Measurement of Mitral Regurgitation in Man from Simultaneous Atrial and Arterial Dilution Curves after Ventricular Injection

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The most direct approach to measurement of the volume of blood regurgitating across an insufficient mitral valve consists of the injection of indicator into the left ventricle and simultaneous sampling of blood from the left atrium and from the aorta or one of its branches. If mixing is complete in the left ventricle, the distribution of indicator to upstream and downstream collection sites is a function of the volumes of blood flowing in these directions.

This principle has been used in experimental animals and in man by a number of investigators.1-5 Their data demonstrate a relationship between the calculated values of regurgitant flow and the clinical or surgical estimates of the severity of insufficiency. The studies referred to, however, involve only 33 patients with clinical mitral disease. Fewer than half of these had any appreciable regurgitation as judged by clinical, surgical, and physiologic criteria. Figures for actual backflow in liters per minute are provided only in one preliminary report4 of a small series. In 20 of the cases,4 the essential dilution curves were not obtained simultaneously. In no clinical case was a duplicate measurement described, and available data on reproducibility of this method are limited to studies of surgically produced lesions of short duration in dogs6 and of tricuspid insufficiency in a small number of patients with lesions of limited severity.6

The present study was designed to evaluate this direct method for the quantification of clinical mitral insufficiency.

Materials and Methods

Twenty-four studies were performed in 16 patients with rheumatic disease of the mitral valve. Two of the patients were demonstrated at cardiac catheterization to have severe aortic stenosis, which was confirmed at surgery. Clinical, fluoroscopic, and physiologic evidence of aortic regurgitation was absent in all patients. The mitral lesion was classified as pure mitral stenosis (MS), predominant mitral stenosis with mild to moderate insufficiency (MSmr), predominant and moderate to severe insufficiency (MRns), or pure and severe mitral insufficiency (MR). In six patients in whom surgery was not performed, classification was based on clinical information and physiologic data not including the method under study.7-9 In the 10 patients who underwent surgery, classification was based on the clinical, physiologic, and surgical findings.

Indicator-dilution curves were obtained during catheterization of the left side of the heart, performed by the percutaneous transdorsal route with the patient in the prone position and under mild barbiturate sedation. Evans-blue dye (4 to 5 mg.) was injected rapidly from a calibrated pipette10 through a polyethylene catheter (internal diameter 0.76 mm.) into the left ventricle. Beginning shortly before the injection of dye, blood was collected simultaneously from a 7-inch, thin-walled, 16-gage needle in the left atrium and a thin-walled 16-gage Cournand needle in the brachial artery, by one of two methods. In the first method, a pump (Harvard Apparatus Co., Dover, Mass.) drew blood through 40 cm. of polyethylene tubing.
regurgitant sample was obtained by the method of Hamilton.\textsuperscript{14} Mitral regurgitant flow was calculated according to the following formula:\textsuperscript{15}

$$Q_R = \frac{Q_S}{(A_{BA}/A_{LA}) - 1}$$

where $Q_R$ = regurgitant flow, $Q_S$ = systemic cardiac output, $A_{BA}$ = the area under the systemic output curve of the left atrium, and $A_{LA}$ = the area under the left atrial output curve.

In three patients (A.L., N.P., and A.Lo.) the left atrial and brachial arterial curves were obtained by continuous densitometric recording. In two patients (C.W. and A.La.) the left atrial curves were obtained with the densitometer and the brachial arterial curves by fractional collection. In the remaining 11 patients the left atrial curves were obtained by fractional collection and the brachial arterial curves with the cuvette densitometer.

All dilution curves were plotted semilogarithmically and extrapolated to 1 per cent of peak concentration value. Areas were obtained by summation of the concentrations at 1-second intervals. Forward flow was calculated according to the method of Hamilton.\textsuperscript{14} Mitral regurgitant flow was calculated according to the following formula:\textsuperscript{15}

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arterial dilution curve, and $A_{LA} = \text{the area under the early left atrial dilution curve.}$

In eight patients this study was repeated after an interval of 10 to 30 minutes. In all patients, systemic output was also measured independently from a peripheral arterial dilution curve after injection into the left atrium. In six patients, the latter measurement was repeated after an interval of 10 to 30 minutes. Differences between duplicate measurements of regurgitant flow, between duplicate measurements of forward flow with the same injection site, and between measurements of forward flow with the two different injection sites, were evaluated with standard statistical techniques for small samples.\textsuperscript{16} The relationship between estimated $Q_R$ and the diagnostic classification was measured with use of the correlation ratio $\eta_a$, which is applicable whether or not the relationship is linear.\textsuperscript{16} Further details of the techniques employed in these studies have been reported previously.\textsuperscript{17}

Results

The results of this study are presented in table 1.

**Measurements of Forward Flow**

The statistical analysis summarized in table 2 demonstrates that, in this series of patients, the variability in estimates of cardiac output was not greater with left ventricular than with left atrial injections, and that there was no systematic difference in estimate of cardiac output between the two injection sites. In addition, comparison of a coefficient of variation for each patient (with 1 degree of freedom) with that for the entire group (with appropriate degrees of freedom) reveals that none of the individual differences between replicates was statistically significant, and in only one patient (R.S.) did the measurement of systemic flow obtained with atrial injection differ significantly ($p < 0.05$) from that obtained with ventricular injection.

These results permit the conclusion that satisfactory estimates of systemic flow can usually be obtained with injection of indicator into the left ventricle.

**Measurements of Regurgitant Flow**

**Validity**

Figure 1 illustrates the raw data obtained in one patient in each of the four diagnostic groups in whom the dilution curves were considered satisfactory and the estimates of $Q_R$ conformed to the clinical, physiologic, and surgical findings. It is clear that the ratio $A_{LA}/A_{RA}$ increases with increasing severity of mitral insufficiency. In addition, as McClure et al.\textsuperscript{18} have shown mathematically and in a cardiovascular model, the descending limb of the arterial dilution curve exhibits, in the presence of mitral insufficiency, an earlier, steeper slope, representing ventricular wash-

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**Table 2**

Comparison of Paired Measurements of Systemic Flow

<table>
<thead>
<tr>
<th>Item</th>
<th>Replicates with atrial injection</th>
<th>Replicates with ventricular injection</th>
<th>Atrial vs. ventricular injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean absolute difference (L/min.)</td>
<td>0.66</td>
<td>0.82</td>
<td>0.68</td>
</tr>
<tr>
<td>S.E. of observation (L/min.)</td>
<td>0.41</td>
<td>0.44</td>
<td>0.21</td>
</tr>
<tr>
<td>Coefficient of variation (%)</td>
<td>8.4</td>
<td>7.9</td>
<td>4.8</td>
</tr>
<tr>
<td>Significance of mean algebraic difference</td>
<td>$0.4 &lt; p &lt; 0.5$</td>
<td>$0.8 &lt; p &lt; 0.9$</td>
<td>$0.9 &lt; p &lt; 1.0$</td>
</tr>
</tbody>
</table>

For the comparison between atrial and ventricular injection sites, the mean of replicate measurements from either site was used whenever these had been performed. Significance was determined by Student's t-test, comparing mean algebraic difference with standard error. In the atrial and ventricular replications, an identical result is obtained by analysis of variance, comparing the variance due to replication with the error variance due to patient variation in replication.
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Figure 1
Semilogarithmic replots of the dilution curves obtained from one patient in each of the diagnostic categories: pure mitral stenosis (A), predominant stenosis (B), predominant mitral regurgitation (C), and pure regurgitation (D). Left atrial curves are drawn in heavy lines, brachial arterial curves in light lines. To facilitate comparison, the arterial dilution curves are drawn to peak at the same ordinal value and all other concentrations are expressed as a per cent of that peak.

out, and a later, flatter slope representing atrioventricular washout. This is seen most clearly in figure 1D but is also evident in figure 1C and is suggested in figure 1B. Thus, the qualitative and quantitative features of these curves are functions of increasing severity of regurgitation.

The scattergram of figure 2 demonstrates a definite relationship between the estimated \( Q_R \) and the diagnostic classification. The overlap between groups signifies that the classification is, by necessity, an arbitrary ordinal scale for a continuous variable. For the MR and MRms groups, in particular, the data may be pooled, since purity of the lesion does not necessarily signify greater severity. The mean and range of \( Q_R \), expressed as a per cent of estimated total left ventricular output, for patients with pure mitral stenosis, predominant stenosis with mild to moderate insufficiency, and predominant or pure insufficiency, are 6 per cent (0 to 11), 21 per cent (8 to 39), and 58 per cent (28 to 82), respectively. The correlation ratio \( \eta \) is 0.87, signifying that three fourths \((\eta^2 = 0.75)\) of the variability in estimated \( Q_R \) is a function of the changes in severity of the regurgitant lesion expressed in the diagnostic classification.

Reliability

In 10 patients, there were no clinical, physiologic, or surgical grounds for doubting the correctness of the calculated \( Q_R \). However, seven of these 10 were patients with pure mitral stenosis or predominant stenosis with minimal or mild insufficiency, in whom the opportunity for misestimate is limited. Moreover, surgery has not been performed in four of the 10 patients, including two of the three with predominant or pure insufficiency. In these cases, therefore, although the order of magnitude seems correct, the absence of an anatomic estimate of the size of the mitral valve precludes a quantitative assessment of the accuracy of \( Q_R \).

Eight studies, in six patients, gave results that were either mathematically absurd, physiologically incredible, in conflict with diagnostic evidence, or otherwise suspect.
Patient A. Lo, is of particular interest, since he had both evidence of, and a demonstrated reason for, overestimate of his mitral regurgitant flow. The surgical report in this patient was of mild (1+) regurgitation. If the surgeon’s description of the diastolic mitral valve area is accepted, the expected regurgitant flow at the time of study is 2.0 L/min. or approximately 30 per cent of total left ventricular output. The dye-dilution estimate was 2.99 L/min. or 39 per cent of total left ventricular output. In previous studies, however, it was demonstrated, by two independent methods, that this patient (case no. 6 in that study) had a larger-than-normal flow through bronchopulmonary anastomoses resulting in the introduction of dye into the left atrium prior to the appearance of recirculating dye. The measured pulmonary collateral flow at that time amounted to 7.2 per cent and 5.9 per cent of total ventricular output by the two methods. For this reason, it is believed that mitral insufficiency, which is definitely present in this patient but probably mild to moderate in severity, was somewhat overestimated by the dilution study.

Of the two studies in R.S., one produced a mathematically and physiologically absurd result: the area under the early left atrial curve exceeded that under the systemic arterial curve, which corresponds to a regurgitant flow exceeding the total left ventricular output.

The second study in R.S. gave rise to a credible figure for regurgitant flow. However, this study must be regarded as suspect because the net forward flow calculated with the left ventricular injection (2.35 L/min.) differed appreciably from that obtained 14 minutes before (3.75 L/min.) and 14 minutes after (3.76 L/min.) with left atrial injection. In no other study in this investigation did the net forward flow after left atrial injection differ from that after left ventricular injection by more than 25 per cent of the latter, and in only two instances did the difference exceed 20 per cent. None of the differences, except for R.S., is statistically significant. In this case, the difference (60 per cent) is too large (p < 0.05) to be attributed to random variation, and the patient’s status was not apparently altered during the 28 minutes required for the three measurements. The reasonable conclusion is that the estimate of forward flow after left ventricular injection is incorrect in this instance. Therefore, calculation of $Q_{R}$, which involves use of an area related to $Q_{A}$, is invalid.

In patient G.L. (fig. 3), the arterial and atrial curves were technically satisfactory, and the two estimates of systemic cardiac output are in good agreement with a pair of estimates obtained with left atrial injection. There is, however, a striking
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disparity between the magnitudes of the two left atrial curves. The first study gave rise to an estimate of backflow approximately equal to systemic flow. The second study resulted in the incredible value of \( Q_R \) of almost 200 L./min., which is over 1,600 per cent of systemic cardiac output.

The reproducibility of results was poor. After exclusion of the mathematically absurd result in one of the studies in R.S., the differences between duplicate determinations in the remaining seven patients, were large: mean absolute difference = 17 per cent of total left ventricular output and coefficient of variation = 23 per cent. The practical significance of the latter statistic may be illustrated by patient A. Lo. in whose single study the estimated \( Q_R \) was 3 L./min. If systemic and regurgitant flows remain constant, there is approximately one chance in two that a second study will yield an estimate of \( Q_R \) either less than 2 L./min. or greater than 4.5 L./min.

Discussion

A variety of technics is available for assessing mitral insufficiency. Some are semi-quantitative.\(^8\)\(^9\) Others, which attempt quantification, are indirect and empirical,\(^20\)\(^21\) require further validation,\(^22\) or have not yet been applied in man.\(^18\) The method under discussion is direct and theoretically sound and has held promise of providing a valid and reliable quantitative measure of \( Q_R \). From the present study, however, it is clear that, although it may have some semiquantitative clinical utility, it is not a dependable quantitative technic. This conclusion is supported by the mathematically absurd result in one patient, the physiologically incredible result in another, the gross discrepancies between physiologic and surgical findings in two others, the evidence for the influence of other short pathways, and the poor reproducibility in duplicate measurements. That such poor reproducibility is not due principally to temporal variation in \( Q_R \) is suggested by other studies,\(^22\) in which, with a different quantitative approach, the coefficient of variation in measurement of \( Q_R \) was very much smaller. In addition, in that investigation, the coefficient of variation was approximately the same in patients with and without mitral regurgitation, indicating that variation in measurements of \( Q_R \) was a function of experimental error and that actual \( Q_R \) varied little under the conditions of study. Moreover, in the present investigation, the mathematically impossible and physiologically incredible results can only represent error of the method and indicate the extreme proportions that such error can achieve.

It seems obvious that incomplete mixing must be a principal cause of error. There is abundant evidence from cinefluorography in dogs\(^23\)\(^24\) and from indicator dilution studies in vitro,\(^25\) in intact dogs,\(^4\)\(^24\)\(^25\) in congenital heart disease,\(^26\)\(^28\) and in disease of the mitral valve,\(^4\) that anatomically complete mixing is rarely, if ever, achieved in cardiac chambers. The cinefluorographic observations of Swan and Beck\(^24\) are of particular interest, since ventricular nonmixing was found in the presence of mitral regurgitation. Of seven cinefluorograms that showed more than a trace of mitral regurgitation, all showed ventricular nonmixing. It is also a commonplace angiographic observation that, in clinical mitral insufficiency, regurgitated opaque medium does not invariably opacify the entire atrium.

Although the absence of complete and homogenous dispersion constitutes a physiologic limitation to the success of this method, it should be appreciated that such dispersion is not actually essential. What is required is that the amounts of dye sampled from the atrium by the atrial catheter and by the ventricle, and the amounts of dye sampled from the ventricle by the atrium and the aorta (including branches of the latter and the arterial catheter) be proportional to the volumes of blood sampled. This condition can be satisfied, in the absence of uniform physical dispersion, by its mathematic equivalent: random distribution and representative random sampling.

The distinction between complete mixing and its mathematic equivalent is not merely
semantic; it permits recognition that the largest source of technical error lies in the atrial catheter. As with all sampling, representativeness is a direct function of the ratio of sample size to population size. If forward flow, regurgitant flow, and total flow are large in relation to the volume of atrium and ventricle, then randomization of mixing and of sampling will fortuitously provide representative samples of atrial dye to the ventricle and of ventricular dye to the atrium and aorta. However, the flows (samples) obtained through catheters are small in relation to the volumes (populations) sampled. With arterial catheters, this is of negligible importance, (as, indeed, it must be if cardiac output can be correctly estimated from arterial dilution curves), presumably because the ventricular ejectate is homogenized in the aorta. However, information obtained from the atrium, especially if that chamber is enlarged, is subject to profound sampling error. It is in this respect that angiocardiography, although only semiquantitative, may have an advantage over indicator dilution.

The conclusion that the principal error is in atrial sampling is supported by studies performed in dogs by Sinclair et al. They found that reproducibility was negligibly affected by changes in the timing of injection or in the location of the ventricular catheter, but could be profoundly affected by changes in the position of the atrial catheter. The greater reproducibility of results for a given atrial sampling site in their cases as compared to the present series probably reflects the limited atrial enlargement accompanying surgically induced lesions of short duration, and illustrates the importance of the size of the atrial sample in relation to the size of the atrium.

It will also be appreciated that dispersion, whether homogenous or random, need not occur instantaneously. It is necessary only that one or the other of these conditions occurs in the ventricle prior to systole and in the atrium prior to ventricular filling. In this case, however, as has been pointed out by Lacy et al., if the atrial catheter and the left ventricle are to sample the same population, the atrial curve must permit recognition, not of the average atrial concentration, but specifically of the concentration obtaining during ventricular filling. The recording of such a step function is not possible with conventional methods such as were employed in the present study.

An additional source of error is the existence of other short pathways to the left atrium. In an earlier communication, it was pointed out that injection into a ventricle and simultaneous collection from an atrium and an artery was merely a special application of a general principle theoretically applicable to the measurement of a variety of regional blood flows, central and peripheral. In the case of central flows, such as bronchopulmonary anastomoses, intracardiac shunts, and valvular regurgitation, the sine qua non is that the regional flow to be measured empties into a cardiac chamber to produce a dilution curve distinct from those of general circulation and recirculation. The coexistence of two such flows precludes the precise measurement of either. Bronchopulmonary collateral channels, which have been demonstrated to produce an early dilution curve in the left atrium following injection of indicator into the aorta, exist in normal man. In the absence of bronchopulmonary disease, the flow through these collateral channels is only 1 or 2 per cent of left ventricular output, and hence would make only a small contribution to the early dilution curve produced by mitral regurgitation. However, it is conceivable that this regional bed is responsible for the occasional finding of "regurgitated" dye in intact animals and in patients with pure mitral stenosis, as in the studies by Woodward et al. and in the present series. Moreover, the demonstrated enhancement of these collateral channels in certain bronchopulmonary diseases would, if such disease coexisted with the valvular lesion, invalidate measurements of mitral regurgitation by the regional flow method.

The results may possibly be improved by certain technical refinements. The use, for
example, of a blunt-ended catheter with multiple, radially arranged orifices may enhance ventricular dispersion of dye. A comparable improvement in the atrial sampling system can also be conceived. The latter, however, must entail a substantially more rapid sampling rate without a proportional increase in caliber, and hence volume, of the sampling conduits, since the latter will impair the system's dynamic response. The mixing requirements of this method are, moreover, very stringent. It seems unlikely that these and other technical refinements can eliminate the inaccuracy and irreproducibility demonstrated in this study, and permit a single observation to be accepted with a high degree of confidence. Thus, the need for multiple measurements will remain, and the attendant expenditure of time and labor, and the necessary prolongation of left heart catheterization studies will, in all probability, quite properly limit the application of this method. Moreover, methodologic improvements will not eliminate the occasional, possibly appreciable, error arising from the existence of bronchopulmonary collateral channels in some patients with acquired valvular heart disease.

Summary

Measurements of forward and regurgitant flow were obtained in 16 patients with rheumatic disease of the mitral valve by means of simultaneous systemic arterial and left atrial dilution curves after injection of Evans-blue dye into the left ventricle. The results indicate that satisfactory measurements of forward flow may be obtained with injections into the left ventricle and that the calculated regurgitant flow has a good correlation with the severity of mitral insufficiency, as estimated clinically and surgically. The mean and range of regurgitant flow, expressed as a per cent of estimated total left ventricular output, for patients with pure mitral stenosis, predominant stenosis with mild to moderate insufficiency, and predominant or pure insufficiency, were 6 per cent (0 to 11), 21 per cent (8 to 39), and 58 per cent (28 to 82), respectively.

Eight studies in six patients, however, gave results that were either mathematically absurd, physiologically incredible, in conflict with diagnostic evidence, or otherwise suspect. Moreover, in the seven patients in whom satisfactory duplicate studies were obtained, the reproducibility of results was poor: the mean absolute difference in successive measurements was 17 per cent of total left ventricular output and the coefficient of variation was 23 per cent of an observation.

It is suggested that the principal source of error lies in unrepresentative sampling from the left atrium in the presence of incomplete mixing of indicator: with blood in the cardiac chambers. In some patients, an additional and possibly appreciable error may arise from the existence of an enhanced pulmonary collateral blood flow, which provides an alternative short pathway from the left ventricle to the left atrium.

It is concluded that, with conventional sampling technics, this theoretically sound approach is too capricious to be a dependable quantitative method.

References


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