Post-Countershock Arrhythmias in Untreated and Digitalized Dogs

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ABSTRACT
Recent studies suggest that countershock can stimulate cardiac autonomic nerves and that the resulting release of norepinephrine contributes to post-countershock (PCS) arrhythmias. β-Adrenergic receptor blocking agents, reserpine, cocaine, and cardiac-denervated preparations were used to evaluate this hypothesis in dogs under pentobarbital anesthesia. The suitability of the dog as an experimental system was examined. In the normal dog, the duration of PCS arrhythmia caused by a countershock of given energy was increased 100% by ouabain (0.05 mg/kg iv). In both normal dogs and dogs given ouabain (0.05 mg/kg iv), dichloroisoproterenol, pronethalol, and propranolol reduced the duration of PCS arrhythmia; reserpine, a norepinephrine depleter, reduced the duration of PCS arrhythmia; cocaine, a norepinephrine-uptake inhibitor possessing antiarrhythmic properties, increased the duration of PCS arrhythmia; denervation of the heart reduced the duration of PCS arrhythmia. Ouabain (0.05 mg/kg iv) reduced the duration of PCS arrhythmia in dogs with denervated hearts. These findings indicate that PCS arrhythmia in dogs is norepinephrine dependent. Evidence indicated that ouabain has an anti-adrenergic action on the heart also is presented.

ADDITIONAL KEY WORDS
ouabain β-receptor blockade cardiac catecholamines
d-d countershock reserpine cocaine cardiac denervation

As a result of the widespread use of the direct current (d-c) defibrillator in the treatment of cardiac arrhythmias, it became evident that the incidence of arrhythmia after countershock was higher in digitalized than non-digitalized patients (1). By the term “countershock” we mean the electrical discharge of a defibrillator which can be used either to terminate or to originate cardiac arrhythmias.

The sinus slowing and decreased force of atrial contraction which often follow countershock suggest that the electrical discharge stimulates intrathoracic autonomic nerves. Although the sinus slowing shows that the countershock stimulates parasympathetic fibers, it seems reasonable to assume that countershock stimulates both sympathetic and parasympathetic components of peripheral autonomic nerves. Because of the known relationships between the actions of digitalis and those of norepinephrine (2-8) and because of evidence that digitalis inhibits the uptake of norepinephrine by various tissues (9-11) we decided to test the hypothesis that arrhythmias observed immediately after exposure of a digitalized patient to countershock are due in part to the liberation of norepinephrine from nerve terminals by the electrical pulse, and in part to altered release or uptake of norepinephrine by the nerve fibers resulting from the action of digitalis on the nerve membrane or both. These
events would increase the time of exposure of cardiac tissue to catecholamine as well as the mean concentration of amine following a single countershock; under the influence of digitalis, certain cardiac fibers might respond to this condition by developing arrhythmias (12, 13).

To test the hypothesis it first was necessary to determine whether we could develop an experimental preparation which showed enhancement of post-countershock (PCS) arrhythmias by digitalis. Also, to permit quantitative comparison of arrhythmias recorded under a variety of experimental conditions, it was important to perform certain studies on the electrical discharges used and on their electrophysiological effects. In particular, we needed to know the effect of interelectrode impedance on the waveform of the countershock; the relationships between peak voltage, waveform, and energy; the waveform and energy delivered to the heart itself; and the consistency of peak voltage and waveform for a series of pulses of the same energy (14, 15).

After completion of these preliminary studies, we conducted a series of experiments designed to demonstrate whether administration of β-adrenergic receptor blocking agents, de-

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**FIGURE 1**

A block diagram of the electronic circuitry used. This apparatus can be assembled from standard equipment which is available in most laboratories. A is the "trigger in" (15 v) of a Tektronix waveform generator (WFC) operated in the "triggered" mode. The triggering pulse is a 4 msec, 15 v, square wave supplied by the Schmitt trigger. B is the "sawtooth out"; C is the "sawtooth input" of a pulse generator (PC); D is the "pulse output" of a pulse generator; and E is the "gate output" of a pulse generator.
completion of catecholamines by reserpine, or chronic cardiac sympathetic denervation would influence the development of post-countershock arrhythmias and whether inhibition of the uptake of norepinephrine by nerve fibers would enhance these arrhythmias both in the absence of digitalis and after acute and chronic digitalization.

Methods

ELECTRONIC APPARATUS AND CIRCUITS

A d-c defibrillator manufactured by the American Optical Co. (Model 10645) was used for all experiments. This device was synchronized by the circuits shown in Figure 1 to discharge 40 to 60 msec after the R wave of the lead II ECG. We chose to deliver the pulse at this time, rather than during diastole, because heart rate was not controlled and because the effects of strong electrical pulses vary with the time of their application in the cardiac cycle (18). The output of the defibrillator was observed on a Tektronix 564 oscilloscope, using a Tektronix high voltage probe and a dual-trace preamplifier, and photographed with a Polaroid or Grass camera (see Fig. 1).

The defibrillator electrodes were circular stainless steel plates which measured 85 and 105 mm in diameter. They were applied with constant pressure to the shaved, lateral aspects of the dog’s chest by a rubber strap. Good electrical contact was ensured by vigorously rubbing the skin with Sanborn ECG jelly. The impedance of the dog between the electrodes was measured by determining the value of a shunt resistance which would halve the voltage of a 20-cycle/sec constant current test pulse of 4 msec duration applied between the defibrillator electrodes. Although our method for measuring the magnitude of the impedance theoretically cannot be exact, it does enable us to detect relative changes if any occur. Experimentation was not begun until the impedance was constant.

The standard lead II and a filtered lead II of the electrocardiogram were continuously monitored with an Electronics for Medicine DR-8 recorder. Femoral arterial blood pressure was monitored also, using a P23AC Statham pressure transducer and another channel of the DR-8 recorder. Palmer bipolar electrodes and a Grass S4G stimulator with an isolation unit were used to stimulate the cervical vagus.

ANIMALS AND EXPERIMENTS

During these studies on the effects of countershock, 60 mongrel dogs were anesthetized with sodium pentobarbital, 30 mg/kg, iv. In most experiments we first determined a threshold energy of countershock which would cause a post-countershock arrhythmia. This was defined as 4 to 6 “ventricular” ectopic beats. In other instances we determined the relationship between the energy of countershock and number of ectopic beats by employing graded increments in energy. We call the Cartesian plot of this relationship the stimulus-response curve. A period of 3 to 5 min elapsed between countershocks. After control measurements the dog was digitalized and an identical series of countershocks was applied. Acute digitalization was accomplished by an initial intravenous injection of ouabain, 0.025 mg/kg, followed by an intravenous infusion of ouabain, 0.025 mg/kg in 100 ml of isotonic saline, administered during the next 35 to 45 min. The total dose ranged from 0.048 to 0.052 mg/kg. Early in the test series, several animals developed ventricular tachycardia; later in the experimental series the infusion was stopped prior to this event. In the absence of ventricular tachycardia, the effects of countershock were studied beginning 15 to 45 min after the ouabain infusion; when ventricular tachycardia occurred, testing was delayed until 10 to 15 min after the return of sinus rhythm. The second series of tests, demonstrating the effects of countershock after acute digitalization, usually required 40 min. Subsequently, various drugs were administered to test their effects upon the ouabain-induced enhancement of post-countershock arrhythmia. The drugs and the doses used will be discussed in Results; the drugs included pronethalol (Nethalide), dichloroisoproterenol (DCI), d,l, and racemic N-isopropyl-p-nitrophenylethanolamine (INPEA), d-1 propranolol (Inderal), atropine, and phentolamine. Drugs were administered intravenously so that the full effect could be achieved rapidly but at an infusion rate which did not cause any signs of cardiovascular collapse, as can occur if dichloroisoproterenol or pronethalol are given too rapidly. The third series of countershocks, testing the effect of drugs on PCS arrhythmia, required 20 to 30 min and always was finished well within the period of more than 2 to 3 hr during which ouabain enhancement of post-countershock arrhythmia could be demonstrated.

One dog was chronically digitalized by giving 0.1 mg of digitoxin orally, daily for 9 days and then tested. The same dog then was given reserpine, 0.5 mg/kg per day im, daily for 6 days while the digitoxin was continued and then tested again. Subsequently, administration of reserpine and digitoxin was stopped and, after allowing 5 weeks for repletion of catecholamines, the dog was then tested under control conditions and when acutely digitalized with ouabain according to the procedure previously described.

The hearts of 3 dogs were denervated by a
FIGURE 2
Two records taken during the application of 100-wattsecond (wsec) countershocks to dog no. 56 (arrow). On both records the standard ECG was recorded by the upper trace (driven off screen by the countershock). The middle trace recorded the artifact indicating the timing of the countershock. The lower trace, which rapidly returned to the isopotential line, recorded the filtered ECG. A, during testing with control conditions; 9 ventricular ectopic beats occurred. B, obtained 1 hr after the dog received ouabain (0.048 mg/kg, iv). Following the countershock, there were 9 ventricular ectopic beats and then 3 normal beats followed by more than 100 ectopic beats.

Note that the rate of the late occurring ventricular tachycardia shown in B is faster than that of the atria. It is unlikely that this ventricular tachycardia arose because of a sinus bradycardia and the consequent unmasking of the normal ventricular rate by either direct or reflex stimulation of the cardiac vagus.

Modification of a procedure described by Cooper et al. (17). Both vagi and phrenic nerve trunks were isolated and any thoracic connections were transected so that the diaphragm and viscera inferior to the diaphragm remained functionally innervated. All of the great vessels in the thorax were stripped of their adventitia in an effort to sever the autonomic nerves coursing with the vessels. The fascia surrounding the trachea and esophagus was stripped for the same reason. Finally, the cardiac nerves and ansa subclaviai originating from both stellate ganglia were cut. The hearts of 2 other dogs were denervated by a simpler procedure. All intrathoracic branches of both vagi were severed in the manner described above. In addition, the stellate ganglia and thoracic ganglia T1 through T5 were extirpated. In all instances, denervation was performed 1 week after the control experiments and subsequent testing was done 10 to 20 days after denervation.

The effectiveness of the cardiac denervation was tested at the time of the experimental run. Denervation was judged to be adequate if there was no change in sinus rate when: (1) the cervical vagi were strongly stimulated at 20 to 30 cycle/sec; (2) carbachol was administered to the atropinized, cocaineized preparation; (3) there was an increase of 50 to 80 mm Hg in mean femoral arterial pressure during bilateral carotid occlusion; and (4) the stellate ganglia were strongly stimulated at 10 to 60 cycle/sec. Although fulfillment of our criteria for assessment of adequacy of denervation may not indicate complete denervation as defined by Peiss et al. (18), for our purposes these criteria are sufficient to indicate that there had been a marked reduction in myocardial autonomic innervation.
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FIGURE 3

Two typical stimulus-response curves relating the duration of the PCS arrhythmia to energy of countershock. The curves are generated by plotting the duration of the PCS arrhythmia, as the number of ventricular ectopic beats, on the ordinate and the energy of countershock in wattseconds necessary to cause that duration on the abscissa. Curve a, the stimulus-response curve of dog no. 56 tested under control conditions; curve b, the same dog tested 1 hr after the administration of ouabain (0.048 mg/kg).

Working Definition of an Arrhythmia

A beat was said to be ectopic if the QRS complex was aberrant in form and not in proper temporal relation to the preceding P wave, and if the following T wave was aberrant. For the reasons discussed in Figure 2, we searched for ectopic beats occurring immediately following a countershock in the recording obtained from the filtered lead II of the electrocardiogram.

Results

EFFECT OF PULSE ENERGY

If a countershock of sufficient energy is delivered by the defibrillator across the chest of a dog, it causes an arrhythmia which satisfies our definition. Figure 2A is a record of a typical PCS arrhythmia which had a duration of 9 beats. The R wave and the T wave of the filtered lead II are aberrant. The P waves either are absent or not in proper temporal relation to the following R wave. The duration of the arrhythmia, defined as the number of ectopic beats, increases with increasing energy of the countershock. The lower curve in Figure 3 is a typical stimulus-response curve which demonstrates this relationship.

The reproducibility of this arrhythmia is indicated by the data in Table 1 which demonstrate two points: the duration of arrhythmia increases with increasing energy or peak voltage or both, and at a given energy or peak voltage, the duration of the PCS arrhythmia is reproducible. These data were taken from a typical experiment.

EFFECT OF OUABAIN ON PCS ARRHYTHMIA

After administration of ouabain, both the duration of the PCS arrhythmia caused by a threshold discharge and the stimulus-response curve were altered. Tests made between 3% and 3 hr after the end of the ouabain infusion showed an increase in the duration of the PCS

<table>
<thead>
<tr>
<th>Shock no.</th>
<th>Time</th>
<th>Energy (wsec)</th>
<th>No. of ectopic beats</th>
<th>Peak voltage*</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>12:00</td>
<td>50</td>
<td>1</td>
<td>950</td>
</tr>
<tr>
<td>2</td>
<td>12:10</td>
<td>70</td>
<td>2</td>
<td>1100</td>
</tr>
<tr>
<td>3</td>
<td>12:14</td>
<td>100</td>
<td>3</td>
<td>1300</td>
</tr>
<tr>
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<td>140</td>
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<td>1450</td>
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</tr>
<tr>
<td>8</td>
<td>12:50</td>
<td>140</td>
<td>4</td>
<td>1450</td>
</tr>
</tbody>
</table>

*Recorded between the output electrodes of the defibrillator.

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Comparison of chronic and acute digitalization and the effects of β-adrenergic receptor blockade and reserpination in dog no. 25. The duration of the arrhythmia, as the number of ectopic beats, is represented by the ordinate and energy of countershock by the abscissa. A shows 3 curves: a, the control curve; b, following the administration of ouabain (0.05 mg/kg); and c, after propranolol (2.0 mg/kg, iv) following the ouabain test. B shows 3 curves: a, the control curve; b, following the oral administration of digitoxin (0.1 mg/day) for 9 days; c, following the administration of reserpine (0.5 mg/day im) and digitoxin (continued at 0.1 mg/day, orally) for 6 days. The 2 points indicated by arrows show the reduction in the duration of the PCS arrhythmia by propranolol (2.0 mg/kg, iv) in the chronically digitalized and in the reserpine-treated, chronically digitalized dog. See text.

TABLE 2
Effect of Ouabain (0.05 mg/kg) on Duration of PCS Arrhythmia

<table>
<thead>
<tr>
<th>Effect</th>
<th>No. of dogs</th>
</tr>
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<tr>
<td>Increase, &gt; 100%</td>
<td>28</td>
</tr>
<tr>
<td>Increase, &lt; 100%</td>
<td>5*</td>
</tr>
<tr>
<td>No change</td>
<td>2*</td>
</tr>
<tr>
<td>Decrease</td>
<td>0</td>
</tr>
</tbody>
</table>

*These dogs were studied early in the series before we realized that the effect being observed often does not occur until 45 to 75 min after completion of the ouabain infusion. Therefore, probably because the test run had been completed by this time, they showed minimal effects.
studied early in the series and the difference may have resulted because they were tested before the ouabain-induced enhancement was fully developed. In some dogs such enhancement was not apparent until some time after the end of ouabain administration. Often 45 to 75 min were required for the enhancement to develop fully.

Chronic oral digitalization with digitoxin also caused an enhancement of PCS arrhythmia. A 25-kg female German shepherd proved to be far more sensitive to countershock when chronically digitalized with a therapeutic dose of digitoxin than when given a therapeutic dose of ouabain by infusion. The results of this experiment are shown in Figures 4A and 4B.

In initial experiments administration of ouabain sometimes was continued until ventricular tachycardia developed. The possibility that the period of ventricular tachycardia, lasting 1 to 2 hr, might itself cause increased sensitivity to countershock was tested by studying the effect of driving the ventricle or the atrium at rates of 250 beat/min on the duration of PCS arrhythmia. Driving either the ventricle or the sinus region at 250 beat/min for 1½ hr had no effect upon the duration of the PCS arrhythmia at the threshold energy of 80 usec. Testing began immediately after the drive was stopped and the dog had returned to normal sinus rhythm.

### EFFECT OF β-RECEPTOR BLOCKADE

#### 1. In Untreated Dogs

The effects of the β-adrenergic receptor blocking drugs, pronethalol, DCI, propranolol, and INPEA, on the duration of PCS arrhythmia in normal dogs are summarized in part A of Table 3. β-Adrenergic receptor blocking drugs inhibited PCS arrhythmia when it was possible to demonstrate than an effective blockade of the β receptors had been achieved by a lack of response to the administration of an intravenous dose of isoproterenol (1 μg/kg). In experiments in which β-receptor blocking drugs caused no or only slight inhibition of PCS arrhythmia, there always was some increase in heart rate or some decrease in blood pressure in response to the isoproterenol challenge. The decrease in duration of PCS arrhythmia caused by pronethalol (4 mg/
Pronethalol inhibition of PCS arrhythmia in dog no. 14. The ordinate represents the duration of the PCS arrhythmia as the number of ectopic beats. The first bar represents the duration of arrhythmia under control conditions with a countershock energy of 50 wsec. The second bar shows the effects of the same countershock energy after pronethalol (4 mg/kg). The third shows that a countershock of 100 wsec was required to cause an arrhythmia of control duration after pronethalol. The peak voltages of the countershocks used are indicated as is the range of the duration of PCS arrhythmia. The range was determined using 8 to 9 countershocks of constant energy during each condition of testing.

Enhancement of PCS arrhythmia by ouabain and inhibition of the enhancement by dichloroisoproterenol, dog no. 29. The ordinate represents the duration of the PCS arrhythmia as the number of ventricular ectopic beats. The bar labeled C represents control conditions using a countershock of 80 wsec. The bar labeled O represents the response to the same energy of countershock after administration of ouabain (0.05 mg/kg, iv). The bar labeled DCI represents the response to the same energy of countershock when DCI was administered (4 mg/kg, iv) following the test with ouabain. The range of the duration of PCS arrhythmia is indicated. The range was determined as in Figure 5.

Enhancement of PCS arrhythmia by ouabain and the pronethalol inhibition of the ouabain effect in dog no. 21. The ordinate represents the duration of PCS arrhythmia as the number of ventricular ectopic beats. The first bar shows the response under control conditions to a countershock of 60 wsec. The second bar represents the response to the same countershock energy after ouabain (0.05 mg/kg, iv). The third bar represents the response to the same energy of countershock when pronethalol (40 mg/kg, iv) was given following the test with ouabain. The range of the duration of PCS arrhythmia is indicated. The range was determined as in Figure 5.
2. In Digitalized Dogs

The effects of the β-adrenergic receptor blocking drugs upon PCS arrhythmia in dogs digitalized with ouabain (0.05 mg/kg) are summarized in part B of Table 3. Again, these drugs inhibited the arrhythmia if an effective β-receptor blockade could be demonstrated by isoproterenol challenge. When inhibition of PCS arrhythmia did not occur, it was not possible to demonstrate an effective blockade of β-adrenergic receptors of the heart or vasculature (19).

The inhibitory effects of pronethalol (4 mg/kg) and DCI (4 mg/kg), in 2 selected dogs treated with ouabain and countershocked at constant energy, are shown in Figures 6 and 7 respectively. The inhibitory effects of INPEA (20 mg/kg) and propranolol (1 mg/kg) on the stimulus response curves of another dog given ouabain are shown in Figure 8B. Figure 4B shows data obtained from a dog chronically treated with digitoxin. In that dog, propranolol (2 mg/kg) reduced the duration of the PCS arrhythmia by 41%.

Inhibition by β-adrenergic receptor blockade of PCS arrhythmia both in the normal animal and after treatment with ouabain. The ordinate represents the duration of the PCS arrhythmia as the number of ventricular ectopic beats and the abscissa represents the energy of countershock in wattseconds necessary to cause that number. A and B show stimulus-response curves obtained from the same dog. The two sets of curves were defined on successive days. A, from the normal dog, shows 3 curves: a represents the response under control conditions; b represents the response following administration of INPEA (20 mg/kg, iv) and c the response following the administration of propranolol (5 mg/kg, iv). B, from the same dog treated with ouabain, shows 4 curves: a represents the response under control conditions the day after the experiment in Figure 8A; b, the response following the administration of ouabain (0.05 mg/kg); c, the response when INPEA (20 mg/kg, iv) was administered following ouabain; and d, the response when propranolol (5 mg/kg, iv) was administered following ouabain and INPEA.
Synergism between cocaine and ouabain. The ordinate represents the duration of the PCS arrhythmia as the number of ventricular ectopic beats. The abscissa represents the time when the drug was administered and when the subsequent 150 usec countershock tests were applied. This form is used to indicate the sequential administration of drugs and their effects on the PCS arrhythmia. All countershock tests were made at an energy of 150 usec.

The duration of arrhythmia under control conditions is indicated by bar 1. Atropine (1 mg/kg) was given at A. The effect is indicated by bar 2. Cocaine (1 mg/kg) was given at C. The effect is indicated by bar 3. Bar 4 indicates that the effect of cocaine had abated when ouabain (0.05 mg/kg) was given at O. The effect of ouabain is indicated by bar 5. Bar 6 indicates that the effect of ouabain had increased 1 hr after drug administration. At the second C, cocaine (1 mg/kg, iv) was administered again. The effect of ouabain and cocaine acting together is indicated by bar 7. Bar 8 indicates again the duration of the effect of cocaine. At the second O, ouabain (0.05 mg/kg) was administered again and the effect is indicated by bar 9. We concluded that atropine has no effect on the duration of the PCS arrhythmia; that cocaine and ouabain enhance the duration of the PCS arrhythmia when acting alone or together.

EFFECT OF CHRONIC RESERPINE ADMINISTRATION

When a dog given oral digitoxin for 9 days was then given reserpine (0.5 mg/kg per day, im) and continued on digitoxin for the next 6 days, it was found that the stimulus-response curve had shifted down and to the right, indicating that reserpine had reduced the sensitivity of the chronically digitalized dog to countershock. Figure 4B shows data obtained on a dog treated in this manner. Countershock of 200 usec caused the chronically digitalized dog to develop an arrhythmia with duration of 25 beats. After this dog had been treated with reserpine, the duration of arrhythmia was reduced to 8 beats in response to countershocks of the same energy. The effect of reserpine is summarized in part B of Table 3.

EFFECT OF COCAINE ON PCS ARRHYTHMIA

In 2 dogs treated with cocaine, there was a marked increase in the duration of PCS arrhythmia both before and after administration of ouabain. The results of one experiment are shown in Figure 9. All determinations were made with countershocks of the same energy. Cocaine caused a marked increase in the duration of the PCS arrhythmia. Cocaine given after ouabain caused an increase in duration of arrhythmia from 30 to 45 beats.

EFFECTS OF OTHER DRUGS USED

We found during preliminary experiments on 5 dogs that neither atropine nor the α-adrenergic receptor blocking drug, phentolamine, had any significant effect on the duration of PCS arrhythmia in either the normal dog or the dog treated with ouabain (0.05 mg/kg). The dose range of atropine used (0.25 to 1.0 mg/kg) could completely inhibit the effect of strong vagal stimulation. The dose range of phentolamine used (2 to 4
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FIGURE 10
Stimulus-response curves under 4 different conditions of testing, dog no. 56. The ordinate represents the duration of PCS arrhythmia as the number of ventricular ectopic beats and the abscissa represents the energy of countershock in wattseconds necessary to cause that number. a = intact, untreated (control conditions); b = intact, ouabain treated (.048 mg/kg); c = denervated, untreated; d = denervated, ouabain treated (.052 mg/kg).

Ouabain shifts the stimulus-response curve of the intact dog upward and shifts the curve of the denervated dog downward. Denervation shifts the curve downward. See text.

EFFECT OF CHRONIC CARDIAC DENERVATION ON PCS ARRHYTHMIA

Five dogs survived the surgical procedure and were tested 10 to 20 days after completion of denervation. In 4 dogs, denervation caused a shift in the stimulus-response curve downward and to the right. Cardiac denervation thus diminished the PCS arrhythmia. Figure 10 shows stimulus-response curves of 1 of these dogs. After a countershock of 100 wsec was applied to the intact dog, the average duration of arrhythmia was 9 beats. When the dog had been denervated, the average number of beats was reduced to 2 at the same countershock energy.

When ouabain was administered to these dogs prior to denervation, the expected increase in duration of PCS arrhythmia occurred. A countershock of 100 wsec caused an average of 9 ectopic beats under control conditions and 100 after ouabain. When ouabain was administered in the usual manner to the denervated dogs, the stimulus-response curve was shifted downward and to the right so that it lay below the control curve. A 100 wsec countershock in the intact, ouabain-treated dog caused an arrhythmia with an average duration of more than 100 ectopic beats. The same countershock, in the denervated, ouabain-treated dog, caused no ectopic beats. The effect of chronic cardiac denervation was to inhibit the PCS arrhythmia in dogs acutely treated with ouabain. The effect of ouabain treatment in dogs with chronic cardiac denervation was to inhibit PCS arrhythmia. This latter effect is in contrast to the effect of ouabain treatment of the intact dog.

The 1 dog that did not show a decrease in the duration of the PCS arrhythmia following denervation showed some degree of sinus bradycardia and probably was not as completely denervated as the others. Yet this dog, though only partially denervated, also exhibited a decreased sensitivity to countershock after ouabain (0.052 mg/kg). Ouabain thus decreased the sensitivity to countershock in 5 out of 5 dogs after cardiac denervation.

Figure 10 shows the stimulus-response curves for 1 of the 5 dogs in each of the four test conditions. The effect of each maneuver upon the sensitivity of the dog to countershock is clear from the data presented.

EFFECT OF COUNTERSHOCK ON P-P INTERVAL

If a denervated dog was countershocked with an energy which was not sufficient to cause any ectopic beats, the P-P interval of the sinus beats which occurred immediately following the countershock was significantly greater than the P-P interval immediately prior to the countershock. Atropine (0.5 mg/
Records obtained after cardiac denervation, dog no. 52. In the top record, the upper trace is the standard lead II ECG recording. The artifact indicating the timing of the countershock is shown on the middle trace. The lower trace is the filtered lead II ECG recording. In the bottom record, the positions of the 2 ECG traces are reversed. A countershock of 100 usec was delivered at the time indicated by the arrow at the bottom of each record. The top record shows the effect of countershock on the P-P interval under control conditions. Prior to the shock the P-P interval was 510 msec. After the countershock the first P-P interval was 550 msec. The bottom record shows the effect of countershock on the P-P interval after the administration of atropine (0.5 mg/kg, iv). Prior to countershock the P-P interval was 580 msec. After countershock the first P-P was still 580 msec. See text.

kg) abolished this increase in P-P interval in each of 3 dogs tested. While this effect was seen most readily in dogs with cardiac denervation, it was also apparent in the intact dog. In 1 intact dog which exhibited no sinus arrhythmia, countershock augmented the P-P interval by 100 msec. The same dog, when denervated, showed an increase in P-P interval of 1450 msec after countershock. At both times the augmentation was abolished by atropine.

The ECG in Figure 11 was recorded from a dog with its heart denervated and demonstrates the augmentation of P-P interval following countershock. This particular dog exhibited the least prolongation of P-P interval in the 3 dogs examined. Table 4 shows the difference in P-P interval between the last 2 sinus beats before the countershock and the first 2 sinus beats after countershock for each pulse energy used during the experiment. One series of tests was made before and one after atropinization.

**Discussion**

**ADEQUACY AND REPRODUCIBILITY OF TESTING TECHNIQUES**

Studies designed to evaluate the suitability of the testing technique have shown that,
for a discharge of constant energy, peak voltage and waveform are constant if the load is constant. Also, after the first few countershocks of a series, it has been demonstrated that the impedance reaches a steady value. Finally, the peak voltage and waveform recorded directly from the heart bear a reasonably consistent relationship to the voltage and waveform recorded between the chest electrodes (1). Since the time of application of the countershock in the cardiac cycle also was constant, it appears that the technique employed provided adequate control of the input to the system under study.

Studies designed to test the suitability of the anesthetized dog for an investigation of the effects of digitalis on PCS arrhythmias have shown: first, that countershock does cause PCS arrhythmia in the dog; second, that a series of countershocks of constant energy results in reproducible PCS arrhythmias; third, that the duration of the arrhythmia bears a positive relationship to the energy of the countershock; and fourth, that administration of ouabain increases the duration of the PCS arrhythmia. The effect of ouabain could be demonstrated at all energy levels and was both reproducible and consistent. These results indicate that the anesthetized dog probably does provide a suitable experimental model to test the hypothesis advanced. Further support of this conclusion recently has been provided by the studies of Castellanos (personal communication) which demonstrated that, in 2 volunteers, the duration of PCS arrhythmia was related to the discharge energy and was increased by administration of digitalis.

Evidence was obtained that countershocks of the energies employed in these studies do activate efferent cardiac autonomic fibers. It seems clear that the decrease in sinus rate produced by countershock resulted from stimulation of cardiac vagal fibers, since the slowing was greater after elimination of sympathetic innervation by denervation and for both control and denervated hearts the slowing was abolished by atropine.

EVALUATION OF HYPOTHESIS

We believe that all of our results support the hypothesis that PCS arrhythmia is caused, at least in part, by an effect of countershock on cardiac autonomic nerves.

Administration of β-adrenergic receptor blocking drugs reduced the duration of PCS arrhythmia in both control and digitalized animals. One might attribute this action to the quinidine-like or local anesthetic effects of the β-receptor blocking agents employed (20).
However, the drugs used in this study differ markedly with respect to direct antiarrhythmic potency. Moreover, the degree of inhibition of PCS arrhythmia appears to be related to the adequacy of β-receptor blockade. Had the action of these β-receptor blocking agents been due to direct antiarrhythmic or local anesthetic effects, one would expect cocaine to have reduced the duration of PCS arrhythmia. This is so because cocaine has been shown to have direct antiarrhythmic action (13) as well as to inhibit the uptake of catecholamine by postganglionic sympathetic nerve terminals (21-24). However, rather than acting as an antiarrhythmic agent, cocaine caused a marked increase in the duration of PCS arrhythmia under both control conditions and after digitalization. We believe that these results strongly support the hypothesis that the PCS arrhythmias are related to the release of norepinephrine by countershock.

Since depletion of cardiac catecholamines by administration of reserpine (6, 25, 26) decreased the duration of PCS arrhythmia and chronic cardiac denervation had the same effect, we are convinced that the PCS arrhythmia depends upon and may be caused by a release of norepinephrine from cardiac postganglionic nerve terminals in response to countershock.

We do not have any direct evidence which would support the postulate that enhancement of PCS arrhythmia by ouabain is due to the fact that ouabain alters either the release or uptake of norepinephrine by sympathetic nerve terminals. However, although one recent report of studies on the guinea pig heart-lung preparation (27) has provided data showing no effect of digitalis on uptake of exogenous norepinephrine, others (10, 11) have suggested that uptake of norepinephrine by the canine heart is inhibited by ouabain.

It may be that ouabain sensitizes the heart to the effects of norepinephrine; conversely, the dependence of ouabain-induced arrhythmias on availability of norepinephrine has been demonstrated in many studies (2-8). It is likely, however, that the enhancement of PCS arrhythmia by ouabain is quantitatively related to the activation of β receptors. Also, in the case of the chronically denervated heart, the absence of postganglionic sympathetic nerve terminals is associated with a reversal of the effect of ouabain on PCS arrhythmia. These findings and the demonstration that cocaine enhanced PCS arrhythmia lend support to, but do not prove, the proposition that the effect of ouabain on the duration of such arrhythmias is related to an action which increases the activation of the cardiac β receptors. We suppose that this action of ouabain, in part, results from the decreased uptake of catecholamine.

It is not clear from these studies whether activation of efferent autonomic fibers coursing to the heart results solely from a direct effect of countershock on some part of the efferent pathway or from an effect induced by stimulation of afferent nerves. It has been shown that a variety of cardiac arrhythmias results from simultaneous activation of vagal and sympathetic centers or other parts of the brain (28-33). A sudden bombardment of such centers by afferent impulses perhaps might result in arrhythmias similar to those caused by direct stimulation of these same centers. Certainly, if the countershock is sufficient to activate efferent fibers, it seems most likely that afferent stimulation also occurs. Moreover, the drugs we have employed in the other test techniques would not differentiate between effects due to direct activation of sympathetic efferents and reflex activation of cardiac autonomic fibers.

It makes little difference whether the liberation of norepinephrine results solely from efferent activation or from simultaneous activation of both afferent and efferent nerves. In either case the role of norepinephrine liberation in the genesis of the PCS arrhythmia would be the same. However, since the arrhythmia was initiated immediately after countershock, the role of adrenal catecholamine appears to be of little, if any, importance.

**POSSIBLE ANTIADRENERGIC EFFECTS OF OUABAIN**

We were not prepared to find that the administration of ouabain to the chronically de-
nervated dog caused an inhibition of PCS arrhythmia over and above that resulting from the denervation. It was clear that the chronically denervated hearts were supersensitive to the effects of catecholamines since isoproterenol, 0.1 μg/kg, caused a greater change in heart rate than administration of 1.0 μg/kg to the intact animal. If one assumes that denervation never is complete (34) and that there is, therefore, a release of some small amount of norepinephrine by countershock in the denervated dog, the suppression of PCS arrhythmia by ouabain under these conditions may indicate that it has β-adrenergic receptor blocking actions. This conclusion is not unreasonable since evidence supporting an antiadrenergic effect of digitalis previously has been presented by Méndez and his co-workers (35) and by Nadeau and James (36). Further studies of this particular problem seem necessary.

OTHER IMPLICATIONS OF THESE STUDIES

The results obtained have led us to several other thoughts about the use of countershock and its effects on the myocardium. First, since the duration of PCS arrhythmia is consistently related to the energy of countershock, we wonder about the utility of testing digitalized patients with countershocks of extremely low energy in an effort to determine whether or not post-countershock arrhythmia will result. Our results suggest that a lack of arrhythmia following a low energy countershock does not guarantee that prolonged arrhythmia will not result from a countershock of greater energy content.

Finally, further studies are required to demonstrate directly whether or not ouabain has an action on either norepinephrine release or uptake. Our initial attempts to do this were unsuccessful. We could not find any significant change in the catecholamine concentration of blood collected from the coronary sinus during repeated countershock before and after the administration of ouabain (0.05 mg/kg). We believe that if a suitable technique were available for sampling the extracellular fluid in the vicinity of the nerve terminal and adrenergic receptor site, we would be able to demonstrate this point.

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