Measurement of Cardiac Output and Central Volume by a Modified Decholin Test of Circulation Time

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A technic is described for determining mean circulation time, cardiac output, and central blood volume by use of graded dosages of sodium dehydrocholate (Decholin) administered into a peripheral vein. The indicator-dilution curves derived by the technic were compared with radiopotassium-dilution curves obtained simultaneously in 12 patients. The results showed a surprisingly good agreement between the 2 methods and indicate that the traditional Decholin test of circulation time can be modified to provide much more information than it has in the past.

The determination of arm-to-tongue circulation times by the sodium dehydrocholate (Decholin) method has a long history of clinical use. Still it has provided only limited quantitative or diagnostic information about the circulation and, for this reason, has been supplanted to a considerable extent by more complex methods. However, during the course of simultaneous radiopotassium-dilution curve and angiocardiographic studies in patients with rheumatic heart disease, we employed the times of appearance and disappearance of the Decholin test to decide the timing of film exposures. It soon became apparent that we could frequently differentiate between mitral stenosis and insufficiency as well from the “Decholin” times as we could from the subsequently obtained dilution curves or Diodrast opacification patterns. This finding led us to appreciate that the Decholin test is fundamentally an application of the indicator-dilution principle in which Decholin serves as an indicator providing 2 subjective end points, the times of appearance and disappearance of the characteristic bitter taste. Therefore, we considered that these end points might be related to determinable, relatively constant blood concentrations of Decholin; if so, we might obtain multiple onset and offset times from multiple injections of graded doses of Decholin. These various times might then be appropriately related to the proper concentration coordinates so as to give adequate data for complete construction of an indicator-dilution curve. Such a curve would of course provide the same quantitative information on cardiac output and central blood volume as are provided by conventional dye and isotope-dilution techniques.

These concepts were tested experimentally by (1) determination indirectly of the blood concentrations of Decholin associated with the appearance and disappearance of the bitter taste, (2) determination of these times of onset and offset of taste following injections of 3 graded doses of Decholin, (3) construction of Decholin-dilution curves from the data on circulation times and blood concentrations at taste threshold, and finally (4) comparison of the results obtained from these curves with results obtained from radiopotassium-dilution studies carried out simultaneously. Comparisons of curve contour, cardiac output, central blood volume, and mean circulation time were made in 12 patients with and without cardiovascular disease. The correlation between the isotope and Decholin results was surprisingly good and indicates that the Decholin method is capable of providing more information than has been obtained in the past.

Method

Twelve patients were studied—6 with rheumatic mitral valvular heart disease, 1 with aortic aneurysm, 1 with pulmonary hypertension, 2 with arteriosclerotic heart disease, and 2 with no known cardiovascular disease.

Each patient was given a preliminary injection
of Decholin, usually 300 mg., so that he could learn to recognize the Decholin taste and subsequently to better determine its onset and offset times. This material was injected in a total volume of 30 to 40 ml. of physiologic saline into an antecubital vein through either a Robb-Steinberg cannula or a no. 15 hypodermic needle. All injections were made as rapidly as possible, from 1 to 2 sec. usually being required. Following the trial injection, each patient was given in varying order, 300 mg., 600 mg., and 1200 mg. injections of Decholin. Onset and offset times of Decholin taste were determined to the nearest .25 sec. for each injection. The results were plotted, as described under the section on theory, in order to form dilution curves. Terminal slope value, cardiac output, mean circulation time, and central blood volume were calculated. Simultaneously with 1 and sometimes with 2, of the Decholin injections a radiopotassium (K⁴²)-dilution curve was obtained by the addition of about 30 mc. of this indicator to the material injected. This technic has been described elsewhere. Slope value, cardiac output, mean circulation time, and central blood volume were likewise calculated from the K⁴² dilution curves.

With both technics, cardiac output was determined by the Hamilton-Stewart formula and central blood volume by the product of mean circulation time and cardiac output.

**Theorv and Method of Decholin Dilution Curve Construction.** It was first assumed that Decholin can serve as an appropriate indicator for indicator-dilution studies—that is, that it mixes completely somewhere in the central circulation, that no significant amount is lost in the first circulation, etc. as discussed by Newman and by Meier. These assumptions, of course, were to be tested indirectly by the comparison of Decholin and K⁴² results. Then, assuming that Decholin fulfills these requirements, if onset and offset of the subjective taste occur at known constant blood concentrations of Decholin, these 2 concentration-time coordinates establish 2 points on a dilution curve. The constant relationship of blood concentration to taste was experimentally established as described in the results. Then, assuming constant cardiac output and central volumes, a second injection of a larger dose of Decholin will give a second curve of exactly the same (parallel) contour as that with the smaller dose, but one with relatively higher concentration levels at every point on the curve in proportion to the size of the 2 doses. Thus, the onset and offset times of taste will be at lower points on the second curve contour as compared to initial values as plotted on the first curve because of the unchanged concentration of Decholin required for threshold of taste. These second points can be extrapolated so as to become points on the first (or a common) curve by the process of placing the second points at the time intercepts experimentally determined, but at concentration intercepts reduced in proportion from the taste concentration threshold as the size of the second Decholin dose is related to the first. Additional points can be added to a common curve in the same fashion by using a third, still larger dose of Decholin. Theoretically, if enough injections of Decholin of different dosages were given, an infinite number of points reducible to a common curve could be obtained. Practically, the number of points obtainable is limited by the amount of Decholin that can safely be given to patients and by the precision of the end points of the test.

By the use of this technic, 6 experimental values (3 pairs of onset-offset times) were determined in all patients and plotted as described above. With experience we learned that the onset to peak circulation time interval of an indicator-dilution curve is 5 to 6 sec. in normal subjects, 6 to 8 with slight to moderate circulation time abnormalities, and 10 to 12 with
Table 1.—Results Calculated from Decholin (D) and K\textsuperscript{42} Dilution Curves

<table>
<thead>
<tr>
<th>Case</th>
<th>Diagnosis</th>
<th>Slope (%/sec.)</th>
<th>Cardiac output (L./min.)</th>
<th>Mean circulation time (sec.)</th>
<th>Central volume (liters)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D</td>
<td>K\textsuperscript{42}</td>
<td>D/K\textsuperscript{42}</td>
<td>D</td>
<td>K\textsuperscript{42}</td>
</tr>
<tr>
<td>1</td>
<td>MS</td>
<td>23</td>
<td>22</td>
<td>1.05</td>
<td>9.5</td>
</tr>
<tr>
<td>2</td>
<td>MI</td>
<td>1.7</td>
<td>2.3</td>
<td>0.74</td>
<td>1.7</td>
</tr>
<tr>
<td>3</td>
<td>PH</td>
<td>23</td>
<td>24</td>
<td>0.96</td>
<td>10.1</td>
</tr>
<tr>
<td>4</td>
<td>N</td>
<td>17</td>
<td>15</td>
<td>1.13</td>
<td>6.8</td>
</tr>
<tr>
<td>5</td>
<td>N</td>
<td>28</td>
<td>23</td>
<td>1.22</td>
<td>10.5</td>
</tr>
<tr>
<td>6</td>
<td>ASHD</td>
<td>20</td>
<td>21</td>
<td>0.95</td>
<td>6.0</td>
</tr>
<tr>
<td>7</td>
<td>DM</td>
<td>28</td>
<td>26</td>
<td>1.08</td>
<td>9.0</td>
</tr>
</tbody>
</table>

Mean 1.05  Mean 0.93  Mean 1.00  Mean 0.94

N = normal; MS = mitral stenosis; MI = mitral insufficiency; PH = pulmonary hypertension; ASHD = arteriosclerotic heart disease; DM = diabetes mellitus; AAA = abdominal aortic aneurysm.

Moderate to marked prolongations of circulation times. Thus an additional "approximate" point was added by use of these time intervals, via the process of tracing upward the slopes of the apparent ascending and descending limbs of the curve until they intersected at the appropriate time intercept. The descending limb was constructed as the exponential slope best fitting the offset time plots and the ascending limb as the best natural curve through the onset time plots, all plotted on a semi-log scale. In this fashion the complete Decholin-dilution-curve contour was established. This construction is illustrated in figure 1.

Results

It was quickly appreciated that both the onset and offset of taste were consistently recorded (within ±1 sec. and usually +1) at identical levels of K\textsuperscript{42} concentration as recorded from the curves obtained from simultaneous radio-potassium injections. Thus it seemed apparent that onset and offset of taste were likewise occurring at approximately the same Decholin blood concentration levels. Second, it appeared from the curves that these "taste" times were noted at about the same concentration level in each patient. By comparing the blood concentration of K\textsuperscript{42} in relation to the amount given (at the times of appearance and disappearance of taste), with the expected Decholin concentration in relation to the amount of Decholin given, an average concentration of 180 mg./L. was calculated as the threshold level required for appreciation of the Decholin taste. This varied only from 170 to 205 mg./L. in 10 of the 12 patients but was calculated to be 140 mg./L. in 1 and 250 mg./L. in another.

The mean value was subsequently employed for calculating cardiac output central volume from all curves. That is, 180 mg./L. was used as a constant concentration value on the abscissa of the scale at which all times of appearance and disappearance of taste were initially plotted preparatory to construction of a common curve.

The calculated results are shown in table 1. The ascending limbs of the K\textsuperscript{42} and the Decholin curves agreed exceptionally well in all instances although no quantitative analysis of the degree of agreement was attempted. The K\textsuperscript{42} and the exponential values of the Decholin terminal slope agreed in every instance within 26 per cent. The mean difference was only 3 per cent (using K\textsuperscript{42} results as reference standard) so that the mean ratio Decholin slope/K\textsuperscript{42} slope was 1.03. The cardiac output values agreed within ±29 per cent in each instance and the mean difference was only 7 per cent so that the mean ratio of Decholin cardiac output/K\textsuperscript{42} cardiac output was 0.93. If the data on cardiac output...
from patients 2 and 10 are excluded on the grounds that the curves had terminal slopes so flat that recirculating indicator amounts were included in the Decholin curve reconstruction and therefore made calculated output too low to that extent, the ratio increases to 0.98 and the greatest variation between the 2 methods is reduced to 23 per cent. Mean circulation times (\(MCT\)) by the 2 methods agreed in each instance within \(\pm 21\) per cent. The mean difference was 0, the mean ratio of Decholin \(MCT/K^2/MCT\) being 1.00. Central volume (\(CV\)) determinations agreed in each instance within \(\pm 28\) per cent. The mean difference here was 6 per cent and the mean ratio of Decholin \(CV/K^2/CV\) was 0.94.

No further formal statistical analysis was attempted because it is probably erroneous to consider this group as a homogeneous one. For example, the errors noted above due to recirculation are presumably minimal in patients with large flows and small volumes, but apparently appreciable with the reverse. Approximately, however, the standard deviation between the 2 methods with regard to all the calculated parameters appears to be of the order of \(\pm 15\) per cent under conditions in which blood flow and volume derangements were not abnormal in the extreme. It also appears that this random variability is of sufficiently great magnitude to make impossible any demonstration as to whether the differences in individual or mean ratios are indicative of systematic variation (error). It seems logical, however, to anticipate systematic underestimation of blood flow in patients with exceptionally prolonged taste times, since these times must mirror the added concentration of recirculating Decholin, however great it may be.

**Discussion**

The results indicate that a surprisingly accurate indicator-dilution curve can be constructed, at least in many patients, from recordings of the times of appearance and disappearance of the bitter taste following ante-cubital injections of 3 graded dosages of Decholin. Consequently, surprisingly accurate results for cardiac output, mean circulation time, and central volume are also obtained from these curves with the general limitations of any indicator-dilution method and the specific limitations imposed by the technic employed. The pulmonary mixing volume\(^2\) and the amount of valvular regurgitant blood flow\(^4\) can also be calculated subject to the same restrictions and the validity of those methods. With the \(K^2\) method taken as a fixed standard (i.e., one with no random or systematic error), it appears that the Decholin technic gives results for circulation time, blood flow, and central blood volume with a random variability of the order of 15–20 per cent (S.D.) and no demonstrated systematic error in a patient group such as ours. Since the \(K^2\) method obviously has some variability itself, the true standard deviation is presumably even somewhat less. With more extensive testing it seems likely that a significant systematic underestimation of flow can be demonstrated under conditions of severely prolonged circulation times.

The following matters are those that we believe provide the major sources of error. The hemodynamic state of the subject and the speed of Decholin injection, must be essentially constant in order that the 3 determinations can be correlated properly. Second, the test has subjective end points and the patients sometimes do not appreciate the disappearance of the Decholin taste as well as its appearance. Therefore, considerable care must be exerted in making as certain as possible that the recorded “disappearance” times are valid. Even so, gross discrepancies sometimes occur, which in our studies could be resolved only by drawing the best fit through the experimental points. Third, when mixing volumes are large and blood flow is slow, the concentration critical for taste may not be reached, especially with the smallest doses. Under these circumstances injections containing larger amounts are required to obtain the usual number of points. These amounts may be undesirably large. Fourth, since the greatest accuracy in curve construction can be obtained, in most instances, by treating the terminal portion of the slope as a decreasing exponential, unduly flattened slopes may be obtained in patients with prolonged circulation times. This occurs simply because it is impossible to correct properly for recirculating material. In these patients even
though the proper appearance-disappearance times are recorded, the true primary dilution curve may be difficult or impossible to reconstruct. Here the main effect will be a systematic error with calculated output too low and mean circulation times too long. Either more injections of appropriate Decholin dosages or a correction factor is required to improve accuracy. Fifth, limitations are imposed by the time and variations in time required for Decholin in the blood to diffuse sufficiently to activate the taste receptors, for the neuronal circuits to respond, and for the patient to signal appearance and disappearance of taste. The close resemblance of the K42 and Decholin curves suggests, however, that these events do not introduce appreciable error and therefore must all proceed with considerable speed and consistency in most subjects. Sixth, the elevated cardiac output found in several patients suggests that rapid injections of 40 ml. of fluid cause a mild cardiac stress. Thus, if information on the circulatory state under more basal conditions is desired, injections of smaller total volume seem indicated.

In spite of our present inability to evaluate completely and quantitatively the importance of these limitations, the good correlation of the Decholin and K42 results indicates that the net effect does not commonly prevent a valid assessment of the existing dilution-curve slope value, cardiac output, mean circulation time, and central volume. As measurements of these parameters have not, to our knowledge, been attempted from analysis of arm-to-tongue circulation times, this accuracy in quantitation indicates that the Decholin test can be made to yield much more information than it has heretofore.

The obvious advantages of the test are that it can be accomplished without special preparations, recourse to unusual devices or materials, or any appreciable danger to the patient, and furthermore it can be accomplished in a short period of time at the bedside. The test can therefore be done on almost any patient by any member of a ward staff following minimal instruction of each. Whether the accuracy obtainable under “ward” conditions will be sufficiently great, and whether the information gained in proportion to the time required in calculations will prove sufficiently valuable to warrant replacement of the traditional single injection arm-to-tongue Decholin circulation time with the more informative multiple, graded-dose technic remains to be determined.

Summary

A method for constructing an indicator-dilution curve from multiple, graded-dosage Decholin circulation times is presented.

This method was applied in 12 patients for measurement of mean circulation time, cardiac output, and central volume. The results obtained were compared with those obtained from simultaneously recorded radiopotassium-dilution curves.

In all patients every comparison agreed within ±30 per cent. The mean ratios of mean circulation time (Decholin)/mean circulation time (K42), cardiac output (Decholin)/cardiac output (K42), and central volume (Decholin)/central volume (K42) were 1.00, 0.93, and 0.94, respectively. The blood concentration of Decholin associated with appearance and disappearance of the characteristic bitter taste averaged about 180 mg./L.

The results show that at least under several varying conditions a modified measurement of Decholin circulation time can be used to give more quantitative information than it has traditionally been used to provide.

Summario in Interlingua

Es presentate un metodo pro le construction de un curva de dilution del indicator ab multiple tempores circulatori a Decholina in doses graduate.

Iste metodo essea usate in 12 patientes pro le mesuration del tempore circulatori medie, del rendimento cardiac, e del volumine central. Le resultatos obtenite essea comparate con le resultatos obtenite per simultanea registraiones de curvas de dilution de kalium radioactive.

In onme le patientes onne le comparaciones essea de accordo intra un margine de ±30 pro cento. Le proportion medie de tempore circulatori medie per Decholina a tempore circulatori
REFERENCES

1 Conn, H. L., Jr.: Accuracy of a radio-potassium dilution (Stewart principle) method for the measurement of cardiac output. J. Appl. Physiol. 7: 542, 1955.


Nine patients, 6 with disseminated lupus erythematous and 3 with periarteritis nodosa, have been treated with metacortandracin. One patient with periarteritis nodosa died while under treatment. The autopsy showed extensive arterial involvement, both visceral and peripheral. The most remarkable feature in the histologic study was the lack of inflammatory process noted in the diseased arteries. The inference from these studies is that, if this patient had been treated in the early phase of the disease, the outcome would have been more favorable. The other 2 cases of periarteritis nodosa have been converted from very ill people to a status of employability. All 6 patients with disseminated lupus erythematous had previously been treated with either cortisone or corticotropin. All have done much better with metacortandracin. However, in no instance have the L.E. cells disappeared from the bone marrow or from the peripheral blood. All 6 cases carry on their usual activities with little or no restriction. The capacity to tolerate a normal diet, without salt restriction or the addition of the large, gastric-disturbing doses of potassium required with the use of other steroids, is appreciated by these people. The initial dose was 10 mg. every 8 hours in all cases except 1. The dose was decreased by 5 mg. every 5 days until the smallest amount required for maintenance was reached. It was usually 15 to 20 mg./day. All these patients with 1 exception have been observed under treatment for 60 to 120 days. Although the short-term treatment has been favorable, more time will have to elapse before a conclusive opinion can be reached as to long-term treatment of the collagen diseases with this new compound.

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