The Factors Influencing the Circulation Time

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A mathematical analysis of the relationship of cardiac output and heart-lung blood volume to observed circulation time is presented. The theoretic conclusions are substantiated by an experiment in which it is shown that diluting the amount of indicator used prolongs the observed circulation time through the heart and lungs.

The measurement of the circulation time through the heart and lungs is one of the most widely used tests of circulatory efficiency in clinical medicine. Yet, surprisingly, the term is usually poorly defined, and there is certainly considerable disagreement concerning its parameters. As Wiggers' points out, circulation time is not the time required for the blood to make a complete circulation, because any given corpuscle has such a wide variety of paths over which to travel as to make such a concept meaningless. With many authors the term "circulation time" seems to imply a measure of the mean velocity of flow of an injected substance from the point of injection to the place of detection. Blumgart's in his informative review remarks that velocity of blood flow as such cannot be measured and defines the measurable circulation time as being "the interval of time necessary for the fastest particle of a foreign substance to traverse the shortest available path between the point of injection and the place of detection."

If a given amount of indicator is injected at time $T_0$, and the concentration of indicator at the place of detection is plotted against time, then, disregarding recirculation, a curve, as shown in figure 1, will be obtained. This has been demonstrated by Hamilton and co-workers in their studies on an injection method for the determination of cardiac output. Following Blumgart's definition, the circulation time would be the time interval from the instant of injection ($T_0$) to the instant ($T_1$) when the first particle of indicator appears. If the time interval measured were the time of mean appearance of the injection mass then the circulation time on this ideal curve would be from $T_0$ to that point on the curve ($T_3$) when half of the area under the curve was between these two points. However, it would seem that, whether the end point be detected objectively (fluorescein) or subjectively (Decholin), the circulation time is determined neither by the appearance of the first particle of indicator nor by the appearance of half the indicator. Rather it would seem that the circulation time actually observed is the time required for an injected indicator to reach a detectable concentration at the place of detection. If this threshold or minimum detectable concentration be assigned the value ($P''$), then the observed circulation time is the time interval between the injection ($T_0$) and the time ($T_2$) when the concentration ($P''$) is reached. It follows that any discussion of the factors controlling the circulation time must be consistent with this definition.

As mentioned, various parameters have been assigned to circulation time. Wiggers states that the test gives "only rough information regarding changes in the circulation; indeed, an analysis of where and why changes occurred can generally not be made." However, it is almost universally recognized that as a clinical test the circulation time is useful in both establishing diagnoses and following the course of disease. It becomes prolonged in congestive heart failure and returns toward normal with relief of failure, although it is usually normal or rapid in heart failure due to anemia, thyrotoxicosis, beriberi and arteriovenous fistula. Blumgart demonstrated that the circulation time is affected by the cross-sectional area of the pathway traveled, which in turn is a function of the amount of blood in the pulmonary
vascular bed and the condition of its vessels. Other things being constant, it can be seen that a widening of the pathway will allow the same volume per unit time to pass at a diminished speed. However, if narrowing of the vascular caliber significantly impedes flow, slowing will occur. Again Blumgart assigns great importance to the relationship of cardiac output and velocity of flow. Increasing minute output increases the rate of flow (and decreases circulation time) if other factors remain the same.

Decreasing cardiac output has the opposite effect. Thus in myxedema without heart failure the circulation time is prolonged in association with a diminished cardiac output. Conversely, circulation time is notoriously rapid in Grave’s disease, even with heart failure and dilatation of the vascular bed, both of which would tend to prolong it. This must be due to the marked increase in cardiac output which commonly occurs in hyperthyroidism. In the usual case of congestive heart failure circulation time is prolonged even more than it would be in a case of myxedema with the same reduction in cardiac output, because pulmonary engorge-ment adds its slowing effect.

Recently Nylin, following David and Bouvrain, has emphasized the effect of cardiac dilation on circulation time. He suggests that a dilated, poorly emptying heart will prolong circulation time by a diluting effect, and has published studies in which he has correlated circulation time with heart volume as measured by his x-ray technic. Meneely and Chesnut have made a similar study and have found a high degree of correlation between the ratio (transverse diameter of the heart/intrathoracic diameter) and circulation time. They admit that Nylin’s observations in patients with congestive failure of a prolongation of the taste sensation and a flattening of the red cell diu-
injected substance the longer it will take for the threshold concentration to be reached. In other words, the greater the volume of blood between the points of injection and detection, the more gradual will be the ascent and descent of the rising and falling-off curves of concentration plotted against time and the longer it will take for the threshold concentration \( P' \) to be reached (fig. 2). This effect, rather than laminar flow, probably accounts for the "stringing out" phenomenon which has been discussed in the literature. Both the rising and falling-off curves are, to the extent which they are determined by this factor, exponential.

This conclusion is justified by data already in the literature. Nylin's red corpuscle dilution curves show a more gradual ascent and falling off in patients with congestive failure. Also, it is a well recognized clinical observation that, in patients with congestive failure, the end point of a circulation time determination tends to be diffuse rather than sharp, and the effect builds up gradually and may last longer. Further, Hitzig's work on ether to lung circulation times found that if he made the ether dose small enough there was not only a poorly defined, but also a prolonged end point in normals. The effect of dose on time-concentration is shown schematically in figure 3 when \( P' \) is again the minimal detectable concentration.

Other factors affecting circulation time can be discarded or defined in terms of one of the above factors. Blumgart assumes that the path traveled is relatively uniform from patient to patient as is shown by the relatively small range of normal circulation times. And certainly laminar flow must be minimal in a system with pulsations, changing frictions, changing diameters, turns and branchings. The viscosity of the blood will be reflected in the cardiac output, dilution and cross-sectional parameters. For example, in anemia the cardiac output increases and the blood volume decreases with a resulting rapid circulation time. Conversely, in polycythemia the cardiac output is normal, but the plethora causes an increase in cross section of the blood channels and a greater dilution of indicator and so the circulation time may be prolonged. Diminution of the available cross-sectional area will, after a certain point is reached, impede flow. Other things being equal this effect will be mirrored by a diminution in cardiac output. An additional factor suggesting itself is the relation of the time of injection to the phase of the cardiac and respiratory cycles. Even in a case of complete heart block it is difficult to imagine the phase of the cardiac cycle having an effect of more than a second or so, and moderate increases in respiration are known to have little effect on cardiac output.

Breath holding diminishes blood flow in the lungs and should be avoided in performing the test.

Therefore, it would seem that the circulation time, as here defined, is a function of (1) the cross-sectional area of the pulmonary vascular bed (controlled by the volume of blood in the lungs), (2) the cardiac output (itself affected by factors such as peripheral resistance), and (3) the amount of dilution of the injected mass by the blood in the heart and lungs. It can be seen that the blood volume factor affects the observed circulation time in two ways: (1) the simple linear velocity effect controlled by cross-section, and (2) the exponential delay in reaching a perceptible concentration produced by the diluting pool of blood in the heart and lungs. Referring to figure 1, the linear effect results in the time from \( T_0 \) to \( T_1 \) while the exponential or "pool" effect results in the time from \( T_1 \) to \( T_2 \) where a detectable concentration \( P' \) is reached. If the rise in concentration is steep this second effect will be small. On the other hand, if dilution is great and the ascent of the curve is gradual then the dilution effect will assume importance. The relationship of these various factors can be stated more precisely in mathematical form.

Let \( V_r \) equal the total volume of blood between the points of injection and detection. This can be considered as the sum of two component volumes, \( V_1 \) and \( V_2 \). The first, \( V_1 \), is the blood in the vessels and that portion of the heart’s blood that will leave with the following systole. The other volume, \( V_2 \), is the blood in the lungs plus the portion of the heart’s blood not ejected. \( V_2 \) is the blood making up the "diluting pool."

The linear component, \( T_1 \), of the observed
circulation times \((T_0 - T_1\) in fig. 1) is a function of the cardiac output \((C)\).

\[
T_1 = \frac{V_1}{C}
\]

The rate at which the pool, \(V_2\), delivers indicator is a function of the quantity of indicator present in \(V_2\). This quantity, \(Q\), is a resultant of two components.

\[
Q = A - B
\]

when \(A\) is the amount of indicator which has entered and \(B\) the amount which has left. Then

\[
\frac{dQ}{dt} = \frac{dA}{dt} - \frac{dB}{dt}
\]

The value \(\frac{dA}{dt}\) is a function of the dose, \(D\), of indicator, then

\[
\frac{dA}{dt} = kD
\]

where \(k\) is a constant determined by the concentration of indicator in the injecting syringe and the time it takes to empty it.

The rate at which the indicator leaves the pool is a function of the cardiac output \((C)\) and the concentration as it leaves the pool \((P)\), so

\[
\frac{dB}{dt} = CP
\]

Since \(P\) is the pool concentration it is by definition \(\frac{Q}{V_2}\), and

\[
\frac{dP}{dt} = \frac{1}{V_1} \cdot \frac{dQ}{dt}
\]

By substituting equations (4), (5) and (6) in equation 3

\[
\frac{dP}{dt} = \frac{kD - CP}{V_1}
\]

This can be integrated into the form

\[
T_2 = \frac{V_2}{C} \ln \frac{kD}{kD - CP'}
\]

where \(T_2\) is the time from the appearance of the first particle of indicator \((T_1)\) until the time \((T_2)\) when a detectable concentration \((P')\) is reached.

Then the total observed circulation time is the sum of \(T_1\) and \(T_2\) or

\[
T = \frac{V_1}{C} + \frac{V_2}{C} \ln \frac{kD}{kD - CP'}
\]

If this exponential effect is significant, then diminishing the amount of indicator used should prolong the observed circulation time as shown in figure 3. On the other hand, if only the linear relationship holds, changing the dose should not change the circulation time. In order to establish this hypothesis, 33 experiments were performed to study the effect of diminishing the dose of indicator on the observed circulation time.

**Methods**

The circulation times were performed with the patients lying as flat in bed as was comfortable with the arm approximately at heart level. No attempt was made to have the patients in a basal state since each experiment served as its own control. The largest vein in the antecubital fossa was selected and 5 ml. of either 10 per cent or 20 per cent Decholin were rapidly injected through an 18 gage needle. An attempt was made to push the plunger into the syringe at the same rate in each injection. The patients were asked to signify both the onset and disappearance of the bitter taste, and times were noted on a stopwatch. After waiting a few minutes the test was again performed, using that concentration of Decholin not used in the first injection. After waiting another few minutes, in 21 cases the first dose was repeated. It was discovered that it made little difference which concentration was used first nor
TABLE 1.—Comparison of Twenty Per Cent and Ten Per Cent Circulation Time in Patients with Congestive Heart Failure and Normal Subjects

<table>
<thead>
<tr>
<th>Patients with Failure</th>
<th>Onset of Taste (seconds)</th>
<th>Duration of Taste (seconds)</th>
<th>Trans. card. diam. intrathor. diam.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20% Decholin</td>
<td>10% Decholin</td>
<td>20% Decholin</td>
</tr>
<tr>
<td>L.P.</td>
<td>31</td>
<td>36</td>
<td>24</td>
</tr>
<tr>
<td>F.E.J.</td>
<td>27</td>
<td>26</td>
<td>16</td>
</tr>
<tr>
<td>H.B.H.</td>
<td>25</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>E.E.C.</td>
<td>31</td>
<td>39</td>
<td>19</td>
</tr>
<tr>
<td>C.A.G.</td>
<td>20</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>M.M.</td>
<td>24</td>
<td>29</td>
<td>22</td>
</tr>
<tr>
<td>R.R.</td>
<td>26</td>
<td>36</td>
<td>11</td>
</tr>
<tr>
<td>J.M.</td>
<td>33</td>
<td>39</td>
<td>20</td>
</tr>
<tr>
<td>C.G.</td>
<td>21</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td>L.H.</td>
<td>24</td>
<td>33</td>
<td>25</td>
</tr>
<tr>
<td>W.H.</td>
<td>18</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>A.J.</td>
<td>18</td>
<td>22</td>
<td>32</td>
</tr>
<tr>
<td>G.F.</td>
<td>22</td>
<td>—</td>
<td>27</td>
</tr>
<tr>
<td>C.H.</td>
<td>40</td>
<td>—</td>
<td>21</td>
</tr>
<tr>
<td>R.D.</td>
<td>22</td>
<td>29</td>
<td>25</td>
</tr>
</tbody>
</table>

Patients without Failure

<table>
<thead>
<tr>
<th>Patients without Failure</th>
<th>Onset of Taste (seconds)</th>
<th>Duration of Taste (seconds)</th>
<th>Trans. card. diam. intrathor. diam.</th>
</tr>
</thead>
<tbody>
<tr>
<td>G.L.</td>
<td>12</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>C.M.</td>
<td>11</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>W.H.</td>
<td>15</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>D.R.</td>
<td>13</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>G.D.H.</td>
<td>11</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>R.B.</td>
<td>14</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>E.W.</td>
<td>17</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>G.Mc.</td>
<td>17</td>
<td>18</td>
<td>14</td>
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<td>H.R.</td>
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<td>14</td>
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<tr>
<td>G.M.</td>
<td>10</td>
<td>12</td>
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</tr>
<tr>
<td>J.Bu.</td>
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<td>12</td>
<td>10</td>
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<tr>
<td>G.S.</td>
<td>16</td>
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<td>F.V.</td>
<td>10</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>J.B.</td>
<td>18</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>K.M.</td>
<td>13</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>C.W.</td>
<td>15</td>
<td>18</td>
<td>20</td>
</tr>
</tbody>
</table>

was there any consistent or significant difference in the first and third measurements. Presumably dilution and excretion reduce the blood level of Decholin so rapidly that the remainder after two or three minutes does not form any appreciable increment. Cardiac and intrathoracic diameters were determined from standard 6 foot chest films.

RESULTS

The results are presented in table 1. The taste onset was faster with 20 per cent Decholin than with 10 per cent, and this difference was greater in cardiac patients with failure than in patients without failure. The duration of taste was longer with 20 per cent Decholin, and,

Table 2.—Measured Differences

<table>
<thead>
<tr>
<th>Difference Measured</th>
<th>Mean</th>
<th>Probability Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference in taste onset between doses in all subjects</td>
<td>2.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Difference in taste duration between doses in all subjects</td>
<td>4.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Increased difference in failure patients of taste onset between doses</td>
<td>4.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Increased difference in failure patients of taste duration between doses</td>
<td>3.8</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
again, this difference was greater in patients with failure. These differences as well as the probability of obtaining them by chance are presented in table 2. In these experiments the correlation between circulation time and heart volume as expressed by the ratio (transverse cardiac diameters/intrathoracic diameter)\(^3\) is fair (Bravais-Pearson coefficient of correlation = 0.63).

**DISCUSSION**

From these preliminary experiments the tentative conclusion is drawn that the "pooling" effect is one of the factors controlling the observed circulation time. Currently a method is being sought for a suitable method for the continuous recording of time-concentration curves following the injection of an indicator. The equation (9) presented probably is not an exact description of the factors controlling circulation time. For example, \(V_1\) and \(V_2\) are not necessarily distinct quantities, and for the purpose of simplification there is the ad hoc assumption that the time it takes a single rapid particle to traverse the "pool" is very short in comparison with the total circulation time. However, it is thought that the equation gives a good approximate description of the parameters involved. The fair correlation between heart volume and circulation time in this report is only partially in agreement with the work of Meneely and Chesnutt.\(^5\) However, it must be remembered that the heart is only a part of the diluting system. The lungs are probably the more important member. Moreover, it is likely that the linear component \(\frac{V_1}{C}\) consumes the major portion of the observed time interval.

**SUMMARY**

Circulation time is defined as the time that it takes an injected indicator to reach a detectable concentration at the place of detection. A discussion of the factors affecting circulation time is presented with a mathematical analysis. By injecting various amounts of indicator it has been shown that "pooling," an exponential parameter previously not well defined, is one of the factors determining circulation time.

**ACKNOWLEDGMENT**

It is a pleasure to acknowledge indebtedness to Moses Greenfield, Ph. D. for helpful discussions of the mathematical treatment used.

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Circulation. 1952;5:583-588
doi: 10.1161/01.CIR.5.4.583
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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