Cardiac Effects of Isoproterenol, Norepinephrine and Epinephrine in Complete A-V Heart Block During Experimental Acidosis and Hyperkalemia

By Santiago V. Guzman, M.D., Antonio C. DeLeon, Jr., M.D., James W. West, Ph.D., and Samuel Bellet, M.D.

Acidosis was found to diminish the effectiveness of various sympathomimetic amines (isoproterenol, norepinephrine, and epinephrine) in increasing the idioventricular rate in dogs with experimentally induced complete A-V heart block. This diminution was correlated with the degree of acidosis (metabolic and respiratory). Hyperkalemia without significant pH change had no such effect.

Isoproterenol, epinephrine and similar drugs have been shown to be effective in restoring cardiac activity during episodes of Stokes-Adams attacks and cardiac arrest from other causes. However, in some of these states the sympathomimetic amines fail to restore cardiac beating or increase the slow idioventricular rate. Recent reports from our laboratory have shown that molar sodium lactate increased the heart rate in some cases of partial and complete A-V heart block and restored cardiac beating during the cardiac arrest of Stokes-Adams syndrome, hyperkalemia, surgery and in the terminal states when the sympathomimetic amines were ineffective. In those cases which responded favorably to molar sodium lactate, acidosis and/or an electrolyte disturbance was observed prior to therapy. It would seem, therefore, that the nonresponsiveness of the idioventricular pacemaker to the sympathomimetic amines in some cases of cardiac standstill may be the result of electrolyte disturbances. Furthermore, the efficacy of molar sodium lactate in this state may be due not only to the amelioration of the hyperkalemia, but also to the correction of the blood pH towards more normal levels. Studies were therefore undertaken in an attempt to elucidate some of the underlying mechanisms involved in the alteration of cardiac rhythmicity and response to the sympathomimetic amines at various pH levels.

Methods

The experiments were performed under light pentobarbital anesthesia (30 mg./Kg.) on young adult mongrel dogs weighing 15 to 25 Kg. Complete heart block was produced by injecting 2 to 4 ml. of 10 per cent formalin solution into the superior part of the interventricular septum by a direct right atrial needle puncture through a right lateral thoracotomy approach. The exact site of formalin infiltration was the annulus of the septal leaflet of the tricuspid valve, 1.0 to 1.5 cm. anterior to the coronary sinus. This includes the region of the A-V node and its bifurcation into the right and left bundle. Necropsy of the heart showed hemorrhagic and/or fibrotic changes in the lower interatrial and the superior part of the interventricular septum. A mortality rate of 25 to 50 per cent occurred during the first 24 hours post-operatively. Following 7 to 10 days post-operatively, the animals were fully recovered and survival rate at this stage ranged from 80 to 90 per cent.

Systemic blood pressure was recorded from the femoral artery with a Statham strain gage transducer.

From the Division of Cardiology, Philadelphia General Hospital and the Department of Pharmacology, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

Supported by grants-in-aid from the Tobacco Industry Research Committee and the American Heart Association.

Work done during Dr. Guzman's tenure of a Research Fellowship of the American Heart Association.

Received for publication March 13, 1959.
CARDIAC EFFECTS OF SYMPATHOMIMETICS

Fig. 1. Effects of respiratory (A) and metabolic (B) acidosis on the idioventricular rate/min., total CO₂ content (vols. per cent of whole blood), blood pH (whole blood), and serum sodium and potassium (mEq./L.). Note that in respiratory acidosis, there was in addition, a progressive increase in serum potassium and a drop in serum sodium. In both instances, a marked decrease in idioventricular rate was noted. Note also the significant increase in the idioventricular rate following the withdrawal of CO₂ inhalation (A) and partial correction of the metabolic acidosis (B).

Respiratory acidosis was induced by inhalation of 20 per cent carbon dioxide in oxygen through a tracheal cannula for periods of 8 to 12 min. Metabolic acidosis was produced by intravenous (femoral) infusion of 8 to 10 mEq./Kg. of ammonium chloride (40 mEq./100 ml. solution) for a period of 3½ to 4 hours. Hyperpotassemia was produced by infusion of isotonic potassium chloride (0.4 to 0.5 mEq./Kg./min.) over a period of 30 min. to 1 hour. During these experiments, serial arterial blood samples (heparinized) were obtained from a femoral arterial catheter at appropriate periods in each of the different experimental conditions (acidosis and hyperkalemia) for determining changes in pH, CO₂, O₂, K, Na and Cl. Whole blood pH was immediately measured in a Beckman pH meter at room temperature, with a correction of 0.01 pH for each degree below 37 C. Blood O₂ and CO₂ content were determined by the method of Van Slyke and Neil. Serum sodium and potassium were analyzed by an internal standard flame photometer.

In another series of experiments the circumflex branch of the left coronary artery was catheterized through one of the carotid arteries under fluoroscopic guidance. It has been demonstrated previously that drugs injected through the left circumflex artery affects the A-V nodal region, idioventricular pacemaker, and left ventricle. This technic, therefore, enabled us to administer drugs directly to a localized portion of the heart in doses large enough to elicit local response without producing systemic effects.

A total of 22 experiments were made on 12 dogs with chronic complete A-V heart block over a period of 2 months. The effects of intravenous and intracoronary injections of isoproterenol,
levarterenol and epinephrine were studied in the control state and during varying degrees of acidosis and hyperkalemia, as well as after correction of these abnormal states. In a few experiments, small amounts of sodium lactate were given by the intracoronary route to produce a transient change in pH in the area supplied by the left circumflex coronary artery without altering the state of metabolic acidosis.

RESULTS

Ammonium Chloride Acidosis. The blood electrolyte and electrocardiographic alterations resulting from ammonium chloride infusion are shown in figures 1B and 2. The decreases in pH and total blood carbon dioxide content are associated with a significant rise in potassium and a fall in serum sodium levels. The electrocardiographic alterations consist of sinus slowing, atrial tachycardia and, some experiments, cessation of atrial activity, slowing of the idioventricular rate, peaking of the T wave, and progressive widening of the QRS complex (fig. 1B). These electrocardiographic changes are similar to the findings in hyperpotassemia. Partial correction of the acidosis by intravenous infusion of molar sodium lactate (5 to 10 mL/Kg. total dose over a period of approximately 30 min.) resulted in a normalization of the electrocardiographic changes and in some instances an increase in the idioventricular rate which was significantly greater than the control rate (fig. 1B).

Respiratory Acidosis. Figures 1A and 2 show the typical electrolyte and electrocardiographic changes following inhalation of 20 per cent carbon dioxide in oxygen. There was no significant changes in serum potassium or sodium and only a slight to moderate decrease in atrial and ventricular rates; however, there was a marked increase of atrial and ven-tricular rates immediately following cessation of carbon dioxide inhalation. In all experiments the heart rates returned to the control levels 5 to 8 min. after the withdrawal of hypercarbia.

Effects of Sympathomimetic Amines on Heart Rate During Various Degrees of Acidosis. Before acidosis (metabolic or respiratory) was induced, the response of each animal to various intravenous doses of the different sympathomimetic amines was determined. The amounts which increased the idioventricular rate by 30 to 40 per cent or more were as follows: isoproterenol (0.25 to 1 µg/Kg.), levarterenol (0.5 to 2 µg/Kg.) and epinephrine (0.5 to 2 µg/Kg.). The effect of each of these on the idioventricular rate in both types of acidosis is shown in figures 3 and 4. A nearly linear correlation was found between the decrease in response of ventricular rate to the sympathomimetic amines and the
degree of acidosis. In addition, there was a diminished rise in blood pressure.

**Potassium Chloride Infusion.** Acute hyperkalemia induced in 3 dogs showed a progressive decrease in both atrial and idioventricular rates as the serum level rose. The decrease in the idioventricular rate was comparable to the cardiac slowing observed during metabolic acidosis with an elevated serum potassium (fig. 1B). However, the pH level was not altered and the response to the sympathomimetic amines was not significantly changed.

**Intracoronary Drug Injections.** Intracoronary injections were made in 3 dogs to determine if acidosis directly alters the responsiveness of the idioventricular pacemaker to sympathomimetic amines. Isoproterenol (0.002 to 0.05 µg./Kg.), levarterenol (0.025 to 0.1 µg./Kg.), and epinephrine (0.025 to 1 µg./Kg.) injections in these dogs before acidosis was induced resulted in increases in idioventricular rate which were comparable to those observed following intravenous injections of these drugs. During acidosis, the positive chronotropic effect from intracoronary injections of sympathomimetic amines diminished according to the decrease in pH. At this time, injections of small amounts of alkalinizing agents (molar sodium lactate or sodium bicarbonate) were made in the left circumflex coronary artery to produce a transient change in the pH only within the vicinity of the idioventricular pacemaker. This resulted in a marked increase in the idioventricular rate (fig. 5). Intracoronary injections of these alkalinizing agents into the same site were ineffective in increasing the idioventricular rate in the absence of acidosis.

**DISCUSSION**

The decrease in cardiovascular response to the sympathomimetic amines during acidosis has been reported by other investigators.

Their studies dealt mainly on the vascular response, and these investigators, notably Snyder and Campbell, and Burget and Visscher described the diminished pressor effects of adrenalin associated with a drop in pH. More recently, Page and Weil reported similar observations with epinephrine and norepinephrine in dogs with respiratory acidosis.

In our present study, interest was centered upon the influence of pH on the positive chronotropic action of certain sympathomimetic amines. The results obtained demonstrated the decreasing effectiveness of the various sympathomimetic amines in accelerating the idioventricular rate in complete A-V block during acidosis. These findings also strongly
suggest the possible role of acidosis in the precipitation and maintenance of Stokes-Adams seizures. The ancillary studies with respiratory acidosis (decreased pH and normal potassium levels) and hyperkalemia (normal pH with elevated potassium levels), show that the decrease in pH appears to be the most important factor in the results. Furthermore, intracoronary injection of an alkalinizing agent (molar sodium lactate) during acidosis suggests that local correction of the pH in the idioventricular pacemaking center "releases" it from the depressant effect of the acidosis. It is interesting to note that while both acidosis and hyperkalemia depressed the idioventricular pacemaker, only a decrease in pH antagonized the positive chronotropic action of the sympathomimetic amines.

Of further interest is the spontaneous increase in the idioventricular rate with partial correction of acidosis or with local correction of the pH in the pacemaking center by intracoronary injection of small amounts of molar sodium lactate. It would seem that the "release" of the idioventricular focus from depression caused by the low pH resulted in an effective positive chronotropic action from the circulating endogenous epinephrine and/or norepinephrine, since these sympathomimetic amines have been reported to be elevated during hypercapnia.13-15 The occurrence of an identical response to pH correction in metabolic acidosis suggests that a similar mechanism may be present in this state.

Recently, we have observed three clinical cases with complete A-V heart block and
acidosis in whom the response to isoproterenol was minimal and brief. However, after correction of the acidosis with molar sodium lactate, A-V conduction was improved and the chronotropic effect of isoproterenol was more marked and lasting (unpublished observations). This would seem to indicate that the variation in response to molar sodium lactate in complete A-V heart block and Stokes-Adams seizures in man may be influenced in a large measure by the presence or absence of acidosis when therapy is instituted.

**SUMMARY**

The effectiveness of the various sympathomimetic amines (isoproterenol, levarterenol and epinephrine) in increasing idioventricular rate under conditions of metabolic acidosis, respiratory acidosis and hyperkalemia was studied in 12 adult mongrel dogs with chronic complete A-V heart block. It was shown that a decreased effectiveness of the 3 amines to accelerate the idioventricular rate occurred during metabolic or respiratory acidosis. The diminished response paralleled the degree of acidosis. During hyperkalemia no significant change in blood pH occurred and the effectiveness of the sympathomimetic amines remained unaltered. Furthermore, correction of the acidosis with alkalinizing agents (molar sodium lactate) resulted in restoration of the effectiveness of the sympathomimetic amines. Direct injections of molar sodium lactate into the left circumflex coronary artery during acidosis resulted in an increase in the idioventricular rate, suggesting that correction of the pH in the region of the pacemaker may have enhanced its responsiveness to circulating endogenous sympathomimetic amines.

These studies therefore suggest that the refractoriness to the sympathomimetic amines is due to the lowered pH and that correction of the latter restores their effectiveness.

**ACKNOWLEDGMENT**

We wish to express our appreciation to Drs. Clemente Oca and Arthur F. Geis of Hahnemann Hospital for demonstrating to one of the authors (S.V.G.) the technique of producing complete A-V heart block.
Cardiac Effects of Isoproterenol, Norepinephrine and Epinephrine in Complete A-V Heart Block During Experimental Acidosis and Hyperkalemia

SANTIAGO V. GUZMAN, ANTONIO C. DELEON, JR., JAMES W. WEST and SAMUEL BELLET

Circ Res. 1959;7:666-672
doi: 10.1161/01.RES.7.4.666

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1959 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/7/4/666

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at: http://circres.ahajournals.org/subscriptions/