THE EFFECT OF INTRAVENOUS PROCAINE ON THE HEART

JOAN H. LONG, M.D., MORTON J. OPPENHEIMER, M.D., MARY R. WESTER, M.S., AND THOMAS M. DURANT, M.D.†


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There has been increasing use of intravenous procaine in recent years in many conditions. It has been advocated for the treatment of acute cardiac arrhythmias occurring during thoracic operations (1) and cardiac surgery (2), in the treatment of serum sickness (3) and arthritis (4), to promote analgesia in obstetrics (5) and in abdominal operations (6), and to promote diuresis in anuria (7). Because of its use in cardiac surgery and in the treatment of cardiac arrhythmias and ventricular fibrillation (7a) it seemed timely to study the effects of procaine itself on the heart and on the electrocardiogram in particular.

In 1936 Mautz (2) applied procaine to the epicardium of dogs and found that it produced a transient current of injury and that the minimal stimulus to this area necessary to produce extrasystoles was increased. He concluded that procaine reduced cardiac irritability. In 1940 Burstein (8) reported that the ventricular tachycardia of dogs which was induced by epinephrine during cyclopropane anesthesia was both prevented and stopped by the intravenous or intracardiac injection of 5 to 10 mg. per kilogram of procaine hydrochloride. Very little attention has been paid to the careful study of Stutzman, Allen and Orth (9) who found that procaine in doses as high as 16 mg. per kilogram failed to reverse the cyclopropane-epinephrine induced ventricular fibrillation of dogs. These authors thought that the ventricular fibrillation previously described was in reality a ventricular tachycardia from which the dogs would have recovered without treatment.

It was the purpose of these studies on 20 mongrel dogs to discover the effects of varying doses of procaine on the heart. The dose of 4 mg. per kilogram was taken as the usual therapeutic dose (8).

The majority of the dogs were anesthetized with a barbiturate (sodium pentobarbital 35 mg. per kilogram). With the dog in the supine position, procaine hydrochloride in a 2 per cent or 4 per cent solution was injected rapidly into the femoral vein. Simultaneous recordings were made of the electrocardiogram, arterial blood pres-

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† From the Departments of Surgery, Physiology and Medicine, Temple University Medical School, Philadelphia, Pa.
sure (using a critically damped strain gauge), heart sounds and respiration. The left and right precordial leads (roughly CF₁ and CF₂) and lead II were used. When artificial respiration was necessary, it was given by means of an endotracheal tube with positive pressure.

In 6 dogs the blood levels of the injected procaine were determined by the method of Graubard, Robertazzi, and Peterson (10). Samples of blood were drawn at intervals of five, ten, and thirty seconds during the first minute, then every minute for ten minutes, and finally twenty minutes after the injection. The blood levels obtained in the first five to ten seconds at varying doses of procaine are shown in table 1. These levels were apparently not only proportional to the amount injected but also to the speed of injection. The blood level of procaine dropped very rapidly to 20 to 30 per cent of the initial level at the end of five seconds. Within five minutes only 5 to 10 per cent of the original concentration was present. However, at the end of twenty minutes 4 to 5 per cent of the original concentration still remained in the blood.

<table>
<thead>
<tr>
<th>Dose of Procaine Injected, mg/kg</th>
<th>Blood Level within 10 Seconds, mg/ml</th>
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</thead>
<tbody>
<tr>
<td>4</td>
<td>0.043-0.048</td>
</tr>
<tr>
<td>10</td>
<td>0.070</td>
</tr>
<tr>
<td>20</td>
<td>0.174-0.295</td>
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<tr>
<td>30</td>
<td>0.280-1.000</td>
</tr>
<tr>
<td>50</td>
<td>0.950</td>
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<tr>
<td>60</td>
<td>0.660-1.630</td>
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Graubard (10) found that in rabbits there were traces of procaine in the blood twenty minutes after injection. This suggests that in these animals at least a small cumulative effect may occur when injections are as frequent as every twenty minutes.

Serum potassium levels were determined on 5 dogs by the flame spectrophotometer method (11). A series of blood samples was taken from ten seconds to ten minutes after the injection of procaine. No changes were found in the serum potassium level.

With a procaine dose of 4 mg. per kilogram, there was usually no change in the electrocardiogram, the heart sounds, or the blood pressure. Respiration was usually slightly accelerated. Occasionally there was an increase in the height of the T wave. This was the first change to be seen in the electrocardiogram in response to intravenous procaine.

A series of progressive changes occurred as the injected amount of procaine was increased from 4 mg. per kilogram to the fatal dose. The latter varied from 20 to 80 mg. per kilogram in the dogs used. With low doses (4 to 10 mg. per kilogram) electrocardiographic changes occurred from ten to thirty seconds after the injection; as the dose increased the changes occurred more rapidly until with doses of 40 mg. per kilogram or more the changes occurred during the injection. The changes
apparently took place when the blood level of procaine was at its height, and as the level dropped the changes regressed.

Changes in the T wave appeared consistently at doses of 8 to 10 mg. per kilogram about ten to thirty seconds after the injection. Usually the height of the T wave was increased; occasionally it was first flat-termed or inverted and then increased in height. In one dog the T wave in the right precordial lead was inverted while the T wave in the left precordial lead was heighted.

At doses of 8 to 10 mg. per kilogram and more there was usually a lowering of the voltage of R (fig. 1, A). This was often accompanied by an increase in the voltage of S with the formation of a "J" in the
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Precordial leads (fig. 1, B). Depression of the S–T segment sometimes occurred. At the dose of 20 mg. per kilogram the first widening of the QRS complex was seen. With increasing doses the widening increased (fig. 1, C and fig. 2, upper). At doses of 60 mg. per kilogram or more the complex was sometimes five times its original width.

There was an increase in the length of the P–R interval with doses of 30 mg. per kilogram. The increase, which amounted to 0.04 to 0.08 seconds, was not nearly as striking as the increase in the width of the QRS complex.

At doses of procaine of 50 to 60 mg. per kilogram a ventricular tachycardia occurred (fig. 2, lower).

All of the changes described, the T wave changes, the S–T segment changes, the widening of the QRS complex, the lengthening of the P–R interval, and the ventricular tachycardia, were reversible, provided that the respiration was maintained. After a single injection of pro-
caine the changes occurred within the first minute and the electrocardiogram returned to the control state in from one to three minutes, depending upon the amount of the injected dose.

When ventricular fibrillation occurred, however, as it did in 3 of the 20 dogs within five to ten seconds of the injection of 60 to 80 mg. per kilogram of procaine, there was no recovery even if artificial respiration was continued for a long period of time (fig. 3).

There was some evidence to suggest that damaged cardiac muscle was more sensitive to procaine than was normal cardiac muscle. One dog in which portions of the muscle of the left and right ventricles had been removed three weeks before was given the therapeutic dose of 4 mg. per kilogram. Within ten seconds of the injection there was marked diminution of the voltage of the QRS complex which became isoelectric in lead II; the T wave was increased. Ventricular fibrilla-

![Fig. 3. Effects of the intravenous injection of procaine hydrochloride on the cardiovascular system of dogs under sodium pentobarbital anesthesia 35 mg. per kilogram. Dog, 11 kg. Arterial blood pressure, strain gauge. Respiration. EKG, lead II. Heart sounds. EKG, CF. White mark is end of injection of procaine, 72 mg. per kilogram.](image)

tion developed when 40 mg. per kilogram was given. This was a dosage of procaine which had not produced ventricular fibrillation in 17 dogs with normal hearts. A dog with a small superficial infarct of the left ventricle showed only slight lowering of the voltage of R with a 4 mg. per kilogram dose of procaine. A dog with severe distemper did not react differently from the healthy normal dogs.

Changes in blood pressure and pulse pressure were measured by strain gauge technic on 10 dogs simultaneously with the electrocardiographic changes. With small doses of procaine (4 to 10 mg. per kilogram) there was either no change of the blood pressure (fig. 1, B) or a transient drop of 10 to 15 mm. of mercury which was independent of any changes in the electrocardiogram. When widening of the QRS complex occurred there was always a concomitant drop in blood pressure and in pulse pressure (fig. 1, C). The wider the QRS complex the
more profound the drop in blood pressure. When the QRS complex
was widened three or fourfold the diastolic blood pressure ranged from
10 to 20 mm. of mercury. A similar severe drop in blood pressure was
produced in 2 control dogs by the intravenous injection of nitro-
glycerine. In these dogs the only electrocardiographic change was a
flattening of the T wave. There was no change in the width or the
voltage of the QRS complex.

The changes in heart sounds paralleled the changes in blood pres-
sure. As the blood pressure dropped the second sound became weaker
and disappeared completely when the blood pressure reached shock
levels (fig. 1, C).

The changes in respiratory rate were not intimately related to the
cardiac changes. Doses of 4 to 10 mg. per kilogram increased the
respiratory rate for a period of about thirty seconds. Larger doses
decreased the rate. Respiration usually ceased at doses of 40 mg. per
kilogram or more, although the mechanical and electrical events of the
heart continued. The dog died unless artificial respiration was in-
stituted. If artificial respiration were maintained for fifteen to thirty
minutes or longer, spontaneous respiration would be resumed. Inter-
estingly enough, blood pressure and the electrocardiogram returned to
the control state long before this occurred. If the dose of procaine is
large enough to cause ventricular fibrillation, respiration and regular
heart action stop almost simultaneously, although fibrillation may con-
tinue for several minutes.

The type of electrocardiographic change following intravenous ad-
ministration of procaine and the time of onset of this change was the
same with both barbiturate and ether anesthesia. However, there
were differences in the response of the central nervous system to pro-
caine with the different anesthetics. In our series of dogs no convul-
sions occurred at any time under barbiturate anesthesia. With ether
anesthesia, extensor spasm occurred with doses of 10 mg. per kilogram
and convulsions at 20 mg per kilogram.

At necropsy the hearts of the dogs which had died of overdoses of
procaine were greatly dilated. The musculature appeared soft and
flabby.

Comment

Increasing doses of intravenous procaine cause the following electro-
cardiographic changes: usually a heightening, sometimes a flattening
or even an inversion of the T wave; a lowering of the voltage of R, an
increase in the depth of the S wave and the formation of a "J," a
depression of the S–T segment; an increase in the width of the QRS
complex; a prolongation of the P–R interval; ventricular tachycardia,
and, ultimately, ventricular fibrillation. The changes in the S and
the S–T segment were not always seen in lead II, although they were
usually present in the precordial leads. Such changes in the electro-
cardiogram apparently indicate changes in the repolarization of the ventricular musculature, changes in the rate of conduction of the cardiac impulse through the bundle of His and the ventricular muscle, and to a lesser extent changes in the rate of conduction through the A–V node and perhaps through the atrial musculature. The most pronounced of these changes is in the conduction through the bundle of His and the ventricular musculature resulting in bundle branch block.

The lowering of the blood pressure and more particularly the pulse pressure as the QRS complex widens, together with the increasingly weak second heart sound, suggests that there is a loss of tonus and a weakening of the force of the heartbeat in addition to the change in conduction. Procaine lowers blood pressure in the heart-lung preparation (11a). A part of the fall in blood pressure is probably due to the vasodilatation which occurs with procaine, but vasodilatation alone with no change in the cardiac output should not lower the pulse pressure. The greatly dilated heart at necropsy and the flabby condition of the muscle also speak for the effect of procaine on the cardiac musculature. In support of this view is the fact that Hazard (12) reported that procaine decreases the tonus of both striated and smooth muscle and in large doses causes complete muscular paralysis.

If it is true that the cardiac changes due to procaine may be manifest earlier and with smaller doses in abnormal hearts, it becomes important from a clinical standpoint since procaine is being advocated in cardiac surgery and as an antidote for various arrhythmias and tachycardias which occur during anesthesia. The evidence obtained from one experiment is certainly insufficient from which to draw conclusions. Graubard, Kovacs and Ritter (4) in a report on the use of procaine in arthritic patients have also suggested that cardiac changes may be manifested with therapeutic doses of procaine in patients with cardiac disease, but they have not yet presented their evidence. It remains a point to be investigated both experimentally and clinically.

The effect of intravenous procaine on respiration was also shown in these experiments. Small doses (4 to 10 mg. per kilogram) caused an increase in respiratory rate which was independent of any change in blood pressure and which was probably owing to direct effect on the respiratory center. Larger doses (20 mg. per kilogram or more) first increased, then decreased the respiratory rate, suggesting an ultimate depression of the respiratory center with higher blood levels of procaine. With doses of 40 mg. per kilogram or more respiration usually ceased within thirty seconds of the injection.

The distinction has been made by Knoefel et al. (13) that sudden death following the administration of one of the procaine-cocaine group of local anesthetic agents is due to cardiovascular collapse, whereas death which occurs more slowly is primarily the result of a failure of the respiratory center. From our experiments with procaine it would appear that this is true, that the dog dies a cardiac death only if the
injected dose is sufficient to cause ventricular fibrillation. In most cases respiratory failure occurred first; the blood pressure might be in the range of 10 to 30 mm. of mercury and there might be no heart sounds, but heart action would continue for about a minute after respiration had ceased. If artificial respiration was instituted immediately, the mechanical and electrical events of the heart would return to normal within three to five minutes provided ventricular fibrillation had not occurred. Spontaneous respiration would be resumed in fifteen to thirty minutes. Therefore, it would seem expedient if sudden collapse occurs during the use of procaine, or perhaps even of other anesthetics of this type, to institute artificial respiration immediately even if the blood pressure reading is unobtainable and the heart sounds are negligible. There would seem to be a fair chance of recovery if the dose of procaine has not been large enough to cause ventricular fibrillation.

In addition to its action on the respiratory center, procaine also acts on other bulbar centers. According to Hazard (12), it inhibits conduction along the peripheral nerves when applied locally, and acts on the ganglions and at the nerve endings of the autonomic nervous system to depress or inhibit conduction.

The problem of explaining all of these various actions, namely, conduction changes in the nervous system, in the nerves, ganglions, and nerve endings, conduction changes in cardiac muscle and contraction changes in smooth and striated muscle, is an interesting one. All of these changes are reversible. The facts suggest that the mode of action of procaine is in some reversible reaction with the chemical mediators of the nerve impulse and of muscular contraction. Among the compounds concerned with these functions are acetylcholine, cholinesterase, creatine phosphate and the potassium ion.

Attempts to discover the relation of procaine to these compounds has so far been confusing. We were impressed by the similarity in the action of increasing blood concentrations of procaine upon the electrocardiogram to increasing concentrations of serum potassium (i.e. increase in the height of the T wave, A-V block and bundle branch block). Serum potassium levels were followed for ten minutes after the injection of procaine. No changes in serum potassium were found. This is not proof, of course, that there are no changes in potassium concentration at cell surfaces or intracellularly.

Hazard (14) found that procaine inhibited the action of cholinesterase in leech muscle. On the other hand he reported that large doses of procaine weakly inhibit the muscarinic cardio-inhibitors and diminish or suppress the nicotinic effects of acetylcholine (15). Cuny (16) has shown that there is a synergistic action between epinephrine and procaine, the latter prolonging the hypertension produced by the former, despite the difference in the action of the two drugs on the blood vessels. More definitive, perhaps, is the work of Rapp (17) who
reported that the reaction between acetylcholine and creatine-phosphate in nerve extracts is inhibited by procaine. This reaction between acetylcholine and creatine-phosphate has been proposed as part of the mechanism associated with the propagation of the nerve impulse (18).

**Summary**

Intravenous procaine causes the following cardiac changes:

a. Doses of 10 to 15 mg. per kilogram cause changes in the height of R, in the T wave and the S-T segment of the electrocardiogram.
b. Increasing the dose produces, successively, bundle branch block, some slowing of conduction through the A-V node, ventricular tachycardia, and, ultimately, ventricular fibrillation.
c. As the bundle branch block increases, the force of the contraction of the heart is decreased.

The cardiac changes short of ventricular fibrillation are usually reversible if respiration is maintained.

There is some slight suggestion that in hearts with muscle damage cardiac changes may occur with therapeutic doses of procaine.

It is suggested that there is a fair chance of recovery following sudden collapse during the use of procaine if artificial respiration is instituted immediately.

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**References**

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