Detection and Measurement of Experimentally Produced Aortic Regurgitation by Means of Indicator-Dilution Curves Recorded from the Left Ventricle

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Detection of indicator upstream to a cardiac valve immediately after its injection just downstream to the valve is proof of retrograde passage of this indicator across the valve and therefore of some degree of valvular incompetence. The fraction of indicator regurgitated in the case, for example, of the aortic valve is related to the ratio of areas encompassed by dilution curves recorded from the left ventricle after successive injections of equal doses of the indicator into the root of the aorta and into the pulmonary artery, provided that forward flow remains unchanged and uniform mixing of indicator and blood occurs. This ratio, the regurgitant fraction, is also related to the ratio of areas of curves recorded simultaneously from the left ventricle and a systemic (radial or femoral) artery after injection into the root of the aorta. This method has been applied to the detection of mitral regurgitation and of pulmonary and tricuspid regurgitation. In the case of the mitral valve, independent proof of the validity of the method has been obtained in dogs with experimental mitral regurgitation. Hitherto, the validity of this method when applied to aortic regurgitation has not been tested by comparison with measurements of regurgitation by completely unrelated technics. Therefore, a comparison has been made of the regurgitant-fraction method of estimating experimentally produced aortic regurgitation in dogs with values derived from the results of retrograde perfusion of the aorta at necropsy at pressure gradients across the aortic valve comparable to those observed in life.

Methods

A total of 30 mongrel dogs, weighing 16.8 to 22.8 kg, were studied. Six of these animals had no surgical procedure on the aortic valve, 18 were studied before and after operation on the aortic valve, and 15 were studied only after valvular operation. Fourteen of the postvalvotomy studies were carried out immediately after operation on the valve, while in 19 a period of 10 to 61 days elapsed between the creation of aortic regurgitation and the subsequent postoperative study.

The studies were performed without thoracotomy, with the dogs anesthetized with sodium pentobarbital. The animals were lying supine or on the left side and breathing 100% oxygen via an endotracheal tube. In part of the procedures, in which it was desired to study animals with a slower heart rate, 7.5 mg/kg of morphine sulfate was given intramuscularly before complete anesthesia was produced with sodium pentobarbital intravenously. Aortic regurgitation was produced without recourse to thoracotomy by means of a valvotome introduced into a common carotid artery, the method being a modification of that described by Cohnheim. The valvotome, a hook-shaped knife sheathed in a metal tube, was advanced from a carotid artery under fluoroscopic control until the resistance of an aortic cusp could be felt. The sheath was withdrawn, and the cusp was engaged with the hook. The hook was then pulled back into the sheath. Subsequent necropsy showed that a tear was usually produced at the base of the cusp; occasionally it extended to the free margin. Initially, some difficulty was experienced on account of arterial spasm, and six dogs died of hemorrhage through tears in the aortic wall. However, there were no failures in the last 36 dogs, although in three not included in this study a tear involving the anterior leaf
of the mitral valve was inadvertently produced. With increasing experience, the operator (D.E.D.) was able to produce mild, moderate, or severe aortic incompetence at will. In the dogs studied immediately after valvotomy, a test injection of dye was made into the aorta. Success in producing incompetence was gauged by the presence or absence of immediately appearing dye in the left ventricle. In the remaining animals, which were studied 10 to 61 days after valvotomy, widening of the pulse pressure and the development of a diastolic murmur were used to determine whether the aortic valve had been rendered incompetent.

For the dye-curve studies, a 19-gauge needle was inserted into the left femoral artery and two size 6-F Cournand catheters, 50 cm long, were introduced into a jugular vein and advanced so that the tip of one lay in the superior vena cava and that of the other in the pulmonary artery. A size 5-F Lehman cardiac catheter, 100 cm in length and closed at one end with multiple side holes situated near the tip (Rodriguez type), was positioned with its tip in the aorta just downstream to the valve after introduction into the right femoral artery. In order to ensure its correct placement, this catheter was advanced into the left ventricle and then withdrawn, with continuous monitoring by fluoroscopic observation and pressure recordings, to the desired distance downstream to where the pressure changed from left ventricular to aortic. In the early experiments the apex of the left ventricle was punctured percutaneously with a 15-gauge needle via the costal interspace of the left side of the chest just caudal to the apex heat. A size 5-F Lehman-type cardiac catheter, 40 cm in length and of 0.2 ml internal volume, was introduced and positioned so that its tip was in the left ventricular outflow tract, and the needle was then withdrawn from the chest. In later experiments the left atrium and ventricle were entered by means of transeptal puncture from the external jugular vein. The septum was punctured at the fossa ovalis by a curved-tip 13-gauge needle which was advanced into the right atrium while its point was guarded by the slightly protruding tip of a 40-cm long, size 6-F Lehman cardiac catheter. After the septal puncture, this catheter was advanced into the left ventricle via the mitral valve.

The method used in the earlier experiments is an adaptation of that described for man by Brock and associates; the one used later is a modification of that described by Ross. In six dogs, both methods of catheterizing the left ventricle were used, so that dye curves recorded simultaneously at two sites in this chamber could be compared. In six of the control dogs and six of the dogs with aortic regurgitation, an additional catheter was positioned via the right subclavian artery so that its tip was in the brachiocephalic artery close to its origin from the aorta. This catheter was used to obtain a recording of the arterial pulse simultaneously with the injection of indicator via the second aortic catheter. The typical positions of the catheters used are illustrated in figure 1.

With the exception of the closed-end, spray-tip catheter used for the aortic injections, all catheters had birds-eye openings at their tips; all were positioned under fluoroscopic control. An electrocardiogram was recorded continuously, as were pressures, at all sites intubated, the latter by means of strain-gauge manometers. Respirations were recorded as pressure variations in the airway by means of a strain-gauge manometer connected to a side arm of the endotracheal tube. The technic used for recording dilution curves has been described previously; indocyanine-green dye was used throughout. Control and post-
DETECTION OF AORTIC REGURGITATION

Valvotomy dye curves were recorded simultaneously from the left ventricle and the femoral artery following successive injections of indicator into the pulmonary artery and the root of the aorta. In the experiments in which the area of left ventricular volume was compared with that obtained following pulmonary artery injection the injections were usually made within a period of five minutes of each other; during the interval between them, care was taken to avoid any procedure which might alter the animal's condition, for example administration of supplementary doses of pentobarbital.

The aortic injections were made with the tip of the aortic catheter positioned just downstream to the valve, as described earlier, or at positions 1 to 2.5 cm downstream to the site of transition from left ventricular to aortic pressure. Replicate injections were usually made at each site in the aorta, and replicate injections were frequently repeated after withdrawal and subsequent repositioning of the tip of the catheter.

Most injections were made manually with a special syringe containing 2.5 mg of indocyanine green in one ml of distilled water. The dye remaining in the catheter was flushed into the aorta with saline. This injection procedure required one to two seconds and, therefore, depending on the heart rate, extended over one to several cardiac cycles.

In 22 dogs, injections into the aorta were synchronized with the electrocardiogram, and the timing and duration of the injection in respect to the cardiac cycle were adjusted so that the period of injection occupied the entire systolic or the entire diastolic phase or, selectively, one complete cardiac cycle. For this purpose a pneumatically powered solenoid-controlled syringe was used. The plunger of this syringe was coupled to a linear potentiometer so that the instant, volume, and duration of each injection were recorded simultaneously with the electrocardiogram, aortic pressure, pulses, and other variables under study. The air pressure driving the syringe was adjusted so that the volume of dye solution that was injected closely approximated one ml (2.5 mg of indocyanine green) independent of the timing and duration of the injection. Thus, the volume and amount of dye used for these synchronized injections were similar to those for the manual (unsynchronized) injections used in the same and associated procedures.

In 13 of the 22 dogs in which synchronized injections were made, a slower heart rate was obtained by combined sodium pentobarbital and morphine anesthesia. In this group, after the synchronized injections previously referred to were done, the duration of injection was reduced to 40 milliseconds (msec), during which time approximately one mg of indocyanine green was injected in a volume of 0.19 to 0.20 ml. The time of these injections in the cardiac cycle was varied in a random fashion throughout the periods of systole and diastole. Several series of such injections were made in order to obtain repetitive measurements with injections timed to occupy discrete phases of the entire cardiac cycle. In order to minimize difficulties in the timing of injections due to sinus arrhythmias and also to reduce respiratory variations in stroke volume, these particular dogs were ventilated artificially at a rate of about 40 to 60 cycles per minute via auffed endotracheal tube with 99.5% oxygen under intermittent positive pressure of 5 to 10 cm of water.

In most of the experiments the dilution curves from the left ventricle and femoral artery were...
Example of estimation of regurgitant flow from back perfusion of the aortic valve (right panel) and the aortic and left ventricular pressure pulses recorded in vivo (left panel) in dog no. 13. Measurements of the duration of diastole \( t_d \), cycle length \( t_c \), and the mean gradient across the aortic valve \( P_{AV} \) from simultaneously recorded pressure pulses are illustrated in the left panel. The relationship of retrograde flow across the aortic valve \( Q_{AV} \) to the pressure gradient across the valve as determined at necropsy is illustrated on the right. Since regurgitant flow occurs only during diastole, the estimated regurgitant flow in liters per minute in vivo \( Q_R \) is given by:

\[
Q_R = \frac{t_d}{t_c} \times (Q_{AV})_P
\]

where \( (Q_{AV})_P \) is the retrograde flow per minute at a pressure gradient equal to the mean diastolic pressure gradient recorded in vivo of 101 mm of mercury. In this instance \( Q_R = \frac{0.212}{0.384} \times 1.55 = 0.85 \) liters/min.

In parts of the experiments, dilution curves were recorded with cuvette oximeters modified for detection of indocyanine green; relatively slow blood-sampling rates of approximately 20 ml per minute were used. The physical characteristics and dynamic-response characteristics of this instrument were described previously. From 2.1 to 4.2 seconds were required for a 90% response to a step change in dye concentration of the systems used over the range of blood sampling rates encountered in these experiments.

In the 13 dogs in which studies of the time of injection in relation to the cardiac cycle were made, the total triangle formula for estimation of the area encompassed by the dilution curves was used for the calculations of the regurgitant fractions. The accuracy of this procedure was checked by parallel calculations of the total areas of many of these curves by means of the usual Hamilton method of logarithmic extrapolation.

The regurgitant fractions calculated from the dilution curves recorded from the left ventricle following injections into the aorta were \( LVA/LVPA \), the ratio of the areas of dilution curves recorded in sequence from the left ventricle after successive injections of equal doses of dye into the aorta (\( LV_A \)) and the pulmonary artery (\( LV_{PA} \)); and \( LV_A/FA_A \), the ratio of the areas of the curves recorded simultaneously from the left ventricle (\( LV_A \)) and the femoral artery (\( FA_A \)) after injection of dye into the aorta (fig. 2).

Comparison of regurgitant fractions observed after manual injection into the aorta and after the injections were synchronized to occur during systole, diastole, and a complete cardiac cycle was confined to \( LV_A/FA_A \) values. This was done because the unavoidable time lapse between the pulmonary arterial injection and the completion...

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*Model X100A, Medical Equipment Division, Waters Corporation, Rochester, Minnesota.
DETECTION OF AORTIC REGURGITATION

Comparison of dye detected in left ventricle following supravalvular aortic injections during different phases of the cardiac cycle in an 18-kg dog. Top panels: Replicate recordings at a paper speed of 5 mm/sec of indicator-dilution curves and other variables following injections of indocyanine green into aorta; injections were synchronized with electrocardiogram so as to occur during systolic phase, diastolic phase, or over one complete cardiac cycle. Trace labeled "dye injected into the aorta" is a recording of position of plunger of solenoid-controlled syringe used to inject dye and hence shows the instant, duration, and volume of each injection. Bottom panels: Simultaneous recordings taken on a second camera at a paper speed of 150 mm/sec of arterial pressure pulse (left subclavian), position of plunger of dye syringe, and electrocardiogram of individual heartbeats in which injections of dye were carried out. Resulting respective dilution curves are shown in top panels. Aortic valvotomy was performed on this dog 18 weeks prior to this study. Note that indicator was detected in the left ventricle (LV) immediately after injection and about two seconds later at the femoral artery (FA) and that clearance of the indicator from both the LV and FA sampling sites was complete before systemic recirculation occurred. The recordings of concentration of indocyanine green are not corrected for the time delay due to the dead space of the respective densitometer sampling systems. This correction is estimated by the equation $0.6 \frac{V_c}{Q_c}$, in which $V_c$ is the dead space of the catheter-densitometer system in ml and $Q_c$ is the rate of blood flow through the system in ml/sec (traces labeled "flow through cuvette"); 0.6 is an empirically determined factor to correct for the fact that laminar flow occurs in at least portions of the system. This correction was approximately 1.2 and 0.15 seconds for the LV and FA systems, respectively. The amount of immediately appearing indicator detected in the left ventricle, expressed as regurgitant fraction, is given in each panel. Note that it is similar in magnitude for the replicate systolic and full-cycle injections; for this animal, at a slow heart rate of about 50 beats per minute, it was somewhat greater for diastolic injections, a tendency not seen when the heart rate was fast (fig. 12). The animal was under morphine-pentobarbital anesthesia and was ventilated with 99.6% oxygen under intermittent positive pressure.

Circulation Research, Volume XII, March 1962
Eighteen of the dogs were killed by exsanguination immediately after the study, and the aorta was perfused in retrograde fashion with the dog’s own blood in order to obtain an independent estimate of the amount of regurgitation present. To carry out these aortic perfusion studies the chest was opened widely, but the heart and great vessels were left in situ. A large cannula (internal diameter 8.9 mm) was tied in the descending aorta immediately upstream to the first intercostal artery and facing the aortic valve. The left ventricle was cannulated directly through the left atrium (cannula internal diameter 12.5 mm), the mitral valve being removed after inspection. The cannulas were connected to a DeBakey-type roller pump so that the blood, which was warmed to 37°C, flowed into the aorta and through the defect in the aortic valve to the left ventricle and thence to a reservoir on the inlet side of the pump. Ligatures on the left subclavian, braehiocephalic, and coronary arteries prevented the blood from taking any other course. The retrograde flow across the aorta under these conditions was very slightly pulsatile.

A side tube on the outlet side of the pump was connected to a mercury manometer and the chamber of the left ventricle was connected to a second manometer by a cannula inserted through a stab wound and sealed in position with a purse-string suture. For reasons of convenience the flow rate was adjusted primarily, and the pressures generated by the various flow rates were measured. At least eight series of pressure measurements were made, four while the flow rate was increased and four while it was decreased. Previous observations had shown that no backflow is obtained under these conditions when the aortic valve is undamaged. After perfusion, the damaged aortic valve was inspected and the size of the defect or defects in the cusps measured. The method of Lange and Hecht for detection of valvular regurgitation based on comparison of dilution curves recorded from the pulmonary artery and a systemic artery was also studied. For this purpose, dilution curves were recorded simultaneously from the pulmonary artery and femoral arteries of these same 12 and 16 dogs— with and without aortic regurgitation, respectively—and the measurements and calculations were carried out on the curves as described by Lange and Hecht.

Results
QUALITATIVE SIGNIFICANCE OF DETECTION OF IMMEDIATELY APPEARING INDICATOR IN THE LEFT VENTRICLE FOLLOWING INJECTION INTO THE AORTA

An example of the recordings of pressure pulses along with dilution curves recorded simultaneously from the left ventricle and femoral artery of a dog with aortic regurgitation is shown in figure 4. An appreciable quantity of indicator was detected in the left ventricle immediately after the injection, indicating the presence of retrograde flow through

Circulation Research, Volume XII, March 1963
the aortic valve. The following data were obtained concerning the qualitative significance of this finding.

**Dogs With Aortic Regurgitation**

Immediately appearing dye was detected in the left ventricle in all of the 130 dilution curves recorded after manual (unsynchronized) injections just downstream to the aortic valve in the 33 animals studied following aortic valvotomy. The smallest regurgitant fraction observed after valvotomy was 0.07, which was associated with an estimated backflow (from back-perfusion data) of 0.3 liters per min/kg.

**Dogs With Normal Aortic Valves**

A total of 51 dilution curves was recorded from the left ventricle of 22 dogs after manual (unsynchronized) injections of indicator into the aorta just downstream to the valve. No early appearing dye was detected in 38 curves recorded from 15 of these normal dogs. Slight amounts were detected in 13 curves recorded from seven animals. The regurgitant fractions, LVA/FAA and LVA/LVPA, measured from these 13 curves ranged from 0.01 to 0.04 and from 0.01 to 0.03, respectively.

A total of 20 injections synchronized to occur during only the systolic or diastolic phases of the cardiac cycle was made in five dogs with normal aortic valves. Slight amounts of immediately appearing dye (regurgitant fraction: 0.0001 to 0.015) were detected following two of the nine systolic injections and one of the 11 diastolic injections made in these animals. The incidence of detection of immediately appearing dye in the normal animals was increased when the tip of the left ventricular catheter was positioned in the outflow tract of the left ventricle immediately upstream to the aortic valve and the injection was timed to occur during closure of the valve—that is, at the incisura of the aortic pressure pulse.26

Since the quantity of immediately appearing indicator expressed as regurgitant fraction never exceeded 0.04 in normal dogs when manual injections were used, and was 0.07 or greater in every instance in dogs with damaged aortic valves, it is concluded that detection of an appreciable amount of immediately appearing indicator in the left ventricle following its injection into the aorta is a strong qualitative indication of the presence of aortic regurgitation.

**FACTORS AFFECTING MAGNITUDE OF VALUE FOR REGURGITANT FRACTION MEASURED IN DOGS WITH AORTIC REGURGITATION**

**Variability Between Replicate Determinations of Regurgitant Fractions**

An example of dilution curves recorded after replicate injections into the aorta in a dog with aortic regurgitation is shown in figure 4. The values for 22 pairs of replicate determinations of regurgitant fraction in 14 animals with aortic regurgitation are shown in table 1. The arithmetic mean differences
### TABLE 1

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<tr>
<th>Dog</th>
<th>Determinations</th>
<th>LVₐ/FAₐ</th>
<th>Determinations</th>
<th>LVₐ/LV₀ₐ</th>
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**Arithmetic mean difference**: 0.07 ± 0.06
**Standard deviation**: ±0.06 ± 17.1
**Arithmetic mean difference**: 0.108 ± 0.108
**Standard deviation**: ±0.078 ± 18.3

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*Injections were of manual type unsynchronized with the cardiac cycle.
†First minus second determination.
§Percentage of mean of first and second determinations.
¶Indicates that changes in hemodynamic status of animal occurred between determinations.
**Aortic catheter was moved far from the valve and then replaced between determinations.
Based on 22 replicate observations without change in position of the injecting catheter.
Based on 12 observations before and after withdrawal and repositioning of the aortic catheter.

Between the replicate values for the LVₐ/FAₐ and LVₐ/LV₀ₐ fractions were 0.07 ± 0.06 and 0.11 ± 0.10, respectively.

The aortic catheter was withdrawn so that its tip was far-removed from the aortic valve and then repositioned by manipulation of the tip into the left ventricle on 10 occasions. The arithmetic mean differences between regurgitant fractions determined before and after repositioning of the aortic catheter were 0.108 ± 0.078 and 0.186 ± 0.153, respectively (table 1).

The relationship between the regurgitant fraction (LVₐ/LV₀ₐ), calculated as the ratio of the areas of the two curves recorded from the left ventricle following successive injections of equal amounts of indicator into the pulmonary artery (LVₐₚₐₐ) and the aorta (LVₐ), and the regurgitant fraction (LVₐ/FAₐ), calculated as the ratio of the areas of the curves recorded simultaneously from the left ventricle (LVₐ) and the femoral artery (FAₐ) following injection into the aorta is shown in table 1 and figure 5. No systematic difference was demonstrable between these two ratios, and the correlation coefficient between the paired determinations was 0.98.

**Effect of Variations in Site of Injection in Aortic Root**

The relationship of the values for the re-
Effect of variations in the distance of the injection site downstream from the aortic valve on the amount of immediately appearing indicator detected in the left ventricle in 15 dogs with aortic regurgitation. The amount of indicator detected in the left ventricle is expressed as the ratios of the areas of the initial deflections of the dilution curves recorded simultaneously from the left ventricle (LVA) and femoral artery (FAA) following injection of the indicator into the aorta (A). Values obtained after injections just downstream to the valve are plotted on the abscissa against values obtained in the same animal for injections performed after withdrawal of the catheter an additional 1, 2, or 2.5 cm from the valve. The numerals designate individual dogs. Values for multiple comparisons from the same animal are connected by vertical lines. The diagonal is the line of identity for the comparative values. Note that a decrease in regurgitant fraction was usually but not always obtained when the tip of the catheter was withdrawn 2 to 2.5 cm from the valve. Decreases were uniform when the withdrawal distance was increased to 5 cm (values not included in figure).

Regurgitant fractions (LVA/FAA) obtained in 15 dogs with aortic regurgitation following injection with the catheter tip just downstream to the aortic valve and after withdrawal of the catheter 1, 2, or 2.5 cm from this position is shown in figure 6.

There was a significant tendency for less immediately appearing dye to be detected in the left ventricle as the injection site was moved distally, but this was not consistently present in all animals. The differences in regurgitant fractions when the injection site was varied from injection at the valve to injection 2 to 2.5 cm away were usually not large. In one animal, however, which had a very small lesion in the valve with an average regurgitant fraction of 0.13, no immediately appearing dye was detected in the left ventricle following two of four injections made at sites estimated to be 1 and 2 cm downstream to the valve. A decrease in regurgitant fraction was uniformly attained when the tip of the catheter was withdrawn further than 2.5 cm from the valve.

Effect of Variations in the Site of Sampling From the Left Ventricle

The areas under pairs of curves recorded simultaneously from two left ventricular sampling sites after injection into the aorta of five dogs with aortic regurgitation were, with one exception, very similar (fig. 7). The one pair of discordant results was obtained in a dog in which the tip of one of the left ventricular catheters was situated immediately

Circulation Research, Volume XII, March 1968
Effect of time of injection in cardiac cycle on amount of immediately appearing indicator detected in the left ventricle following injections into the aortic root of a closed-chest anesthetized dog (no. 1) with aortic regurgitation. The duration of each injection was 40 msec. The amounts of indicator detected in the left ventricle expressed as the regurgitant fraction \((LV/A)/FA\) are plotted on the ordinate against the time of the injection in the cardiac cycle on the abscissa. The duration of systole is represented on the left half of the abscissa as 100% and the duration of diastole similarly on the right half. Each bar represents a single injection of indicator whose sequence in the series of 17 injections included in the figure is indicated by the respective numeral above each bar. The duration of each 40-msec injection expressed as a percentage of the particular systolic or diastolic phase of the cycle in which it occurred is indicated by the length of the bar. Note that the amount of immediately appearing indicator was maximal for the injections which occurred toward the end of systole or the onset of diastole, with a progressive decrease in this amount as injections occurred earlier in systole or later in diastole.

Effect of Variation in Time of Injection Into the Aorta in Relation to Cardiac Cycle

Regurgitant fractions were determined in seven dogs with aortic regurgitation and six normal dogs after 377 injections of very short duration (40 msec) synchronized electronically to occur during all phases of the cardiac cycle. The results are presented graphically in figures 8 and 9. In the dogs with aortic regurgitation, significant quantities of early appearing dye were detected in the left ventricle following every injection, irrespective of the time in the cardiac cycle in which the injection occurred. However, the quantity of regurgitated dye detected, expressed as regurgitant fraction, varied in a characteristic and uniform fashion with the timing of the injection. Minimal values for the regurgitant fraction were obtained when the injection occurred at the end of diastole and the onset of systole. The values increased progressively as the injections were delayed in order to have them occur later in systole, and they attained a maximal value at the end of systole and through the onset of diastole. The values for the regurgitant fraction then decreased progressively to a minimum as the timing of the injections was delayed progressively in order to have them occur toward the end of diastole (figs. 8 and 9).

The results obtained by carrying out injections of very short duration just downstream to the aortic valve in various phases of the cardiac cycle in normal dogs are shown in the lower portion of figure 9. Very small amounts of immediately appearing indicator were detected in the outflow tract of the left ventricle in four of six animals. Usually, immediately appearing dye was detected in this manner only when the injection was timed to occur just prior to closure of the valve (fig. 10). The maximal value for regurgitant fraction obtained in these six dogs was 0.08 for an injection which occurred just prior to closure of the valve. The minimal value obtained in the seven dogs with aortic regurgitation was 0.07 for an injection which occurred just prior to closure of the valve. There was no overlap between the values from the normal dogs and those from the dogs with aortic regurgitation when similarly timed injections were used (fig. 9).

It is apparent from these data that in the
DETECTION OF AORTIC REGURGITATION

FIGURE 9

Effect of time of injection in cardiac cycle on amount of immediately appearing indicator detected in left ventricle following injections into the aortic root. Values from seven dogs with aortic regurgitation, indicated by numerals, and from six normal dogs, indicated by letters, are included. The duration of each injection was 40 msec. See legend of figure 8 for definition of ordinate and abscissa values. The numbers or letters above each bar designate the individual dogs from which each value was obtained. Animal 7 had a second series of determinations designated as 7' after withdrawal and replacement of the aortic catheter at the valve. Average values of replicate injections were used for the instances when these occurred at the same phase of systole. Note that uniformly in the dogs with aortic regurgitation the minimal amount of immediately appearing indicator was detected in the left ventricle when the injections occurred near the end of diastole or the onset of systole, and, with exception of dog 6, the maximal amounts were detected for injections occurring at the end of systole and the onset of diastole. In dog 6 the maximal values were obtained following injections occurring in the midportion of systole. Note that the ordinate scale for the normal dog values is expanded 20 times over that used for the dogs with aortic regurgitation. Only traces of or no immediately appearing dye were detected in the left ventricle of normal dogs following injections during diastole. Slightly greater amounts were detected in four of the six dogs for injections during systole. See text for discussion.

Case of injections of very short duration, the time of the injection in the cardiac cycle is an important determinant of the amount of regurgitated indicator which can be detected in the left ventricle. It is of considerable practical importance in this regard, however, that the average of the values for the regurgitant fraction for the multiple short-duration injections which would be required to cover all phases of systole would be approximately equal to the average of the analogous values covering all phases of diastole (figs. 8 and 9).

It might be expected therefore that, if the duration of the injections were extended to the full period of systole and the full period of diastole, the values for the regurgitant fraction would be of similar magnitude for both the systolic and the diastolic injections.

Data in this regard were obtained by comparing the values for regurgitant fraction which were obtained following successive injections synchronized electronically to coincide with only the full systolic or the full diastolic phases of single cardiac cycles in 12
FIGURE 10
Demonstration of retrograde passage of indicator across the aortic valve during closure of valve in a normal 21-kg dog under morphine-pentobarbital anesthesia without thoracotomy. Note that immediately appearing indicator in the left ventricle was detected only when the injection (40-msec duration) occurred just prior to the incisura of the aortic pressure pulse caused by closure of the valve. No immediately appearing dye was detected when similar injections occurred at the peak of the aortic pressure pulse (left panel) or just after the incisura at the onset of diastole (right panel).

dogs with aortic regurgitation (fig. 4) and in five normal dogs. The values for regurgitant fraction obtained with these systolic and diastolic injections were also compared with (1) values obtained in most of these dogs for injections synchronized to cover the period of one complete cardiac cycle and (2) values from all of the dogs obtained with manual (unsynchronized) injections, which, depending on the heart rate, occurred over a period occupying one to several heartbeats. All of the values for regurgitant fraction obtained in three dogs from these various types of injections are shown in figure 11. These values have been plotted against heart rate since variations in the relative duration of systole and diastole might be expected to affect the amount of indicator regurgitated when the injection is timed to occupy one or the other of these two phases of the cardiac cycle. In these three animals with severe, moderate, or mild degrees of aortic regurgitation, respectively, no clearly evident systematic difference was obtained with these different types of injection. The average results for all of the animals studied are plotted similarly in figure 12. In the dogs with relatively slow heart rates and severe degrees of aortic regurgitation, the regurgitant fractions obtained by diastolic injections tended to be higher than those obtained for systolic injections, while the estimates from full-cycle and unsynchronized injections gave intermediate values (fig. 12).

Effect of Dynamic Response of Densitometer Catheter Systems Used
Dilution curves from the left ventricle were recorded simultaneously on nine occasions by withdrawing blood from the same site through a rapidly responding densitometer, for which a rapid rate of blood flow was used, and through a second, slower-responding instrument, for which a slow flow rate was utilized. The curves recorded with the faster-responding instrument showed large variations in concentration of indicator with each heartbeat while these cyclic variations were largely damped out by the slow system. The areas under the pairs of curves were, however, closely similar; thus, as might be expected,
DETECTION OF AORTIC REGURGITATION

The regurgitant fractions obtained by the two instruments were closely similar. Since this investigation was based primarily on comparisons of areas of dilution curves, no extended effort was made to obtain an accurate reproduction of the higher-frequency changes in concentration of indicator occurring at the sampling sites under study.

Correlation of Regurgitant Fraction from Dilution Curves Obtained in Vivo with Estimates of Severity of Aortic Regurgitation Based on Back-Perfusion Data at Necropsy

The data from the 18 dogs with aortic regurgitation that were studied by back perfusion of the aortic valve at necropsy are given in table 2. The animals have been arranged in order of increasing magnitude of regurgitation on the basis of the back-perfusion data. There is an evident correlation among the estimates of regurgitation from the dilution curves, the back-perfusion data, and the estimated severity of the anatomic defects found in the cusps of the valve after completion of the studies of back perfusion.

The estimated values of regurgitation based on the back-perfusion data and expressed as percentage regurgitation—that is, \((100 \times \text{backflow})/(\text{forward} + \text{backflow})\)—and as liters per min/10 kg of body weight are plotted in figure 13 against the regurgitant fractions obtained by the dye method after aortic valvotomy as compared with values obtained from 22 dogs studied with intact aortic valves. The values for forward flow used for estimation of the percentage regurgitation from the back-perfusion data were determined from
femoral arterial dilution curves recorded after injections of indocyanine green into the pulmonary artery. A similar degree of positive correlation was obtained between the regurgitant fractions and the estimates of regurgitation based on the back-perfusion data when these values were expressed either as a percentage of total forward flow across the valve or in absolute units of liters/min and when either of the two values for regurgitant fraction (LVA/FAA or LVA/LVPA) was used. The correlation coefficients for the regurgitation values expressed as liters per min/10 kg and the values for regurgitant fraction were 0.92 for the LVA/FAA fractions and 0.89 for LVA/LVPA values, while the values in relation to regurgitation expressed as a percentage of total flow were 0.92 and 0.89, respectively.

The regression equations shown in figure 13 were calculated with the use of the average values for regurgitant fraction obtained for each animal. The variability of these average values for regurgitant fraction from the regression line is such that the statistical likelihood of a similar value for LVA/FAA falling more than 15%, or 0.36 liters per min/10 kg, away from this line is less than 5%. The analogous figures for the variability of LVA/LVPA values are 19% and 0.40 liter per min/10 kg.

The relationship of the regurgitant fraction obtained after injection 1 to 2.5 cm downstream to the aortic valve to the percentage regurgitation estimated from the back-perfusion data in 15 of these dogs is shown in figure 14. The coefficient of correlation of 0.87 for these data and the standard error of the estimate of 8.9% were similar to the values ob-

---

**Figure 12**

Effect of the time of injection in the cardiac cycle on the amount of immediately appearing indicator detected in the left ventricle following injections just downstream to the aortic valve in anesthetized dogs studied without thoracotomy. Twelve dogs with aortic regurgitation, indicated by numerals, and ten normal dogs, indicated by letters, are included. See legend of figure 11 for definition of ordinate and abscissa values. Note the tendency in the dogs with severe degrees of aortic regurgitation and slow heart rates for the regurgitant fractions to be higher for diastolic than for systolic injections; the values obtained for full-cycle and manual injections tend to be intermediate between these values. Traces of immediately appearing indicator were detected in the left ventricle of three of the normal dogs with no consistent relationship to the type of injection used.

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**Figure 13**

Circulation Research, Volume XII, March 1963
DETECTION OF AORTIC REGURGITATION

Comparison of values related to severity of aortic regurgitation determined by back perfusion of the valve at necropsy and by left ventricular dilution curves recorded in vivo following injections of indicator just downstream to the aortic valve. Data from 22 dogs with normal aortic valves and 18 dogs with aortic regurgitation are included in each of the panels. The values for regurgitant flow determined (fig. 3) from data obtained by back perfusion of the valve at necropsy are plotted on the ordinate. These values are expressed as a percentage of total (effective plus regurgitant) flow across the valve in the left panels and in liters/min in relation to body weight in the right panels. The effective forward flows were determined from dilution curves recorded at the femoral artery in vivo. The regurgitant fractions plotted in the top panels are expressed as the ratio of the areas encompassed by the initial deflections of left ventricular (LVA) and femoral artery (FA) curves recorded simultaneously after injections into the aorta (A) just downstream to the valve. In the bottom panels the analogous values are expressed as the ratio of the areas encompassed by the initial deflections of the left ventricular curves (LV A and LV PA) recorded in succession after aortic (A) and pulmonary arterial (PA) injections. Values from individual dogs are designated by numbers, and replicate values are connected by lines. The calculated linear regression line with its equation is included in each panel. The dashed lines include the regions covered by doubling the standard errors of the estimate on either side of the respective regression lines. Note that the distribution of the experimentally determined points is similar for the different methods used to express the data obtained.

METHODS FOR ESTIMATING VALVULAR REGURGITATION BASED ON SYSTEMIC ARTERIAL DILUTION CURVES

The relationships of the ratios of expected to observed variance and slopes by the Korner-Shillingford method20, 21 to the back-perfusion estimates of aortic regurgitation are shown in figure 15. The range of values obtained in the normal dogs overlapped completely the values obtained from animals after aortic valvotomy. Similar lack of correlation was obtained for the C/C ratios,22 the disappearance slope ratios,2 23 and the several other empirical ratios studied in these animals. The results were not demonstrably im-
TABELE 2
Relationship of Size of Defects in Aortic Cusps to Magnitude of Regurgitant Fraction of Indicator (LVA/FAA) and Estimates of Regurgitation Based on Back Perfusion of Valve at Necropsy

<table>
<thead>
<tr>
<th>Dog</th>
<th>Weight, kg</th>
<th>Average heart rate, beats/min</th>
<th>Regurgitant fraction LVA/FAA from dye curves</th>
<th>Regurgitation from back perfusion, liters/min</th>
<th>Length of defect in aortic cusps, mm</th>
<th>Coronary</th>
<th>Non-coronary</th>
<th>Estimated severity of lesion</th>
<th>Time of study</th>
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<tr>
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</table>

*Arranged in order of increasing severity of aortic regurgitation from back perfusion data.

†Average values of replicate determinations used in 14 dogs (table 1).

‡Graded on basis of 0 to 5; 0: no defect; 5: very severe defect.

§A, studied immediately after creation of defect; O, studied 10 days or more after creation of defect.

**Avulsed valve cusp.

a Two orifices in the same cusp.

b Flap-like orifice in the cusp.

c First study.

d Second study.

Comment

All attempts to verify the validity of various indicator-dilution techniques proposed for detection and quantitation of valvular regurgitation have suffered from the fact that there is no accepted independent method for quantitative measurement of valvular regurgitation under physiologic conditions in intact animals or human beings. Lack of an independent method applicable in vivo led, for the purposes of this study, to the recourse of back perfusing the valve at necropsy under conditions reasonably similar to those pertaining during the diastolic phase of the cardiac cycle during life. The back-perfusion studies were carried out within two hours after death; the animals' own blood was used, supplemented on some occasions by a relatively small volume of blood from another animal when this was needed to obtain the volume necessary to fill the perfusion system.

The values for backflow per minute at various pressure gradients obtained by these necropsy studies were corrected to the same mean diastolic pressure gradients and diastolic times per minute as measured during life. It is recognized that the exact relationship between these values and the actual regurgitant flows per minute which existed at any given period during the dilution studies carried out just prior to the death of the animal is unknown. It is believed, however, that the nature of the defect in the valve is the major determinant of both the in vivo and the necropsy values and, therefore, that, although a systematic difference in the actual flow values...
probably exists, a reasonably reproducible quantitative relationship must pertain between the actual regurgitant flow during life and the estimates of this value calculated from the back-perfusion data and the diastolic pressure and time data measured during the particular in vivo period under study. Consequently, if a quantitative relationship is established between values based on indicator-dilution curves recorded during life and estimates of regurgitant flow for this period from the back-perfusion studies at necropsy, it follows that the values from the indicator-dilution curves do indeed bear a quantitative relationship to the degree of valvular regurgitation present.

Although some variability was found, the results reported herein demonstrate that such a relationship does exist under the conditions of these studies (figs. 13 and 14). Presumably, therefore, within the limits of the variability obtained, the regurgitant fraction determined by dilution curves recorded simultaneously from the left ventricle and a systemic artery following injections of indicator downstream to the aortic valve will provide a valid estimate of the presence and degree of aortic regurgitation, although a one-to-one relationship may not pertain between the actual regurgitant flows in vivo and the values estimated by the dye method.

The present results were obtained in dogs with both acute and chronic regurgitation. The technics required for obtaining the necessary dilution curves are applicable to studies on man. The question as to the validity of the method in estimating the degree of aortic regurgitation in clinical patients must, however, await further studies.

REGURGITANT FRACTION, GENERAL CONSIDERATIONS

The regurgitant fraction has three potential advantages over other methods of measuring regurgitation that are based on indicator-dilution technics. Firstly, since only the areas encompassed by the dilution curves are required, the values obtained are largely independent of the dynamic-response characteristics of the sampling and recording systems used. Secondly, it is potentially capable of giving a measure of aortic backflow in the presence of other lesions of the valve. Finally, unlike other methods, which depend on a quantitative measurement of a change in a component or components of dilution curves normally present, the regurgitant fraction is based on detection and measurement of something not normally present—namely, immediately appearing dye in the left ventricle. When the valve was intact, only trivial amounts of immediately appearing dye were detected in the left ventricle and then in only 13 of 51 occasions. The backflow of small amounts of indicator across the aortic valve in some normal dogs probably results from the small amount of blood which must flow retrograde across the undamaged aortic valve in the brief interval between the onset of left ventricular relaxation and the closure of the cusps of the aortic valve. The findings in this study suggest that, in dogs, a regurgitant fraction of more than 0.1 should always be considered indicative of aortic incompetence. No false negative findings were obtained after the injection of dye at, or 1 cm downstream to, the aortic valve in dogs after aortic valvotomy. Two false negative results were seen following injection of dye at a distance of 2...
emu downstream to the valve in one dog after valvotomy. The regurgitant flow in this animal was only 0.3 liter per min/10 kg and its percentage regurgitation, 20%.

**RELATIONSHIP OF REGURGITANT FRACTION TO TIME OF INJECTION**

The studies in normal dogs suggest that the detection of small amounts of indicator in the outflow tract of the left ventricle in these animals is related to the closure of the aortic valve. If indicator injected at the valve is not totally washed away before closure of the valve, the initial backflow of blood in the aorta at the onset of diastole may entrap dyed blood in the left ventricle by closure of the aortic leaflets. In this situation it has been found that in normal dogs the positions of the tips of the injecting and sampling catheters may be important determinants in the detection of the very small amount of regurgitant flow into the left ventricle (that is, immediately appearing indicator) associated with closure of the cusps of the valve.

In dogs with aortic regurgitation the progressive increase in the regurgitant fraction \((LVA/FAA)\) as injections of short duration (40 msec) are made later in systole is related both to the decrease in velocity of systolic ejection toward the end of systole and to the decrease in the period of forward flow remaining in the particular systolic phase of the cycle in which the injection was made. The velocity of blood flow in the aorta and its branches increases progressively in the first third of systole and then decreases progressively throughout the last two thirds of systole. Thus, indicator injected during the first third of systole will travel farther from the valve and be diluted in a greater quantity of blood because there is a longer duration of forward flow at a relatively higher velocity than when indicator is injected during the last two thirds of systole.

When dye is injected at the onset of systole, it is dispersed along the central arterial system for a distance determined by the stroke
DETECTION OF AORTIC REGURGITATION

volume of that particular systole and the degree of dispersion of the indicator in this stroke volume. At the termination of this systole, the highest concentration of indicator will be located peripherally toward the head of the column of ejected blood; the concentration will decrease proximally to a minimal value or zero at the tail of this column, which, at the end of systole, will be just downstream to the aortic valve. With the onset of diastole, regurgitation begins, and at this instant the concentration of indicator in the regurgitated blood will be zero or a minimal value, depending upon how completely the indicator was washed out of this area by the preceding systolic ejection. Since the pressure gradient from aorta to ventricle producing regurgitation is at a maximum at the onset of diastole and then decreases progressively until the onset of the next systole, the volume rate of regurgitant flow through a defective valve will vary in the same manner. In the situation under consideration, therefore, the concentration of indicator in the regurgitated blood will be zero or at a minimal value during the initial part of diastole, when the volume rate of regurgitation is at a maximum. The concentration of indicator will then increase progressively as increasing volumes of the column of blood in the aorta and central vessels ejected in the previous systole flow back into the ventricle. However, as the concentration of indicator in the regurgitated blood increases, the volume rate of regurgitation decreases toward the end of diastole.

It is evident, therefore, that the fraction of indicator returning to the ventricle following its injection just downstream to the aortic valve would be expected to vary considerably with the time of the cardiac cycle in which the injection occurs. For the reasons pointed out in the preceding paragraph, this fraction should be at a minimal value when the period of injection is limited so as to occur just at the end of diastole or the onset of systole, and it should be at a maximal value when an equivalent injection is timed to occur at the end of systole or the onset of diastole. In the latter instance the concentration of indicator when regurgitation begins at the onset of diastole would be maximal in the aortic blood occupying the region just downstream to the aortic valve; accordingly, a coincidence of the maximal concentration of indicator in regurgitated blood and maximal rate of regurgitant flow would then occur and thus produce the maximal regurgitation of indicator into the left ventricle. The results obtained with the use of short-duration injections confirm these considerations (figs. 8 and 9).

Similar considerations were proposed by Warner and Toronto to explain their findings that the detection of retrograde flow of indicator to the left subclavian artery following short-duration injections at downstream sites in the descending aorta is dependent on the phase of the cardiac cycle in which the injection occurs.

The finding that the fractions or indicator detected in the left ventricle were similar when the results of longer-duration injections synchronized to cover the full diastolic or the full systolic phase of a single cardiac cycle were compared is at first consideration surprising. The values for regurgitated indicator that are found after multiple injections of very short duration which have been spaced to cover all phases of the cycle are, however, compatible with these results. This finding must result from the interplay of (1) the progressive decrease in the volume rate of regurgitation toward the end of diastole, 2) the variations in the concentration of indicator in blood being regurgitated at any instant during diastole, and (3) the fact that the volume rate of blood flow from the ventricle varies greatly during the period of ejection, decreasing to a low value during the last part of systole.

Because of the last-mentioned factor, the fraction of indicator injected into the aorta during the last third of systole remains in relatively close proximity to the aortic valve, where it is highly susceptible to regurgitation during the subsequent diastolic period. Contrariwise, because of the decrease in rate of regurgitant flow during the latter part of diastole, only a relatively small portion of
the indicator injected during this phase is regurgitated into the ventricle, and the remaining nonregurgitated portion is then washed far downstream to the aortic valve during the subsequent systole. This relative similarity in regurgitant fractions for holosystolic and holodiastolic injections is a fortunate situation from the practical viewpoint since it is the basis for the finding that representative reproducible values for regurgitant fraction can be obtained by the usual manual injection techniques without recourse to a mechanical, electronically synchronized injection assembly.

**SELECTION OF INJECTION AND SAMPLING SITES**

The data from dogs with aortic regurgitation suggest that, when the tip of the injecting catheter is not more than 2 cm downstream from the aortic valve, its exact position in relation to the valve is not of great importance. It is the belief of the authors that the optimal position is obtained by withdrawing the aortic catheter approximately 1 cm downstream to the point at which the change from left ventricular to aortic pressure occurs. In a few isolated instances the area encompassed by dilution curves recorded from the femoral artery following injections thought to be just downstream to the aortic valve were discordantly smaller than the areas of similar curves recorded after injections into the pulmonary artery. It is believed that this finding resulted from an occasional preferential injection into the ostium of a coronary artery. This finding was not encountered when the tip of the injecting catheter was positioned by withdrawing 1 cm downstream to the site of transition from ventricular to aortic pressure.

The data for dogs with aortic regurgitation suggest that the exact position of the tip of the sampling catheter in the left ventricle was not of great importance. A position in what appeared to be the middle of the left ventricle was preferred. Apparently the regurgitant jet into the left ventricle produces better mixing in these animals than occurs in normal dogs.

Theoretical considerations suggest that the regurgitant fraction is a measure of the proportion of the total left ventricular output that regurgitates. If this were strictly the case, it might be expected that an approximately one-to-one relationship would have been obtained between the percentage regurgitation by the back-perfusion method and the regurgitant fraction converted to per cent by multiplying by 100. The fact that the percentage of the regurgitant fraction systematically exceeded the back-perfusion values by a factor of approximately two (figs. 13 and 14) suggests that the assumptions, such as that of uniform mixing, upon which quantitative derivations of the regurgitant fraction have been based, do not conform to the actual situation and that a more complicated relationship between the various factors must pertain. This relationship is, however, sufficiently uniform from animal to animal so that a reasonably close correlation can be demonstrated under the conditions of these experiments between the values from the regurgitant fraction-dye method and the values for regurgitation by back perfusion.

In the course of the studies reported herein, the correlation has been investigated between the degree of aortic regurgitation and the various features of systemic arterial dilution curves such as the disappearance slope, the variance, and other parameters of the curves which are frequently distorted in the presence of valvular regurgitation. Such correlations were either not demonstrable or very poor and therefore provide no support for the use of these parameters of dilution curves as a basis for detecting and quantitating the severity of valvular regurgitation. These findings are in harmony with the results of studies of mechanical and mathematical models of the circulation which indicate that the severity of valvular regurgitation cannot be quantitated on the basis of a single dilution curve recorded downstream to the site of injection of the indicator.

On the other hand, considerable support for the use of the regurgitant fraction-indicator dilution method to detect and estimate the severity of regurgitation has recently been obtained by comparison of forward and back-
DETECTION OF AORTIC REGURGITATION

ward flows in the ascending aorta recorded by means of an electromagnetic flowmeter with the regurgitant fraction-dye values determined simultaneously before and after creation of aortic regurgitation. It has also been found that there is a close correlation between values for aortic regurgitation determined by the method of left ventricular regurgitant fraction and values determined by the method described by Warner and Toronto based on detection of the quantity of indicator in the left subclavian artery following injections of the indicator into the descending aorta at sites downstream to the origin of the subclavian artery. The validity of these technics of upstream sampling has also received support from study of mathematical models of the circulation with the use of an analogue computer.

Summary

In dogs studied without thoracotomy the detection of immediately appearing indicator in the left ventricle following its injection approximately 1 cm downstream from the aortic valve can be used as a reliable index of the presence or absence of aortic regurgitation.

With this type of injection and under the conditions of these experiments, the ratio of the area encompassed by the immediately appearing portion of the dilution curve recorded from the left ventricle to the area encompassed by the primary portion of the curve recorded at the femoral artery bears a close positive correlation (correlation coefficient: 0.9) to the severity of aortic regurgitation as estimated by back perfusion of the valve at necropsy.

Within limitations, the position of the tip of the sampling catheter in the left ventricle in dogs with aortic regurgitation is not an important determinant of the amount of immediately appearing indicator detected in this chamber. Furthermore, although the amount of indicator detected in the left ventricle following injections of very short duration is time-dependent, if the duration of the injection is extended to cover the full systolic or diastolic phase of one heartbeat or continues over one or more heartbeats, the exact timing of this injection in relation to the cardiac cycle is not an important determinant of this variable.

It is concluded that under these conditions the positive correlation established between the amount of immediately appearing dye detected in the left ventricle (expressed as the regurgitant fraction) and the severity of aortic regurgitation determined by back perfusion at necropsy can be used as a valid means of estimating the severity of aortic regurgitation in dogs.

The applicability of this indicator-dilution method to the study of clinical aortic regurgitation merits further study.

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Detection and Measurement of Experimentally Produced Aortic Regurgitation by Means of Indicator-Dilution Curves Recorded from the Left Ventricle
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Circ Res. 1963;12:269-290
doi: 10.1161/01.RES.12.3.269

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