An Appraisal of the Double Indicator-Dilution Method for the Estimation of Mitral Regurgitation in Human Subjects

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The shape of an indicator-dilution curve is determined by at least 4 variables: cardiac output, the volume between the injection site and the sampling site, the presence of a left-to-right intracardiac shunt, and the presence of valvular regurgitation. In the absence of an intracardiac shunt and valvular regurgitation, one can predict the downslope of the arterial dilution curve, using the calculated values of cardiac output and "central blood volume." Several investigators have tried to estimate the amount of regurgitation in man by measuring the deviation of the observed downslope from the predicted downslope. Lange and Hecht have presented evidence suggesting that an estimate of mitral regurgitation may be obtained by comparing the dilution curves recorded simultaneously from the pulmonary artery and the femoral artery. There is evidence from studies on dogs with simulated valvular regurgitation that supports the validity of this technique.

This is a report of the results of the double-dilution-curve technic in the estimation of mitral regurgitation in 50 patients.

Materials and Methods

Fifty adult patients were studied during right heart catheterization. Indocyanine dye (5 to 12.5 mg) was injected in an antecubital vein; the dilution of indicator at the pulmonary artery and the femoral artery was measured by drawing a continuous sample from each site through a cuvette oximeter at a rate of 32 ml per minute. The proximal sample was drawn from the right ventricle in 2 patients in whom it was not possible to enter the pulmonary artery. The output of each oximeter was simultaneously registered on a cathode-ray photographic recording system at a paper speed of 5 mm per second. The downslopes of the curves were extrapolated after they were replotted on semi-logarithmic paper. The regurgitant flow, expressed as a fraction of the effective forward flow (QH/QF), was calculated by means of the equation derived by Lange and Hecht:

\[ Q_H/Q_F = \frac{\Delta MCT - \Delta AT - 0.6}{\Delta AT} \]

in which \( \Delta MCT \) = time (seconds) between mean circulation times of two curves \( \Delta AT \) = time (seconds) between appearance times of the two curves.

The amount of mitral regurgitation in each patient was also estimated by the use of a combination of other criteria. Each patient was examined by one or more of the authors and the degree of mitral regurgitation was estimated on the basis of the physical examination, the electrocardiogram, and the x-ray findings. Patients with aortic regurgitation were excluded. Twenty-six patients had percutaneous left atrial puncture by the method of Bjork and co-workers, and an estimate of the relative importance of mitral regurgitation was made by dividing the extent of the y descent in the first 0.1 second by the mean left atrial pressure. Twenty-three patients had operative exploration of the mitral valve.

On the basis of all available information, exclusive of the indicator-dilution curves, the degree of regurgitation was graded in each of the 50 patients (table 1).

Results and Discussion

The ratio of regurgitant flow to forward flow (QH/QF) varied from 0 to 2.43. There was usually a marked difference between the curves recorded from patients with little or no regurgitation and the curves recorded from patients with severe regurgitation. The similarity between the pulmonary and femoral arterial dilution curves recorded from a patient with slight regurgitation (group 1) is illustrated in figure 1. The curves recorded from a patient with severe mitral regurgita-

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tion (group 3) are shown in figure 2. The decrease in the maximum concentration and the more prolonged downslope in the femoral artery curve were consistent features in patients with severe regurgitation.

The amount of regurgitation estimated from the clinical and surgical data is plotted against the $Q_R/Q_F$ from the dilution curves in figure 3. The relationship is not a perfect one, but it is significant that only 1 patient with moderate (grade 2) or severe (grade 3) regurgitation had a $Q_R/Q_F$ ratio below 0.40.

The 6 points marked by $x$ in figure 3 are of special significance in that each point represents a discrepancy between the estimate of the regurgitant flow by the dilution technic and the estimate of the amount of regurgitation by clinical and operative means. The one discrepancy in group 0 ($Q_R/Q_F = 0.97$) had severe heart failure with no evidence of valvular disease; the etiology was obscure after intensive study, including right and left heart catheterization. There were 3 patients in group 1 with high $Q_R/Q_F$ ratios. The patient with a $Q_R/Q_F = 0.90$ had shown little improvement following a mitral valvulotomy and had clinical evidence suggesting a mixed lesion with predominant stenosis. It is possible that this patient may need to be reclassified into another group after re-operation. Another patient ($Q_R/Q_F = 0.71$) had autopsy evidence of severe subaortic stenosis but no valvular disease. The third exception in group 1 ($Q_R/Q_F = 2.0$) had good clinical evidence of severe predominant mitral stenosis. This impression was confirmed at operation, and only a minimal regurgitant jet was present. The patient had marked sustained improvement following the correction of the mitral stenosis. The one patient in group 2 with an unusually high regurgitant ratio ($Q_R/Q_F = 1.68$) had heart failure of indeterminate etiology. A moderately loud systolic murmur was present at the apex, and on the basis of this rather tenuous evidence the patient was classified as group 2. The relatively low level of confidence in the classification of this patient makes it difficult to be certain regarding the cause of the discrepancy in this instance. The other discrepancy in group 2 was in a patient in whom the calculated regurgitant ratio seemed unusually low ($Q_R/Q_F = 0.20$). All studies in this patient, except the dilution curves, indicated moderate mitral regurgitation: loud systolic murmur, evidence of left ventricular hypertrophy on physical examination and on the electrocardiogram, and a left atrial pressure pulse in which the ratio $R_y$ (0.1 sec.) was over 0.6.

### Table 1

**Classification of Patients**

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Diagnosis</th>
<th>Method of Grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>18</td>
<td>10 No heart disease</td>
<td>Clinical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 Rheumatic heart disease</td>
<td>Operative 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Heart failure of indeterminate etiology</td>
<td>Clinical 1</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>14 Rheumatic heart disease</td>
<td>Operative 11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Subaortic stenosis</td>
<td>Clinical 3</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>10 Rheumatic heart disease</td>
<td>Operative 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Heart failure of indeterminate etiology</td>
<td>Clinical</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>Rheumatic heart disease</td>
<td>Operative 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clinical 4</td>
</tr>
</tbody>
</table>
Pulmonary and femoral artery dilution curves from patient with severe mitral stenosis and minimal (grade 1) mitral regurgitation.

Right ventricle and femoral artery dilution curves from patient with severe mitral regurgitation.

It seems almost certain that the double-dilution technic provided a gross overestimate of the amount of regurgitation in the patient with subaortic stenosis (group 1, $Q_R/Q_F 0.7$), and in the patient with severe mitral stenosis (group 1, $Q_R/Q_F 2.0$). It is probable, although not so certain, that the amount of mitral regurgitation was overestimated by the double-dilution technic in 2 other patients (group 0, $Q_R/Q_F 0.97$; group 1, $Q_R/Q_F 0.90$). It is significant that each of these 4 patients had unusual enlargement of the left side of the heart; this is demonstrated in figure 4, an angiocardioanogram showing a giant left atrium in the patient with operatively proved mitral stenosis and a $Q_R/Q_F$ of 2.0.

The two other discrepancies between the two estimates of regurgitation (group 2, $Q_R/Q_F 1.68$ and 0.20) are less extreme, and the reasons for them are obscure at the present time. They may be due to errors in the grouping of the patients. It is possible that these discrepancies may be related to changes in the degree of mixing of the regurgitated indicator in the receiving chamber or changes in the distensibility of the receiving chamber.13

These data are interpreted as indicating that there are at least two factors that may alter the shape of an indicator-dilution curve after its formation in the pulmonary artery: left-sided valvular regurgitation and the presence of a large volume between the pulmonary artery and the femoral artery. In patients without great left-sided enlargement the effect of volume is insignificant, and the equation

$$\frac{\triangle MCT - \triangle AT}{\triangle AT} = Q_R/Q_F$$

is equal to a figure near zero in the absence of mitral or aortic regurgitation. The pulmonary and femoral arterial dilution curves become more dissimilar as the degree of mitral regurgitation increases, and the equation provides a
clinically useful estimate of the amount of regurgitation. This information may be of
great value in the selection of patients for surgical treatment, since patients with more
than slight regurgitation are probably best treated by open valvulotomy with the extra-
corporeal pump-oxygenator, rather than by conventional mitral valvulotomy.

A comparison of the results with the double-
dilution technic and the ratio

\[ \frac{R_y (0.1 \text{ sec.})}{\text{mean left atrial pressure}} \]
described by Morrow and associates\textsuperscript{12} for each
of the 26 patients who had left atrial catheteriza-
tion is illustrated in figure 5. The corre-
lation with the degree of regurgitation was
substantially less impressive with the pres-
sure method than with the dilution method.

The effect of an unusually large volume be-
tween the pulmonary artery and the femoral
artery may be a cause of falsely elevated re-
gurgitant ratios and therefore limits the value
of the double-dilution technic. There is exper-
imental evidence indicating that a large vol-
ume between the pulmonary and femoral
artery would be the dominant factor in de-
termining the downslope of the femoral artery
curve and would thus produce differences
between the pulmonary artery and femoral
artery curves in the absence of valvular
regurgitation.\textsuperscript{14}

**Summary**

The amount of mitral regurgitation was es-
timated in 50 patients by an indicator-dilution
technic and by the usual clinical, catheteriza-
tion, operative, and autopsy criteria. There
was a good correlation between the two esti-
mates. Patients with significant mitral regur-
gitation (grade 2 or grade 3) had, with one
exception, \( Q_R/Q_F \) ratios above 0.41. There
were at least two instances where the calcu-
lated \( Q_R/Q_F \) was almost certainly falsely high.
It seems likely that these discrepancies are
related to the presence of an unusually large
volume between the pulmonary artery and the
femoral artery.

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Though we can never hope to attain to the complete knowledge of the texture, or constituent frame and nature of bodies, yet may we reasonably expect by this method of experiments, to make farther and farther advances abundantly sufficient to reward our pains. And though the method be tedious, yet our abilities can proceed no faster; for as the learned author of the Procedure of Human Understanding observes, "All the real true knowledge we have of Nature is entirely experimental, insomuch that, how strange soever the assertion seems, we may lay this down as the first fundamental unerring rule in physics, That it is not within the compass of human understanding to assign a purely speculative reason for any one phaenomenon in nature." So that in natural philosophy, we cannot depend on any mere speculations of the mind: we can only with the mathematicians, reason with any tolerable certainty from proper data, such as arise from the united testimony of many good and credible experiments.—STEPHEN HALES, B.D., F.R.S. Haemastatics. Preface, Vol. II, London, 1733.
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