Time and Concentration Components of Indicator-Dilution Curves Recorded Following Central Injections of Dye in Normal Human Subjects

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Indicator-dilution curves were recorded by oximeters at the ears and the right radial artery following the injection of Evans blue (T 1824) into the superior vena cava and pulmonary arteries of 37 subjects who had no evidence of cardiovascular disease. The variability and ranges of various time and concentration components of these dilution curves are presented. These values can be used as standards of reference in the interpretation of abnormal dilution curves. Some of the factors responsible for the variability of these values in healthy subjects are assessed and discussed.

The recording of concentration-time curves at a peripheral arterial site following injection of an indicator into the heart and great vessels provides a valuable tool for the study of normal and abnormal circulation. Its increasing use in diagnostic and research laboratories attests to its efficacy. When this technic is used, it is desirable to have a normal standard of reference with which the values obtained from individual subjects can be compared. The present communication reports the values and the variability of various time and concentration components derived from indicator-dilution curves recorded during catheterization of the right side of the heart in a series of healthy human beings.

Methods and Subjects

The right side of the heart was catheterized by the methods previously described,1 2 with the subjects resting in the supine position. They had a light meal prior to the study and were given as premedication 30 mg. of codeine sulfate and 100 mg. of secobarbital sodium at the beginning of the procedure. Evans blue (T 1824) 3 was used as the indicator. Ten milligrams of the dye in 2 ml. of solution was injected into the superior vena cava, main pulmonary artery, right pulmonary artery, or left pulmonary artery. The subjects were breathing 100 per cent oxygen during the recording of the dilution curves, in order to avoid interference due to fluctuations in the oxygen saturation of arterial blood.

Dye-dilution curves were recorded photographically by means of ear oximeters placed on one or both ears and a cuvet oximeter connected to a 20-gage needle in the right radial artery. The sensitivity of the system was such that dye concentrations of 1 mg. per liter gave a deflection of 0.4 to 0.7 cm. for the radial artery curves and 0.2 to 0.8 cm. for the ear oximeter curves.

Time components of the curves recorded by the cuvet oximeter were corrected for the volume of the instrument between the tip of the arterial needle and the middle of the detecting photocell. The time taken for dyed blood to travel from the needle tip in the artery to the detecting element was calculated from the volume of this "dead space" and the flow rate of blood withdrawn through the cuvet system. This time correction was then subtracted from the appropriate time components of the dilution curve. The dead space and physical dimensions of the oximeters were specified in a recent communication.3 Each milliliter of flow through the oximeter was signaled on the photographic record. The flow rates averaged approximately 23 ml. per minute.

The cardiac output was estimated by the Fick method in 24 subjects while they were breathing 100 per cent oxygen. The average interval between this procedure and the recording of dye-dilution curves after injection into the main pulmonary artery was 7.6 minutes, with a range of 1 to 23 minutes. This interval exceeded 12 minutes in 4 subjects.

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TIME AND CONCENTRATION COMPONENTS

The concentration and time components of the dilution curves that are the subject matter of this presentation are illustrated in figure 1. Cardiac output, central blood volume, and mean transit time were calculated from the radial artery curves by the Stewart-Hamilton method. In addition the portion of the central blood volume related to the curve proper was calculated from the ratio of the amount of dye injected in milligrams (I) to the peak concentration in milligrams per liter (Cp) as described by Keys and co-workers. This calculation was made only for the curves recorded following injection into the main pulmonary artery. Except for the ratio of least concentration to recirculation concentration obtained from deflections in centimeters, values for concentration components were not measured from the earpiece curves owing to the difficulty of establishing an accurate quantitative relationship between deflection and blood-dye concentration for this instrument.

A group of 37 subjects was studied. It consisted of 17 patients referred to the laboratory to exclude a cardiac lesion as a diagnostic possibility, and 20 healthy physicians. All patients included in this report were considered to have normal cardiovascular systems on the basis of the final evaluation of the clinical and catheterization data. The number of dye curves recorded in these subjects varied from 1 to 4. Intervals between consecutive injections varied from 3 to 57 minutes, with an average of 16 minutes. Only 3 pairs of consecutive curves were separated by more than 30 minutes.

For reasons that will be evident from the results, subjects were divided into subgroups of 23 adult males, 7 adult females, and 7 teen-age subjects (2 females and 5 males). The average ages were 31 (range 26 to 41), 34 (range 22 to 47), and 16 (range 14 to 19) years respectively for the 3 subgroups.

In order to assess the variability of the components of the dye-dilution curves that may occur during the course of the procedure, 5 to 11 consecutive curves recorded in 6 additional resting normal subjects after injection of indicator into the same site (main pulmonary artery or superior vena cava) were analyzed. The interval from the first to the last injection varied from 24 to 60 minutes in these subjects.

RESULTS

Table 1 shows the mean and standard deviation of various time components of the curves recorded at the radial artery following injection into the superior vena cava or pulmonary arteries in 37 subjects who constituted the main experimental group. Considerable variability is evident. The averages of the various time components of the curve obtained after injection into the superior vena cava other than the recirculation time and the least concentration time were all greater than those obtained following injection into the main pulmonary artery or its branches. Paired comparisons revealed that the average differences between the time components of the curves recorded following injection into the superior vena cava and the main pulmonary artery were 1.4, 0.9, 3.8, and 2.8 seconds respectively for the appearance time, build-up time, disappearance time, and mean transit time.

Fig. 1. Time and concentration components of an indicator-dilution curve with extrapolation of the declining slope of concentration, according to the method of Hamilton, to eliminate the estimated effect of recirculated indicator. Time in seconds is represented on the abscissa while the logarithm of concentration is shown on the ordinate. This dilution curve was recorded for the radial artery following injection of Evans blue into the pulmonary artery of a normal subject.

AT = appearance time, BT = build-up time, Cl = least concentration, Cc = peak concentration, Cr = recirculation concentration, DT = disappearance time, LCT = least concentration time, PCT = peak concentration time, PT = passage time, RT = recirculation time.
Table 1.—Averages and Variability of Time Components of Dye-Dilution Curves Recorded at the Radial Artery in Normal Subjects*

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Subjects</th>
<th>Site of Injection</th>
<th>Mean</th>
<th>S.D.</th>
<th>Mean</th>
<th>S.D.</th>
<th>PCT Mean</th>
<th>S.D.</th>
<th>DT Mean</th>
<th>S.D.</th>
<th>PT Mean</th>
<th>S.D.</th>
<th>MTT Mean</th>
<th>S.D.</th>
<th>LCT Mean</th>
<th>S.D.</th>
<th>RT Mean</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult male</td>
<td>11</td>
<td>RPA</td>
<td>10.9</td>
<td>1.8</td>
<td>6.1</td>
<td>0.9</td>
<td>17.0</td>
<td>2.5</td>
<td>19.8</td>
<td>4.2</td>
<td>25.9</td>
<td>5.0</td>
<td>19.1</td>
<td>2.9</td>
<td>13.1</td>
<td>2.5</td>
<td>21.8</td>
<td>2.7</td>
</tr>
<tr>
<td>Adult female</td>
<td>10.0</td>
<td>2.3</td>
<td>5.8</td>
<td>1.0</td>
<td>15.8</td>
<td>3.0</td>
<td>17.1</td>
<td>4.3</td>
<td>22.9</td>
<td>4.9</td>
<td>17.7</td>
<td>3.9</td>
<td>12.1</td>
<td>2.5</td>
<td>20.2</td>
<td>2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teenage</td>
<td>16</td>
<td>MPA</td>
<td>11.7</td>
<td>2.2</td>
<td>6.1</td>
<td>1.0</td>
<td>17.8</td>
<td>3.0</td>
<td>20.3</td>
<td>4.4</td>
<td>26.4</td>
<td>5.2</td>
<td>19.5</td>
<td>3.3</td>
<td>12.8</td>
<td>2.3</td>
<td>21.4</td>
<td>3.4</td>
</tr>
<tr>
<td>9</td>
<td>SVC</td>
<td>13.2</td>
<td>3.0</td>
<td>7.0</td>
<td>0.9</td>
<td>20.4</td>
<td>3.5</td>
<td>23.8</td>
<td>4.6</td>
<td>30.8</td>
<td>5.1</td>
<td>22.7</td>
<td>4.3</td>
<td>12.6</td>
<td>1.5</td>
<td>21.5</td>
<td>1.9</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: AT = appearance time, BT = build-up time, PCT = peak concentration time, DT = disappearance time, PT = passage time, MTT = mean transit time, LCT = least concentration time, RT = recirculation time, RPA = right pulmonary artery, LPA = left pulmonary artery, MPA = main pulmonary artery, SVC = superior vena cava, and S.D. = standard deviation.

†p < 0.01 for difference from male subgroup.
‡p < 0.05 for difference from male subgroup.

Considerable variability of the time components following injection at any one site is also evident in table 1. An attempt was made to relate this variability to differences in cardiac output, blood volume, and body size encountered in these subjects. Figure 2 shows the relationship of the appearance time, build-up time, and recirculation time from the curves recorded at the radial artery after injection into the main pulmonary artery to the cardiac output as estimated by the Fick method, the part of the central blood volume related to the curve proper (I/Cp), and the surface area. The appearance time increased with the blood volume (I/Cp) and the surface area, but showed no correlation with cardiac output. Build-up time and recirculation time, on the other hand, correlated with cardiac output, and build-up time also correlated well with surface area. Build-up time and recirculation time also correlated well with cardiac index (p < 0.01), whereas no definite correlation of appearance time with cardiac index could be demonstrated. Most of the time components were significantly shorter in the adult female and teen-age subgroups than in the adult male subgroup. However, the surface area was significantly larger in the adult males than in the adult females and the teen-age subjects. Correction of the appearance time, build-up time, and recirculation time for the surface area by dividing these time components in seconds by the surface area in square meters eliminated the correlation with surface area. However, the average values for the corrected appearance time and recirculation time, but not for the build-up time, were significantly greater in the adult male subgroup than in the other 2 subgroups. The over-all average values for the corrected time components were 5.4, 3.1, and 10.5 seconds per square meter for the appearance time, build-up time and recirculation time, and the standard deviations of these values were 1.4, 0.5, and 1.9 seconds per square meter respectively.

The data on cardiac index, central blood volume, disappearance slope, and various concentration components of the same curves are shown in table 2. Paired comparisons revealed that the central blood volume, the least concentration, and the ratio of the least concentration to the recirculation concentration were significantly larger, whereas the peak
concentration and the disappearance slope were significantly smaller in the curves obtained after injection into the superior vena cava than after injection into the main pulmonary artery. On the other hand, paired comparisons of cardiac index calculated from the dye curves from various sites did not show any systematic differences. The differences in the various components shown in table 2 among the 3 subgroups of subjects did not attain statistical significance, except for the difference in the disappearance slope of the curves recorded after injections into the superior vena cava in the male subgroup as compared with the female subgroup, which might be related, at least in part, to the higher mean cardiac index in the latter subgroup.

The values for various time components and the ratio of the least concentration to the recirculation concentration for the curves re-
corded at the left ear are presented in Table 3. The differences between subgroups and injection sites were similar to those obtained from radial artery curves.

The appearance time was longer in the curves recorded from the radial artery than those recorded at the ear, while no significant systematic difference was evident in the other time components. Furthermore, as illustrated in Figure 3, the difference between the appearance times of the curves recorded at the radial artery and at the ear increased with the absolute value of the appearance time.

Comparison of the time components recorded at the right and left ears showed no systematic differences. The mean differences did not exceed 0.1 second.

The variability, with time, of repeated determinations of appearance time, build-up time and recirculation time of the dye-dilution curves recorded at the left ear and right radial artery following successive injections into the same site in 6 subjects is illustrated in Figure 4. In some subjects these components showed no systematic change with time while in others there was some progressive prolongation or shortening during the period of observation. However, the appearance time and build-up time remained relatively stable and usually did not vary by more than 2 seconds, whereas the recirculation time frequently showed wider variation.

**Discussion**

The variability of such parameters as those that form the basis of the present study can be due to technical or biologic factors. Technical factors involved in the recording and analysis of dye-dilution curves include potential errors in the measurement of records or signaling of the exact moment of dye injection, correction for the "dead space" of the indicator-dilution system between the artery and photocell, calibration of the instruments in terms of dye concentration, possible differences in dynamic response among various oximeters used, and variation in the same instrument with time. These factors ordinarily could account for only a small part of the variability that has been demonstrated and that can be exemplified by a range of 5.8 to 15.3 seconds in the case of appearance time recorded at the radial artery following the injection of dye into the main pulmonary artery.

The greatest part of this variability is most likely due to the biologic intra-individual and interindividual differences. Many components of indicator-dilution curves vary in the same
individual when the injection sites or sampling sites are changed. Differences observed in the present study between the components of dilution curves recorded after injection into the superior vena cava and those recorded after injection into the main pulmonary artery and its branches confirm the observations of Hetzel, Swan, and Wood, who found that as the injection site was moved peripherally, the time components other than the recirculation time were prolonged, peak concentration was reduced, and central blood volume was increased. However, their report was based mainly on a group of patients with cardiac abnormalities. The present study, which is based on subjects without cardiac disease, demonstrates in addition that the least concentration time was also independent of the injection site, similar to the finding in respect to recirculation time. These authors ascribed their findings to the longer anatomic path between injection and sampling sites which is traversed by the dye and to increased longitudinal dispersion of the dye as it passes from the more peripheral to the central injection site. Similarly, appearance times in curves recorded at the radial artery that were longer than those recorded at the ear probably reflect the longer anatomic pathways to the radial sampling site. The finding that this difference increased with the absolute value for the appearance time is consistent with this explanation. The absence of systematic differences in the value for cardiac output obtained by the dilution technic following injection of indicator into the various sites, which was also reported by Hetzel and co-workers, allows estimation of cardiac output from dye-dilution curves recorded after injection at these various sites.

When the injection sites and the sampling sites are the same, intra-individual variations apparently still occur probably because of changes in the hemodynamic status of the subject. The present study showed that the appearance time and build-up time changed relatively little and were more stable than the recirculation time in a series of repeated dye-dilution curves. Small intra-individual variability of various circulation times and more recently of the appearance time and the peak concentration time has been reported previously. These considerations are important with respect to the validity of comparing components of dye-dilution curves recorded successively following injection into different sites. Such comparisons may be of practical importance; for example, comparison of appearance times following injection into the venae cavae, branches of the pulmonary artery and pulmonary veins is of value in the diagnosis of anomalous pulmonary venous drainage. In adult and teen-age patients differences in the appearance time of less than
2 seconds between any two curves may not be significant. Care must be exercised in comparing time components of curves recorded at longer time intervals, such as 30 or 40 minutes, in view of the tendency exhibited by some subjects to progressive prolongation or shortening of the time components with time.

Assessment of interindividual variation reveals lack of definite correlation of the appearance time with cardiac output, but good correlation with surface area and blood volume (I/Cp). Direct comparison with the "central blood volume" was not carried out because the values for appearance time and also build-up time are included in the calculation of "central blood volume." The blood volume (I/Cp) that was correlated with the time components is calculated independently of any measurement of time components of the dilution curve and is a measure of the dispersion of the injected indicator during its passage from the injection site to the sampling site. Dispersion of the indicator in turn is thought to be dependent in part upon the volume of blood between the injection site and the sampling site. Good correlation of appearance time with blood volume (I/Cp) and surface area, which is in turn correlated with total blood volume of the subject, suggests strongly that a large part of the interindividual variability for appearance time is due to the differences in central blood volume.

A good negative correlation of build-up time and recirculation time with cardiac output is probably due to the lesser dispersion of the indicator in subjects with high rates of flow. Furthermore, in subjects with the same total blood volume an inverse relationship between cardiac output and the time required for dyed blood to make a complete circuit of the vascular system (systemic recirculation time) would be expected. Positive correlation of build-up time with surface area could be explained again by greater dispersion of the indicator in subjects with greater blood volume, as indicated by greater surface area. Lack of correlation of build-up time and recirculation time with blood volume (I/Cp) is difficult to explain. Metabolic rate and heart rate are known to be related to the velocity of the circulation, and undoubtedly several unexplored parameters of the circulation and body size in addition to those that have been discussed enter into the determination of interindividual variability. Because of the good correlation of appearance time and build-up time with surface area and a trend in that direction in the case of recirculation time, the expression of various circulation times as circulation "indexes" in seconds per square meter may allow a more valid comparison of the time components of the indicator-dilution curves in various patients.

All the time components in the adult males were longer than those in the adult females and the teen-age subgroup (mainly male). Blumgart and Weiss previously reported short circulation times in teen-age subjects, and Dees and co-workers' found shorter circulation times in females than in males. However, the body size of our male subgroup was significantly greater than in the other 2 subgroups, which probably accounts, at least in part, for the longer time components in the adult males. Correction for body size by dividing the appearance time, build-up time,
and recirculation time by the surface area did not abolish significant differences in the appearance time and recirculation time between the male subgroup and the other 2 subgroups. This means either that factors other than differences in body size are responsible for part of the observed difference or that the correction for body size on the basis of surface area was not complete. Dees and co-workers\textsuperscript{11} found, further, that the time components were longer in the subjects more than 40 years of age. Only a few subjects were in this older group in the present study. However, no systematic difference could be demonstrated between males more than 30 years of age and those less than 30 years of age.

Although considerable variability of various components of indicator-dilution curves exists in normal subjects, gross changes occur in conditions such as congestive heart failure, thyrotoxicosis, and others,\textsuperscript{13, 14} and result in components outside the range encountered in normal man. Deviations from normal are particularly evident and of practical importance in patients with congenital heart defects or valvular heart disease.\textsuperscript{15} Values that exceed 2 times the standard deviation from the mean as set forth in the present study should be considered abnormal.

A special consideration has been given to the ratio of the least concentration to the recirculation concentration of the curves re-
corded at the radial artery, since it has been shown to be increased in patients with predominant valvular regurgitation and in those with left-to-right shunt. All the values recorded in the present group of normal subjects were less than 0.60 for the curves recorded after injection into the pulmonary artery and less than 0.85 after injection into the superior vena cava. The finding of larger values should therefore arouse suspicion that one of these lesions exists. Curves recorded by ear oximeters appear to be less reliable for this purpose.

Summary

Indicator-dilution curves were recorded by oximeters at the radial artery and at the ears, following injection of Evans blue (T-1824) into the superior vena cava and the pulmonary arteries of 37 subjects who had no evidence of cardiovascular disease.

The variability and range of various components of these curves are reported. Curves recorded following injection into the superior vena cava showed significantly longer time components, other than the recirculation time and the least concentration time, than the curves recorded following injection into the main pulmonary artery. Also, the “central blood volume,” the least concentration, and the ratio of the least concentration to the recirculation concentration were larger, whereas the peak concentration and the disappearance slope were smaller in the curves recorded after injection into the superior vena cava. The values for cardiac output calculated from the curves following injection into the superior vena cava showed no systematic difference from those following injection into the pulmonary arteries.

The appearance time was significantly shorter in the curves recorded at the ears than in the curves recorded at the radial artery, whereas other time components showed no systematic difference.

The time components of the curves recorded at the right and left ears were practically identical.

The appearance time and the build-up time remained relatively stable when injection of the indicator into the same site in the same subject was repeated several times over a period of 30 to 60 minutes, whereas the recirculation time showed wider variations.

Significantly longer time components of the curves recorded in the adult males as compared to the adult females and teen-age subjects are thought to be related chiefly to the larger body size of the adult males.

Rather large interindividual variability of various components of indicator-dilution curves recorded in normal subjects could be accounted for in large part by the differences in body size, blood volume, and cardiac output.

Acknowledgement

This study was made possible by the unstinting cooperation of many professional and technical colleagues. The authors are particularly indebted to Miss M. Koelsch, Mrs. J. Frank, Miss L. Cronin, and Mr. W. F. Sutterer for their help and interest in this study.

Summario in Interlingua

Curvas del dilution de colorante indicatori esseva registrate per oxymetros al arteria radial e al aures post le injection de blau de Evans (T-1824) in le vena cave superior e le arterias pulmonar de 37 subjectos qui exhibiva nulle signo de morbo cardiovascular.

Le variabilitate de diverse componentes de iste curvas es reportate. Curvas registrate post injectiones in le vena cave superior exhibiva significativamente plus longe componentes temporal—aparte le tempore de recirculation e le tempore del concentration minimal—que le curvas registrate post injectiones in le principal arteria pulmonar. In plus, le "volume de sanguine central," le concentration minimal, e le proportion inter le concentration minimal e le concentration de recirculation esseva plus grande, durante que le concentration maximal e le inclino de disparition esseva plus miere in le curvas registrate post injection in le vena cave superior. Le valores del rendimento cardiac, calculate ab le curvas post injectiones in le vena cave superior, non differeva systematicamente ab le valores calculate post injectiones in le arteria pulmonar.
Le tempore de appariation essava significativemente plus breve in le curvas registrate al aures que in le curvas registrate al arteria radial, durante que le altere componentes temporal non differeva systematamente.

Le componentes temporal del curvas registrate al aure dextere e al aure sinistre esseva praticamente identic.

Le tempore del appariation e le tempore de accumulation remaneva relativemente stabile quando le injection del indicator in le mesme sito in le mesme subjecto esseva repetite plure vices intra un periodo de 30 a 60 minutas. Le tempore del recirculation monstrava plus grande variationes.

Le constatation de significativemente plus longe componentes temporal del curvas registrate in masculos adulte in comparation con le constatationes in adulte femininas e in adolescentes es interpretate como primarmente un effecto del plus grande dimensiones corporee in masculos adulte.

Un satis grande variabilitate interindividua de varie componentes del curvas del dilution de colorante indicatori in subjectos normal esseva explicable in grande parte per differentias del dimensiones corporee, del volumine de sanguine, e del rendimento cardiace.

REFERENCES


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