hand, a false indication of incompetence, i.e., a regurgitant fraction greater than 1 per cent, was obtained in normal animals only rarely and then in specific circumstances in which it might reasonably be explained on the basis of the mixing of atrial and ventricular contents during a long diastole.

Among the factors investigated in the abnormal dogs for their possible effect on the measurement of regurgitation, the timing of the left ventricular injection proved unimportant, but cardiac arrhythmias did produce variations in the amount of dye that regurgitated. Changes in the mechanics of ventricular contraction, especially during an extrasystole, may produce uneven mixing of the two streams of blood leaving the left ventricle, and the regurgitant fraction would then lead to an erroneous estimate of regurgitation. Alternatively, the changes in pressure relationships between the left ventricle and the two chambers into which it empties, together with the changes in duration of systole, may produce a true physiological variation in regurgitation, especially at fast heart rates. The estimate of regurgitation obtained by the dye-dilution method at that time may be correct for the particular time, but it would not be representative of the general condition.

Injection into different regions of the left ventricle did not affect the proportion of dye regurgitated, even when injection was made into the outflow tract as close as possible to the aortic valve and during ventricular systole. Thus the dye must have spread into the main stream of blood passing from the ventricle to both the atrium and the aorta, although it need not have mixed with the entire content of the left ventricle. Widespread dispersion of dye may have been assisted by the use of the special "spray tip" catheter for injection. The type of regurgitation created by punching a hole in the anterior cusp of the mitral valve, which produced a defect between the outflow tract of the left ventricle and the left atrium, could have contributed to the surprisingly high regurgitant fraction obtained after injection in the outflow tract. This seems unlikely, however, since similar results were obtained when the anterior leaflet of the mitral valve was intact and the incompetence was created by tying back the chordae tendineae.

Reasonably stable values for the regurgitant fraction were obtained by sampling from a wide range of positions in the left atrium. However, unduly high and unduly low concentrations of dye were obtained on some occasions. Low concentrations, resulting in falsely low estimates of the regurgitant fraction, may be expected when the sampling catheter approaches the inflow from the pulmonary veins. The high concentrations obtained in the cephalad and left lateral regions of the atrium presumably resulted from prefer-
Figure 9

Mean values of regurgitant fractions estimated from restoration of sampling catheters to a particular position. a. Left ventricular injecting catheter. b. Left atrial sampling catheter. Even after long intervals estimates showed little change.

Dye-dilution curves recorded near the valve were shown to afford valid and reproducible estimates of the degree of mitral regurgitation.

On the other hand, it was not possible to establish an accurate relation between the estimates of regurgitation made by the hydraulic formula and those made by any other method in current use. The left atrial pressure curves were analyzed, but mean left atrial pressures were mostly less than the level at which the better empirical indices, such as the amplitude of the v wave derived for man,1,17 have proved useful in clinical studies. No method of analyzing the left atrial pressure pulse showed a significant correlation with the degree of regurgitation in these dogs. The dye-dilution curves recorded at the femoral artery after injection into the right ventricle were also examined. The ratio of the least concentration to the peak recirculation concentration, the $C_L/C_R$ ratio of Marshall and associates,1 was abnormal only in the animals with the most severe regurgitation. Another index applied by these authors, which makes use of the "disappearance ratio" and the peak concentration, was equally insensitive. A more detailed analysis of slope in the manner of the original suggestions of Korner and Shillingford18 showed almost complete overlap between the values for backflow calculated for normal animals and those obtained for animals with mitral regurgitation, although there was some statistical relationship between the area of the hole and the calculated backflow ($r = 0.75$). It was not possible to apply the more rigorous conditions under which Korner and his associates19 20 recently showed the method to be more accurate. However, these conditions are so rigorous that they are in practice applicable only to animal studies in which the measurements made on an individual animal before the production of regurgitation can be used as the control for studies in the same animal after regurgitation is produced.

The unique advantage of the dye-dilution technique is that it depends upon detection in the atrium of a substance not normally present, rather than on qualitative changes of a function differing from the normal. Specific conditions used in this study were: the injection through a "spray tip" catheter, the establishment of reasonable rates of atrial sampling, and the restriction of sampling to the region near the mitral valve. Misleading results may still be obtained in the presence of extrasystoles, slow fibrillation, or an un-
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usual tachycardia. However, two of the conditions previously thought most important may perhaps be disregarded: the left ventricular injection site can be varied extensively without consequence, and the presence of a voluminous left atrium may matter less when the sampling site is accurately placed near the mitral valve. In a recent review Conn21 drew much the same conclusion.

Thus the experiments in animals demonstrate some specific conditions under which the findings in the rigorously controlled experiments in models may be most usefully applied to laboratory investigations in man, in whom rigorously controlled experimentation of this type is almost precluded.

Theoretical Considerations

Consider a system of two chambers in series through which flow is uniform and continuous and in which the chambers are so arranged that part of the inflow into the downstream chamber is returned to the upstream chamber and no recirculation occurs. If an indicator is injected into the downstream chamber and sampled continuously from the upstream chamber and from a site distal to the downstream chamber, forward and backward flow can be measured in the following way:

Let $F$ and $R$ volumes per unit time represent the forward and regurgitant flow respectively, and let the instantaneous concentrations of indicator in the upstream and downstream chambers be $C_u(t)$ and $C_d(t)$ at time $t$ after injection of indicator into the downstream chamber. During a very small time interval, $\Delta t$, the concentrations may be assumed to be constant, and hence the quantity of dye entering the upstream chamber in the interval $t$ to $t + \Delta t$ is $RC_u \Delta t$ units. In the same interval, $(F + R) C_d \Delta t$ units pass from the upstream to the downstream chamber. When all of the dye has passed out of the upstream chamber, the total dye that entered this chamber must equal the total dye that has left it, and therefore:

$$\Sigma RC_u \Delta t = \Sigma (F + R) C_d \Delta t$$

or, as $\Delta t \to 0$

$$R \int_0^\infty C_u dt = (F + R) \int_0^\infty C_d dt$$

The effect on estimates of regurgitation of timing in the cardiac cycle of injection of dye into the left ventricle, as demonstrated by pairs of simultaneous dilution curves recorded from the left atrium and femoral artery in an animal (20 Kg.) with moderate mitral regurgitation. Timing of injection can be estimated from recordings inserted before each panel showing travel of syringe and simultaneous electrocardiographic tracing. The regurgitant fraction remained similar (about 15 percent) in the three instances in which the timing of the injection varied from systole, to diastole, to full duration of cardiac cycle.

$$\frac{R}{F + R} = \frac{\int_0^\infty C_u dt}{\int_0^\infty C_d dt}$$

This ratio has been called the "regurgitant fraction."11

As all of the indicator eventually passes the distal sampling site, the forward flow may be calculated by the standard method:

Forward flow = \frac{\text{quantity of indicator}}{\text{area of curve from distal site}}

Thus the regurgitant flow may be calculated as an absolute value.

This analysis has considered only uniform continuous flow. However, Lacy and co-workers15 have shown that the same relationship can be derived for discontinuous flow by considering flow in terms of strokes. This replaces the very small time interval $\Delta t$ by an interval characteristic of the system, namely, its cycle length.

In deriving the above-mentioned calculation, the curve recorded from the distal site
is used as a measure of indicator entering the upstream chamber. Thus, regurgitant blood is assumed to be similar at all times to blood passing to the periphery. If this condition is satisfied, incomplete mixing of dye and blood in the downstream chamber is not a source of error.

The area of the indicator-dilution curve from the upstream chamber is taken as a measure of the dye returning from it into the downstream chamber. This assumption is more subject to error. The portion of the continuous sample withdrawn from the upstream chamber during systole may contain too high a concentration of indicator, because regurgitant blood has not had time to mix adequately with the residual blood in this chamber. Even in their model containing a mechanical stirrer, Lacy and associates observed large concentration peaks in the "atrium" in "systole."

Variations in concentration during systole or diastole may also distort the curve from the upstream chamber, because the rate of blood flow between the two chambers varies, whereas samples are withdrawn at a uniform rate. Consequently, blood that passes the sampling catheter rapidly is not represented as much as is blood that passes slowly.

In their model Lacy and his co-workers were able to use a system of high dynamic response and so to measure concentrations in diastole only. They assumed that mixing in the upstream chamber in diastole was fairly complete, so that indicator concentrations then represented correct values for the whole cycle; their assumption was well supported by their results.

Warner has recently described a more realistic mathematical model of the left heart than that used by Lacy. Equations based on this model have been derived for predicting the time-course of the concentration of an indicator in the left atrium and aorta after an injection into the left ventricle in the presence or absence of mitral or aortic regurgitation. The results of solutions of these equations obtained by Warner with the use of an analogue computer indicate that the ratio of the areas of dilution curves recorded from the left atrium and the ventricle is closely related to the ratio of the backflow to the total forward flow across the mitral valve. These results based on theoretical considerations are therefore in harmony with the results reported herein that were obtained in vivo in dogs with chronic mitral regurgitation.

Some of the conclusions drawn from experiments in models can be applied to the investigation of mitral regurgitation in man. However, in the absence of thoracotomy, sampling from the left atrium requires the use of narrow tubes of substantial length and precludes a system with an inherently high dynamic response. Recently it has been demonstrated that the original curve that existed at the tip of the catheter may be reconstructed from the recorded curve and from the measured response of the catheter-transducer-recording system to a stepwise change in concentration of indicator. However, the approach adopted in this study has been to test the method with techniques and instrumentation more likely to be used in practice, by varying some of the factors that might affect either the amount of dye entering the left atrium through an incompetent mitral valve or the amount detected by the left atrial sampling system.

Summary

Indicator-dilution curves were recorded simultaneously from the left atrium and the femoral artery during injections of indocyanine green into the left ventricle in normal dogs and in dogs with chronic mitral regurgitation. A study was made—without the use of thoracotomy—of the effect of the following factors on the amount of early appearing indicator detected in the left atrium: (a) the timing of the injection of indicator in relation to the cardiac cycle, (b) the position of the injecting catheter in the left ventricle, and (c) the position of the sampling catheter in the left atrium. It was found that the time and site of the injection into the left ventricle had little effect on the amount of early appearing dye detected in the left atrium and that, although the position of the sampling catheter in the left atrium was important, reproducible results were attained when the sampling site was restricted to a region in close proximity to the mitral valve. A close correlation was
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demonstrated between the volume of regurgitation determined independently on a hydraulic basis and the volume estimated from the fraction of early appearing indicator detected in the left atrium. It is concluded that further work with this upstream-sampling technique is justified in order to study its possibilities as a practical method for detecting and quantitating mitral regurgitation in human beings.

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