Radiopotassium Indicator-Dilution Studies During Angiocardiography

By Hadley L. Conn, Jr., Claude R. Joyner, Donald F. Heiman and Harry F. Zinsser

In an attempt to learn more about the physiologic changes in the cardiovascular system during angiocardiography and the nature of mixing of radio-opaque dyes with blood, radiopotassium and Diodrast I\(^{131}\) dilution curves were obtained before and during angiocardiography. Studies in patients without valvular disease and with mitral valvular disease indicated an increased cardiac output during angiocardiography, but the increases were not statistically greater than those following control injections. No difference in indicator-dilution patterns of potassium and Diodrast was demonstrable, suggesting identical circulatory mixing patterns.

Angiocardiography with the use of radio-opaque dyes is a successful and widely used method for the diagnosis of many cardiovascular abnormalities. One of its uses has been as an ancillary tool in the diagnosis of mitral stenosis and regurgitation. Although this application has led to considerable speculation, no firm conclusions have been reached as to the factors responsible for the observed chamber density patterns, particularly in the left side of the heart. The simplest approach is to consider radio-opaque dyes as indicators and to consider that, following their injection, multiple indicator-dilution curves of the circulation are recorded on film. As a consequence, the temptation is severe to explain observed results in the light of conclusions based on T-1824 and isotope dilution curve data from the same kinds of patients, and to presume that rate and character of blood flow and chamber volume would be the major factors controlling angiocardiographic patterns. Unfortunately there is a basis for some suspicion that iodopyracet (Diodrast) curves should be viewed somewhat differently from T-1824 curves obtained in resting subjects. This suspicion arises from knowledge that varying concentrations of Diodrast may be required for chamber or vessel visualization, from uncertainty as to whether radio-opaque dyes mix with blood in the same fashion as the commonly used highly soluble indicators, and from data, both collected and reviewed by Rowe, suggesting that marked change in circulatory physiology can occur during angiocardiography.

We have attempted to learn more about these matters by simultaneous angiocardiographic and isotope dilution studies in patients with and without rheumatic heart disease. Cardiac output, circulation times, and dilution curve contour were determined before and during angiocardiography, and the relative rates of passage from peripheral vein to peripheral artery for potassium and Diodrast were measured, these rates presumably relating to over-all similarities, or lack thereof, in the mixing of the indicators with blood. The results fail to show dilution curve differences attributable to differences in mixing characteristics of the two indicators with blood, but do show that increased cardiac output and velocity of flow usually occur with the performance of angiocardiography. They also show that dilution curves obtained with either indicator during angiocardiography may be somewhat distorted for reasons that have not been clearly demonstrated.

Methods

Fifteen studies were carried out on patients undergoing angiocardiography. Nine comparisons of radiopotassium (K\(^{42}\)) dilution curves were obtained during saline (control) and subsequent Diodrast injections. Seven of these patients had rheumatic mitral valvular disease, 1 had arteriosclerotic heart disease, and 1 no demonstrable heart disease. The
actual disease states and data obtained are indicated in table 1. Six studies, in which $K^6$ and Diodrast $I^{131}$ were simultaneously administered, were made during Diodrast angiocardiography. These studies were on 5 patients with rheumatic mitral valvular disease and 1 with no demonstrated heart disease. The actual disease states in these patients are indicated, along with the data obtained, in table 2.

The procedure was as follows: One of the antecubital veins was surgically exposed and a Robb-Steinberg cannula inserted. An indwelling Cournand Needle was placed in a femoral artery. About 30 $\mu$C of $K^6$ contained in 1 ml of saline. Injection times were 1 to 3 sec. In 6 approximately 45 ml of 70 per cent Diodrast to which had been added $30 \mu$C of $K^6$ contained in 1 ml of saline. Injection times were 1 to 3 sec. In 6 patients, about $30 \mu$C of Diodrast $I^{131}$ were also added, being mixed in the syringe with the remainder of the nonradioactive Diodrast. In the latter studies the dilution curve was obtained only up to the time of recirculation. After the dilution curve had been recorded, the amount of radioactivity in the total volume of blood collected was determined. This amount was considered to represent the sum of all $K^6$ and $I^{131}$ activity resulting from the first passage of potassium and Diodrast. After 3 days the sample was again counted and, after proper decay corrections, the result was considered to show the amount of $I^{131}$ activity present, since $K^6$ ($T_{1/2} = 12.4$ hours) would at this time have only about 1 per cent of its initial activity. In this manner the proportions of $K^6$ and Diodrast $I^{131}$ contributing to the dilution curve sample activity were determined. Then the ratio of amounts of $K^6$ to Diodrast $I^{131}$ obtained experimentally was compared (table 2) with the predicted ratio calculated from the amounts of each administered when based on the assumptions that each indicator was diluted in the same fashion, and that labeled and unlabeled molecules behave in the same fashion.

The cardiac output and index (by the Hamilton-Stewart method), mean circulation time, and terminal slope constant value ($k$) were determined from the dilution curves obtained during the saline (control) injections and from the dilution curves obtained during the Diodrast injections, and the results compared (table 1). All blood sampling and counting was done with a special unit consisting of mercury gravity vacuum pump, scintillation counter, logarithmic counting rate meter, and Brown recorder, which has been described elsewhere.

**RESULTS**

**Comparison of Data from Saline and Diodrast Injections**

In 7 of 9 patients the isotope dilution curve obtained with Diodrast injection had an appre-
**TABLE 2.—** Relative Amounts of Diodrast I\(^{131}\) and K\(^{42}\) in Arterial Sample Aliquots Following Simultaneous Injection During Angiocardiography Compared with Predicted Results.

<table>
<thead>
<tr>
<th>Patient no., diagnosis</th>
<th>Percentage of Diodrast I(^{131}) and K(^{42}) arterial blood aliquots</th>
<th>Per cent deviation from predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Predicted†</td>
<td>Calculated</td>
</tr>
<tr>
<td>1. No heart disease</td>
<td>31 60 31 62</td>
<td>0 0</td>
</tr>
<tr>
<td>2. Rheumatic heart disease, MI†</td>
<td>45 54 45 55</td>
<td>2 2</td>
</tr>
<tr>
<td>3. Rheumatic heart disease, MS§</td>
<td>28 72 32 68</td>
<td>14 5</td>
</tr>
<tr>
<td>4. Rheumatic heart disease, MS, NSR</td>
<td></td>
<td>44 56 44 56</td>
</tr>
<tr>
<td>5. Rheumatic heart disease, MS, NSR</td>
<td>28 72 28 72</td>
<td>0 0</td>
</tr>
<tr>
<td>6. Rheumatic heart disease, MS, AF</td>
<td>43 57 43 57</td>
<td>0 0</td>
</tr>
<tr>
<td>Mean deviation...</td>
<td>2 1</td>
<td></td>
</tr>
</tbody>
</table>

* Predicted on basis of relative amounts of each isotope injected into antecubital vein and assumption of same mixing pattern.
† Mitral insufficiency.
‡ Atrial fibrillation.
§ Mitral stenosis.
|| Normal sinus rhythm.

(though frequently only slightly) slower onset of activity time, peak of activity time and mean circulation time, with a flatter terminal exponential slope than was seen with the isotope-saline curves. In 1 patient (study 8), on the other hand, the terminal slope was appreciably steeper with the Diodrast injection. In the other patient, curve differences were negligible. In many instances the changes could be correlated with the estimated relative speed of injection of the two substances, the faster the injection the “faster” the various components of the curves. If the terminal slope exponential constant values (k’s) obtained in association with saline injections are taken as unity (or controls), the curve slope constants (k’s) obtained in association with Diodrast injections averaged only 0.87. That is, the slopes were some 13 per cent flatter on the average. Further, if the results from study 8 are excluded from the analysis, on the basis that they change the statistical significance of the whole series and on the basis that the saline injection speed here was recognizably delayed, the ratio becomes 0.79, which is significantly (t = 3) different from unity. That is, applied to the entire series, the K\(^{42}\) curve terminal slopes during angiocardiography were statistically significantly flatter than those resulting during the control injections. By the same mathematical procedures the mean of the mean circulation times during Diodrast injection averaged 11 per cent more than during saline injection. This change, just reaching statistical significance at the 5 per cent level (t = 2.3), indicates that mean circulation time as determined during the Diodrast injection was on the average significantly, albeit only slightly, prolonged.

In 6 of the 9 patients the cardiac index was more than +1 S.E. above a normal of 3.1 ± 0.4 L./M²/min. during both the saline and Diodrast injections. The other 3 patients failed to show this response; but they had very severe rheumatic heart disease, however, which very possibly may have made them unable to increase cardiac output to such a level. Perhaps of more interest was the failure to demonstrate that the cardiac indices during angiocardiography showed a consistent change when compared to the saline control results, the former averaging 0.92 when the mean of the latter is taken as unity. This difference, when analyzed statistically, fails to reach commonly accepted levels of statistical significance (t = 1.14). Thus, cardiac index or output was elevated in most patients during both procedures, but was not significantly different when the two technics are compared.

The results from the 2 subjects who did not have rheumatic valvular heart disease are essentially the same as those from the subjects who did have rheumatic valvular disease.

**Simultaneous Diodrast I\(^{131}\) and K\(^{42}\) Injections Along with the Angiocardiographic Dye**

As far as was discernible, the addition of labeled Diodrast I\(^{131}\) to the nonradioactive Diodrast and K\(^{42}\) did not give rise to any change in the shape of the dilution curves as
judged by a comparison of these curves with those obtained using K₄² alone with Diodrast (both during angiocardiography). Further, as shown in table 2, the amounts of Diodrast and I¹³¹ and K₄² recovered from the femoral arterial blood up to time of recirculation agreed in each of the 6 studies within 14 per cent of that predicted from the amounts injected (assuming the same type of dilution). The mean deviations of the calculated from the predicted amounts were only 2 per cent and 1 per cent.

The 1 subject with no heart disease showed the same result as those with rheumatic valvular disease.

**DISCUSSION**

The results showed clear-cut information on three points. First, dilution curves obtained during angiocardiography showed a slight but definite distortion, with lowering of peak concentrations and “smearing” to the right, when compared to dilution curves obtained with control K₄²-saline injections. Second, there was usually an increased cardiac index (or output) during angiocardiography. But there was also a similar increase in output in association with an immediately previous saline injection of similar volume and given at a similar rate of speed. Third, the amounts of I¹³¹ Diodrast and of K₄² reaching the peripheral arteries with respect to time after a simultaneous intravenous injection were almost identical when corrections were made for the relative amounts of each initially injected.

The reasons for the first finding are not entirely known. It has been noted that such a change or “smearing” in curve contour usually occurs following peripheral injections, when compared with curves obtained following central injections. This apparently occurs when the peripheral injections are not made with sufficient speed to put essentially all the indicator into the right heart in one cardiac cycle. Thus the relative speed of injection of the two materials is suggested as one cause for the difference in curve contour.

This view is supported by two observations: First, the estimated time required for Diodrast injection was usually slightly longer than for saline injection. Second, one notable exception occurred in study 8 in which the Diodrast injection time was the shorter and the resultant dilution curve was “faster” and had a steeper terminal slope than the control saline curve. The slightly longer injection time required for 70 per cent Diodrast, as compared to saline, may in turn be due to the fact that Diodrast is somewhat more viscous, as tested in a viscometer (unpublished observations). Still another factor that could not be well evaluated is spasm in the vein near the site of injection, which may sometimes contribute a great deal in slowing the entrance of injected materials into the right heart and thereby produce distortion of dilution curves. In fact, most workers doing angiocardiography can predict from the occurrence, immediately after Diodrast injection, of sudden severe arm pain, a symptom of severe venospasm, that there will ensue a dye hang-up with dye visualized in the arm and consequently there will frequently be poor heart chamber visualization. This was illustrated in patient 2 in whom the injection speeds of the Diodrast and the saline were not exceptionally different. However, the patient complained bitterly of pain in the arm immediately after the Diodrast injection. As might have been predicted, the K₄²-Diodrast curve showed the most marked aberration in circulation time, peak concentration, and terminal slope observed in the whole series, although calculated cardiac output was little affected. Thus we feel that the present studies add further weight to the concept that speed of injection and degree of venospasm are two important factors affecting the indicator-dilution curve, i.e., the pattern of dilution of indicator, whether opaque or nonopaque, in the circulatory system.

The increases in cardiac output found during angiocardiography merely emphasize that this test per se causes some degree of cardiovascular stress. It is presumed that those patients with mitral disease who failed to show above-normal outputs were simply incapable, because of their cardiac status, of increasing output beyond normal or even subnormal levels. The reasons responsible for change in flow remain in doubt, but the interesting finding that saline given in the same manner produces almost
identical results for cardiac output apparently shows that Diodrast per se is not the major factor. Moreover, there is evidence that very rapid intravenous injections of 50 ml. volume may cause temporary slight rises in right atrial and pulmonary arterial pressure, and perhaps ventricular volume and pressure. According to the Starling law, a temporarily increased ventricular output could be expected from a heart capable of responding. Further evidence favoring the volume-rate etiology can be adduced from our findings that similar K42 injections during “right-heart” catheterization rarely evoke flow-pressure changes when the injected volumes are small (1 to 5 ml.). Nevertheless, as we do not know whether the elevated cardiac outputs were present either before or after the immediate 30 sec. testing period, no certain conclusion can safely be drawn. Since most of the events surrounding an angiocardiographic study are in themselves conducive to the production of a stress response, we suspect that excitement can be the most important factor determining cardiac output at this time and that heart output may actually be increased throughout the procedure from start to finish.

The findings of similar dilution curve contours and almost identical amounts of Diodrast I131 and of K42 in peripheral arterial samples up to the time of recirculation provide no evidence that the physical properties of Diodrast solutions are unique, beyond the reasons previously mentioned, in the matter of comparative indicator mixing with blood. The findings therefore are compatible with the concept that Diodrast and radiopotassium, once they have arrived in the central circulation, undergo the same pattern of dilution. They are compatible with the concept that indicator-dilution principle theories could be applied to explain angiocardiographic patterns, if the degree of dye opacification in any area could be well correlated with dye concentration present. Nevertheless, the possibility is not completely eliminated that Diodrast and potassium can mix with blood differently in different parts of the circulation and yet in such a manner that the net result, as found in the peripheral artery, may be very similar. Of more importance, the arterial curves provide essentially no evidence bearing directly on how mitral stenosis and mitral insufficiency affect the character of blood flow and the nature of mixing in the left atrium and ventricle. Only the total amount of insufficiency present across all valves between injection and sampling sites can be approximated, with use of the method of Korner and Shillingford:

**SUMMARY**

Isotope dilution curves, using radio potassium and Diodrast labeled with I131 singly or in combination as indicators, were carried out before and during Diodrast angiocardiography in patients with and without valvular heart disease. The results showed that the dilution curves generally were delayed in onset, had lower peak activities, and flatter terminal slopes and indicated a longer mean circulation time during angiocardiography than was found with control dilution curves. Relative speeds of injection and venospasm due to Diodrast were two factors implicated as responsible.

Cardiac index was usually above normal during both control and angiocardiographic studies, and to essentially the same extent. The very rapid addition of relatively large volume of fluid to the right side of the circulation, or excitement associated with performance of the studies, may be responsible.

Simultaneous injections of K42 and Diodrast I131 with angiocardiography provided no evidence that the two materials have different mixing patterns with flowing blood.
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Le indice cardiac esseva usualmente supra le normal tanto durante le studios de controlo como etiam durante le studios angiocardio-

graphic, e a essentialmente le mesme grado. Le rapidissime addition de relativemente grande volumines de fluido al latere dextere del circulating o le excitation associate con le execution del studios esseva possibilemente le factores responsabile.

Le injection simultanee de K42 e de Diodrast a I131 durante angiocardiographia non supportava le conclusion que le duo materiales differe in lor modo de mixtion con sanguine circulante.

REFERENCES


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