Effects of Quantitatively Controlled Left Ventricular-Atrial Regurgitation on Indicator-Dilution Curves in the Dog

By DANIEL S. LUKAS, M.D., LUCIEN I. ARDITI, M.D., A. LEE WINSTON, M.D., AND CHARLES W. PEARCE, M.D.

Regurgitation of blood through an insufficient valve disturbs the normal sequential dilution of an indicator substance as it traverses the heart. Studying this effect in a model of the circulation, Korner and Shillingford observed that several parameters of dye-dilution curves varied quantitatively with rate of regurgitation and could be used to measure the backflow. Subsequently, incomplete dispersion of the regurgitant jet within the upstream chamber was found to lessen the effects of regurgitation on dilution curves. This finding has led to serious doubt about the applicability of the Korner-Shillingford method to the measurement of valvular regurgitation in man.

A stringent assessment of the quantitative variations in dilution curves produced by known rates of regurgitation in the mammalian heart is lacking. Recently, Eich, Staib, and Enerson demonstrated that small rates of backflow altered the downslope of indicator-dilution curves in dogs, but these investigators did not extend their observations to flows greater than 38 per cent of the cardiac output.

In the present study, dye-dilution curves were recorded in dogs with controlled, constantly measured left ventricular-atrial regurgitation ranging from 29 to 209 per cent of cardiac output.

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Methods

Mongrel dogs weighing 20 to 30 Kg. were anesthetized with pentobarbital (26 mg. per Kg.) administered intravenously. Ventilation was maintained by a piston pump respirator with 100 per cent oxygen via an endotracheal tube. Left thoracotomy was performed and a circuit for left ventricular-atrial regurgitation created by a modification of the method of Braunwald, Welch, and Sarnoff (fig. 1). An 8 to 10 cm. segment of semirigid plastic (Tygon) tubing, 1 cm. O.D., 0.8 cm. I.D., was inserted into the apex of the left ventricle through a stab wound and fixed by sutures. A piece of similar tubing was inserted into the left atrial appendage and secured by a purse-string suture. Mounted on the intraatrial end of the tube was a rubber flutter valve which permitted blood to flow into, but not out of, the atrium. The circuit was completed by a short angle of wide-bore glass tubing and a specially constructed one-half inch Potter electro-turbimometer, which were held in place by cuffs of soft plastic tubing. All tubings were filled with saline solution prior to positioning. The volume of the circuit was kept down to 16 ml. A screw clamp on one of the tubes permitted regulation of flow. Output from the frequency converter of the flowmeter was led into a D.C. amplifier of a Sanborn polyviso recorder.

The flowmeter was calibrated beforehand with water and with blood varying in hematocrit from 23 to 43 per cent. Amplitude of deflection in the record varied linearly with flow over a range of 0.8 to 10 L. per minute and was identical for water and blood of different hematocrit, as well as for constant and pulsatile flows. Repeated calibrations over a period of several months remained constant. In calibrating, vacuum aspiration was used to provide constant flow, and a Sigmanotor pump run at varying pulse rates was used for pulsatile flow. Since flow from the pump was characterized by a positive phase alternating with a short negative phase, a one-way valve was incorporated in the system to prevent backflow. The resulting pattern of flow was similar to that of ventricular-atrial regurgitation in that a positive pulse alternated with a phase of no flow. Maximum pump output was 3.0 L./min. Although the Potter meter record failed to indicate the changing pattern of instantaneous flow...
in the pulsatile system, mean flow was measured reliably, as indicated by identity of the calibrations for constant and pulsatile flows of various frequencies.

A polyethylene catheter of 1.67 mm. I.D. was inserted retrogradely into the descending aortic arch via the femoral artery. Another catheter, 1.4 mm. I.D., was passed into the left atrium via a small segmental pulmonary vein of the left upper lobe. Heparin, 4 mg. per Kg., was administered intravenously prior to opening the ventricular-atrial circuit, and in 1 mg. per Kg. doses every hour thereafter.

Indicator-dilution curves were obtained by injection of 1.97 ml. of 0.1 per cent T 1824 into the left atrium via the catheter. In two dogs, 0.125 per cent indocyanine green was used. The dye and a subsequent flush of 12 ml. of isotonic saline were injected within 0.6 to 0.8 second. The average escape velocity of the indicator and flush was 1,110 cm. per second. To record the dye curves, blood was drawn from the aortic catheter at the rate of 0.5 or 1 ml. per second through a cuvette and Electronics for Medicine oximeter, the output of which was led to a D.C. amplifier of the polyviso. The time lag in the catheter-cuvette system at a withdrawal rate of 0.5 ml. per second was 2.2 seconds. The cuvette was calibrated both before and after each experiment with dilutions of dye in arterial blood calculated to cover the entire range of concentrations encountered. No significant drift in the calibrations was noted throughout the five- to six-hour course of each experiment. Blood withdrawn for each curve was reinfused. To maintain blood pressure, blood lost by oozing was estimated visually and replaced periodically by transfusion from a donor dog.

The procedure varied somewhat from experiment to experiment, but, in general, after two or more control dye curves had been recorded, four to five different levels of regurgitation were induced and dilution curves recorded at each level (fig. 2). The shunt was closed and the sequence repeated until the animal died or sufficient data were obtained. If the electrocardiogram or arterial pressure indicated a change in state of the animal during the run, control curves were repeated. In five dogs curves were recorded after injection of dye into the pulmonary artery.

Dye curves were reconstructed on semilogarithmic paper. Since recirculation in the curves obtained after left atrial injection occurred late in the course of primary circulation, it was necessary to extrapolate only the last 0.5 to 1.0-second segment of the downslope (fig. 2). An exception was a dog (no. 19A) with an aortic-pulmonary fistula of congenital or traumatic origin. Early recirculation of indicator through the shunt was evident in the dye curves and necessitated extrapolation of a larger segment of the downslope. Cardiac output, transit volume, reciprocal of slope, and variance were calculated from the reconstructed curves. The order of reproducibility of these variables in nine pairs of control curves recorded after left atrial injection within 15 minutes of each other is shown in table 1.

Results

Fifty dye curves were recorded following left atrial injection in seven dogs with regurgitant flows varying from 0.95 to 3.32 L. per minute. In each dog, as regurgitant flow...
increased, the downslope became more prolonged, i.e., reciprocal of the slope, 1/s, increased (fig. 3). Except at large rates of backflow, cardiac output generally remained at control levels when regurgitation was induced. To include the effects of any concomitant decrease in forward flow on 1/s, 1/s for each dog was plotted against the net cardiac output (forward flow minus regurgitant flow), as suggested by Korner and Shillingford1 (fig. 4). Reciprocal of the slope varied inversely with net cardiac output. At all levels of net cardiac output, 1/s was greater in those animals with larger transit volumes (fig 4). Since no consistent relationship between transit volume and regurgitant flow was apparent in any of the dogs, increase in 1/s with increasing regurgitation was not dependent on associated change in transit volume.

Having established a relationship between net cardiac output and 1/s, regurgitant flow was calculated from the formula suggested by Korner and Shillingford:1

\[ Q_r = Q_f \left( \frac{1/s}{1/s_0} - 1 \right), \]

where \( Q_r \) is regurgitant flow, \( Q_f \) is the cardiac output, \( 1/sr \) is the reciprocal of the slope recorded during regurgitation, and \( 1/s_0 \) is the reciprocal of the slope in the absence of regurgitation. For each calculation, \( 1/s_0 \) was obtained from a control curve from the same animal. The control curve employed was the one in which cardiac output and transit volumes most clearly matched the output and volume present during recording of the regurgitant curve. Regurgitant flow calculated in this manner correlated closely (R = 0.91) with simultaneously recorded flowmeter values (fig. 5). The mean difference between the two methods was 0.10 ± 0.27 L per minute (mean ± S.D.). In 36 of the 50 comparisons, calculated and measured \( Q_r \) agreed within 0.3 L per minute.

Variance of the curves increased with increasing regurgitation, and, as in the case of 1/s, a definite inverse relationship was observed between variance and net cardiac output for each dog. Regurgitant flow was calculated by substituting variance for 1/s in the previously cited equation. Values so calculated correlated less well with measured flows (fig. 6).

Among 32 curves recorded with the shunt closed, correlation between 1/s and cardiac output appeared to be poor. However, within restricted ranges of volume, 1/s varied inversely with cardiac output, and for any level of cardiac output 1/s increased with transit volume (fig. 7). Since the number of data was relatively small and the scatter considerable, no attempt was made to develop a multiple regression formula relating these three variables.

In 21 dye curves recorded after injection into the pulmonary artery, 1/s and variance varied directly with rate of regurgitation and inversely with net cardiac output, but with more scatter than in the case of the left atrial injections. Estimates of regurgitant flow by the slope method were not as accurate as with left atrial injection, and usually were less than the metered values (fig. 8).

Appearance time of dye both after left atrial and pulmonary arterial injection was not shortened by regurgitation. The ratio of minimum dye concentration to maximum re-
Table 1
Reproducibility of Data Calculated from Paired Dye Curves Recorded within Fifteen Minutes of Each Other

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Cardiac output, L./min.</th>
<th>Transit volume, ml.</th>
<th>I/slope</th>
<th>Variance</th>
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<tbody>
<tr>
<td>16A</td>
<td>1.37</td>
<td>94</td>
<td>2.60</td>
<td>4.52</td>
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<td>151</td>
<td>1.51</td>
<td>98</td>
<td>2.87</td>
<td>5.70</td>
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<tr>
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<td>1.63</td>
<td>96</td>
<td>1.21</td>
<td>2.63</td>
</tr>
<tr>
<td>160</td>
<td>1.60</td>
<td>96</td>
<td>1.37</td>
<td>2.71</td>
</tr>
<tr>
<td>18A</td>
<td>3.63</td>
<td>121</td>
<td>1.23</td>
<td>1.12</td>
</tr>
<tr>
<td>3.61</td>
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</tr>
<tr>
<td>3.65</td>
<td>112</td>
<td>1.22</td>
<td>1.19</td>
<td></td>
</tr>
<tr>
<td>3.09</td>
<td>116</td>
<td>1.21</td>
<td>1.18</td>
<td></td>
</tr>
<tr>
<td>19A</td>
<td>2.66</td>
<td>102</td>
<td>1.49</td>
<td>1.62</td>
</tr>
<tr>
<td>2.58</td>
<td>95</td>
<td>1.43</td>
<td>1.31</td>
<td></td>
</tr>
<tr>
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<tr>
<td>3.78</td>
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<tr>
<td>3.38</td>
<td>225</td>
<td>1.90</td>
<td>2.29</td>
<td></td>
</tr>
<tr>
<td>23A</td>
<td>3.74</td>
<td>249</td>
<td>1.87</td>
<td>2.25</td>
</tr>
<tr>
<td>3.78</td>
<td>221</td>
<td>1.74</td>
<td>2.13</td>
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<td>28A</td>
<td>4.87</td>
<td>300</td>
<td>1.33</td>
<td>1.56</td>
</tr>
<tr>
<td>4.84</td>
<td>258</td>
<td>1.43</td>
<td>1.48</td>
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</table>

circulation concentration did not correlate with the presence or absence of regurgitation. Other parameters of the dye curves were not correlated with regurgitant flow.

Discussion
The assessment of methods for measuring valvular regurgitation in man has been limited seriously by the lack of an independent and quantitatively reliable method. Surgical and clinical methods for estimating regurgitation are so gross that they cannot be considered to provide adequate reference standards for evaluating data obtained by indicator-dilution and other techniques.

This difficulty has led to the use of "circulation models," or physical analogues of the circulatory system. Although these models permit control of certain variables, such as volume and rates of forward and regurgitant flow, they do not faithfully reproduce the central circulation. In common with all physical and mathematical analogues which fail to include certain naturally present variables, they may lead to erroneous conclusions about the behavior of the system they intend to mimic.

The preparation used in this study was devised originally to observe the effects of controlled left ventricular-atrial regurgitation on cardiovascular function in the dog. It also differs from naturally occurring mitral valvular incompetence in several respects, and does not reproduce the wide range of anatomical and hemodynamic abnormalities encountered. Nevertheless, the preparation affords the advantages of studying the effects of known amounts of regurgitation on indicator-dilution curves in the cardiovascular system of the living animal.

Korner and Shillingford's definition of the alterations in indicator dilution produced by regurgitation was based on observations made in a model in which volume, forward flow, and backflow were known and could be varied independently. Subsequently, using a model of different design, Hoffman and Rowe demonstrated that backflow had little effect on indicator dilution if the regurgitation jet was not permitted to mix with the fluid in the upstream chamber. The extent to which the severe restriction of mixing achieved in their model applies to the living heart remains to be demonstrated.
Comparison of regurgitant flow calculated from change in slope of dye curves with regurgitant flow measured by flowmeter. Dye injected into left atrium. (Open circles) are values derived from data of Eich, Staib, and Enerson. (Oblique line) represents theoretical perfect agreement between two methods.

In our preparation, dispersion of indicator and regurgitated blood within the left atrium was not a limiting factor. It was possible to confirm the essential observation by Korner and Shillingford that rate of forward flow and transit volume affect the downslope and variance of an indicator-dilution curve obtained by injecting indicator upstream and recording downstream from the site of backflow. The increase in reciprocal of slope and variance in the presence of regurgitation was demonstrated not to be due to concomitant change in forward flow or transit volume. In the same animal, for a given level of forward flow and volume, deviation in the slope could be used to measure regurgitant flow with reasonable accuracy.

Recently, Eich and co-workers found that small degrees of regurgitation prolonged the downslope of indicator-dilution curves in dogs with a left ventricular-atrial shunt similar to the type we employed. In the restricted range of regurgitant flow (0.17 to 0.64 L. per minute) that they studied, no relationship between backflow and slope appeared. However, in the eight instances in which these authors present sufficient data to permit calculation of backflow by the slope method, we found that the calculated values and the measured values agreed within 0.3 L. per minute. Their data, plotted as open circles in figure 5, fill in a range of regurgitant flow we could not study because of limitations of our flowmeter.

In the present investigation, injection of dye into the pulmonary artery provided less accurate estimates of regurgitant flow than injection into the left atrium. The estimates from pulmonary artery injection tended to fall short of the metered values. This may have been related to increased cyclic altera-
tions in blood flow through the lungs secondary to the intermittent positive pressure breathing. The possibility exists that intermittent backflow in the pulmonary capillaries was induced during the phase of positive pressure and prevented recording of control curves free of any effects of backflow. Emanuel, Lacy, and Newman also have noted in dogs with surgically created mitral incompetence that the downslope of dilution curves recorded from the aorta was relatively less affected by the incompetence when dye was injected into the superior vena cava and first traversed the lungs, than when it was injected into the left atrium. 8

In contrast to the observations of Korner and Shillingford, variance was considerably less reliable than slope in measurement of regurgitation in our dogs. Estimates based on variance averaged 78 per cent greater than meter values. A correction factor could have been employed to bring the variance estimates into line with metered flow, but a greater degree of scatter, as compared with slope estimates, would have persisted. The reason for the greater effect of backflow on variance than on slope is not apparent.

If more control data had been obtained, it might have been possible to develop a multiple regression equation relating reciprocal of slope to volume and forward flow, and to use this formula in predicting control slope. However, data were so scattered and differences from dog to dog so marked, that use of predicted rather than determined values for control slope in each animal would have decreased considerably the accuracy of estimating backflow. Since values for reciprocal of slope were small, absolute changes of slight magnitude were quite significant. Eich, Staib, and Enerson also found that effects of regurgitation on indicator-dilution curves could not be identified without a control curve from the same animal for comparison.

Recognition is taken of the fact that the catheter-detector system employed has a low frequency response, which prevents distortionless reproduction of the indicator-dilution events. Since the technique of recording dye-dilution curves was held constant, this distortion does not preclude comparison of curves. Thus, with regard to slope, the error produced by the system would have the effect.

Figure 7
Relation of reciprocal of dye curve slope to cardiac output at dye transit volumes less and greater than 200 ml. No regurgitation. Dye injected into left atrium.

Figure 8
Comparison of regurgitant flow calculated from change in slope of dye curves with regurgitant flow measured by flowmeter. Dye injected into pulmonary artery. (Oblique line) represents theoretical perfect agreement between two methods.
of multiplying the numerator and denominator of the regurgitant slope/control slope ratio by a constant; this would not change the value of the ratio. Data on distortion of indicator-dilution curves empirically derived by Milnor and Jose\textsuperscript{12} indicate that at the volume/flow ratio of 2.2 for the sampling system used in this study, slope was prolonged by only 1 to 3 per cent. On the other hand, since calculation of variance involves finding the sum of products of concentrations and squared time intervals under the curve, time delays arising in the detector system, even though small, would distort variance increasingly as this parameter grew larger. It is possible that the observed greater effect of regurgitation on variance than on slope is related to these time errors. The degree of prolongation of mean transit time (corrected for delay in arrival time) by the detector system\textsuperscript{12} makes it probable that the transit volumes in this study are 5 to 10 per cent too large. This error would not alter the essential observation that transit volume did not vary consistently with rate of regurgitation.

Although the results of this investigation hold some promise for the usefulness of indicator-dilution curves in quantifying valvular regurgitation, they apply strictly to the dog with a particular type of left ventricular-atrial regurgitation. The applicability to other varieties of experimental regurgitation or to valvular insufficiency in man remains to be defined.

Summary

Dye-dilution curves were recorded from the aortic arch of dogs with left ventricular-atrial regurgitation produced surgically by a shunt from the apex of the left ventricle to the left atrial appendage. Rate of regurgitation was monitored by an electroturbameter and was varied from 0.9 to 3.3 liters per minute. In each dog, reciprocal of the downslope and variance of curves obtained after injection of dye into the left atrium varied directly with rate of backflow and inversely with net cardiac output. These effects of regurgitation were not due to change in transit volume. Estimates of regurgitation based on change in reciprocal of slope correlated closely with flowmeter values and were more accurate than estimates based on change in variance. Backflow was underestimated by curves recorded after injection of dye into the pulmonary artery.

References

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