Calculation of Cardiac Output from Indicator-Dilution Curves in the Presence of Mitral Regurgitation

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MEIER and Zierler have lucidly presented the theory underlying the application of indicator dilution to the measurement of flow in the vascular bed. This theory is not violated by the presence of valve incompetence provided that indicator particles that recirculate and reenter the vascular system can be excluded from the primary indicator-concentration-time curve.

Valve incompetence results in an increased dilution volume and a slowed clearance of indicator from the heart. Indicator-dilution curves in such circulatory systems show reduced magnitudes of concentration and a prolonged disappearance phase when compared to dilution curves obtained from similar systems without valve incompetence. Previous studies of indicator-dilution curves in patients with mitral incompetence have been concerned with the detection of the incompetence or with the estimation of the amount of regurgitation. The calculation of forward or systemic blood flow hitherto has not been considered in detail.

The present study was initiated to ascertain whether the validity of the concept of Meier and Zierler is borne out in practice. Cardiac output was calculated from indicator-dilution curves according to the accepted methods of Stewart and Hamilton after injection of indicator into the pulmonary artery, left ventricle, and ascending aorta in patients with mitral incompetence and in a control group without valve incompetence. The dilution curve with injection into the ascending aorta is unaffected by the presence of incompetence of the mitral valve during the inscription of the primary indicator-concentration curve. The dilution curves obtained after injection into the left ventricle and pulmonary artery are affected by the valvular incompetence and by the enlargement of the cardiac chambers that accompanies it.

Material and Methods

The data were obtained on 28 patients undergoing diagnostic cardiac catheterization (table 1). Of these, 15 had no hemodynamic abnormalities or had only mild or minimal aortic stenosis or mitral stenosis and were considered as controls. The remaining 13 patients had pure mitral incompetence and included both children with congenital mitral incompetence and adults in whom the incompetence was acquired.

Technic

Indocyanine green in doses of 2.5 to 5.0 mg. was injected through cardiac catheters (Lehman, sizes 5 through 7; NIH, sizes 7 through 10) as a single rapid injection using a special syringe assembly, which allows the expulsion of an accurately known volume of the dye solution.

The injection sites were the pulmonary artery, left ventricle, and ascending aorta. The sampling site was always the femoral artery, which was connected to the polythene lumen of a cuvette oximeter by an indwelling needle. Blood was withdrawn at constant flow rates of 12 to 18 ml. per minute continuously before, during, and after the dye injection, each milliliter being signaled on the recording paper. The change in optical density associated with the passage of dye was amplified (Preac magnetic amplifier model M5724) and recorded on photographic paper by

*Cardio-Green, Hynson, Westcott, Dunning, Baltimore, Maryland.
†Model XC50B, Waters Corp., Rochester, Minnesota.
a galvanometer-oscillograph assembly using a Visicorder (Minneapolis Honeywell Co., Model 1012). The cuvette was calibrated for dye concentration by using the patient's own blood. The frequency response of the optimally damped galvanometer* is 24 cps.

The dynamic response of the system was determined experimentally for needle-oximeter and catheter-oximeter systems. The delay to square-wave variation in dye content of whole blood6 of the cuvette oximeter using a needle, and 100 cm. lengths of 6 F and 7 F cardiac catheters and the "time constants" (63 per cent of peak response) of the various systems are given in table 2. The delay values so determined were used in the evaluation of curves obtained by withdrawing blood from the central circulation. The additional damping imposed by the use of catheter-oximeter systems was considerable.

The effect of recirculated dye during cardiac output calculation was eliminated by the method of Hamilton and co-workers,6 and cardiac output (CO) was calculated according to the conventional formula

\[ CO = \frac{60I}{\bar{c}t} \]

in which \( I \) is the amount of injected dye, and \( \bar{c} \) is the mean concentration during the primary circulation for the period \( t \). The cardiac index (L,.min./M.2) was obtained by dividing the cardiac output by the body surface area (M.2).

**Procedure**

A "set" of dilution curves is defined as a group of dilution curves obtained in a patient in rapid succession (within 5 to 15 minutes) after injection into the pulmonary artery, left ventricle, and ascending aorta. In some of the patients with mitral incompetence, "sets" were obtained after injection into the left ventricle and ascending aorta only. In some patients, a second "set" of dye curves was also obtained between 10 and 15 minutes after angiocardiography with the patient under anesthesia; this involved injections of large amounts of pharmacologically active contrast material and caused significant changes in cardiac output.7 In a few subjects, cuvette calibrations were recorded using blood obtained both before and 2 to 5 minutes after injection of contrast medium. No significant difference in the response of the instrument to dye was found. Such a second "set" was regarded as a separate comparison of cardiac outputs. The comparisons of cardiac outputs to be reported were made within, and not between such "sets" of dilution curves.

**Results**

Mitrval regurgitation causes a decrease in peak concentration of dye and prolongation of the disappearance phase of the dilution curve when the indicator is involved in the regurgitant flow in its primary circulation (fig. 1). These effects increase proportionately to the magnitude of the regurgitation and to the degree of chamber enlargement.

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>Age, yr. Mean</th>
<th>Range</th>
<th>Body surface area, M.2</th>
<th>Mean</th>
<th>Range</th>
<th>Indicator-dilution curves, number of &quot;sets&quot;*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Mitrval Insufficiency</td>
<td>15</td>
<td>23</td>
<td>5.5 to 58</td>
<td>1.3</td>
<td>0.8</td>
<td>1.98</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>41</td>
<td>5 to 69</td>
<td>1.5</td>
<td>0.76</td>
<td>1.78</td>
<td>18</td>
</tr>
</tbody>
</table>

*Comparisons of dye curves from different sites obtained in one individual within 5 to 15 minutes.

*To 63 per cent of peak concentration.
†Six milligrams per liter of blood.
INDICATOR-DILUTION CURVES

Figure 1
Arterial indicator-dilution curves after injection of indicator into ascending aorta (solid line) and left ventricle (broken line) in normal person and in patient with mitral regurgitation. The changing concentration of dye with time is shown following injection of indicator at T₁.

Figure 2 shows comparison of the cardiac indices obtained within the "sets" after injection of dye at the three different sites. A wide range of cardiac indices was observed in both the control group and in the patients with mitral insufficiency, related not only to the differing basal cardiac output in such patients but also to the differing circulatory states under conditions of sedation, anesthesia, and after angiocardiography. Fewer comparisons of cardiac index from pulmonary-artery dye curves were available in the mitral insufficiency patients. The mean cardiac indices are given in table 3. They illustrate the lower blood flow rates obtained in patients with mitral incompetence. The averages of paired differences for injection sites are given in table 4 for control and mitral insufficiency groups. These differences are statistically significant in regard to the aorta injection site for the mitral insufficiency patients. For the control group, the P value approaches 0.1 in the case of aortic minus pulmonary artery dilution curves.

Discussion
There is good correlation of cardiac indices within a set of dye curves both in the control group and in mitral incompetence. In general, differences are within the reproducibility of indicator-dilution calculations of flow measurements. A systematic and significant difference exists between the cardiac indices obtained from the ascending aortic and left ventricular dye curves in mitral regurgitation, in that estimates from the aortic injection site exceed values for the left ventricular injection by 20 per cent. Insignificant differences of small magnitude were seen for the other comparisons.

Employment of standard technics and sampling site and the absence of a significant difference in cardiac indices from the three sites in the control series minimize the possibility that random instrumentation and calculation errors, streamlining of blood flow, nonmixing of the dye, dynamic response of the detector, and the effect of background dye are significant causes of the difference in cardiac index that is estimated for the aortic and left ventricular dye curves in mitral re-
gurgitation. This difference was not related to the absolute level of cardiac index.

The cardiac index obtained with the injection of indicator into the ascending aorta correlates well with that obtained with injection of indicator into the left ventricle in the control group. In mitral insufficiency, this is the only dye curve in which the indicator is not involved in the regurgitant process during the inscription of the primary indicator concentration curve. Therefore, the discrepancy in cases of mitral insufficiency is likely to be due to an underestimate of cardiac index from the dye curve after left ventricular injection.

The range of difference between cardiac indices obtained from ascending aortic and left ventricular dye curves in mitral incompetence was 2 to 40 per cent, but in 13 of the 18 comparisons (72 per cent) the difference was less than 20 per cent. Therefore the estimate of forward flow from indicator-dilution curves in the resting state when the indicator is involved in the regurgitant flow in its primary circulation is likely to result in an error of underestimation less than 20 per cent in the majority of instances. The error of the other accepted method for estimating cardiac output in intact man (Fick principle) is in the range of 10 to 15 per cent.9,10

**Nature of Difference in Patients with Mitral Regurgitation**

It follows from Meier and Zierler1 that if the cardiac output from the left ventricular dye curve is erroneously low, then the time-concentration dilution curve as submitted to computation includes extra dye particles. The likely source of such particles would be the recovery of recirculated indicator.

**The Effects of Coronary Recirculated Indicator Particles**

The coronary-circulated indicator has been shown to be one of the earliest returning par-

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**Table 3**

*Cardiac Indices with Injection of Indicator into the Three Sites and Comparison of Percentage Difference of Cardiac Index Values in Patients with and without Mitral Regurgitation*

<table>
<thead>
<tr>
<th>Cardiac index, mean ± S.D.</th>
<th>Control</th>
<th>Mitral insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary artery</td>
<td>4.50 ± 2.03</td>
<td>2.86 ± 1.58</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>4.69 ± 2.19</td>
<td>3.10 ± 1.39</td>
</tr>
<tr>
<td>Ascending aorta</td>
<td>4.83 ± 2.34</td>
<td>3.88 ± 1.84</td>
</tr>
<tr>
<td>Difference, per cent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascending aorta minus left ventricle</td>
<td>3.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Left ventricle minus pulmonary artery</td>
<td>4.0</td>
<td>7.7</td>
</tr>
<tr>
<td>Ascending aorta minus pulmonary artery</td>
<td>7.0</td>
<td>26.0</td>
</tr>
</tbody>
</table>

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**Table 4**

*Mean Differences of Paired Cardiac Index Values with Injection of Indicator into the Three Sites in Controls and in Mitral Insufficiency*

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Mean</th>
<th>Standard error</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aorta—left ventricle</td>
<td>20</td>
<td>0.090</td>
<td>0.207</td>
<td>&lt;0.7 and &gt;0.6</td>
</tr>
<tr>
<td>Left ventricle—pulmonary artery</td>
<td>20</td>
<td>0.190</td>
<td>0.190</td>
<td>&lt;0.4 and &gt;0.3</td>
</tr>
<tr>
<td>Aorta—pulmonary artery</td>
<td>20</td>
<td>0.325</td>
<td>0.244</td>
<td>&lt;0.2 and &gt;0.1</td>
</tr>
<tr>
<td>Mitral insufficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aorta—left ventricle</td>
<td>18</td>
<td>0.779</td>
<td>0.154</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricle—pulmonary artery</td>
<td>9</td>
<td>0.077</td>
<td>0.103</td>
<td>&lt;0.5 and &gt;0.4</td>
</tr>
<tr>
<td>Aorta—pulmonary artery</td>
<td>9</td>
<td>0.651</td>
<td>0.101</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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**INDICATOR-DILUTION CURVES**

In conditions of reduced cardiac output, the traversal time through the coronary vascular bed may not differ greatly from normal in contrast to other systemic vascular beds. Also, in such cases the proportion of the cardiac output traversing the coronary circulation probably is increased, as may be calculated from the data of Blain and associates. Hence, the coronary recirculated indicator deserves particular attention. Figure 3 is derived from dilution curves in a patient without mitral regurgitation and in one with

**Figure 3**

Indicator-dilution curves recorded at femoral artery and in coronary sinus from patient with mitral stenosis (left panel) and mitral insufficiency (dominant) with mitral stenosis (right panel). Dashed vertical lines represent the instant when the indicator is in the ascending aorta for the first time. Dash-dot vertical lines represent the arrival of the first coronary recirculated indicator particles at the femoral artery. For all femoral dilution curves, the instant Te is the point of extrapolation defined when the curve was analyzed by the Stewart-Hamilton method. Curves immediately below the top curves were recorded via catheter positioned in coronary sinus, transposed in time allowing for the catheter dead space, at a volume flow rate of 12 ml./min. Transit time from ascending aorta to the coronary sinus is x. The curves to the right of the dash-dot lines are coronary sinus curves transposed (but not further distorted or corrected for catheter distortion) by transit time from right atrium to femoral artery (y). This, then, places the returning coronary sinus blood in a possible temporal relationship to the disappearance phase of the primary circulation of indicator. For the aortic injection site for each curve, although coronary recirculated indicator may appear prior to Te, the disappearance phase of the curve is virtually complete and very little if any coronary recirculated particles are included in the extrapolated downslope. On the other hand, for femoral dilution curves with injection into the left ventricle and more particularly the pulmonary artery (the two lower curves), coronary recirculated particles may appear shortly after peak concentration of primary dilution curve and may influence its downslope materially. In mitral incompetence, the appearance of coronary recirculated particles may occur at peak concentration of dilution curves injected as centrally as pulmonary artery and influence the dilution curve for the complete downslope. For the dilution curves on the left the differences of cardiac index, aorta minus pulmonary artery, was 11 per cent, and for the dilution curves on the right, 32 per cent. For the patient on the right, cardiac index, aorta minus left ventricle, is 21 per cent.
mitral regurgitation. It demonstrates that coronary recirculated particles ordinarily may be recovered from the disappearance slope of the primary curve. The position, magnitude, and dispersion of these particles will be dependent on the injection site, the temporal dispersion of the primary dilution curve, and the ratio of coronary to systemic flow. The coronary recirculated particles can be included in cardiac output calculation in normal subjects with pulmonary artery injection and to a larger extent in mitral incompetence with both pulmonary artery and left ventricular injection. This is supported by the data of Jose and associates who found in normal subjects that the cardiac output was 7 per cent lower with pulmonary artery injection than with left atrial injection. Likewise, in normal subjects, our data indicate that the cardiac output is lower from pulmonary artery injection curves than from left heart injection curves. From the data of other au-

Figure 4

Schematic representation of effects of coronary recirculated particles on disappearance slope of arterial indicator-dilution curve with pulmonary artery injection in a patient without mitral incompetence (left panel) and with left ventricular injection in a patient without mitral incompetence (center panel) and with mitral incompetence (right panel). The coronary recirculated particles have been drawn in (dotted area), assuming their peak concentration to be 5 per cent of peak concentration of arterial dilution curve. If it is assumed that coronary recirculated particles may appear in indicator-dilution curves with injection into pulmonary artery and at times with injection into the left ventricle, the rapid appearance and disappearance of coronary particles in the absence of mitral incompetence will lead to the inclusion of these particles and few other systemically recirculated particles in the primary concentration curve (unlikely with left ventricular injection) and therefore result in an error related approximately to the magnitude of coronary blood flow. In a prolonged and distorted dilution curve such as occurs with mitral incompetence with injection at or upstream to the chamber involved in a regurgitant process (right panel), the long tail concentration of such a dilution curve may give rise to erroneous extrapolation with inclusion of significant quantities of dye which has recirculated from parts of the body other than the coronary circulation.

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...thors,14-17 the mean cardiac output from indicator-dilution curves (injection into the pulmonary artery) is calculated to be 4 per cent to 9 per cent lower than that obtained by the Fick method; this difference could be accounted for by the inclusion of the coronary recirculated indicator particles in cardiac output calculation.

Time-Course of Recirculated Particles

The time-course of return of indicator from various regions is a damped version of the input curve to those sites. Thus, the time-course of return of systemically recirculated particles in patients with mitral incompetence will differ from normal in the characteristic feature of such curves—the slow clearance of dye and prolonged disappearance phase. The potential effects of such an alteration in the time-course of return of recirculated indicator particles on indicator-dilution curves is shown in diagrammatic form in figure 4. The prolonged disappearance phase will not allow accurate separation of coronary recirculated particles from other components of recirculated dye. Thus, coronary recirculated particles either will continue to influence the downslope of the primary dilution curve if a wide discrepancy is present between the coronary arrival time and the arrival time from other regions or will tend to merge inseparably with the rest of the systemically recirculated indicator if the circulation times are similar. In either event, under the conventional system of analysis, this will lead to the false inclusion of a significant additional component of systemically recirculated indicator other than that which traverses the coronary circulation. Although speculative (but supported by the temporal relations of few dilution curves recorded from the coronary sinus as figure 3), this appears to be the most reasonable explanation for the lower cardiac output, defined by dilution curves involved in the regurgitation process in its primary circulation.

Summary

Cardiac output was determined by the indicator-dilution technic with injection of indicator into the ascending aorta, left ventricle, and pulmonary artery in 13 cases of mitral incompetence and in 15 control cases (normal or mild valvular obstruction). The ascending aortic dye curve is not involved in mitral incompetence in its primary circulation and was used for comparison.

In normal subjects, there is no significant difference between the cardiac output obtained by injection of indicator into the ascending aorta and the left ventricle.

The cardiac output obtained from indicator-dilution curves affected by mitral regurgitation in its primary circulation is underestimated by approximately 20 per cent.

The effects of the coronary recirculated indicator particles on the disappearance slope would best explain the discrepancy. Even in the normal circulation, the inclusion of the coronary recirculated particles leads to a small underestimation of the cardiac output when the indicator is injected into the pulmonary artery.

References

7. RAHMTOOLA, S. H., BROWN, R., DAVIS, G. D.,
Famous General Practitioners

It is not sufficiently realized either by doctors or by the lay public, that many of the great advances of medicine during the past century and a half have been directly due to the acute observation, masterly deduction, and in some instances accurate experimentation of general practitioners.

Immunity, bacteriology, tropical medicine, epidemiology, orthopaedics, cardiology and even neurology have benefited by the work of such men.—ZACHARY COPE, KT. Some Famous General Practitioners and other Medical Historical Essays. London, Pitman Medical Publishing Co., Ltd., 1961, p. vii.
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