Clinical Use of Ascorbic Acid as an Indicator of Right-to-left Shunt*

With a Note on Other Applications

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Many indicator dilution techniques have been employed within recent years in the detection of right-to-left shunts (Nicholson, Burchell, and Wood, 1951; Cooper *et al.*, 1960; Long, Braunwald, and Morrow, 1960; Symposium, 1958). The indicator most commonly used for this purpose at present is indocyanine green (Symposium, 1958). Although the latter has proved to be satisfactory for many purposes, there remain disadvantages in its use: (a) there is blood loss associated with withdrawal of samples (a disadvantage particularly pertinent where total blood volume is small, as in infants); (b) difficulties may be encountered in the cannulation of small vessels, a frequent problem in infants and children, resulting in a less than adequate sampling speed; (c) the recording system is expensive, as is the dye itself; (d) the method requires relatively complex instrumentation. Another method, originally described by Clark *et al.* (Clark *et al.*, 1960; Clark and Barger, 1959), using ascorbic acid (Frommer, Pfaff, and Braunwald, 1961) or dissolved hydrogen as an indicator, overcomes all the objections listed above in regard to the use of indocyanine green, and is also superior to the krypton method for essentially the same reasons. The purpose of the

present report is to demonstrate the application of ascorbic acid for the detection of right-to-left shunts in a diagnostic cardiovascular laboratory and to describe some modifications of the original technique. In addition, its applicability in cases with left-to-right shunts and those with valvular regurgitation will be demonstrated.

SUBJECTS AND METHODS

During cardiac catheterization, carried out for a variety of reasons, 51 observations were made in 22 patients with various types of congenital heart disease. In 16 patients these studies were done to prove the presence or absence of a small right-to-left shunt (Table I). The method was also used in 4 patients to demonstrate a left-to-right shunt and in 2 to verify the presence of valvular regurgitation. The data on these latter 6 patients appear in Table II.

A schematic diagram of the circuit used is seen in Fig. 1. The circuitry is minimal and can be constructed for under 10 dollars. The principle of operation relies on the electrical potential that appears at a platinum electrode in the presence of a strong reducing agent such as ascorbic acid.

An indifferent electrode of pure silver is fastened to the patient's skin and connected to one input terminal of a conventional electrocardiogram amplifier through a connexion box (Fig. 1 and 2). The D.P.D.T. switch of the connexion box serves to ground both input terminals of the amplifier while connexions are being made to the patient. The other input terminal of the electrocardiogram amplifier is connected through a lead with an alligator clip to a braided platinum wire which has been inserted in the brachial artery. The latter is exposed and

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TABLE I
CATHETERIZATION STUDIES IN 16 PATIENTS WITH RIGHT-TO-LEFT SHUNT

Case No.	Age (yr.)	Diagnosis*	Right ventricular pressure (mm. Hg)	Brachial artery pressure (mm. Hg)	Peripheral O ₂ sat. (%)	Injection site	Appearance time (sec.)		Injection site	Appearance time (sec.)		Shunt site as determined by	
							1st	2nd		1st	2nd	Ascorbic acid	Cine-angiography
1	2 6/12	PS	110/6	80/42	95	SVC	1.7	—	RV	3.9	—	Atrial	No VSD; No RA inj.
2	3/12	PS	115/8	110/56	90	RA	0.8 1.2	3.0 3.4	RV	2.8	—	Atrial	No VSD; no RA inj.
3	4 6/12	PS	204/15	132/68	92	RA	1.7 2.0 1.3	—	RV	4.2 3.9 3.8	—	Atrial	No VSD
4	7/12	PS	140/8	98/53	74	RA	2.7	—	RV	6.6	—	Atrial	Atrial
5	6 11/12	PS	200/11	122/70	98	RA	3.5	—	RV	4.0	—	None	No VSD
6	9 6/12	PS; VSD	88/4	100/62	93	—	—	—	RV	2.9	5.0	Ventr.	VSD
7	11	PS; PR; VSD	70/8	110/50	95	RA	3.4	7.0	RV	4.4	6.8	Atrial†	probable Not done
8	3 6/12	PS	180/13	80/40	97	RA	5.6	—	—	—	—	None†	None
9	10 10/12	PS; VSD	105/	116/77	82	RA	4.6 4.1	—	RV; Pulm. art.	3.0 7.3	—	Ventr.	Ventr.
10	1 8/12	PS	180/8	100/42	95 (pulm. vein 100)	RA	2.6	—	RV	4.4	—	Atrial†	Atrial
11	4/12	PS	80/6	96/40	94	RA	1.0	—	—	—	—	?Level	No VSD
12	1 6/12	PS; TR; ASD	180/	88/48	69	RA	2.2 2.8	—	RV	1.6 2.3	7.8 8.6	Atrial	Atrial
13	5	VSD; Pulm. vasc. obstr.	88/4	100/62	93	—	—	—	RV	2.9	5.0	Ventr.	Not done
14	22	VSD; Pulm. vasc. obstr.	100/	106/64	91	RA	2.6	—	RV	2.9	8.7	Ventr.	Ventr.
15	7 9/12	VSD; Pulm. vasc. obstr.	85/5	98/58	92.5	RA	2.9	—	RV; Pulm. art.	1.5 3.9	—	Ventr.	Ventr.
16	8 2/12	Ebstein's deformity	22/7-12	100/70	87.0	RA	4.9	—	RV	9.2 9.0	—	Atrial	No VSD

* PS is pulmonary stenosis; VSD is ventricular septal defect; PR is pulmonary regurgitation; TR is tricuspid regurgitation; ASD is atrial septal defect.

† Confirmed by indocyanine green injection.

cannulated by a No. 21 or No. 20 arterial needle. The puncture site affords easy introduction of the wire which has a globular tip to avoid damage to the intima (Fig. 3).

The standard platinum wire can be constructed by twisting seven strands of No. 34 AWG platinum wire and fusing the end with an oxygen burner (Fig. 3). If the wire is stranded, its flexibility is such that once inserted

TABLE II
CATHETERIZATION STUDIES IN 4 PATIENTS WITH LEFT-TO-RIGHT SHUNT, AND IN 2 WITH VALVULAR REGURGITATION

Case No.	Age (yr.)	Diagnosis	Injection site	Sampling site	Appearance time (sec.)		Conclusions	Confirmation by cine-angiograms
					1st	2nd		
17	17	VSD; TR; PR	RV	RA RV	0.2 0.2 Immed.	8.5 7.7 8.5	Consistent with tricuspid regurgitation	Not done
18	24	VSD; Pulm. vasc. obstr.; PR	Pulm. art.	RV	1.3	4.0	Consistent with pulm. regurg. and vent. septal defect	Not done
19	6	VSD (small)	LV	RV	1.0	—	Consistent with L-R shunt at ventricular level	Yes
20	14	(VSD small)	LV LV	RV RA	0.6 2.0	— —	Consistent with L-R shunt at ventricular level	Yes
21	11 1/12	VSD	LV LV	SVC RV	6.4 0.2 0.2	— — —	Consistent with L-R shunt at ventricular level	Yes
22	11 8/12	VSD; PS	Aorta	Pulm. art.	0.2 No curve	— —	Consistent with absence of aortopulmonary shunt	Not done

FIG. 1.—Schematic display of simple circuit used in ascorbic acid studies.

in the lumen of a vessel it can be easily advanced without danger of perforating the vessel wall. Although an even greater electrical signal can be obtained if platinum black is deposited on the wire (Clark and Barger, 1959), it

has been our experience that “blackened” electrodes are easily “poisoned” and rendered unresponsive. An adequate signal can be obtained with plain braided platinum if the above described wire is advanced a distance of 5 or

FIG. 2.—(A) Lead joining silver (indifferent) electrode to connexion box. (B) Lead joining platinum electrode to connexion box. (C) Connexion box with double-pole double-throw switch.

FIG. 3.—Photograph of braided platinum wire with terminal bead, displayed against millimetre scale.

more centimetres into the lumen of the artery to avoid blockage of the flow. The tissue impedance is such that no insulation of the platinum wire is required. Electrical contact between the alligator clip and the patient's skin or wound must be avoided. To prevent this, dry gauze sponges can be used to advantage as electrical insulators.

The lead joining the connexion box to the platinum electrode should be electrically shielded and insulated with a material that can be autoclaved. Such small flexible shielded leads are not generally available but can be constructed easily by shielding a section of No. 24 AWG teflon-covered stranded wire with 3/64 in. (0.1 cm.) shielding (Belden). One end is attached to a miniature plug (Switchcraft) and the other to a miniature alligator clip. The lead joining the connexion box to the silver electrode, consisting of a rubber-covered single-conductor shielded wire, need not be autoclaved and may also be connected to the silver electrode by a miniature alligator clip. A small bar of pure silver will serve well as a reference electrode, though a well-cleaned standard electrocardiographic electrode may also be used. A photograph of the connexion box and leads is shown in Fig. 2. A 1 5/8 × 2 3/4 × 2 1/8-in. (4 × 7 × 6 cm.) aluminium box (Middletown) is adequate in size. Appropriate receptacles (Switchcraft) can be obtained for the miniature plugs. The box is grounded to the amplifier through a three conductor jack.

Small amounts of ascorbic acid (50–200 mg.) can be used safely and amounts up to 800 mg. have been injected without complications. In the studies to be described, the indicator was injected through a catheter into the appropriate cardiac chamber either after filling the injecting catheter with ascorbic acid and using an additional 100 mg. as a flush or by following a bolus of ascorbic acid with a flush of saline. The exact moment of injection was marked by hand and the arrival time at the platinum electrode detected by the system described.

Some of the studies were performed using a commercially available platinum-tipped catheter* placed in the various cardiac chambers. In these cases, the circuitry described above remained exactly the same

* U.S. Catheter Corp., Glens Falls, New York.

except for substitution of the electrode catheter for the braided platinum wire.

RESULTS

Table I gives the results in 16 patients in whom right-to-left shunts were suspected. In all cases the appearance of the ascorbic acid was detected by the braided platinum wire in the brachial or femoral artery. Double-peaked curves resulting from the ascorbic acid reaching the peripheral artery by two pathways (i.e. across the shunt and through the pulmonary circulation) were seen in only 5 patients (Cases 2, 6, 7, 13, and 14). In 7 patients with single-peaked curves the presence of a shunt at either atrial or ventricular level could be determined only by the different appearance times of ascorbic acid, depending on whether the injection was made "upstream" or "downstream" to the site of the defect (Cases 1, 3, 4, 9, 10, 15, 16). The remaining 4 (Cases 5, 8, 11, 12) illustrate evidence which can be helpful but by itself may not be considered diagnostic. Injections of the ascorbic acid into the right atrium and right ventricle of Case 5 gave the same appearance time. Since angiocardiology and arterial oxygen saturations did not indicate any right-to-left shunt, despite the presence of a right ventricular pressure of 200/11 mm. Hg, ascorbic acid curves in this case confirmed the absence of any right-to-left shunt. Likewise, in Case 8, in whom the probability of a right-to-left shunt had been excluded by other means, the appearance time of 5.6 seconds after right atrial injection was considered confirmatory evidence. Since in the entire group of 22 (most with multiple injections) the longest appearance time of ascorbic acid through a proven right-to-left shunt was 4.9 seconds, it appears that single curves delayed

beyond 5 seconds may be considered as confirmatory evidence of the absence of any right-to-left shunt. In Case 11 there is again a single curve after a right atrial injection. Here the appearance time was 1 second. Since the shortest appearance time found in patients without a shunt was 2.7 seconds and the shortest pulmonary circulation time (PA to LA) was 2.1 seconds (Case 6), this early appearance time in a single curve is consistent with the presence of a shunt. In Case 12 there was marked tricuspid regurgitation as well as an atrial septal defect. Although the presence of a shunt was established, its precise site could not be determined by differential appearance times after right ventricular and right atrial injections. In this case cine-angiocardigraphic evidence was required to establish the exact diagnosis.

The details of the findings in the remaining 6 of 22 patients, where the method was applied for a variety of reasons, appear in Table II. In these the ascorbic acid was used in conjunction with sampling platinum catheters to establish the presence or absence of left-to-right shunting or valvular regurgitation.

DISCUSSION

The single most frequent, and important, use of this technique in our laboratory was in the detection and localization of small right-to-left shunts in patients with pulmonary stenosis (Cases 1 to 12, Table I). A decreased arterial oxygen saturation, while suggestive, is not diagnostic by itself of the presence of a shunt. In order for saturation data to establish conclusively the presence and the site of a right-to-left shunt, multiple blood samples from left ventricle, left atrium, and pulmonary veins would have to be obtained. Furthermore, with small shunts, oxygen data alone may be equivocal, as noted in many of the cases described. In many instances localization of the site of the shunt is not possible without angiocardigraphic means or indicator dilution curves, which may be time-consuming and cumbersome.

In this laboratory, ascorbic acid has proved to be a simple, practical, and efficient indicator with which to localize right-to-left shunts. While it may take multiple injections to obtain conclusive results, if there is not an obvious double-peaked curve indicative of a right-to-left shunt, these can be accomplished in rapid succession, and from different injection sites, to confirm an early appearance of the indicator.

Since almost all of the curves obtained with ascorbic acid show a prolonged downslope, a fact probably related to the nature of the reaction at the

electrode site, the delay in the downslope of an early curve appears to be the reason for the frequent observation of single rather than double-peaked curves in patients with established right-to-left shunts. The curves illustrated in Fig. 4 demonstrate the usefulness of single curves when analysing their appearance times only. About one-half of the cases showing a right-to-left shunt displayed the familiar double-peak configuration (Fig. 5). Analysis of the curves from the entire series suggests that in dealing with single-peaked curves, an appearance time of 5 seconds or greater should be considered strong evidence against a right-to-left shunt and an appearance time of 2 seconds or less can be used as evidence in favour of a right-to-left shunt.

In the cases described, indocyanine green dye would have, in all probability, demonstrated the right-to-left shunt equally well. However, the disadvantages previously mentioned, particularly with regard to blood loss, limited its use to only 4 of the entire series of 22 patients. In none of these 4 was information obtained by indocyanine green that was not recorded by the ascorbic acid method. The problems of adequate sampling, blood loss, and its replacement, inherent in multiple extravascular samplings through a photoelectric system, are particularly well illustrated in the eight small children described in Table I (Cases 1-4, 8, 10-12).

Other applications of ascorbic acid as an indicator are in patients with suspected valvular regurgitation or left-to-right shunts. An example is given in Case 17 (Table II), a patient with tricuspid regurgitation, in whom ascorbic acid was injected through a platinum electrode catheter in the right ventricle and sampled from a similar catheter in the right atrium (Fig. 6). Here the larger curve of each pair is inscribed from the right ventricular catheter, recording the moment of injection of the indicator, while the smaller curve with a slightly later onset is recorded from the right atrial catheter and reflects the presence of regurgitation. Quantitation of regurgitation was not attempted by this method. A similar situation existed in Case 18 (Table II), a patient with pulmonary regurgitation. Here a double-ringed platinum-tipped catheter was employed instead of separate sampling and injecting catheters. The disadvantage of this type of catheter is the fixed distance between the electrodes, which, if large, may preclude the demonstration of small degrees of regurgitation. In a patient suspected of having a patent ductus arteriosus (Case 22—Table II) ascorbic acid was injected into the aortic arch and sampling was carried out by the electrode catheter in the main and left pulmonary artery. Late appearance times excluded the presence of an appreciable left-to-right shunt through a ductus.

FIG. 4.—(A) Injection of ascorbic acid into superior vena cava with sensing wire in peripheral artery. (B) Injection of ascorbic acid into right ventricle with sensing wire in peripheral artery. Short appearance time (1.7 sec.) from SVC as compared to RV (3.9 sec.) illustrates right-to-left shunt at atrial level in a 2½-year-old boy with pulmonary stenosis (Case 1—Table I).

A similar use was shown in Cases 19, 20, and 21 (Table II) where a left-to-right shunt through a small ventricular septal defect was demonstrated by injecting the indicator into the left ventricle and sampling from the right ventricle. It is of interest

that in one of these studies, the appearance time from left ventricle to right ventricle was 0.6 sec., from left ventricle to right atrium 2.0 sec., and from the left ventricle to superior vena cava a normal 6.4 sec. This suggested the presence of tricuspid

FIG. 5.—Example of double-peaked curve with injection of ascorbic acid into right atrium and peripheral sampling but only single curve with injection into right ventricle. Appearance time of secondary curve in RA injection. (AT_2) is similar to appearance time of RV injection, representing main bolus of ascorbic acid traversing pulmonary circulation. This 3-month-old child had right-to-left shunt at atrial level with pulmonary stenosis (Case 2—Table I).

FIG. 6.—Example of tricuspid regurgitation (Case 17—Table II) demonstrated by use of two platinum electrode catheters. The right ventricular catheter was used for injection of the ascorbic acid and records its presence in the RV instantaneously. The right atrial catheter records the indicator almost simultaneously. Arrow indicates time of injection on two occasions. The smaller secondary curves recorded from both electrodes represent a recirculation.

regurgitation. The left ventricle to right ventricle time in the other two patients was 1.0 sec., and 0.2 sec., respectively. These measurements, unaffected by sampling delays, give some insight in average intracardiac circulation times and confirm some of the physiological measurements made earlier with hydrogen as an indicator (Hugenholtz *et al.*, 1963).

The major difference between this technique and that described earlier by Clark and Barger (1959) lies in the use of a simple braided and very pliable platinum wire (Fig. 3). This change provides the large surface area needed for developing a sufficient potential to be detected with a standard electrocardiograph pre-amplifier. Furthermore, it avoids the erratic results of "platinizing" recommended by Clark, and it corrects the rigid characteristics of the Clark electrode permitting sampling in small arteries. Finally, with this modification there appears to be no need, at least for qualitative work, to use the more complex circuitry designed by Frommer *et al.* (1961) which utilizes a polarizing voltage on the electrode.

The present simple circuit is identical to that reported from this laboratory for the detection of left-to-right shunting using hydrogen gas as an indicator (Hugenholtz *et al.*, 1963). The combined use of ascorbic acid injections and hydrogen inhalation has proved so practical in the detection and localization of shunts in either direction that it has

superseded all other screening methods. These techniques are frequently used before the usual routine of obtaining intracardiac pressures, oxygen saturations, and cine-angiography, and have proved helpful in shortening the duration of the catheterization procedure. Clark originally proposed a preparation of hydrogen dissolved in water as an indicator superior to ascorbic acid (Clark *et al.*, 1960). Since ascorbic acid is available as a prepared and inexpensive solution, it proved much simpler to use and was just as satisfactory. In addition it has obvious advantages for laboratories unwilling to store hydrogen gas. The same precautions as noted in the study using hydrogen gas (Hugenholtz *et al.*, 1963) and by Weinberg *et al.* (1962) with regard to the hazard of inducing ventricular fibrillation via an internal electrode should be followed, particularly with the use of the platinum catheter. Details of such precautions have been given before (Hugenholtz *et al.*, 1963).

SUMMARY

The use of ascorbic acid has been demonstrated in 51 indicator dilution curves obtained in 22 patients with a variety of cardiac defects. Its advantages over the more commonly used dye dilution methods were enumerated and its application in the detection of right-to-left shunts, valvular regurgitation, and left-to-right shunts was demonstrated. Certain modifications of the original method of Clark have been described.

This method is as simple as the hydrogen inhalation technique previously described and uses the same electrical circuit. These two indicators and techniques appear to be a most satisfactory combination for the purpose of screening patients suspected of having intracardiac shunts in either direction, and for the study of these problems in infants and children where the usual indicator dilution techniques cannot be used.

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