Mitral Regurgitant Flow and Left Ventricular Function in Patients with Mitral Valve Disease


INABILITY to measure mitral regurgitant flow has greatly limited the hemodynamic evaluation of mixed mitral valve disease, and of any associated myocardial disease. A direct dye-dilution measurement of regurgitant flow by recording simultaneous left atrial and arterial dilution curves after injection of dye into the left ventricle was suggested 6 years ago, and several theoretical analyses of the method have appeared since. Only two studies have been published describing its application in man. Each has concluded that the measurement is in practice subject to large and unpredictable errors, and has attributed these to inherent poor mixing of the injected dye in either the ventricle or atrium.

It is predictable, however, that imperfect ventricular mixing of dye is unlikely to cause major errors in the measurement, and this was recently confirmed in practice by study of the method in dogs. This same study also showed that reproducible atrial curves and accurate measurements of regurgitant flow were obtained if the atrial sampling needle was kept close to the mitral valve, but not when a more peripheral sampling site was used. In both the human studies referred to, access to the left atrium was gained by dorsal percutaneous puncture, and a peripheral sampling site in the atrium was therefore very likely. Another feature of both studies was that left ventricular injections of dye were made through plastic catheters introduced from the left atrium. In our hands, such catheters frequently recoil into the atrium during injection, and in fact may wash in and out of the ventricle spontaneously in the presence of mitral incompetence. Such an occurrence would very likely pass unnoticed during an injection, and would give a totally false result to the measurement of regurgitant flow.

It seemed possible, then, that the poor results obtained in human application arose through technical features of these studies, and were not inherent to the method. The use of transseptal left atrial puncture makes possible a sampling site close to the mitral valve; we chose in addition to use direct percutaneous puncture of the left ventricle to obtain reliable access and delivery of dye into that chamber. This report describes our results with these approaches in the study of patients with mitral valve disease.

Methods

Thirty-nine patients have been studied, aged from 12 to 59 years, all with rheumatic mitral valve disease. Mitral incompetence was suspected on clinical grounds in every patient and was clearly present in the majority. Some degree of mitral stenosis was present in about half the group, and aortic stenosis in two. Patients with obvious aortic incompetence were excluded, although in five of the 39 patients studied, soft early diastolic basal murmurs were present. A diagnosis was in each case made from information independent of that gained by the present study; in 12 patients this has included a surgeon’s findings at mitral valvotomy. The functional status of each patient was classified by accepted criteria.

Patients were studied supine under light sedation, under local anesthesia. A catheter was passed from the right arm into the main pulmonary artery. An 18-gage Courmand needle was placed in the left femoral artery. A 17-gage Ross needle was passed into the right atrium from the right long saphenous vein, and the atrial septum was punctured as low as practicable, leaving approximately an inch of needle projecting into the left atrium. The left ventricle was then punctured at the apex anteriorly with a 22-gage needle in which were drilled two terminal side-holes.

Simultaneous pressure measurements were made from the left atrium, left ventricle, femoral artery, and pulmonary artery. A small calibrated volume of indocyanine green dye was then injected rapidly into the left ventricle, and dilution

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curves were recorded continuously from the left atrium (through the Ross needle) and femoral artery (through the Cournand needle). The left ventricular puncture needle was then removed, usually after a period of 2 to 3 minutes.

Pressure measurements were made with Statham P23-G pressure transducers and recorded, together with an electrocardiogram and the dye-dilution curves on a Sanborn multichannel direct-writing recorder. Midchest level was used as the zero reference for all pressures, and all readings were made from the records during respiratory end-expiration. Mean pressure gradients were computed by planimetry from superimposed equisensitive records.

The dye-dilution curves were recorded and calibrated, by methods previously described, with cuvette densitometers. For the left atrial curves, the total volume of the sampling system up to the cuvette was 1.1 ml. and the rate of blood withdrawal 0.45 ml/sec. For the arterial curves these figures were 0.4 ml and 0.7 ml/sec. The downslope of dilution curves is slowed less than 2 per cent by either of these systems.

The forward cardiac output (Fp) was calculated in the usual way from the amount of dye injected and the area of the extrapolated arterial dilution curve (A FA). The area beneath the left atrial curve (A LA) was similarly computed, and the mitral regurgitant flow (FR) was calculated from the formula:

\[
F_R = \frac{A_{LA} \times F_p}{A_{FA} - A_{LA}}
\]

The total left ventricular output (FV) was then the sum of forward cardiac output and mitral regurgitant flow: FV = FP + FR.

It is convenient here to define the *regurgitant fraction* as the proportion of total left ventricular output that is regurgitated, i.e., the ratio FR/FV. This fraction is equal to the ratio of the areas of the two dilution curves, A LA/A FA.

The functional areas of the mitral valve, both in diastole and in systole, were calculated by substituting the appropriate blood flow (in ml/sec.) and pressure gradient (in mm. Hg.) in the formula:

\[
\text{Functional valve area} = \frac{\text{blood flow}}{0.7 \times 44.5 / \text{mean pressure gradient}}
\]

For this and subsequent calculations, the periods of diastolic mitral valve flow and mitral regurgitant flow were identified and measured from superimposed simultaneous pressure tracings from the atrium and ventricle.

From the above information, the minute work of the left ventricle (MWLV) was estimated, both pressure and flow work, both forward and regurgitant. Pressure work was calculated from the formula:

\[
\text{Work (Kg.M./min.)} = \frac{\text{Mean LV pressure (cm. Water)} \times \text{blood flow (L./min.)}}{100}
\]

Forward pressure work was obtained by use of the mean LV pressure during aortic ejection with the minute forward flow Fp, and regurgitant pressure work by the mean LV pressure during regurgitation with the minute mitral regurgitant flow FR.

To calculate flow work, the mean velocity imparted to blood forward and backward was derived from the appropriate forward or regurgitant stroke volume, aortic or mitral systolic valve area, and duration of forward or backward flow. Thus,

\[
\text{stroke volume (ml.)} = \frac{\text{valve area (sq. cm.)} \times \text{flow period (sec.)}}{\text{Mean velocity (cm./sec.)}}
\]

The flow work was then calculated from the formula:

\[
\text{Work (Kg.M/min.)} = \frac{\text{blood flow (L./min.)} \times (\text{mean velocity})^2}{2 \times 9.8 \times 10,000}
\]

Except in two patients who had aortic stenosis and in whom this valve area was separately calculated, an aortic systolic valve area of 6 sq. cm. was assumed.

In 12 of the 39 patients, duplicate measurements of mitral regurgitant flow were made to assess the reproducibility of this figure. In five of these, the left ventricular needle was removed and replaced between measurements, the transseptal puncture needle was not moved.

**Results**

**General Features**

This technic has proved both feasible and
MITRAL REGURGITANT FLOW

Figure 1
Left. Original recordings of simultaneous division curves from femoral artery and left atrium after injection of dye into the left ventricle. Right. Some pair of curves replotted on logarithmic scale of concentration. (Patient I.D., Cardiac output 2.81 L/min., regurgitant fraction 0.38, regurgitant flow 1.73 L/min., regurgitant orifice 0.30 sq. cm., stenotic orifice 1.4 sq. cm.)

reliable as a routine procedure. Successful studies resulted in 38 of the 39 patients. The one failure arose through inability to enter the left ventricle in a patient with severe pulmonary hypertension and predominant mitral stenosis. With careful local anesthesia, the procedure causes little discomfort to the patient; measurements are therefore made in a relaxed state and in the supine position.

The morbidity is not high. Mild precordial pain may follow left ventricular puncture for some hours in less than half the patients. Fever over 100 F. appeared in four patients some 24 hours after the study. In three, this fever persisted with or without some chest pain, subsiding spontaneously in 3, 5, and 10 days respectively; no evidence of infection was found, nor any change in serial electrocardiograms. This complication resembled somewhat the pericarditis that may follow myocardial infarction.20

Patients with No Mitral Incompetence

In six patients no early appearing dye was detected in the left atrial curve. This negative result was duplicated by a second dye injection in two patients. Four of the six have undergone mitral valvotomy (patients S.J., L.K., F.C., and V.R., table 2), and in none was any mitral regurgitation found.

Patients with Minimal Mitral Incompetence

In two patients small irregular deflections were seen in the left atrial record, with an appearance time wholly accounted for by the transit of blood through the sampling needle and cuvette (1.7 sec.). In one of these patients, a second injection of dye into the ventricle gave an identical left atrial record. These results were interpreted as showing minimal mitral incompetence; no attempt was made to calculate the regurgitant flow. Both patients had soft apical systolic murmurs, and both later underwent surgery (patients K.N., G.W., table 2); the surgeon found "a barely palpable regurgitant jet" in one, but was unable to detect regurgitation in the other.

Patients with Measurable Incompetence

In the remaining 30 patients, the left atrial curves recorded were smooth in contour, and clearly indicated the regurgitation of significant amounts of dye into the atrium. A typical pair of curves is shown in figure 1, both in their original form and replotted with a logarithmic ordinate. Better seen when replotted, the downslope of the arterial curve is initially rapid, later slow, and finally interrupted by systemic recirculation. The second component of this downslope is parallel to
Table 1
Successive Forward and Regurgitant Flow Measurements in Nine Patients with Measurable Regurgitation, Indicating the Order of Reproducibility Obtained

<table>
<thead>
<tr>
<th>Patient</th>
<th>Forward flow (L./min.)</th>
<th>Regurgitant flow (L./min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L.Ka</td>
<td>4.28</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>4.16</td>
<td>0.53</td>
</tr>
<tr>
<td>W.M.</td>
<td>4.56</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>4.58</td>
<td>0.42</td>
</tr>
<tr>
<td>K.G.</td>
<td>3.76</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>3.26</td>
<td>0.65</td>
</tr>
<tr>
<td>P.B.</td>
<td>2.80</td>
<td>1.21</td>
</tr>
<tr>
<td></td>
<td>2.39</td>
<td>0.96</td>
</tr>
<tr>
<td>W.B.</td>
<td>4.78</td>
<td>1.50</td>
</tr>
<tr>
<td></td>
<td>4.72</td>
<td>1.58</td>
</tr>
<tr>
<td>M.F.</td>
<td>6.10</td>
<td>1.78</td>
</tr>
<tr>
<td></td>
<td>5.56</td>
<td>1.63</td>
</tr>
<tr>
<td>C.B.</td>
<td>6.84</td>
<td>2.11</td>
</tr>
<tr>
<td></td>
<td>6.31</td>
<td>1.96</td>
</tr>
<tr>
<td>A.O’C</td>
<td>2.66</td>
<td>3.11</td>
</tr>
<tr>
<td></td>
<td>2.75</td>
<td>3.43</td>
</tr>
<tr>
<td>S.M.</td>
<td>4.07</td>
<td>5.66</td>
</tr>
<tr>
<td></td>
<td>4.12</td>
<td>6.96</td>
</tr>
<tr>
<td>Mean difference between paired measurements</td>
<td>0.26</td>
<td>0.35</td>
</tr>
<tr>
<td>S.D. of difference</td>
<td>0.23</td>
<td>0.36</td>
</tr>
</tbody>
</table>

0.26 L./min. (S.D. 0.23 L./min.). For paired measurements of regurgitant flow, the mean difference was 0.35 L./min. (S.D. 0.36 L./min.).

Valve Area Calculations
The mean pressure gradient from left ventricle to left atrium during the period of regurgitation was measured from superimposed pressure tracings. From this and the measured regurgitant flow, the systolic valve area (regurgitant orifice) was calculated. The diastolic valve area (stenotic orifice) was obtained from the mean diastolic pressure gradient and the total diastolic valve flow.

Thirty patients had measurable amounts of regurgitation, and in them the regurgitant orifice ranged from 0.04 to 2.0 sq. cm. Fourteen patients had a stenotic orifice less than 3.0 sq. cm., and eight of these also had measurable regurgitation. The relationship of regurgitant to stenotic orifices in these eight patients is shown in figure 2. No patient with a stenosis less than 3 sq. cm. had a regurgitant orifice greater than 0.45 sq. cm., while for a stenosis less than 1.5 sq. cm. the largest regurgitant orifice was 0.3 sq. cm.

Correlation with Surgical Findings
Descriptions of the mitral valve during surgery were available in 12 of the patients studied, the operation preceding study in five and following it in seven. These data are summarized in table 2.

No patient with very severe incompetence has undergone surgery. The regurgitant flow appeared ‘‘significant’’ to the surgeon by digital palpation when the regurgitant orifice was greater than 0.1 sq. cm., ‘‘severe’’ between 0.2 and 0.3 sq. cm., and ‘‘gross’’ at 0.45 sq. cm. It is notable that in only one of five patients explored in whom the regurgitant orifice was 0.18 sq. cm. or more did the surgeon feel that mitral valvotomy was feasible, despite the presence of significant stenosis in three of the five. In this one patient (W.B.), successful relief of stenosis was possible without increased incompetence; this was confirmed by re-study 3 weeks after operation (table 2).
Left Ventricular Work

Four components of the total external work of the left ventricle were calculated—the forward pressure work and forward flow work and the regurgitant pressure work and regurgitant flow work. Excluding two patients with coincident aortic stenosis, the flow component of forward work was only a very small proportion of the total forward work (average 0.9 per cent, range 0.2 to 3.4 per cent). In contrast, the flow component of regurgitant work was a much more significant part of the total regurgitant work (average 24 per cent, range 10 to 32 per cent). This regurgitant flow work ranged up to 4.65 Kg.M./min., and was over 2.0 Kg.M./min. in eight of the 30 patients with measurable incompetence. The total regurgitant work ranged up to 19.0 Kg.M./min., constituting up to 77 per cent of the total work of the left ventricle.

Correlation of Hemodynamic Data with Functional Capacity

For this purpose, patients with obstructive lesions were excluded; 24 patients in the study had "pure" mitral incompetence (mitral stenotic orifice over 3 sq. cm. and pulmonary vascular resistance less than 400 dynes sec. cm.\(^{-5}\)).

In this group, it could not be shown that functional impairment was related to the severity of mitral incompetence, whether this was expressed by the regurgitant fraction (fig. 3A), by the regurgitant flow (fig. 3B), or by the regurgitant valve orifice (fig. 3C). In fact, there was a tendency for the patients with the worst incompetence, by these definitions, to appear only in the least incapacitated groups. In figure 3D, the same phenomenon is apparent, the left ventricular minute work being highest only in patients with relatively little functional impairment.
There was found, however, a definite relationship between disability and elevation of the left ventricular end-diastolic pressure (fig. 4A), and the latter was regularly accompanied by elevation of the right atrial pressure (fig. 4B).

**Discussion**

Previous attempts to apply this direct dye-dilution method for measuring mitral regurgitation have given occasional results grossly discordant with known findings,\(^7\)\(^8\) throwing considerable doubt on its value in clinical studies. It appears, however, that the modifications introduced in the present study have eliminated such grossly misleading results, and have permitted a better appraisal of the method's reliability in practice. Left ventricular puncture has given reliable delivery of dye into the body of the ventricle without the possibility of catheter recoil into the atrium during injection. The transseptal approach to the atrium has ensured a sampling site close to the mitral valve, away from the periphery of a large atrium where the mixing of dye might be less uniform.

Our accuracy attained in the measurement of regurgitant flow is impossible to assess, since no alternative standard is available, but we have not had reason to think that the results were in any case qualitatively wrong. The reproducibility of paired measurements (table 1) gives some idea of reliability, and this is tolerable for such a measurement. In this regard it is worth considering the variability expected in such a calculation. The figure for regurgitant flow is derived from a quotient of the areas of two dilution curves, each of which probably has a significant and independent variability. The quotient then will have a variability that depends

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**FUNCTIONAL CLASS**

*Figure 3*

*Relationships between symptom severity and various hemodynamic findings in 24 patients with “pure” mitral incompetence.*

(A) regurgitant fraction, (B) regurgitant flow in L./min., (C) regurgitant orifice in square centimeters, (D) total left ventricular work in Kg.M./min.
MITRAL REGURGITANT FLOW

Table 2

Calculated Valve Orifices (MVA) in Square Centimeters during Systole and Diastole, Related to the Findings at Operation

<table>
<thead>
<tr>
<th>Patient, age, sex</th>
<th>Estimated MVA Diastole</th>
<th>Estimated MVA Systole</th>
<th>Surgical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.J. 48F</td>
<td>1.4</td>
<td>0</td>
<td>Tight MS, no MR</td>
</tr>
<tr>
<td>L.K. 48F</td>
<td>1.7</td>
<td>0</td>
<td>Moderate MS, no MR</td>
</tr>
<tr>
<td>F.C. 14M</td>
<td>1.8</td>
<td>0</td>
<td>Tight MS, no MR</td>
</tr>
<tr>
<td>V.R. 41F</td>
<td>&gt;3</td>
<td>0</td>
<td>*Tight MS, excellent valvotomy with no residual MR</td>
</tr>
<tr>
<td>K.N. 39M</td>
<td>1.3</td>
<td>NC</td>
<td>Tight MS, trace MR</td>
</tr>
<tr>
<td>G.W. 38M</td>
<td>0.9</td>
<td>NC</td>
<td>Tight MS, no MR felt</td>
</tr>
<tr>
<td>B.W. 42F</td>
<td>&gt;3</td>
<td>0.12</td>
<td>*Tight MS, no MR. Extensive valvotomy produced</td>
</tr>
<tr>
<td>P.B. 29M</td>
<td>1.3</td>
<td>0.18</td>
<td>*Moderate MS and severe MR. No valvotomy attempted</td>
</tr>
<tr>
<td>L.D. 22F</td>
<td>1.4</td>
<td>0.3</td>
<td>*Tight MS, some MR. Valvotomy stopped because MR increased</td>
</tr>
<tr>
<td>H.B. 29M</td>
<td>2.5</td>
<td>0.3</td>
<td>Mild MS, severe MR—<em>inoperable</em></td>
</tr>
<tr>
<td>W.B. 42M</td>
<td>1.6</td>
<td>0.3</td>
<td>Moderate MS, moderate MR. Successful valvotomy with no increase of MR</td>
</tr>
<tr>
<td>W.B. (post-op.)</td>
<td>&gt;3</td>
<td>0.2</td>
<td>Re-studied 3 weeks after operation</td>
</tr>
<tr>
<td>R.M. 28M</td>
<td>2.8</td>
<td>0.45</td>
<td>*Little MS, gross MR. No valvotomy attempted</td>
</tr>
</tbody>
</table>

*Signifies that operation preceded the hemodynamic study; MS, mitral stenosis; MR, mitral regurgitation; NC, minimal mitral incompetence, no calculation made.

not only on those of the two component curves, but that increases also with the magnitude of the quotient itself. This would account for the poorer reproducibility observed when the regurgitant flow was large.

The assumptions made in this calculation have been clearly set out in the analysis by Lacy et al. and the extent to which they are fulfilled in the present study is difficult to evaluate. Mixing of dye in the left atrium is clearly not adequate in what we have defined as minimal incompetence, since the atrial curves recorded were irregular. With larger regurgitant flows, however, atrial mixing must be encouraged, and the experimental study by Newcombe et al. suggests that it does become adequate to fulfill the assumptions made, provided sampling is performed close to the mitral valve. It is probably important in this regard that the atrial volume in which mixing must be uniform need not be the total atrial volume, provided it remains functionally constant.

The smooth curves obtained from the atrium are clearly not the required curves of diastolic atrial concentration, since the distortion imposed by the blood sampling gives a mean of systolic and diastolic concentrations. This effect must produce a consistent over-estimate of regurgitant flow, but probably not a major one.

The curves recorded from the femoral artery should satisfactorily represent central aortic curves in area, provided that their relatively smooth contour does not lead to incorrect extrapolation of the downslope. Predictable identity of the “correct” extrapolation with that of the left atrial curve helps to prevent such errors.

The values obtained for mitral regurgitant
flow have all been within a credible range when compared with the known magnitude of regurgitant flows tolerated by experimental animals. One of the few checks on our order of accuracy has been in those patients with measurable mitral incompetence and stenosis in whom a surgeon's description of the valve in diastole was available. It has been encouraging that the calculation of diastolic valve area has corresponded to the surgeon's estimate equally well in the patients with marked incompetence as in those with pure stenosis. From the diagnostic viewpoint, it is in this group of patients where the results of study have been most helpful, since their clinical evaluation is most difficult.

We chose to use an empirical constant of 0.7 in the hydraulic formula for mitral valve area calculation both during diastole and systole. As discussed by Gorlin and Dexter, there is less certainty in choosing this constant for calculation of the regurgitant orifice, since the orifice is probably not fixed during systole; however, the figure of 0.7 is unlikely to be greatly in error. Since the systolic and diastolic flow periods are measured directly in this study, as are the pressure gradients across the valve, the assumptions made in applying the hydraulic formulas and in determining the empirical constant are fewer than were originally necessary. In particular, the original assumption that left atrial mean systolic pressure could be represented by a mean pulmonary capillary wedge pressure has often in our patients proved in error by as much as 20 mm. Hg.

The fact that a regurgitant orifice of only 0.3 sq. cm. gave rise to "severe regurgitation" as estimated by the surgeon is very relevant to surgical repair of incompetent valves. The aim of the surgeon must clearly be to leave no visible leak whatever, and this may be difficult to achieve in the open nonbeating heart.

The magnitude of external work done by the left ventricle in mitral incompetence is very considerable. In severe cases this is more than in the largest left-to-right shunts through a ventricular septal defect or patent ductus arteriosus, and equals the external work done in most cases of aortic stenosis. It is hard on these grounds to assign a benign course to mitral incompetence, and it is predictable that the maintenance of forward output and clinical well being of the patient will depend largely on the integrity of left ventricular function.

The relationships shown in figures 3 and 4 emphasize further the importance of left ventricular performance in determining the functional status of the individual patient. The regurgitant fraction and regurgitant orifice were frequently large in patients with little disability and small hearts, as well as...
in those with severe symptoms and large hearts. Raised end-diastolic pressure in the left ventricle was only seen in patients with severe symptoms. In the same patients, total left ventricular output and minute work tended to be lower than in less disabled patients with the same regurgitant valve orifice. These findings in man, are in accord with the experimental work of Braunwald et al., 23 who showed in dogs that the acute effects of any given mitral regurgitant flow on left ventricular end-diastolic pressure and volume were determined by the ventricular function at that time.

There was no consistent correlation between symptom severity and the patient's age or duration of disease as far as this could be judged. In fact, in a number of patients the disability apparently dated from the original attack of rheumatic fever and the development of the valve lesion. While such large work loads on the left ventricle must ultimately cause failure of even a normal ventricular muscle, it appeared in this group of patients that the disability was dependent most on the amount of rheumatic myocardial disease acquired during the rheumatic activity.

No attempt has been made to present here the related clinical and radiologic findings on our patients. From a study of these, however, it has become clear that the usual clinical estimate of the "severity" of mitral incompetence tends to be an estimate of ventricular failure and dilatation accompanying the valve lesion, rather than of the regurgitant valve orifice or regurgitant flow. It is also apparent that the various changes seen in arterial dilution curves in the presence of mitral regurgitation, long used by many authors 16, 24-26 to assess its severity, correlate better with ventricular status than with valve status, inasmuch as these two are separated by our present methods. Since it is presumably the valve status and regurgitant flow upon which the selection of patients for surgical treatment should be based, the adoption of a direct technic for their measurement such as used in the present study would seem desirable.

Summary
A direct indicator-dilution principle for measurement of regurgitant flow has been applied in the study of 39 patients with mitral valve disease.

Certain technical modifications in the procedure appear to have abolished the grossly anomalous results encountered previously, enabling a degree of reliance to be placed on the quantitative measurement.

With use of the measurement obtained, together with other hemodynamic data, the functional status of patients with mitral incompetence has been analyzed. The findings confirm that left ventricular failure, not mitral incompetence itself, underlies many of the criteria presently used to determine the severity of the disease, i.e., the presence of symptoms, the clinical and radiologic signs, and abnormalities in arterial dye dilution curves. These criteria are therefore probably not optimal ones on which to base selection of patients for surgical treatment, or to follow its results.

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References


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