Circulation Time End Points

A Quantitative Comparison of Saccharin and Radioiodinated Albumin as Indicators

By Richard N. Pierson, Jr., M.D., Michael Grieco, M.D., Neil Swinton, M.D., and Michael Dubin, M.D.

Arm-to-tongue circulation time is widely used as a clinical test for the presence of cardiac failure.¹  To our knowledge, there have been no objective studies relating the actual time of arrival of an injected substance to its subjectively reported end point. Preliminary observations suggested that a delay of several seconds occurs. Since this represents a significant fraction of the total circulation time, the current study was undertaken to provide more precise information concerning the relationship between the arrival of an indicator and its subjective end point. In patients with cardiac failure and without heart disease, saccharin was injected together with albumin ¹³¹I (IHSA) and the arrival time, as noted by taste, was compared with that recorded by an external radiation monitor over the tongue. The characteristics of the radioisotope indicator-arrival curve were also analyzed for each subject.

Methods

Circulatory studies were performed in 13 patients with congestive heart failure and in 15 patients without cardiovascular disease. The subjects were studied in the supine position after a 12-hour fast. A 56-cm polyethylene catheter, internal diameter 0.8 mm, was passed percutaneously into the basilic or cephalic venous system via a no. 14 thin-walled needle which was subsequently withdrawn over the catheter. The catheter was passed, without fluoroscopy, an estimated 2 cm beyond the axilla. Multiple injections of the radioisotope-saccharin mixture were made with no discomfort to the patient; the patient was usually unaware of the injection.

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*Intracath 1914, C. R. Bard, Summit, New Jersey.

A 5-ml reservoir of polyethylene tubing was filled with 4 ml of a 62.5% saccharin solution† (2.5 g) and approximately 1 ml of IHSA‡ (5 to 50 μc). This mixture was flushed through the catheter with 10 ml of 5% dextrose in water from a syringe electrically wired to activate a marking pen when 2 ml had been delivered. The injection was usually accomplished in 1.5 seconds. The patient was instructed and given practice in the use of an electric hand switch to signal the taste end point. Blood volume was measured 15 minutes prior to the circulation-time study by the standard method of tracer albumin dilution using approximately 5 μc of IHSA.

Peripheral time-concentration curves of IHSA transit were monitored by a broadly collimated 2 by 2 inch sodium iodide crystal, gamma ray spectrometer, and a ratemeter.§ The output of the ratemeter was recorded at 30.5 cm per minute with a time constant of 2.0 seconds. The monitoring probe was placed over the angle of the jaw directed toward the tongue.

The subjective saccharin-circulation time was measured directly from the tracing by measuring the time elapsed between injection signal and the patient-activated signal.

Data Analysis

The following measurements were used for the analysis of the isotope arrival curves.

Time Measurements

Figure 1 shows an actual tracing, and figure 2 displays the method of analysis of the output of the tongue monitor.

Arrival time is denoted by the first major deflection of the pen from the base line. This time, while relatively exact, is not always easily defined owing to the slowly rising initial portion of

†Supplied by courtesy of E. R. Squibb and Company, New Brunswick, New Jersey.


§Nuclear-Chicago Corp. DS 5 probe; 132 B spectrometer; and 1629 ratemeter. Texas Instrument Company galvanometer-chart recorder.
Radioactivity at the tongue, externally monitored. Tracing reads from right to left, two small boxes per second. Arrows indicate electronic marking signals for time of injection and taste.

The curve and becomes more difficult to measure in congestive heart failure when the concentration of radioactivity rises at a slower rate. Therefore, the radioisotope-circulation time was also measured by utilizing the time at which half of the peak concentration of radioactivity was recorded. Since the concentration is always rising sharply at the time when half of the peak concentration is reached, this intercept can always be accurately measured on the time axis. In an analysis of 6 successive IHSA arrival curves in each of three subjects under steady state conditions, the time of half-peak concentration was found to vary less than 1 second and was a more reproducible end point than the arrival time.

Concentration Measurements

Since both the amount of IHSA injected and the blood volume are known, the concentration of radioisotope circulating in the blood at equilibrium time can be calculated. By equating the deflection of the recording pen after equilibration of radioactivity in the circulation has occurred with the calculated concentration of radioactivity in the blood at this time, a factor was obtained from which the relative concentration of radioactivity in the blood under the monitor can be estimated at any time during the inscription of the curve.

Since the injected mixture also contains a known amount of saccharin which, during the first circulation, bears a known relationship to the quantity of 131I injected, the concentration of saccharin in the blood in view of the monitor may be estimated at any point on the curve during the first passage prior to dilution of a significant amount of saccharin in extravascular pools.

The actual concentration of radioisotope or saccharin in arterial and capillary blood at the taste organ during the early portion of the arrival will differ from the estimated concentration for two reasons: first, a tendency to overestimate the saccharin concentration results since the factor used to estimate its concentration is measured at the time of equilibration of IHSA and depends on arterial, capillary, and venous blood volumes in view of the monitor, while smaller volumes involving only the arterial and capillary phase are filled during the rising portion of the concentration curve.

Second, a counteracting tendency to cause underestimation of first-passage saccharin concentration is introduced by the rate at which the small saccharin molecule leaves the intravascular compartment during the 10 to 50 seconds of its transit from arm to artery by way of the capillary circulation of the lung.

Neither of these variables was measured in this study; thus the reported “saccharin concentration” represents an estimation of the actual concentration, and was used in making comparisons between results in similar patients studied with the same method.

Results

Table 1 shows a comparison of IHSA and subjective saccharin-arrival times in 15 normal subjects as well as a detailed analysis of each IHSA arrival curve. In all cases, the saccharin arrival was reported during the ascending limb of the radioisotope concentration curve. The mean IHSA arrival time was

Figure 1

Figure 2

Indicator concentration at the tongue. Diagram of methods of analysis.
Table 1

Normal Subjects

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<th>Pt</th>
<th>SCT (sec)</th>
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<th>SHT—IHSA arrival time (sec)</th>
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<th>PC (mg/100 ml)</th>
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Mean and standard deviation:

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Abbreviations: SCT = saccharin circulation time; PCT = peak concentration time; PC = peak concentration; TT = taste threshold; and BSA = body surface area.
6.9 ± 1.8 seconds, varying from 3.1 to 8.5 seconds. In each case, the saccharin circulation time was reported later than the IHSA arrival time. The mean saccharin-circulation time was 10.6 ± 2.1 seconds with individual values from 5.0 to 14.0 seconds. The delay in reporting saccharin-circulation time, after the arrival of radioactivity at the tongue, was 3.7 ± 1.3 seconds and varied from 1.5 to 5.5 seconds, as shown in figure 3.

Figure 4 displays separately the means of curve characteristics for all normals and for all patients in cardiac failure. In each group, the mean values for arrival time, for time of half-peak concentration, and for peak concentration were used to plot these averaged curves. The arrows indicate the time and the relative saccharin concentration at which the taste and end point occurred.

There was no difference between the mean of saccharin-circulation times and the mean of times of half-peak concentration of IHSA (10.6 ± 2.4 seconds.) Figure 5 shows the relationship of each individual saccharin end point to the concurrently measured time of half-peak concentration of IHSA. When each saccharin end point is compared with the concurrent objective IHSA time of half-peak concentration, there is a standard deviation of 1.4 seconds between these measured times.

Other aspects of the arrival curve are also presented in table 1. The peak concentration, expressed in terms of saccharin concentration, varied from 70 to 130 mg/100 ml (because of limitations in accuracy of this approximation, each concentration is given to the nearest 10 mg). The calculated saccharin concentration at which the taste was reported was 42 ± 22 mg/100 ml, varying from 15 to 80 mg/100 ml.

The mean rate of increase of saccharin concentration in this group of normal subjects was estimated to be 12.1 ± 3.1 mg/100 ml/second.

The IHSA arrival time and the saccharin-circulation time were prolonged in 13 patients with clinical evidence of severe congestive failure (table 2). Pulmonary rales, cardiomegaly, and dependent edema were uniform characteristics of patients chosen for this study group. The mean IHSA arrival time was 14.5 ± 2.8 seconds with a range from 10.5 to 19 seconds. This compared with the mean in the normal group of 6.9 ± 1.8 seconds. In each patient, a delay occurred between IHSA arrival and the report of saccharin taste. This delay in heart failure was
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Mean and standard deviation:

- 22.0 ± 3.8
- 14.5 ± 2.8
- 7.5 ± 3.3
- 22.3 ± 3.3
- 30.5 ± 3.3
- 72.7 ± 16
- 34.6 ± 1.6
- 5.1 ± 1.6
- 65.5 ± 1.65

**Abbreviations:** SCT = saccharin circulation time; PCT = peak concentration time; PC = peak concentration; TT = taste threshold; and BSA = body surface area.
7.5 ± 3.3 seconds, varying from 2.0 to 13.5 seconds, compared with the normal mean delay of 3.7 ± 1.3 seconds. The saccharin-circulation time in heart failure was accordingly prolonged even more than would be expected from the prolongation of the IHSA arrival time alone, the mean saccharin-circulation time being 22.0 ± 3.8 seconds with a range of 15.5 to 29.0 seconds, compared with a mean time in normal subjects of 10.6 ± 2.1 seconds.

It is of interest that the mean saccharin taste end point was again reported in the midportion of the rising slope of the mean IHSA concentration curve. As seen in figure 4, this curve differed from that of the normal not only by a delayed arrival, but also by a slower rate of buildup. As in the normal subjects, the saccharin-circulation time was similar to the time of half-peak concentration of radioisotope recorded over the tongue. This latter objective value in heart failure was 22.3 ± 3.3 seconds, varying from 17.3 seconds to 27.3 seconds, which compared with the concurrent mean saccharin-circulation time of 22.0 ± 3.8 seconds. In nine of 13 patients, the saccharin-circulation time was within 2 seconds of the time of half-peak concentration. However, in the remaining four patients, wide individual variations were found (fig. 5) with saccharin end points preceding by as much as 6.0 seconds and following by as much as 6.8 seconds the time of half-peak concentration. Thus in five of 28 subjects (18% of the group studied) there was a difference of more than 4 seconds between a subjective and an objective circulation time.

The calculated saccharin concentration at which the taste end point was reported was similar on the average in normals and in heart failure, being 41.7 ± 21.7 mg/100 ml in the normals and 34.6 ± 16.3 mg/100 ml in congestive failure. The range of the threshold concentration for saccharin was from 10 to 80 mg/100 ml in the normals and was estimated as 10 to 65 mg/100 ml in patients with cardiac failure. The calculated rate of rise of saccharin concentration is seen to be approximately twice as great in normal subjects as in patients with congestive failure: 12.1 mg/100 ml/second in normals compared with 5.1 mg/100 ml/second in subjects with heart failure.

**Discussion**

The circulation time is much used in clinical medicine as a safe, convenient, repeatable, bedside measurement of cardiac function. Indeed, the circulation time is a theoretically attractive measurement of congestive heart failure since it is prolonged by both the prominent hemodynamic lesions of congestive failure, low cardiac output, and increased blood volume. However, the interpretation of a given result is often hindered by the wide range of normal, usually quoted at from 9 to 17 seconds, for most of the indicators sensed at a peripheral arterial-capillary bed. The circulation time might find its most significant use in delineating early failure before obvious clinical changes have occurred if the normal variation in the measurement could be rendered smaller.

The times consumed in transit of the indicators, saccharin and IHSA, through the vessels from vein to tongue were estimated from the measurements made in this study. It is interesting that more than 20% of the normal total circulation time in this study occurred after the first arrival of saccharin at the tongue before it was tasted. The range of such delays, from 1.5 to 5.5 seconds in the normal subjects and from 2.0 to 13.5 seconds in those with cardiac failure, provides the subjective circulation-time measurement with a non-cardiac variable of significant magnitude. This

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**Figure 6**

*Schematic diagram of the circulation time: (A) interval between injection and arrival; (B) delay between arrival and the taste end point in normal subjects; (B1) shortest delay; (B2) average delay; and (B3) longest delay.*

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component of the circulation time may be appreciated graphically in figure 6 which defines a period of time, A, during which the transit time of a bolus of indicator through the blood vessels and heart is precisely dependent on cardiac output and the volume of blood in which the indicator is diluted in transit. A second period of time, B, defines the time from the first arrival of the indicator to the end point, and varies, in the normal subjects of this study, from 15 to 45% of the total circulation time, A plus B. In the patients studied with congestive heart failure, the variation was even greater, with the time varying from 13 to 56% of the total circulation time.

**Taste Threshold**

The wide variation in the delay between arrival of saccharin at the tongue and report of its taste appears to depend on individual differences in taste threshold. Such threshold variations are indicated by estimation of saccharin concentration at the tongue at the instant of taste in this study. It is clear that the variable of taste threshold affects the circulation time only at the most distal anatomic segment of the transit pathway from arm vein to tongue. Indeed this distal segment is beyond the heart and lungs where the most significant hemodynamic lesions involving cardiac output and increased volume occur in heart failure. Thus taste threshold, a variable of major quantitative proportion without apparent relation to cardiac function, is a co-determinant of the circulation time. Furthermore, the variations in normals measured in this study are sufficient to explain the observed wide variations between 9 and 17 seconds.

**In Search of an End Point**

To avoid the uncertainty in interpretation attending the end points achieved with subjective indicators, radium C, radioactive sodium, fluorescein, vital dyes, cold or normal saline, and many other substances have been used. When peripheral arterial arrival has been measured as an all-or-none event, exactly the same dose dependence and, therefore, threshold effect applies to objective indicators. The arrival of the indicator material will be followed by a gradually increasing concentration until the arbitrary sensing threshold of the counter, cuvette, or other instrument has been exceeded. For a larger patient with a greater volume of blood diluting a given standard injected dose, a longer circulation time will be measured. In a smaller patient, a similar dose will be more concentrated at arrival and surpass a concentration threshold at an earlier time during the concentration buildup. These objective indicators succeed in eliminating dependence on patient cooperation, but so long as a single all-or-none end point is used, the delay between first arrival and end point signal is dependent on a noncardiac variable, the threshold setting.

An additional defect of single end point methods derives from the fact that they measure primarily delay in arrival, giving less weight to the slowed concentration buildup so evident in the studies in heart failure reported here. This defect subtracts from the sensitivity of the method in detecting less severe heart failure.

**Time of Half-Peak Concentration**

The time when half the peak concentration is reached provides an easily measured point where rapid buildup favors an accurate measurement along the time axis. Coincidentally, the time of half-peak concentration is similar to the subjective circulation-time end points in this study. This chance identity between end points does not deserve great stress since it refers only to a mean value which carries a wide standard deviation. In addition, it is apparent that varying the dose of the subjective indicator could alter this relationship, this end point being threshold-dependent. In fact, an arbitrary dose of saccharin was used in this study without correction for patient size or blood volume. Nonetheless, the usefulness of an easily measurable, repeatable, objective end point occurring in the buildup phase of an indicator-dilution curve provides a useful measurement.
for comparative purposes. Unlike the endpoint of any subjective indicator, which will tend to be shortened by increasing the dose until high levels are reached, the time of half-peak concentration is independent of dose so long as adequate count rates above background noise are recorded.

**Saccharin as an Indicator**

Saccharin has been suggested as a circulation-time indicator because it usually provides a clear end point and is safe. A disadvantage, recognized by neuropsychologists but perhaps not by most physicians, is that taste for saccharin is a threshold characteristic with wide ranges of variation. Since threshold is unlikely to change in a given subject over a short period, repeated tests for comparison in the same subject can be usefully interpreted, a finding supported by the good repeatability shown by Schwartz and his colleagues. The wide range of threshold values estimated in the 28 subjects of this study suggest, however, that saccharin is not a generally reliable indicator. Definition of the threshold variations between different subjects provides a quantitatively feasible explanation of the wide ranges of normal circulation time usually quoted. Examination of the other possible physiological explanations, individual differences in cardiac index or central blood volume, was beyond the scope of this study.

**Summary**

Ideal measurements are both simple and precise. The subjective circulation time has provided more simplicity than precision to three generations of physicians attempting to analyze cardiac function. Other more complex and less available measurements have displaced the circulation time from its prior vogue, probably because of the wide ranges of normal circulation time values. Yet, no other bedside measurement of cardiac function reflects both cardiac output and central blood volume with a single result.

The peripheral arrival characteristics of radioisotope-labeled albumin are described in 15 normal subjects and in 13 patients with heart failure. These circulation-times are compared with the taste end point of the saccharin indicator simultaneously injected.

Taste threshold, a variable not dependent on cardiac status, determines a significant proportion of the circulation time in both normal and failing circulations.

The wide availability of instruments which measure radioactivity, dye density, or thermal change as a function of time could reinvest the circulation time with a new precision, in return for a modest loss of simplicity. Bypass of the noncardiac variable taste threshold may be added to the other well-described advantages of an objective circulation-time measurement by use of the time of half-peak concentration as the end point in recording the circulation time.

**References**

Circulation Time End Points: A Quantitative Comparison of Saccharin and Radioiodinated Albumin as Indicators

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