The Use of Ascorbate Dilution Curves in Cardiovascular Diagnosis

Applications of a Technic for Direct Intravascular Detection of Indicator

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At the present time, indicator-dilution curves are one of the most important technics employed in the investigation of the circulation. The earliest of these studies were carried out by the rapid serial collections of blood samples and their subsequent photometric analysis. This ingenious but cumbersome method was replaced by the continuous withdrawal of blood in front of a photoelectric cell, thus permitting the direct inscription of time-concentration curves. Although this approach has greatly facilitated application of the indicator-dilution principle, a number of drawbacks have remained. Most of them are related to the unavoidable physical separation of the intravascular sampling site and the external detector. Thus, the loss of blood may become significant, particularly when multiple dilution curves are necessary. Secondly, distortion of the curve results during transit from sampling site to the detector. Finally, it may be difficult to obtain dilution curves from the central circulation, since the blood sample must traverse a long catheter. Accordingly, considerable effort has been directed toward the development of technics that permit placement of the detector directly into the blood stream.

Clark and his associates have recently introduced a new group of indicators, chemical reducing agents, that can be detected with intravascular platinum electrodes. This report describes the technics and instrumentation employed in this laboratory with sodium ascorbate as an indicator; particular emphasis is placed on the dilution curves obtained from an electrode incorporated into a catheter introduced into the central circulation.

Theory and Instrumentation

Following the injection of ascorbate into the circulation, its concentration at any intravascular site may be measured by the increase in current that it produces between an intravascular platinum sensing electrode at this site and a reference electrode on the skin. The basis for this signal is the oxidation of ascorbate ion, which occurs upon its contact with a positively charged platinum surface, and the resultant release of electrons. The current produced is proportional to the ascorbate ion concentration at the electrode surface, but it is also affected by the previous physical, chemical, and electrical treatment of the electrode, its size and shape, and the voltage applied to it, as well as a number of other influences. During the inscription of an ascorbate dilution curve, however, the factors other than the concentration of the indicator remain virtually constant.

The system employed (fig. 1) consists of a bright platinum sensing electrode incorporated on a cardiac catheter (1), or (2) threaded through a modified Courand needle (3), and connected to a control box (4). A silver reference electrode (5) is placed on the skin. The control box applies +1 volt to the platinum electrode and the current flowing between the sensing and reference electrodes develops a voltage across a series resistor, and this voltage is applied to a recorder (6). A sterilized clip lead (7) is used to protect the sterile field.

The cardiac catheter is a commercially available* Courand catheter with a 90 per cent platinum-10 per cent rhodium electrode, 2 mm. in width, encircling the catheter several millimeters proximal to its tip. The wire to the electrode is embedded in the catheter wall, leaving the lumen patent. The arterial electrodes are prepared by melting one end of a 0.010-inch diameter platinum wire into a sphere, slightly less than 0.030 inch in diameter. Thirty-gage, thin-wall Teflon tubing is

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Figure 1
Schematic diagram of the instrumentation employed for the recording of ascorbate-dilution curves. Numbers are described in the text.

threaded over the wire and sealed to the electrode with Hysol cement.* A small metal contact is soldered to the other end of the platinum wire. The electrode tip is cleaned with acetone, rinsed with water, and prepared for autoclaving. The tip of the no. 18 Cournand needle is modified by blunting the bevel and removing all internal burrs (fig. 2).

Within the control box, (fig. 3), a transistor circuit maintains a 1-volt potential across the electrode terminals. The transistor also prevents the electrode current from ever exceeding 0.6 ma., thus limiting the hazard of cardiac stimulation. The electrode current is measured across one of the series resistors, R11 to R20. A resistor is selected across which not more than 10 mv. is developed by the peak current of the inscribed curve. Thus the electrode voltage always remains within 10 mv. of its original value. A much larger change, e.g., 50 mv., would often introduce significant distortion into the curves. For similar reasons, if a zero offset is desired, the controls of this box are used, rather than the centering controls of the recorder.

Because of their availability, a standard recording potentiometer or an amplifier-galvanometer combination† was used. However, any system would be satisfactory that can produce a full-scale deflection for a current as small as 0.5 microampere without developing more than a 10-mv. drop across the current-measuring element.

Procedure
The electrode is cleaned with saline before it is inserted into the blood stream. Following the introduction of the electrode, the sensitivity on the control box is set so that the baseline current produces approximately one fifth of the full-scale deflection. The current flow stabilizes gradually following the application of voltage to the electrode. It is often convenient to shorten this period of stabilization by first applying an excessive voltage (approximately 1.34 volts) for about 30 seconds before dropping to the 1.0 voltage. If the baseline is still falling, it may be necessary to reapply the overvoltage briefly, or if it is rising excessively, a brief period of short circuiting the electrodes (0 volts) is helpful. It is desirable to avoid frequent interruptions of the voltage applied to the electrode.

The indicator, buffered sodium ascorbate,* is injected at concentrations of 50 or 100 mg. per ml., in doses ranging between 25 mg. and 300 mg., depending on the size of the patient, the hemodynamic state, the volume of blood between the site of injection and sampling, and the intrinsic sensitivity of the electrode.

Results
The linearity of the electrode current with the ascorbate concentration in the blood stream was examined in dogs in which various doses of sodium ascorbate were injected intra-venously. The peak amplitudes, as well as the areas beneath the arterial dilution curves were found to be linearly related to the doses (fig. 4).

Sodium ascorbate dilution curves have been recorded in 25 dogs and in a total of 90 patients. There have been no febrile reactions or other detectable toxicity. In more than one half of the patients studied, the sodium ascorbate curves were compared with indocyanine-green dye-dilution curves, with identical injection and sampling sites; the dye-dilution curves were recorded immediately

‡Model 301 D. C. amplifier and rectilinear recorder, Texas Instrument Co., Houston, Texas.

*Supplied as "Ascorbic Acid" by Lederle Laboratories, Pearl River, New York.

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Figure 2
Schematic diagram of the platinum electrode, the Teflon covering, and the short-beveled Cournand needle.
ASCORBATE DILUTION CURVES IN CARDIOVASCULAR DIAGNOSIS

Circuit diagram of control box.

ALL SWITCHES ARE SHORTING CONTACT TYPE.
ALL MERCUERY BATTERIES.
R 21 TO R 29 0, 10 M, 3.3 M, 1 M, 330 K, 100 K, 33 K, 10 K, 3.3 K - 10 %.
FOR 10 MV RECORDER R 11 TO R 20: 50, 100, 200, 500, 1 K, 2 K, 5 K, 10 K, 20 K, 0
1% PRECISION RESISTORS. (DEPOSITED CARBON).
* SET FOR 1.00 V OUTPUT

Figure 3

before or after the ascorbate curves. For the paired curves, the initial portions, representing the passage of indicator through the central circulation and through any shunt in either direction, were essentially identical. It is this portion of the curve that is of diagnostic significance. In the later portions of the ascorbate curves, generated by indicator that had passed through the peripheral capillary bed and had recirculated, the peaks were smaller than the corresponding peaks in the dye curves.

Comparing the quality of the tracings on systems of equal frequency response, there were generally less artifacts coincident with the pulse in the ascorbate than in the dye curves. With the platinum electrode advanced into the thoracic vessels, these artifacts were more apparent and a signal coincident with respiration was often present, especially in tracings from the right atrium. Intracardiac electrocardiograms were present in high-frequency recordings. Occasional artifacts were noted coincident with movements of the patient. In some instances, the curves had to be repeated in order to distinguish a very small shunt from a respiratory artifact; otherwise these artifacts created no problems.

Ascorbate dilution curves sampled in a peripheral artery following injection into the right atrium of a patient without any cardiac shunt or valvular regurgitation are reproduced in figure 5. In a patient with the tetralogy of Fallot, the presence of a right-to-left cardiac shunt is evidenced by the characteristic early peak in the curves reproduced in figure 6, which were obtained following injection into the right ventricle and sampling from a systemic artery. Figure 7 is an arterial dilution curve obtained following injection into a pulmonary vein of a patient with a left-to-right shunt through an atrial septal defect. There is a sudden inter-
Figure 4

Relationship between peak signal and dose of sodium ascorbate injected.

Figure 5

Ascorbate (left) and indocyanine green dye (right) dilution curves recorded in rapid succession from a systemic artery in a patient without a circulatory shunt following injection of the indicators into the right atrium at the time indicated by the vertical arrows.

Figure 6

Ascorbate (left) and indocyanine green dye (right) dilution curves recorded from a systemic artery in a patient with the tetralogy of Fallot.

Ascorbate dilution curve obtained in a patient with an atrial septal defect following injection into a pulmonary vein (pulm. V.) and sampling from the femoral artery (F.A.). The first peak (1) represents the indicator that followed the normal circulatory path, while the second peak (2) represents the indicator that was shunted through the defect.

Figure 7

Ascorbate (left) and indocyanine green dye (right) dilution curves recorded from a systemic artery in a patient with the tetralogy of Fallot.

Ascorbate dilution curve obtained in a patient with an atrial septal defect following injection into a pulmonary vein (pulm. V.) and sampling from the femoral artery (F.A.). The first peak (1) represents the indicator that followed the normal circulatory path, while the second peak (2) represents the indicator that was shunted through the defect.

Fracture of the descending limb, followed by the abnormally early recirculation curve, a pattern characteristic of arterial dilution curves following injections into the left side of the heart proximal to the origin of such a shunt. A series of intracardiac ascorbate dilution curves obtained in a patient with a large ventricular septal defect are reproduced in figure 8. In each instance the sensing electrode was near the tip of the catheter through which the injections were made. Each curve is characterized by a large, sharp, initial deflection resulting from the reaction of the electrode to the injection of ascorbate. In the curves obtained from the pulmonary artery and the right ventricle, a second peak is apparent; this is due to the early recirculation of indicator through the shunt, and it occurs only in areas at or distal to the site of entry of the shunt into the right side of the heart. In contrast, in the right atrium, a chamber proximal to the site of entry of the shunt, no second peak is exhibited. These curves may be compared to those reproduced in fig.
Figure 9, which were obtained from a patient with an atrial septal defect, in whom the abnormal shunt curve (peak 2) is present both in the curve from the right ventricle and in the curve from the right atrium, thus localizing the entry of the shunt to a point upstream to the tricuspid valve. A distinct systemic recirculation curve (peak 3) is also present.

A series of intracardiac dilution curves following peripheral vein injection in the patient with the ventricular septal defect are reproduced in figure 10. The site of entry of the left-to-right shunt into the right ventricle is localized by the technic previously described. The curves from the pulmonary artery and right ventricle exhibit a distinct interruption of the descending limb, signifying the recirculation of shunted indicator; this is not present in the curve from the right atrium, although the small degree of accompanying tricuspid regurgitation may have been responsible for the slight distortion of the descending limb of the dilution curve obtained from this chamber.

Discussion

Hydrogen, sodium ascorbate, and a number of other substances may be employed as indicators when platinum electrodes are used for direct intravascular detection. The use of hydrogen was not extensively investigated in this laboratory, since the inert foreign gases (N₂O or Kr⁸⁵), which are not associated with an explosive hazard, permit not only the detection and localization of small left-to-right shunts, as does inhaled hydrogen, but also allow determination of the magnitude of the shunt. Similarly, although hydrogen dis-

Figure 8

Intracardiac ascorbate dilution curves obtained from a patient with a large ventricular septal defect with injection into and sampling from the pulmonary artery (P.A., top), right ventricle (R.V., center) and right atrium (R.A., bottom). The vertical arrows represent the onset of injection. The initial deflections (1) represent the injection of ascorbate, and the second deflections (2) represent the ascorbate that recirculated through the shunt.
Intracardiac ascorbate dilution curves obtained from a patient with an atrial septal defect. Injection into and sampling from the right ventricle (R.V., left) and right atrium (R.A., right).

Figure 9

solved in saline may be injected into the right side of the heart for the detection of right-to-left shunts, earlier observations utilizing solutions of Kr in a similar manner indicated the practicality of quantifying such shunts.

It would appear likely that ascorbate equilibrates rapidly with the interstitial fluid and that a significant fraction escapes from the vascular bed during its passage through the systemic capillaries, but that only negligible amounts leave the pulmonary capillaries. Although little clinical significance should be attributed to the amplitude of the peripheral recirculation peaks of the ascorbate curves, the apparently negligible loss of this indicator from the pulmonary circulation suggests that the shunt-to-pulmonary flow ratio may be computed.

As indicated in figure 4, when the current flowing between the electrodes is measured (rather than the potential developed), a linear relationship exists between ascorbate concentration and deflection. Work currently in progress suggests that in spite of the fact that gradual alterations in the sensitivity of the electrode take place, calibration of ascorbate dilution curves is possible, thus permitting quantification of cardiac output.

In the clinical applications of the ascorbate technic in this laboratory, the recording of
curves from a catheter inserted directly into the heart or great vessels has been found particularly valuable. The applications have been facilitated by the availability of electrode catheters that permit both the injection and sampling of indicator through a single catheter. Although the injection of dye into the pulmonary artery and sampling of its concentration through a second catheter in the right side of the heart has proved to be a sensitive technic for the detection and localization of left-to-right shunts, the use of two catheters has, in this laboratory, proved technically cumbersome. The single catheter technic described herein provides a convenient method
for simultaneously introducing both the indicator and the sampling element into the central circulation, thus permitting detection and localization of left-to-right shunts. When the sensing electrode is placed several centimeters behind the tip, the ascorbate technic may also be employed in the study of valvular regurgitation. The indicator is injected distal to the valve under study, and its concentration is detected in the chamber proximal to it. Furthermore, the ascorbate technic has also been found useful in the study of patients with aortic regurgitation and those who have left-to-right shunts originating from the aorta. In these applications the electrode is introduced into the right brachial artery or the central aorta, and ascorbate is injected by means of a second catheter into the aorta at a more distal site, as described previously.

A distinct advantage of the ascorbate-dilution technic is the ease with which curves may be repeated. As many as 23 dilution curves have been carried out in the course of a single catheterization; the injection of up to 6.5 Gm. of sodium ascorbate has resulted in no detectable side effects. The cost of this indicator is considerably less than indocyanine-green dye. Finally, the ability to record dilution curves without the need for complex detecting devices (densitometer, oximeters, scintillation crystals) should prove advantageous in many laboratories and under many experimental and clinical circumstances.

Summary

The instrumentation and clinical applications, in this laboratory, of Clark’s sodium ascorbate dilution technic are described. With this method the sensing device, a platinum electrode, is introduced directly into the blood stream, and a reducing agent, sodium ascorbate, is used as the indicator. Time-concentration curves may be obtained without the withdrawal of blood. Observations in 90 patients have indicated that the contours of the dilution curves are essentially identical to indocyanine-green dye-dilution curves, except for diminished peripheral recirculation peaks.

The ascorbate-dilution technic has been found of particular value when the sensing electrode is incorporated into a cardiac catheter. This method permits injection and sampling of the indicator from the central circulation and greatly facilitates the study of circulatory shunts and of valvular regurgitation.

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References


The basis of the practice of medicine will always be the study of disease at the bedside by every available method, and since Sydenham is the archetype of those who believe that the most successful way of studying disease is at the bedside, his name will forever endure.

The epitaph on his monument in St. James' Church, Westminster, is magnificent and true:

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