Assessment of an Indicator-Dilution Technic for Quantitating Aortic Regurgitation by Electromagnetic Flowmeter

By Donald A. Meloody, M.D., David E. Donald, B.V.S., M.R.C.V.S., Ph.D. in Physiology, Hiram W. Marshall, M.D., and Earl H. Wood, M.D., Ph.D.

In the presence of aortic regurgitation, if dye is injected into the aortic root, some of it regurgitates and can be detected almost immediately in the left ventricle. If simultaneous dilution curves are recorded from the left ventricle and a systemic artery, the ratio of the area of the immediately appearing portions of the left ventricular (LVA) and the femoral artery (FAA) dye curves has been termed the "regurgitant fraction" (LVA/FAA). Theoretically, this fraction expresses the ratio of the regurgitant volume to total stroke volume, or the fraction of total left ventricular stroke volume which regurgitates if uniform mixing of indicator and blood occurs. Since the introduction of this upstream sampling technic for quantitating valvular regurgitation in 1956,1 a growing experimental and clinical experience has confirmed the usefulness of this method.2-5 Independent estimates of regurgitation using hydraulic formulas or backflow perfusion showed a good correlation with estimates obtained by the dye-dilution technic both for experimental mitral regurgitation1,3 and experimental aortic regurgitation.4 Detailed studies on the factors affecting the technic such as the timing of the injection of indicator and the position of the injecting and sampling catheters have been reported.5,6 The availability of the square-wave electromagnetic flowmeter developed by Denison, Sponsor, and Green7 made it possible to extend assessment of the dye-dilution technic by comparison of the values obtained by these two independent methods.

Methods

The methods used in the measurement and photoplethysmographic recording of various physiological variables and indicator-dilution curves have been reported previously.8-10 Figure 1 schematically depicts the experimental design used in this project. Nine mongrel dogs, ranging in weight from 12.3 to 20.2 kg were studied. Intramuscular injection of morphine (5 mg/kg) and intravenous injection of pentobarbital (35 mg/kg) were used for anesthesia with supplemental doses of pentobarbital administered as required. Respiration was maintained via auffed endotracheal tube connected to a Palmer respirator with 99.5% oxygen administered under an inspiratory positive pressure adjusted to ensure adequate inflation of the lungs as determined with the thorax opened.

After median sternotomy was performed, catheters of the Rodriguez-Alvare spray tip type* (no. 5 F) for injection of indocyanine green were positioned in the main pulmonary artery, via a small branch, and at the aortic root 1 cm distal to the aortic valve via a femoral artery. The aortic root catheter was positioned by reintegrating passage into the left ventricle as indicated by pressure monitoring, and then withdrawn to a position 1 cm distal to the point where an aortic pressure pulse contour was first noted. Catheters with bird's-eye openings at their tips (no. 6 F, Command) for pressure recordings and blood sampling were introduced to the body or apex of the left ventricle and into the junction of the aortic and left subclavian arteries via a pulmonary vein and the internal mammary artery, respectively. A polyethylene cannula 10 cm in length and 1 mm in internal diameter was introduced into the left femoral artery. All catheters were connected to strain gauge manometers for the recording of pressure. No capacitance transducers were used, thus avoiding the zero error connected with the presence in

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FIGURE 1
Assembly for obtaining simultaneous measurements of aortic regurgitation by flowmeter and upstream sampling indicator-dilution methods. The catheter used for injection of indicator into the pulmonary artery for determinations of systemic flow is not shown.

The circumference of the ascending aorta was measured as close to the heart as possible by means of a circumferential tie, and a noncannulating flowmeter probe (Square-Wave Electromagnetic Flowmeter Model 201B) was selected and positioned at this site to give a stable recording as monitored on a direct writing Sanborn polyvinyl recorder. Pressures were recorded from the left ventricle and the aorta distal to the probe before and after the application of the probe and at intervals throughout the procedure. Pressures recorded from the left ventricle and from the aorta distal to the probe at existing heart rates before and after the production of aortic regurgitation are recorded in table 1. No gradients were detected across the probe during the control state before the production of regurgitation. After regurgitation, small systolic gradients were noted in some experiments as indicated in table 1. Probe electrode balance was conducted according to the technique recommended by Denison, Spoo, and Green and was checked at frequent intervals throughout the procedure. A magnet current of one ampere was used, and phasic flow was recorded throughout the procedure for all flowmeter measurements.

Injection of indicator into the aortic root in the control state showed no early appearing dye in the left ventricle in this series of experiments and proved the absence of aortic regurgitation in the control state in each experiment. A series of dye curves for the determination of cardiac output was done by injecting into the main pulmonary artery and sampling from the femoral artery at existing heart rates and at slower heart rates (table 2) which were obtained by stimulating the peripheral cut end of the right vagus nerve with a Grass Physiologic Stimulator; the frequency and voltage were varied to attain the desired heart rate. Simultaneous recording of phasic flow with the flowmeter was used to obtain a calibration factor for com-

*Supplied through the courtesy of Hynson, Westcott & Dunning, Inc., Baltimore, Maryland, under the trade name of Cardio-Green.
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Simultaneous Pressures in the Left Ventricle and Aortic Arch During Recording of Flow in the Ascending Aorta with a Square-wave Electromagnetic Flowmeter Before and After Creation of Aortic Regurgitation

<table>
<thead>
<tr>
<th>Dog</th>
<th>Weight, kg</th>
<th>Heart rate range studied, beats/min</th>
<th>Blood pressure, max mm Hg</th>
<th>Mean diastolic pressure gradient* with regurgitation, mm Hg</th>
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<tr>
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<td>Aortic root</td>
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<td>135/0-3</td>
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*Aorta to left ventricle.

Table 1

Table 1

<table>
<thead>
<tr>
<th>Dog</th>
<th>Weight, kg</th>
<th>Heart rate range studied, beats/min</th>
<th>Blood pressure, max mm Hg</th>
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*Aorta to left ventricle.

The zero flow, zero voltage reference line, was established by vagal arrest of the heart. Aortic regurgitation was then produced by means of a valvulotome introduced via a carotid artery. Success in the production of aortic regurgitation could be gauged by the detection of immediately appearing dye in the left ventricle after an aortic root injection, and also by the presence of a negative phase (retrograde flow) during the diastolic phase of the flowmeter tracing. Two injections into the aortic root were alternated with a single injection into the pulmonary artery for the determination of the regurgitant fraction (LV/Ao) and of the cardiac output in close temporal relationship, respectively. A series of determinations was conducted at spontaneously occurring heart rates and then additional determinations were carried out at slower heart rates produced by vagal stimulation. All nine dogs were studied at existing heart rates, while only six dogs were studied with vagal slowing. An additional zero flow reference line could be obtained at the termination of the experiment by vagal arrest of the heart. The heart was arrested for a period sufficient for pressures to equilibrate between the left ventricle and the aorta. The absence of a transvalvular gradient during arrest was assumed to indicate the attainment of zero flow by the simultaneously recorded flowmeter tracing. The maximal variation between the zero flow reference line established before and after the production of the regurgitation did not exceed 2 mm per hour of elapsed experimental time which represented an apparent change in flow averaging 210 ml per minute per hour. The animal was killed by exsanguination, and the blood was saved for use in the perfusion calibration to eliminate any change in sensitivity of the flowmeter due to changes in hematocrit of the perfusate. Necropsy confirmed the position of the injecting and sampling catheters, and allowed the site and size of the defect in the aortic valve to be estimated.

In vitro calibration of the flowmeter was carried out at the termination of each experiment using the apparatus devised by one of us (D.E.D.) which is depicted schematically in figure 2. The flowmeter probe was removed and the ascending aorta dissected free and removed. The maximal possible extent of the proximal end of the aorta was obtained so that adequate length was available for cannulation without interference, with repositioning of the flowmeter probe as close as possible to the position which had pertained in the in vivo portion of the study. Blood saved from exsanguination of the animal was used to prime the apparatus. The heat exchanger was adjusted to maintain the temperature of the perfusing blood at 37° C and the saline water bath was maintained at this same temperature. Pressure within the isolated aorta was measured by means of a catheter connected to a strain gauge manometer. The pressure was adjusted by the screw clamp (B) to approximate the mean arterial pressure level observed in vivo, although the actual pressure level was not found to be critical if good contact was maintained between the vessel wall and the probe electrodes. A zero flow reference line was ob-
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Calibration of aortic flowmeter by perfusion of excised aorta (dog 9) using the apparatus shown in figure 2. The negative signs indicate values obtained during perfusion of the aorta in the retrograde direction and vice versa. Note the linear relationship between flow and galvanometer deflection and that this calibration line passes through zero. Therefore, the same calibration factor can be used for measurement of retrograde and forward flows.

The following formulas were used to obtain the regurgitant fraction \((L/V_A/FA_A)\) by the total triangle method:

\[ (L/V_A/FA_A) = \frac{PT_F \times OA}{PF_A \times OA} \]

and by the forward triangle method:

\[ (L/V_A/FA_A) = \frac{BF \times OA}{GF_A \times OA} \]

Cardiac output was calculated from dye curves recorded at the femoral artery after injection into the pulmonary artery, by the routine Hamilton method of semilogarithmic extrapolation. Cardiac output also could be obtained by flowmeter after the production of regurgitation by calculating the effective stroke volume as the difference between the total stroke volume (the area enclosed by the positive systolic portion of the flowmeter tracing and the zero flow reference line) and the regurgitant stroke volume (the area enclosed by the negative diastolic portion of the flowmeter tracing and the zero flow reference line) and dividing by the cycle length. Flowmeter regurgitant flow in milliliters per second was calculated by dividing the average regurgitant stroke volume (milliliters) by the average cycle length (seconds). Regurgitant flow by dye curve in milliliters per second was calculated from the cardiac output (milliliters per second) and the total triangle regurgitant fraction \((L/V_A/FA_A)\) by means of the following formula:

\[ \text{Regurgitant flow by dye curve} = \text{cardiac output} \times \left(\frac{0.82 \times L/V_A/FA_A}{L - 0.82 \times L/V_A/FA_A}\right) \]

The derivation of this formula relating regurgitant fraction to regurgitant flow follows:

\[ Q_R = \text{Regurgitant flow} \]
\[ Q_F = \text{Effective forward flow, systemic flow} \]
\[ Q_T = \text{Total forward flow across valve} \]
\[ Q_B = Q_T - Q_R \] by definition
\[ Q_R = \frac{Q_B}{Q_T} \]
\[ Q_B = \frac{Q_R}{Q_T} + Q_F \] (1)
\[ Q_B = \frac{Q_R}{Q_T} + Q_F \] (2)
\[ Q_B = \frac{Q_R}{Q_T} \]
\[ Q_F = Q_T - Q_B \]

The origin of the constant 0.82 will be described subsequently.

The area enclosed between the positive systolic portion of the flowmeter tracing and the zero flow reference line represents the total stroke volume (TSV) if coronary systolic flow is ignored. Similarly, the area enclosed by the negative diastolic portion of the flowmeter tracing and the zero flow reference line represents the regurgitant stroke volume (RV) if coronary diastolic flow is ignored. The areas indicated by shading in figure 4 were measured planimetrically on 5 to 15 beats (depend-
Figure 4

Recordings used for simultaneous determinations of aortic regurgitation by flowmeter and dye-dilution techniques at two different heart rates in dog 5. The dog's weight was 14.6 kg and the estimated area of the defect in the aortic valve from measurements at necropsy was 0.15 sq cm.

The lower middle panel illustrates the method used to obtain the zero-flow reference line of the flowmeter after the production of regurgitation. The heart was arrested by vagal stimulation for a period sufficient for the pressures to equilibrate between the aorta and the left ventricle. In this instance, the transvalvular gradient fell to zero at an equilibrium pressure of 18 mm Hg and flow was assumed to be zero at this point. The degree of aortic regurgitation was determined by the ratio of the regurgitant volume (RV) to total stroke volume (TSV) as indicated by the shaded areas in the flowmeter recordings in the right and left lower panels. The regurgitant fraction determined by the flowmeter was compared with the ratio of the simultaneously recorded areas of the immediately appearing portion of the left ventricular dilution curve (LV A) and the femoral artery curve (FA A) shown in the upper panels. These comparisons were made at the animal's spontaneously occurring heart rate (left panels) and at slower heart rates during vagal stimulation (right panels). The length of the horizontal line connecting the two vertical arrows marking the time of injection of indocyanine green indicates the delay in the appearance time of the left ventricular dilution curve due to the dead space of the catheter-densitometer sampling system. The corresponding delay for the femoral artery system was 0.2 second. Note that different paper speeds, indicated by the vertical lines, were used in different panels.

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Assemble for calibration of aortic flowmeter by forward and retrograde perfusion at known rates of flow. A, B, C, and D represent clamps. By opening C and D and simultaneously closing A and B and vice versa, the direction of flow through the aorta could be reversed at will without changing other conditions in the system. P and P' indicate manometer systems, strain gauge type.

Maintained with the pump turned off and with the mean intra-aortic pressure maintained at the desired level. This was repeated before and after each set of forward and retrograde perfusions at the same flow level. By changing the clamps from position A-B to C-D, forward and retrograde perfusions of the aorta at the same dial setting on the pump could be obtained immediately interchangeably. The actual volume flow through the system was determined by occluding the flow line at F and measuring the inflow into the calibrating cylinder over an interval timed by stopwatch and by signals on the photokymographic record. A sequence of forward and retrograde flows was recorded in the range encountered during the experiment. A calibration obtained using this apparatus is shown in figure 3.

To obtain a calibration factor for stroke volume measurements, the perfusion flow in milliliters per second per centimeter of flowmeter deflection is multiplied by the time in seconds represented by 1 cm on the horizontal axis of the photokymographic record. A sequence of forward and retrograde flows was recorded in the range encountered during the experiment. A calibration obtained using this apparatus is shown in figure 3.

The calibration factor for rate of flow based on the dye-curve determinations of cardiac output was obtained by dividing the volume calibration factor for stroke volume measurements by the time in seconds represented by 1 cm on the horizontal axis of the photokymographic record. This is indicated in the following formula:

$\text{Flow calibration factor by dye curve (ml/sec per cm deflection)} = \frac{\text{volume calibration factor (ml/square centimeter)}}{\text{average flowmeter beat area (sq cm)}}$

The dye-curve regurgitant fraction ratios $L_{RV}/F_A$ were assessed by three methods: the semi-logarithmic extrapolation method of Hamilton, the total triangle method of Warner and Wood, and the forward triangle method of Hetzel and associates. Both the left ventricular and femoral artery dye curves were measured by extrapolation of the disappearance slope of the curves to less than 2% of peak concentration. For the total and forward triangle methods, each dye curve is considered as a triangle and the area is calculated from the base (the passage time [PT] or buildup time [BT]) and the height (the peak concentration [CP], expressed in milligrams per liter) measured directly on the photokymographic record.
through zero flow, the calibration factor for converting flowmeter beat areas to stroke volume measurements which appears in both the numerator and denominator of the RV/TSV ratio is identical and hence will cancel out. Therefore, if linearity pertains and zero flow coincides with a galvanometer deflection of zero, this ratio is independent of the sensitivity of the flowmeter. If the regurgitant volume (RV in milliliters) and the total stroke volume (TSV in milliliters) are divided by the cycle length (seconds), the mean regurgitant flow in milliliters per second \( (Q_{\text{R}}) \) and the mean total forward flow in milliliters per second \( (Q_{\text{F}}) \) will be obtained. Since the factor of cycle length is common to both the numerator and denominator, the ratio of RV/TSV is identical to the ratio of \( Q_{\text{R}}/Q_{\text{F}} \).

Maximal forward and maximal regurgitant flows are represented by the peak and nadir deflections of the flowmeter tracing from the zero flow reference line. The duration of forward flow was measured on the flowmeter tracing on the zero flow line between the points of intersection of the positive systolic portion of the flowmeter tracing with the zero flow line. Similarly, the duration of regurgitant flow was measured on the zero flow line between the points of intersection of the negative diastolic portion of the flowmeter tracing with the zero line. Mean systolic forward flow was calculated by dividing the total stroke volume in milliliters by the duration of forward flow in seconds. Mean diastolic regurgitant flow was calculated by dividing the regurgitant volume by the duration of regurgitant flow.

The mean aortic pressure during the interval between the inscription of the incisura and the onset of the upstroke of the pressure tracing \( (P_{\text{A}}) \) was measured by planimetry. The mean left ventricular pressure during the corresponding period \( (P_{\text{LV}}) \) was measured similarly, and the mean gradient across the aortic valve during the period of regurgitation expressed in millimeters of mercury \( (P_{\text{A}} - P_{\text{LV}}) \) was derived by subtraction.

The aortic regurgitant orifice \( (A_{\text{RO}}) \) in square centimeters was calculated from the hydraulic formula of Gorlin using an orifice contraction coefficient for the aortic valve of 0.65 (as advocated by Rodrigo, Gorlin and associates)\textsuperscript{20-22} which, in combination with the square root of the mercury conversion factor of 1.17, results in a "C" factor of 1. The final form of this equation is:

\[
\text{Area of aortic regurgitant orifice, } A_{\text{RO}} = \frac{44.5 \times \sqrt{P_{\text{A}} - P_{\text{LV}}}}{Q_{\text{F}}}.
\]

Regurgitant flow was measured at the spontaneous

\[
(44.5 \times A_{\text{RO}} \times t_{\text{D}}). 
\]

Comparison of stroke-volume values determined simultaneously from dilution curves of indocyanine green and by an electromagnetic flowmeter on the ascending aorta of nine anesthetized dogs with open chests. The flowmeter values were obtained by measuring the area above the zero-flow reference line encompassed by each recorded flowmeter beat and converting these to stroke volume by multiplication by a calibration factor obtained by perfusion of the excised aorta at known flows at necropsy (figs. 2 and 3). The numerals designate the individual dogs from which each pair of the simultaneous determinations were made. The diagonal line represents the loci of identical values for the two methods. In five dogs, the average difference between the two methods for stroke volumes was not statistically significant \( (P > 0.05) \). In four dogs, there was a statistically significant systematic difference \( (P < 0.05) \) (see table 2 and text for additional details). The values shown were obtained before aortic valvulotomy was performed.

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TABLE 2
Comparison of Stroke-Volume Values Determined Simultaneously from Dilution Curves of Indocyanine Green and by an Electromagnetic Flowmeter on the Ascending Aorta in Anesthetized Dogs with Open Chests

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<tr>
<th>Dog</th>
<th>Stroke-volume from dye curve, ml</th>
<th>Average stroke-volume from dye curve, ml</th>
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</table>

*Values in parentheses give the range of values obtained in each dog; other figures are average values.

P values of less than 0.05 were taken to indicate a statistically significant difference between stroke volumes calculated from dye curves and stroke-volume determinations by the flowmeter using the calibration factor determined by perfusion of the aorta at necropsy.

Results
Calibration and Validity of Flowmeter Values. The in vivo method of calibration based on measurements of stroke volume by dye curve was compared with the in vitro method of calibration by perfusion of the aorta at necropsy by plotting stroke volumes calculated by the two methods in 95 simultaneous determinations in the nine dogs. These data are shown in figure 5 and table 2. The excellent correlation between the two methods is evident, and in five dogs, indicated by the numerals 1, 3, 4, 7, and 8, the differences between these two completely independent methods for measurement of stroke volume were not statistically significant (P greater than 0.05). In four dogs, indicated by the numerals 2, 5, 6, and 9, the stroke volume measurements showed a small but statistically significant systematic difference (P less than 0.05) by the two methods of calibration. For purposes of this study, the in vivo determined calibration factor was used to convert the flowmeter beat areas to stroke volume measurements. The in vivo determined calibration factors for converting the flowmeter beat areas to stroke volume measurements ranged from 0.45 to 2.22 ml per square centimeter of beat area and averaged 1.18 ml per square centimeter. Corresponding calibrations for rate of flow...
DYE DILUTION IN AORTIC REGURGITATION

TABLE 3

Average Flow Values Determined by Electromagnetic Flowmeter in Dogs Before and After Surgical Production of Aortic Regurgitation*

<table>
<thead>
<tr>
<th>Dog</th>
<th>Control</th>
<th>After injection</th>
<th>Regurgitant volume, ml/beat</th>
<th>Total stroke volume, ml/beat</th>
<th>Average degree of regurgitation, RV/TSV ( \times 100 )</th>
<th>Area of orifice, sq. cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.32</td>
<td>0.98</td>
<td>1.3</td>
<td>8.0</td>
<td>19</td>
<td>0.01</td>
</tr>
<tr>
<td>2</td>
<td>2.23</td>
<td>1.58</td>
<td>22.8</td>
<td>41.3</td>
<td>65</td>
<td>0.28</td>
</tr>
<tr>
<td>3</td>
<td>1.32</td>
<td>2.62</td>
<td>17.3</td>
<td>39.4</td>
<td>85</td>
<td>0.98</td>
</tr>
<tr>
<td>4</td>
<td>0.60</td>
<td>1.71</td>
<td>29.7</td>
<td>39.4</td>
<td>68</td>
<td>0.96</td>
</tr>
<tr>
<td>5</td>
<td>1.10</td>
<td>1.05</td>
<td>12.0</td>
<td>27.8</td>
<td>48</td>
<td>0.15</td>
</tr>
<tr>
<td>6</td>
<td>2.15</td>
<td>1.75</td>
<td>23.3</td>
<td>33.5</td>
<td>76</td>
<td>0.39</td>
</tr>
<tr>
<td>7</td>
<td>1.39</td>
<td>0.47</td>
<td>1.4</td>
<td>5.6</td>
<td>25</td>
<td>0.03</td>
</tr>
<tr>
<td>8</td>
<td>1.73</td>
<td>1.81</td>
<td>1.0</td>
<td>6.8</td>
<td>29</td>
<td>0.02</td>
</tr>
<tr>
<td>9</td>
<td>1.77</td>
<td>0.62</td>
<td>1.0</td>
<td>13.0</td>
<td>79</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*Based on determinations at spontaneously occurring heart rates.

TABLE 4

Rates of Forward and Regurgitant Flow in the Ascending Aorta of Dogs After Surgical Production of Aortic Regurgitation

<table>
<thead>
<tr>
<th>Dog</th>
<th>( Q_p ) ml/min</th>
<th>Maximal diastolic, ml/diast. sec</th>
<th>Maximal systolic, ml/syst. sec</th>
<th>( Q_u ) ml/min</th>
<th>Maximal diastolic, ml/diast. sec</th>
<th>Maximal systolic, ml/syst. sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>120</td>
<td>5.9</td>
<td>8.2</td>
<td>120</td>
<td>12.1</td>
<td>16.4</td>
</tr>
<tr>
<td>2</td>
<td>3240</td>
<td>94.3</td>
<td>117.0</td>
<td>5030</td>
<td>183.3</td>
<td>292.9</td>
</tr>
<tr>
<td>3</td>
<td>2850</td>
<td>82.7</td>
<td>106.0</td>
<td>1090</td>
<td>173.3</td>
<td>275.0</td>
</tr>
<tr>
<td>4</td>
<td>3840</td>
<td>125.0</td>
<td>169.0</td>
<td>4900</td>
<td>188.3</td>
<td>251.0</td>
</tr>
<tr>
<td>5</td>
<td>1040</td>
<td>57.7</td>
<td>69.8</td>
<td>4170</td>
<td>125.0</td>
<td>199.0</td>
</tr>
<tr>
<td>6</td>
<td>3820</td>
<td>122.6</td>
<td>172.0</td>
<td>5930</td>
<td>188.0</td>
<td>250.0</td>
</tr>
<tr>
<td>7</td>
<td>294</td>
<td>10.3</td>
<td>14.4</td>
<td>1350</td>
<td>24.4</td>
<td>67.7</td>
</tr>
<tr>
<td>8</td>
<td>205</td>
<td>8.8</td>
<td>15.6</td>
<td>1290</td>
<td>89.1</td>
<td>80.8</td>
</tr>
<tr>
<td>9</td>
<td>2050</td>
<td>61.3</td>
<td>81.5</td>
<td>2420</td>
<td>91.2</td>
<td>160.0</td>
</tr>
</tbody>
</table>

The areas of the valvular defects ranged from 0.01 to 0.39 square centimeter. Simultaneous flow determinations were made by flowmeter and the dye methods at heart rates ranging from 39 to 216 beats per minute, the slower heart rates being obtained by vagal stimulation. The values obtained for cardiac output, mean and maximal forward flows and other parameters...
Comparison of values for regurgitant fraction determined simultaneously by flowmeter and the upstream sampling indicator-dilution technique (231 simultaneous determinations in nine dogs). The areas of the early appearing portion of the left ventricular (LV) curve and the primary deflection of the femoral artery (FA) dye curves were measured by the semilog replot, the total triangle, and the forward triangle methods. The ratios of the areas encompassed by these dye curves (LV/LFA) designated according to the method of measurement used are given in the left, middle, and right panels respectively. The dye values are plotted against the simultaneously determined ratios of regurgitant volume (RV) to total stroke volume (TSV) by flowmeter at the animal’s spontaneously occurring heart rates (upper panels) and at slower heart rates obtained by vagal stimulation (lower panels). Control values for the nine dogs are plotted at the origins of the graphs. The numerals indicate the individual animals studied as listed in table I. Note the good correlation between these two independent methods of measuring the degree of regurgitation and the systematic differences between the values obtained. This correlation holds over a wide range of heart rates in spite of the large attendant variations in transvalvular diastolic pressure gradients and effective forward flows. The three values for dog 7 indicated by the asterisks are believed to have resulted from preferential injections of indicator into the defect since withdrawal of the injecting catheter 2 cm returned the dye-curve values to those indicated by the numeral 7 obtained earlier in the experiment.
Comparison of flowmeter and dye-curve measurements of the degree of aortic regurgitation at different heart rates obtained by varying degrees of electric stimulation of the right vagus nerve (231 simultaneous determinations in nine dogs).

The overall correlation coefficient for these determinations is 0.91 irrespective of heart-rate variations. The regression equation indicates that the systematic difference between the flowmeter and dye-curve determinations would be corrected by a factor of 0.82 times the dye-curve determination with a standard error of estimate (SEM) of 0.11 regurgitant fraction units being obtained. The calculated regression line passes through zero. The total triangle method was used for calculation of the regurgitant flow from the dilution curves.

Making a total of 272 measurements. At slower heart rates ranging down to 39 beats per minute obtained by vagal stimulation, 59 simultaneous measurements of the regurgitant fraction by the two methods showed a similar correlation. In one dog (no. 6), four determinations of the regurgitant fraction by dye curve could not be measured accurately because of a nearly horizontal disappearance slope of the femoral artery curve, which could not be accurately extrapolated owing to the irregularities occasioned by the extremely low cardiac output (70 ml/min) with vagal slowing of the heart. All data comprising 231 determinations are graphed according to heart rate ranges in Figure 7, the dye curve regurgitant fraction being measured by the total triangle method. The correlation coefficient for the 231 determinations was 0.91 and the linear regression equation was $Q_R/Q_P = 0.82 L_V/F_A$. The standard error of estimate of the regression equation is 0.13 regurgitant fraction units.

Comparison of Regurgitant Flow Determinations by Flowmeter and Upstream Sampling Indicator-Dilution Technique. Regurgitant flow determinations by flowmeter and dye techniques were obtained as indicated under the section on methods. Owing to the nature of the relationship between the regurgitant frac-
Regurgitant flow (Qr) and regurgitant fraction illustrated in figure 8, the errors, in estimation of regurgitant flow tend to increase with increasing regurgitant fractions.

The relationship between the magnitude of the regurgitant fraction and the error in measurement of regurgitant flow by the upstream sampling dye technic is illustrated in figure 9 by plotting the differences in regurgitant flow values obtained by dye and flowmeter against the regurgitant fraction value obtained by the dye method. For the 108 simultaneous determinations at regurgitant ratios values of less than 0.6 these differences, with two exceptions, were less than 1.0 liter per minute. However, at regurgitant fractions of more than 0.6, the magnitude of the differences in these regurgitant flow values increased several fold, as might be expected from the relationship shown in figure 8.

The results of a statistical analysis of the relationship between the differences in values for regurgitant flow determined simultaneously by flowmeter and by the upstream sampling dye method are shown in figure 10. If it is assumed that the errors in determination of regurgitant flow by the flowmeter are negligible, the flowmeter values can be used as a basis for estimating the magnitude of the errors in determining this flow by the dye method. In the dogs studied the average regurgitant flow, as determined by flowmeter associated with a regurgitant fraction of 0.5, was approximately 600 ml per minute and the standard deviation of the differences in the determinations of this flow by the flowmeter and the dye method was 150 ml per minute. The magnitude of this standard deviation increased with increasing degrees of regurgitation so that in the range of regurgitant fractions of 0.9 to 1.0 by dye curve (average regurgitant flow of more than 2.7 L/min) the standard deviation of the differences between flowmeter and dye values approached 1.3 L per minute (fig. 10).

Effect of Changes in Heart Rate on the Degree of Regurgitation and Related Parameters. Measurements of the degree of regurgi-
DYE DILUTION IN AORTIC REGURGITATION

The relation of the magnitude of the regurgitant fraction to the error in measurement of regurgitant flow by the upstream sampling dye method. The regurgitant flows by the dye-curve method, \( Q_r \), were calculated using the equation given in the lower left quadrant of the graph. \( Q_0 \) indicates cardiac output determined from the dye curve recorded at the femoral artery. Values from 231 simultaneous determinations of aortic regurgitation in nine dogs by the flowmeter and dye methods are included.

Note the increase in magnitude of the differences between the values for regurgitant flow obtained by these two independent methods at increasing levels of regurgitant fraction and that this effect was not appreciably different at different heart rates.

Three factors are involved primarily as hydrodynamic determinants of the regurgitant volume per beat: (1) the size of the defect, (2) the duration of diastole, and (3) the square root of the transvalvular pressure gradient during diastole. The typical effects of variations in heart rate on the two of the factors which would be expected to change with heart rate are illustrated in figure 12 for a dog with a small defect in the valve (dog 9) and a dog with a large defect (dog 8). The small defect was a nearly circular hole, 2 mm in diameter; in one case the large
The relation of the magnitude of the regurgitant fraction determined by the upstream sampling indicator-dilution technique to the level of regurgitant flow through the aortic valve determined by flowmeter and the variability of the differences (error) in the values obtained for this flow by the flowmeter and dilution techniques are indicated. The tabular and plotted data are average values based on 221 simultaneous determinations by the flowmeter and dye methods made in nine dogs.

The mean flow values listed in the table are metered regurgitant flows expressed in liters per minute associated with the designated levels of regurgitant fraction. Each tabulated and plotted flow and regurgitant fraction value is an average figure for all determinations covering the range from 0.05 to 0.094 above and below each successive 0.1 unit step in regurgitant fraction extending over the range of observed values from 0 to more than 1.0. The stippled area extends over the region covering plus and minus 1 standard deviation of the differences between the regurgitant flow values determined simultaneously by the flowmeter and the dye methods.

Note that when the regurgitant fraction is less than 0.5 there is a relatively small degree of variability between the values for regurgitant flow measured by these completely independent methods, but that the degree of this variability increases to large values as the regurgitant fraction approaches 1.0.

defect was a tear in the cusp from apex to base. The increase in duration of diastole with decrease in heart rate was not significantly different for dogs with either large or small defects (fig. 12). The mean pressure gradient across the valve during diastole decreased with slowing of the heart rate for both small and large defects, being nearly parallel for the two situations for heart rates from 200 down to 100 per minute. At slower heart rates the pressure gradient across the larger defects dropped to much lower levels, since the regurgitant flow through the defect was of such large magnitude as to result in an approach to equilibration of pressure between aorta and left ventricle toward the termination of a long diastole (fig. 12).

Comparison of Metered Values for Aortic Regurgitation with Those Calculated from the Hydraulic Formula. The values for regurgitant flow per beat in the six dogs studied at different heart rates were estimated hydraulically using the area of the regurgitant ori- fice measured at necropsy and the duration of diastole and mean aortic-left ventricular pressure gradient measured at each heart rate. These hydraulically determined values for regurgitant flow were compared with the metered values obtained at each of the heart rates studied and an excellent correlation obtained both for dogs with large and with small defects in the aortic valve (fig. 13). This agreement indicates that changes in the volume of aortic regurgitation with changes in heart rate follow straightforward hydrodynamic considerations, and that flow changes estimated from...
DYE DILUTION IN AORTIC REGURGITATION

Effect of heart-rate variations by vagal stimulation on flowmeter measurements of regurgitant volume, regurgitant fraction (RV/TSV or Q/R/QF), and metered effective forward flow. The pattern of increase in regurgitant stroke volume with slowing of the heart rate for dogs with small and large defects is indicated by comparing the trends in dogs 7, 8, and 9 (regurgitant orifice sizes varying from 0.93-0.93 sq cm) with dogs 2, 4, 5, and 6 (second study), and 3 (regurgitant orifice sizes varying from 0.15-0.93 sq cm). The increase in regurgitant fraction (RV/TSV) with slowing of the heart rate is less evident than regurgitant stroke volume, since total stroke volume also increases with slowing of the heart rate. Note that the metered effective forward flows decreased to exceedingly low levels at slow heart rates in dogs with large valvular defects. In spite of these wide ranges of heart rate and concomitant large variations in regurgitant stroke volumes, regurgitant fractions and effective forward flows, the correlation between values obtained by the dye and flowmeter methods was not demonstrably altered by these changes in rate (Fig. 7).

Comparison of the effect of heart rate on parameters which affect the degree of aortic regurgitation in a dog with a small defect (dog 9) and one with a large defect in the aortic valve (dog 8). Note that the increase in duration of diastole with decrease in heart rate would be expected to produce approximately the same percentage increase in the volume of regurgitation per beat in the two dogs. However, the magnitude of the expected increase in regurgitation due to the increase in duration of diastole is diminished by the decrease in the mean diastolic pressure gradient across the aortic valve which is particularly striking in the dog with the large defect in which equalization of pressures between the left ventricle and aorta was approached toward the termination of the long diastoles associated with unusually slow heart rates.
hydraulic formula based on the hydrodynamics of steady flow show a close correlation with actual flowmeter measurements in a biological system with pulsatile continuously varying flow.

**Comment**

**Validity of Flowmeter Measurements.** Extensive studies by Denison and Spencer and their co-workers\(^7\)\(^2\)\(^3\)\(^4\) have validated flow contours registered by the square-wave electromagnetic flowmeter from various sites on the aorta including the ascending aorta\(^2\)\(^5\) by relating these to simultaneous measurements of pressure gradient. In addition, Womersley and McDonald\(^2\)\(^6\)\(^2\)\(^8\) found good agreement between the actual flowmeter tracings and the theoretically predicted flow curves from pressure gradient data. Studies on the linearity and stability of this type of flowmeter have been reported by Denison, Spencer, and Green\(^7\) as well as by Shirer, Shackelford, and Jochim\(^8\) and by Ferguson and Wells,\(^9\) the latter team using a modified version of the instrument.

Additional data were obtained in this study validating the use of this instrument for stroke-volume measurements. The good correlation between stroke-volume measurements obtained by the dye-dilution technic and stroke-volume measurements using the flowmeter beat areas and a calibration factor determined by perfusion of the aorta (fig. 5) validates the use of the positive systolic area of the flowmeter tracing as a measure of total stroke volume. In addition, hydraulic estimates of the regurgitant volume over a wide range of heart rates showed a good correlation with actual flowmeter measurements obtained in dogs with small and large valvular defects as indicated in figure 13.\(^3\)\(^4\) These data support the validity of the negative diastolic area of the flowmeter tracing as a measure of the regurgitant stroke volume.

The forward and retrograde perfusion technic demonstrated linearity of the flowmeter calibration for forward and retrograde flows in addition to providing a calibration factor for stroke-volume measurements determined in vivo. When linearity of calibration through zero flow pertains, the ratio of regurgitant volume to total stroke volume is independent of the sensitivity of the flowmeter and of the calibration factor for converting the flow.
DYE DILUTION IN AORTIC REGURGITATION

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meter beat areas to stroke-volume measurements. When the actual regurgitant volume in milliliters or any of the flow measurements are calculated, however, a calibration factor must be used to convert the flowmeter deflections or areas to flow or volume measurements.

The calibration factor, based on in vivo measurements of stroke volume by the dye-dilution technic in the control state before the production of regurgitation, was used in these experiments. Only small quantitative variations, if any, and no directional changes in the results would have pertained if the calibrations based on perfusion of the excised aorta had been used. In five dogs, including the animal whose perfusion calibration showed different slopes of the calibration line for forward and retrograde perfusion, the in vitro and in vivo calibrations were not significantly different statistically. In the four experiments in which small statistically significant differences were found between the two calibration technics, complex environmental factors including motor electrolytic and motor thermal potentials as discussed by Wyatt32 probably account for the small systematic differences observed between the in vivo and in vitro methods of calibration for stroke-volume measurements. The fact that a calibration factor obtained after the aorta was removed from the body, cannulated and suspended in a water bath was the same or only slightly different from that which had pertained when the meter was in place on this vessel in vivo, is convincing proof of the validity of the measurements of flow obtained by this meter.

The use of the areas enclosed by the flowmeter tracing and the zero flow reference line to represent the total stroke volume and the regurgitant volume ignores the effect of coronary flow on these volumes, since the probe is necessarily placed distal to the origin of the coronary vessels. Since the area under the positive systolic portion of the flowmeter tracing represents a small underestimate of the total stroke volume by the amount of coronary systolic flow volume, and the area within the negative portion of the flowmeter tracing and the zero line represents an overestimate of the regurgitant volume by the amount of coronary diastolic flow volume passing retrogradely through the probe, the use of the ratio of regurgitant volume area to total stroke-volume area directly represents a systematic overestimation of the ratio of actual regurgitant volume to total stroke volume with respect to the left ventricle. Use of the data of Wegria and co-workers33 for coronary flow in dogs with acute aortic regurgitation, and assuming the maximal observed increase in coronary flow of 36% noted by these workers together with apportionment of this flow in a 1:2.58 ratio for coronary systolic and coronary diastolic flow, indicates that the average overestimate of the ratio of actual regurgitant volume to total stroke volume is 0.02 regurgitant fraction units. While this would indicate that the systematic difference between the flowmeter and dye-curve regurgitant fractions is slightly larger than the differences observed, the overall correlation of regurgitant fraction measurements by the two methods would not be affected.

Although the use of this type of flowmeter provides an almost ideal standard of comparison for the indicator-dilution method, the large size of the flowmeter probes available for this study required an open-chest preparation. There is, however, no evident reason to expect that significantly different results would have been obtained if it were possible to carry out such studies without thoracotomy.

Regurgitant Fraction Determinations by Flowmeter and Dye-Dilution Technics.

The upstream sampling technic for quantitating aortic regurgitation evolved from the concept reported in 1956 that the fraction of dye passing retrogradely through the aortic valve is proportionate to the regurgitant fraction of blood. That this is true is indicated by the correlation of the dye-curve ratio of LV/FAA with the independent measurement of the Qa/Qa ratio by flowmeter. Measurements of the regurgitant fraction, LV/FAA, by the total-triangle method indicate that this correlation is linear and through zero. The forward
TABLE 5

<table>
<thead>
<tr>
<th>Regurgitant fraction, LVA/FA,</th>
<th>Distance catheter tip withdrawn from aortic valve, cm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>0.75</td>
</tr>
<tr>
<td>5</td>
<td>0.83</td>
</tr>
<tr>
<td>6</td>
<td>0.80</td>
</tr>
<tr>
<td>7</td>
<td>0.27, 0.91</td>
</tr>
<tr>
<td>9</td>
<td>0.20</td>
</tr>
</tbody>
</table>

*Average of 23 determinations prior to vagal arrest of heart. Value of 0.91 obtained after arrest of heart and just prior to withdrawal of catheter is believed due to a preferential injection into the valve defect.

The triangle method exhibits a similar correlation but shows more variability, especially when the degree of regurgitation is high. The Hamilton replux ratio of LVA/FA, suggests that this correlation is curvilinear (fig. 6). Systematic differences between the regurgitant fraction determinations by dye curve and flowmeter are clearly evident in figure 6. A likely explanation for the systematic differences observed is the fact that a dye curve recorded by sampling from the bloodstream through a catheter represents the time-average concentration of indicator rather than the desired volume-average concentration of indicator. From the data at hand, it is impossible to designate the exact source of the systematic differences between the dye curve and flowmeter values for the regurgitant fraction. Regression analysis of the total triangle data for regurgitant fraction measurement indicates that a factor of 0.82 would eliminate the systematic differences between the two methods with the standard error of estimate being 0.11 regurgitant fraction units.

Occasionally discordant results have occurred from markedly preferential injection of dye toward the regurgitant orifice as in animal 7 (fig. 6). In this animal an excellent correlation was obtained between simultaneous dye and flowmeter values for regurgitant fraction for the first 23 of 26 determinations at the animal’s spontaneous heart rate and at the slower rates produced by vagal stimulation. Then after a period of complete arrest of the heart by vagal stimulation, three replicate injections of dye into the aorta were carried out at the animal’s spontaneous heart rate of about 200 beats per minute. These injections gave discordantly high values for the regurgitant fraction, averaging 0.91 as compared to the average value of 0.37 obtained at these heart rates earlier in the experiment. The aortic catheter was then withdrawn 2 cm and indicator was injected into the aorta. The regurgitant fraction value of 0.27 obtained was strikingly less than the immediately preceding determinations, but it was in agreement with the simultaneously recorded flowmeter values and the dye and flowmeter values obtained earlier in the experiment. This large decrease in the value for regurgitant fraction with withdrawal of the aortic catheter 1 to 2 cm is in contradiction to previously reported findings and to the results obtained in the four additional animals in which no systematic decrease was obtained until the withdrawal distance exceeded 2 cm (table 5). Therefore it is believed that a preferential injection of indicator into the defect must have occurred during these three determinations in this animal. This

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instance supports the suggestion of Armezli
and co-workers that, in the practical appli-
cation of this method, replicate determinations
should always be made at least at two sites:
one, approximately 1 cm downstream and the
second, about 2 cm downstream to the aortic
valve. These workers also stressed the nec-
essity of ensuring that the period of injection
of indicator encompasses at least one full car-
diac cycle.

The effects of changes in heart rate caused
by vagal stimulation indicate that slowing
of the heart rate produces an absolute increase
in the regurgitant volume per beat, an increase
in the RV/TSV ratio, and a diminution of
effective forward flow (fig. 11). The mean
diastolic pressure gradient tends to decrease
with slowing of the heart rate by vagal stim-
ulation (fig. 12). These changes did not affect
the correlation of regurgitant fraction deter-
minations by the two methods; however, at
slow heart rates care must be taken that the
period of the injections of indicator into the
aorta extends over at least one full cardiac
cycle.

Comparison of Regurgitant Flow Determi-
nations by the Upstream Sampling Technic
and by Flowmeter. Determinations of regur-
gitant flow (\(Q_R\)) by the dye technic require
the determination of the regurgitant fraction
\(\frac{LVA}{FAA}\), the cardiac output (\(Q_s\)) and the
use of the equation: \(Q_R = Q_s \left( \frac{Q_L}{Q_F} \right) \left( 1 - \frac{Q_L}{Q_F} \right) \). This mathematical relationship
of the regurgitant fraction \(Q_R/Q_F\) to the re-
gurgitant flow \(Q_L\), which is given in figure 8 indi-
cates that a given error in the determination
of the regurgitant fraction would cause a pro-
gressively greater error in the calculated value
for regurgitant flow as the magnitude of the
regurgitation fraction increased with severer
degrees of regurgitation. The observed stand-
ard deviations of the differences between dye
curve regurgitant flow and flowmeter regur-
gitant flow ranged from 0.00 L per minute
(controls) to 1.27 L per minute at the highest
degrees of regurgitation. The facts that this
method makes it possible to detect small de-
grees of aortic regurgitation and that errors
in the estimate of the regurgitant flow asso-
ciated with mild-to-moderate degrees of regur-
gitation are relatively small support its pos-
sible value in the detection and assessment of
the severity of clinical aortic regurgitation.

Summary

The square-wave electromagnetic flowmeter
was used to assess the upstream sampling dye-
dilution technic for quantitating aortic regur-
gitation by simultaneous determinations of the
regurgitant fraction by flowmeter, as given
by the ratio of regurgitant volume to total
stroke volume (RV/TSV) and the identical
ratio of regurgitant flow to total forward flow
(\(Q_R/Q_F\)), and the regurgitant fraction by dye
curve, as given by the ratio of the areas of the
immediately appearing portion of the left ven-
tricular curve to the area of the femoral
artery dye curve (\(LVA/FAA\)) after injection
of indicator approximately 1 cm downstream
to the aortic valve. A good correlation (\(r =
0.91\)) was found between these two independ-
ent methods which can be represented by the
regression equation \(Q_R/Q_F = 0.82 (LVA/FAA)\).
This correlation indicates that the concept
that the regurgitant fraction of indicator
(\(LVA/FAA\)) is proportionate to the regurgi-
tant fraction of blood (RV/TSV) is valid. The
observed systematic difference between flow-
meter and dye-curve regurgitant fractions
may be due to the fact that time-average
rather than volume-average concentrations of
the indicator are obtained by sampling of
blood through catheters.

Two different and independent calibration
technics were used to establish a calibration
factor for converting recorded flowmeter de-
formations to volumetric units for measurement
of rates and volumes of blood flow in the as-
cending aorta. The first technic involved
simultaneous recording of dye-dilution curves
and velocity pulses in the ascending aorta by
the flowmeter before the production of aortic
regurgitation. The second involved bi-intra-
cional perfusion of the isolated aorta at known
rates of blood flow with simultaneous flow-
meter recordings at the termination of each
experiment. The data obtained validated the
use of the flowmeter for measurements of total stroke volume and regurgitant stroke volume. The close correspondence between flowmeter recordings of the regurgitant flow and hydraulic estimates of regurgitant flow, based on the size of the defect in the aortic valve measured at necropsy and continuous records of the pressure gradient across the valve, also lent strong support to the validity of these measurements.

The relationship \( Q_B = Q_s \left( Q_k/Q_p \right) / \left( 1 - Q_k/Q_p \right) \) can be used to estimate regurgitant flow from values of the regurgitant fraction \( Q_r/Q_p \) and the systemic flow \( Q_s \). The mathematical relationship of the regurgitant fraction to regurgitant flow, determined by the dilution-curve technique, plus the variability obtained between simultaneous flowmeter and dilution-curve estimates of regurgitation, indicate that the error in the estimation of regurgitant flow by the dye-dilution technique is least for small-to-moderate degrees of regurgitation and increases progressively with the severe degrees of regurgitation associated with regurgitant fractions of greater than 0.6.

On the basis of 231 simultaneous determinations by the indicator-dilution and flowmeter techniques carried out in nine dogs, and assuming that the flowmeter values were uniformly correct, it was estimated that the standard deviation of the errors in measurement of regurgitant flow by the upstream sampling dye-dilution method was 0.15 L per minute for regurgitant fractions below 0.6, and that this variability increased so that the standard deviation was 1.3 L per minute at regurgitant fraction levels of 0.9 to 1.0.

The results of determinations carried out over a range of heart rates from 39 to 216 beats per minute indicate that the indicator-dilution method is applicable over a wide range of heart rates. The observed changes in aortic regurgitation with variation in heart rate correlated closely with the changes estimated by hydraulic equations based on the hydrodynamics of steady flow through an orifice.

The increase in regurgitant stroke volume with increased duration of diastole at slow heart rates was disproportionately greater than the increase in total stroke volume, so that the effective forward (systemic) flow fell to extremely low levels at slow heart rates, particularly in dogs with large defects in the aortic valve.

The applicability of the upstream sampling indicator-dilution technique to the detection and estimation of the severity of aortic regurgitation in human beings merits further study.

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References

DYE DILUTION IN AORTIC REGURGITATION


Assessment of an Indicator-Dilution Technic for Quantitating Aortic Regurgitation by Electromagnetic Flowmeter

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