Validity of Indicator-Dilution Determinations of Cardiac Output in Patients with Mitral Regurgitation

By Philip Samet, M.D., William H. Bernstein, M.D., and Cesar Castillo, M.D.

The indicator-dilution method has been widely employed for determination of cardiac output since its introduction by Stewart and Hamilton and associates. The effect of unrecognized recirculation of indicator particles upon the primary indicator time-concentration curve has caused concern as to whether this method may be employed in such conditions as mitral regurgitation and as to whether the right heart may be employed with validity as an injection site when systemic arterial sampling sites are utilized. A previous study from this laboratory has demonstrated that left ventricular cardiac outputs were virtually identical when the pulmonary artery and the left atrium were used as injection sites with sampling from systemic arterial sites. The purpose of this report is to examine data as to the effect of mitral regurgitation upon the validity of the indicator-dilution curve for the determination of cardiac output employing right atrial injection and systemic and pulmonary artery sampling.

Methods

Indicator-dilution curves were recorded from the pulmonary artery and a systemic artery after right atrial injection. Indocyanine green in doses of 2 to 5 mg was injected into the right atrium via an 80-cm size 5 Lehman catheter. Blood was sampled from the pulmonary artery through a 100-cm size 6 Lehman catheter and from the systemic artery through a Cournand indwelling arterial needle employing a Harvard constant infusion-withdrawal pump and Gilford densitometers. The curves were recorded on an eight-channel (Electronics for Medicine) recorder. Outputs were calculated by semilogarithmic replotting of the primary data. The curves were calibrated by three concentrations of dye in blood.

A total of 532 separate catheterization studies are included in this report. Each pulmonary and systemic arterial value for cardiac output represents the mean of two separate determinations; thus a total of 2,128 dye curves were analyzed. The subjects were divided into four groups. The first group (78 studies) included normal subjects, a few with hyperthyroidism but without cardiomegaly, and patients who had had prior correction of various types of congenital cardiac lesions and in whom shunts were excluded postoperatively. The second group (91 studies) included patients with pulmonary emphysema with or without cor pulmonale. The third group (140 catheterizations) included patients with varying degrees of mitral regurgitation with or without other valvular lesions. This group was divided into four subgroups (grades I to IV of progressively increasing degrees of mitral insufficiency). There were 71, 33, 26, and 10 studies in these four subgroups, respectively. The fourth and last group (223 studies) included patients with valvular lesions, including aortic regurgitation, but without mitral regurgitation. Patients with known or suspected tricuspid or pulmonic regurgitation were excluded from this study.

The pulmonary artery cardiac index was taken as the standard since early dye-particle recirculation in mitral regurgitation could not be expected to distort the downstroke of this curve as may be possible in the case of the systemic arterial curve. If the cardiac indices after right atrial injection and simultaneous pulmonary and systemic arterial sampling are of similar magnitude, the theoretical objections of Rahimtoola and Swan would be of little practical import though of considerable theoretical interest.
Results

The mean cardiac indices and the standard deviations for the four groups of patients after pulmonary and systemic arterial sampling are shown in table 1. There is no significant difference in these two values (0.3 > P > 0.2) for the first group. The differences are small but significant for the last three groups: 0.01 > P > 0.001 for group 2, and P < 0.001 for groups 3 and 4. These small differences, however, are of limited physiological import and are less than 3% overall even in the group with mitral regurgitation (group 3).

The data are illustrated in figures 1 to 8. In figures 1 to 4, the indices determined from pulmonary and systemic arterial sampling are plotted along the abscissae and ordinates, respectively. The center line is the line of identity while the others represent 10 and 20% deviations from the line of identity. It is evident that there is little systematic deviation in any of the four groups of patients and that the small differences are not of physiological importance. The per cent deviations of the systemic arterial indices from the pulmonary artery indices are plotted in figures 5 to 8. The values from the systemic and pulmonary sampling sites are virtually identical. It must be emphasized that these comments apply only to dilution curves which permit a straight-line semilogarithmic extrapolation. If the data do not fall on such a straight-line extrapolation, then calculations of the cardiac output and indices are not possible.

These data have also been analyzed from another viewpoint. The magnitude of the pulmonary-systemic arterial differences were compared for the four different groups defined. None of the differences were significant; group 1 versus group 2, 0.3 > P > 0.2, group 1 versus group 3, 0.05 > P > 0.02, and group 1 versus group 4, 0.3 > P > 0.2. The results

Table 1

<table>
<thead>
<tr>
<th>Sampling site</th>
<th>Cardiac index, L/min/m²</th>
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<tbody>
<tr>
<td></td>
<td>Group 1</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>3.19 ± 0.7*</td>
</tr>
<tr>
<td>Systemic artery</td>
<td>3.17 ± 0.7</td>
</tr>
</tbody>
</table>

*Mean, ± standard deviation.

Figure 1

Comparison of cardiac indices on use of pulmonary (P.A.) and systemic (S.A.) arterial sampling sites in group 1. See text.

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emphasize that the indicator-dilution technique is equally useful in all four groups of subjects as long as the aforementioned limitations are recognized.

The data for the four subgroups of patients with mitral regurgitation are shown in table 2, and figures 9 to 12. The maximum difference between the pulmonary and systemic arterial indices was about 5% (table 2). The pulmonary artery index is significantly greater than the systemic arterial index for grade-I mitral regurgitation, \( P < 0.01 \). The difference is not significant for grade II, \( 0.1 > P > 0.05 \). The differences are significant for grades III and IV, \( P < 0.01 \) and \( P = 0.01 \), respectively. There is, however, no progressively greater

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**Figure 3**
Comparison of cardiac indices on use of pulmonary and systemic arterial sampling sites in group 3. See text.

**Figure 4**
Comparison of cardiac indices on use of pulmonary and systemic arterial sampling sites in group 4. See text.

**Figure 5**
Distribution of per cent differences between pulmonary and systemic arterial sampling sites in group 1.

**Figure 6**
Distribution of per cent differences between pulmonary and systemic arterial sampling sites in group 2.

**Figure 7**
Distribution of per cent differences between pulmonary and systemic arterial sampling sites in group 3.
difference between the systemic and pulmonary arterial indices as the severity of the mitral insufficiency increases. The pulmonary and systemic arterial indices did not differ significantly between grades I and II ($P > 0.05$), between grades I and III ($0.2 > P > 0.1$),

**Figure 8**
Distribution of per cent differences between pulmonary and systemic arterial sampling sites in group 4.

**Figure 9**
Comparison of cardiac indices on use of pulmonary and systemic arterial sampling sites in group 3 patients with grade-I mitral regurgitation. See text.

**Figure 10**
Comparison of cardiac indices on use of pulmonary and systemic arterial sampling sites in group 3 patients with grade-II mitral regurgitation. See text.

**Figure 11**
Comparison of cardiac indices on use of pulmonary and systemic arterial sampling sites in group 3 patients with grade-III mitral regurgitation. See text.

**Table 2**
Cardiac Indices Determined on Use of Pulmonary and Systemic Arterial Sampling Sites in Patients with Mitral Regurgitation of Varying Severity

<table>
<thead>
<tr>
<th>Sampling site</th>
<th>Cardiac index, L/min/m² in mitral regurgitation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade I</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>2.49 ± 0.6*</td>
</tr>
<tr>
<td>Systemic artery</td>
<td>2.44 ± 0.6</td>
</tr>
</tbody>
</table>

*Mean, ± standard deviation.
Comparison of cardiac indices on use of pulmonary and systemic arterial sampling sites in group 3, patients with grade-IV mitral regurgitation. See text.

between grades I and IV (P > 0.05), between grades II and III (P > 0.05), between grades II and IV (0.2 > P > 0.1), or between grades III and IV (P > 0.05).

Discussion

The recent paper of Rahimtoola and Swan has raised serious doubts as to the validity of indicator-dilution determinations of cardiac output in patients with mitral regurgitation if the indicator is injected upstream (proximal) to the aortic valve and sampled in a peripheral arterial site. A systematic 20% difference in output was observed in patients with mitral insufficiency on use of the left ventricle from that on use of the ascending aorta as the injection site. In normal subjects, no significant difference in values was found on use of these two injection sites with systemic arterial sampling. The difference between the control subjects (15 in all) and the 13 patients with mitral regurgitation was attributed to the greater effect of coronary recirculation of indicator particles after left ventricular (and presumably right heart) injection in the latter group; such recirculation would not be present, of course, after injection of the indicator in the ascending aorta.

Unrecognized recirculation of dye would result in increase of the area under the primary curve with consequent underestimation of cardiac index. The problem presented by such early dye recirculation would be more serious in patients with lower cardiac indices, that is, those with mitral regurgitation, than in control subjects.

There is, however, a critical technical objection to Rahimtoola and Swan's study. Indicator injection into the ascending aorta with systemic arterial sampling may not permit uniform dye recirculation between injection and sampling sites. Interposition of a ventricular mixing chamber is desirable to avoid the potential pitfall of nonuniform mixing. We have in this laboratory on occasion noted nonuniform mixing even after left ventricular injection with systemic arterial sampling. Rahimtoola and Swan have minimized the problem of nonuniform mixing by noting that use of left ventricular and aortic injection sites resulted in similar cardiac indices in control subjects. It is our feeling, however, that left atrial injection ensures adequate indicator mixing more than does the left ventricular or ascending aorta injection. The data in the present study do not demonstrate any physiologically significant differences between pulmonary artery and systemic artery sampling sites after right atrial injection. These results show that the cardiac index may be readily calculated from systemic arterial sampling sites after use of the right or left heart as the injection site in patients with varying degrees of mitral regurgitation (grades I to IV), if a semilogarithmic, straight-line extrapolation is feasible. The divergent results from those of Rahimtoola and Swan are attributed to mixing problems after aortic injection.

The potential problem of distortion of the downstroke of the pulmonary artery dye curve by coronary artery dye recirculation requires analysis. The proximity of the injection and sampling sites after right atrial injection and pulmonary artery sampling compared to the relatively prolonged circuit via pulmonary artery, left heart, coronary artery and sinus, right atrium and then to pul-
monary artery suggests that the pulmonary artery downstroke is not distorted by early coronary artery recirculation of dye. The major portion of the pulmonary artery curve, including the downstroke, is usually inscribed by the time the femoral curve is recorded. These time relationships decrease the effect of possible coronary recirculation problems. In severe mitral regurgitation, the pulmonary artery curve is often completed before inscription of the systemic arterial curve is even begun. Furthermore, coronary blood flow is in all probability less than 10% of total blood flow so that the quantitative effect of such potential, early coronary recirculation of dye would be further minimized. Since the error of the dye-dilution method is itself of the order of 5 to 10%, the problems introduced by possible coronary recirculation are attenuated. In addition, use of the ascending aorta injection site does not remove the latent problem of early coronary recirculation of dye, since ascending aorta dye may be washed back to the aortic valve area and enter the coronary bed during late systole or early diastole or both. These considerations have buttressed our conviction that the right atrial-pulmonary artery circuit is in all likelihood as free of the problem of coronary artery dye recirculation as is the ascending aorta-systemic arterial circuit.

A recent study by Krovetz and Benson\(^7\) has provided experimental data bearing on the adequacy of aortic injection sites (with systemic arterial sampling) for indicator-dilution determination of cardiac output. Paired simultaneous dilution curves were recorded from two sampling sites in the dog. The injection sites were the superior vena cava, right atrium, left ventricle, aortic root, and the descending thoracic aorta. The average difference of the paired outputs following right heart injection was 5.8%. Left ventricular injection resulted in an average difference of 6.3%, which rose to 9.9% after aortic root injection, and to 23.1% after injection into the thoracic aorta. These data were interpreted as evidence for incomplete mixing after aortic injection.

One further point deserves some comment. Several observers\(^4,5\) have suggested that pulmonary artery indicator injection with systemic arterial sampling results in lower output values than left atrial injection. Previously published data from this laboratory\(^6\) have not confirmed this thesis. In 110 patients in sinus rhythm, the cardiac indices after dye injection into the pulmonary artery and left atrium were 2.78 and 2.73 L/min/m\(^2\) respectively. In 59 patients in atrial fibrillation, the mean cardiac index was 2.01 after both pulmonary artery and left atrial injection. These data also minimize the problem of early recirculation of dye particles in the calculation of cardiac output.

The similarity in pulmonary artery and systemic arterial cardiac indices (right and left ventricular output, respectively) also reveals little difference in output from the two ventricles in the four groups of patients studied. It may be inferred, therefore, that bronchial artery flow comprises only a small fraction of total cardiac output under these circumstances.

**Summary**

A total of 532 groups of indicator-dilution determinations of cardiac index were performed in four groups of patients, many with mitral regurgitation. The indicator, indocyanine green, was injected into the right atrium and sampled from both the pulmonary and systemic arterial trees. The potential problem imposed by early recirculation of indicator particles was present in the latter but not the former dilution curves. The absence of physiologically significant differences between the two sampling sites demonstrates that even severe mitral regurgitation does not vitiate indicator-dilution determination of cardiac output after right heart injection and systemic arterial sampling if the downstroke of the primary dilution curve permits a straight line semilogarithmic extrapolation.

**References**

1. Stewart, G. N.: Researches on the circulation time and on the influences which affect it.


For many years medical workers have written of a gross irregularity of the ventricular and arterial pulsations, occurring especially in patients in whom cardiac failure is imminent, and in whom cyanosis, venous engorgement and dropsy are outstanding features. You all know these patients; you have all seen the picture, hung from time to time as it is in the galleries of disease which our wards constitute: the body raised with pillows, the haggard and anxious countenance; the glistening eye, its white oft tinged with yellow; the flushed cheeks; the full, plum-coloured and open lips; the laboured breathing; the prominent precordial bulging; the confused and wavy impulses which hurry from interspace to interspace; the swollen legs and belly. Here it is but rarely that one seeks in vain the pulse which bears distinctive qualities. Its rapid action, the utter disorder of rhythm, the hopelessly jumbling of strong pulsations with quick runs of almost imperceptible beats, the changing length of intervening pauses, are all characteristics.—Thomas Lewis: A Lecture on Evidences of Auricular Fibrillation, Treated Historically. Brit M J 1:57, 1912.
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