Left-to-Right Shunt Detection by an Intravascular Electrode with Hydrogen as an Indicator

Abstract. Hydrogen gas crosses the pulmonary membrane and dissolves in blood, and it therefore appears immediately and in high concentration in the left heart and later and in lower concentration in the right heart. The hydrogen-sensing, platinum black-tipped catheter is uniquely sensitive in detecting the left-to-right shunts.

An electrode sensitive to a foreign gas in aqueous solution should have several applications in biological and medical research. The classic hydrogen reference electrode principle has been applied to measure gaseous hydrogen concentration (pH_2), instead of hydrogen ion activity, according to the equation:

$$2H^+ + 2e \rightleftharpoons H_2$$

Preliminary studies (*1*) have indicated that, contrary to what might be expected on the basis of the sensitivity of colloidal platinum to "poisoning," a platinum black electrode produces very sizable potentials, with respect to a reference electrode, when exposed to blood containing hydrogen. Potentials of up to 300 mv are observed, and these are, of course, relatively simple to measure and record even in the presence of the potentials generated by the heart.

A number of types of platinum and palladium electrodes were prepared and tested. Platinum black electrodes were found to be satisfactory. They were prepared by making the platinum the cathode (1.5 v) in a 5-percent solution of platinic chloride while using a platinum electrode of similar area as an anode until a perceptibly grey coating was deposited. They retained their sensitivity to hydrogen over a period of several weeks even though allowed to become dry, repeatedly exposed to blood, cleaned, and sterilized by soaking in 70-percent alcohol or by autoclaving. The most convenient reference electrode was found to be a silver chloride coated silver plate cut in the shape of an "L" with the parts long enough to prevent the generation of abnormal reference potentials by fluids contacting a solder joint. This silver–silver-chloride reference was brought into contact with the skin through a saline-soaked pad. Measurements of potential were obtained by connecting the reference and platinum directly to a model G Beckman *p*H meter, to a 100-mv-span model G-11A Varian, or to a multichannel Electronics for Medicine recording oscilloscope, using any of the d-c amplifier circuits available with this instrument.

A membrane electrode, similar in principle of design to that described by Clark (*2*), was used to give a signal when hydrogen gas flowed by its tip. In a dog, one platinum black-tipped catheter was placed in the aorta just distal to the aortic valve; the other was placed in the superior vena cava near the right auricle. The membrane electrode was placed in a tracheal window. Figure 1 is a simultaneous recording of the potentials developed by these electrodes following one breath of 100-percent hydrogen.

The subject for the observation shown in Fig. 2 was a child known to have a pulmonary valvular stenosis and a ventricular septal defect and a predominant left-to-right shunt. Curves *RV* and *IVC* were obtained by moving the electrode-tipped catheter from one location to another, with an inspiration of hydrogen at each location, as described in the legend. The 2-second-delay fast-slope curve obtained for the right ventricle demonstrates the existence of the left-to-right shunt (subsequently established by blood oxygen analysis and cineangiography).

Although the potential developed by the platinum black-tipped catheters used is not strictly quantitative, the differences in timing, rate of response and final potential developed are so great that little difficulty is encountered in distinguishing between left heart blood and right heart blood after inspiration of hydrogen.

The application of this technique in the detection of left-to-right shunts is being explored in a variety of patients. We are attempting to design a multiple elec-

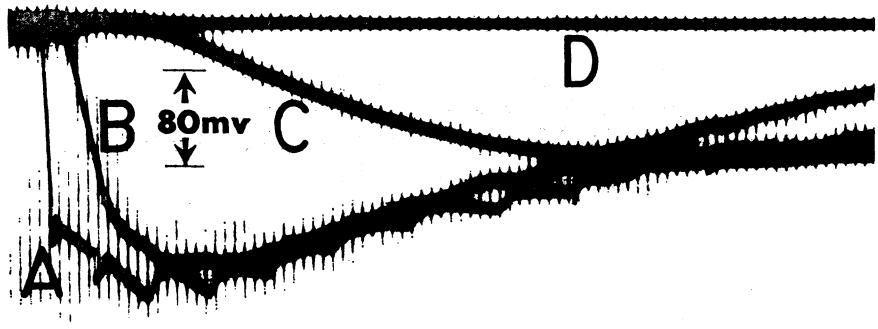

Fig. 1. Potentials developed by tracheal, aortic, and vena caval platinum black electrodes in an anesthetized dog. (*A*) Trachea. This potential signals the appearance of hydrogen in the trachea. Note also the changes in hydrogen concentration in the trachea as the lungs are cleared of hydrogen by respiration. (*B*) The increase in hydrogen content of blood in the aorta begins 2 seconds after passage of hydrogen through the trachea is detected. Maximum response occurs in approximately 12 seconds. (*C*) Increase in hydrogen in the vena cava begins about 8 seconds after hydrogen appears in the aorta and reaches a maximum in about 1 minute. At higher paper speed, the pattern of the electrocardiogram is useful in locating the position of the catheter tip. (*D*) Base line. Vertical marks are 1-second intervals.

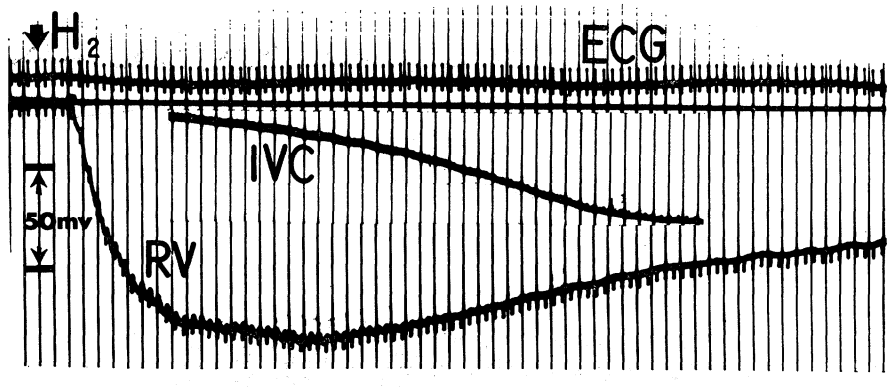

Fig. 2. Hydrogen potentials from right ventricle and vena cava of a patient with a ventricular septal defect and pulmonic stenosis, having a left-to-right shunt. At the point indicated by the large arrow, one breath of hydrogen was administered by mask. The sudden increase in potential from the catheter tip in the right ventricle (curve *RV*) indicates the presence of left heart blood flowing directly into the right ventricle. The superimposed curve (*IVC*) was obtained later from the same catheter after the tip was withdrawn to the inferior vena cava and a second breath of hydrogen was given. The large arrow also indicates the hydrogen inhalation point for the *IVC* curve. The vertical lines show 1-second intervals. Note that the electrocardiogram (*ECG*) is superimposed on the *RV* curve but is barely detectable on the *IVC* curve. Note also the lack of effect of one breath of hydrogen on the electrocardiogram.

trode catheter whereby hydrogen potential measurements may be made simultaneously at various points and where blood samples and pressure measurements can be taken at the same time (*3*).

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References and Notes

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2. L. C. Clark, Jr., *Trans. Am. Soc. Artificial Internal Organs* 2, 41 (1956).
3. This research was supported by U.S. Public Health Service grants H-3109 and H-2602 (C-2). We express our appreciation for the interest and encouragement of Dr. Champ Lyons.

Note added in proof: Since this report was submitted for publication, a large number of diagnostic catheterizations have been completed, by means of the hydrogen electrode catheter; these are described in a report in *Surgery* (in press).

13 April 1959

Potentiation of Epinephrine and Norepinephrine by Iproniazid

Abstract. The effects of pretreatment with iproniazid on the toxicity and cataract-producing ability of epinephrine and norepinephrine were studied. The epinephrine and norepinephrine were administered in such a way that a slow, prolonged rate of absorption was achieved. Under these conditions, the lethality and cataract-producing ability of these amines were shown to be significantly enhanced by the action of iproniazid.

To explain the psychic effects of iproniazid, it has been postulated that this substance potentiates the effects of certain physiological amines by inhibiting monamine oxidase (*1*). Although potentiation of serotonin (*2*) and dihydroxyphenylalanine (*3*) has been produced by preadministration of iproniazid, significant potentiation of the effects of epinephrine and norepinephrine by iproniazid has not been shown previously.

To demonstrate potentiation by iproniazid, a slow, prolonged rate of absorption of epinephrine and norepinephrine was attained in three ways: by subcutaneous administration, by repeated intraperitoneal injection, and by slow intravenous perfusion of the amines. At more rapid rates of absorption, no potentiation could be shown. For example, we were not able to show potentiation of single intraperitoneal doses of norepinephrine by iproniazid in rats, nor were we able to show a significant difference in the amount of norepinephrine required to kill rats perfused intravenously at a relatively rapid rate.

In the experiments described below, doses of iproniazid reported to inhibit completely monamine oxidase were used (*4*). Mice routinely received 100 mg/kg, and rats, 50 mg/kg. In each case, enough time was allowed for the iproniazid to inhibit the monamine oxidase before the catechol amines were administered. Doubling the dose of iproniazid in mice did not further potentiate the effects of the amines.

The results given in Table 1 show that iproniazid potentiates the toxicity and cataract-producing ability of subcutaneously administered epinephrine and norepinephrine. Both multiple small doses and a single larger dose of these amines were effective in demonstrating the potentiation. Griesemer had found incidentally that a single subcutaneous dose of 0.5 mg of epinephrine per kilogram which killed none of 15 controls, killed 21 of 41 rabbits that had been injected with 50 mg of iproniazid per kilogram 12 hours and 2 hours prior to the administration of epinephrine (*5*).

Using a total of 130 rats, we could show no potentiation by iproniazid of epinephrine given in single doses intraperitoneally. The results of the studies of subcutaneously administered amines prompted us to administer the norepinephrine in divided doses intraperitoneally to obtain a more prolonged rate of absorption. One-half milligram of norepinephrine was given every 15 minutes for 13 doses to rats pretreated with iproniazid and to control rats pretreated with saline. Thirteen of 20 rats pretreated with iproniazid and four of 20 controls died of this treatment ($p = < 0.01$).

In the studies in which the catechol amines were administered subcutaneously and intraperitoneally, the potentiation by iproniazid could have been due to the fact that the iproniazid prevented the amines from being destroyed before they were absorbed from the injection site. To test this possibility, the amines were infused intravenously at a slow rate. Unanesthetized rats were used, to avoid the effect of drugs which depress the central nervous system, which have been shown to antagonize the toxicity of epinephrine (*6*). The jugular veins of the rats were cannulated under light ether anesthesia, and an hour was allowed for complete recovery from the anesthetic. The weights of the animals in the two groups were identical. The animals were perfused with DL-norepinephrine bitartrate at a rate of 1 mg/cm^3 per 85 minutes. The rats pretreated with iproniazid died after having received 0.73 ± 0.66 mg, the controls, after having received 4.66 ± 1.74 mg ($p = <0.01$). The heightened sensitivity of rats pretreated with iproniazid to intravenously administered norepinephrine indicates that the potentiation seen in the studies in which the amines were administered subcutaneously and intraperitoneally was not due solely to a difference in the amount of intact amine available for absorption.

Seven controls and seven rats pretreated with iproniazid, when perfused with 1.5 mg of DL-norepinephrine per cubic centimeter per 85 minutes failed to show a significant difference in response, although, on the average, less of the amine was needed to kill the animals pretreated with iproniazid (0.83 ± 0.44 mg, as opposed to 2.0 ± 1.33 mg).

It has been shown that iproniazid profoundly alters the metabolism of epinephrine and norepinephrine, presumably by inhibiting monamine oxidase (*7*). Such inhibition provides a possible explanation for the potentiation of these catechol amines by iproniazid. It may be that the amines must be absorbed slowly in order to show the potentiation because the monamine oxidase system slowly deaminates the amines in vivo, as it does in vitro (*8*). At faster rates of absorption the monamine oxidase system may have little opportunity to inactivate any of the dose administered before a toxic level is reached; therefore, control animals and animals pre-

Table 1. Effects of iproniazid on the incidence of mortality and of cataract produced by catechol amines given subcutaneously.

Drug and No. of doses*	Total dose (mg/kg)	Species	No. dead at 24 hours per No. used		No. with cataract per No. of survivors at 4 hours	
			Animals pretreated with iproniazid	Controls	Animals pretreated with iproniazid	Controls
Epinephrine, 4	8	Mouse	17/20	5/20 †	7/8	5/17 ‡
Epinephrine, 6	6	Rat	18/18	9/18 †	4/6	0/16 ‡
Norepinephrine, 5	20	Rat	5/8	0/8 ‡	5/8	0/8 ‡
Norepinephrine, 1	12.5	Rat	10/10	4/10 ‡		

* Interval between doses, ½ hour. † $p < 0.01$. ‡ $p < 0.05$.