Electrophysiological Effects of Direct Current Countershock before and after Ouabain Sensitization and after Diphenylhydantoin Desensitization in the Dog

By Richard H. Helfant, M.D., Benjamin J. Scherlag, Ph.D., and Anthony M. Damato, M.D.

ABSTRACT

The effects of synchronized direct current countershock on ventricular automaticity, intraventricular conduction, and atrioventricular conduction were studied before and after ouabain administration and after diphenylhydantoin. At the level of electrical energy that induced ventricular arrhythmias, averaging 159 watt-seconds, countershock transiently increased ventricular automaticity and prolonged both intraventricular and atrioventricular conduction time. Immediately after ouabain-induced ventricular tachycardia returned to regular sinus rhythm, underlying ventricular automaticity and intraventricular and atrioventricular conduction times were increased. An average of 23 watt-seconds produced overt and persistent ventricular tachycardias due to enhanced automaticity or re-entry. Atrioventricular and intraventricular conduction times were also prolonged, and transient complete heart block occurred in two experiments. Diphenylhydantoin administration at this time depressed ventricular automaticity, caused a speeding of atrioventricular and intraventricular conduction times and increased the electrical energy necessary to produce ventricular tachycardia to 355 watt-seconds.

ADDITIONAL KEY WORDS intraventricular conduction heart block ventricular automaticity atrioventricular conduction re-entry

Synchronized direct current countershock is an accepted procedure for the termination of a number of cardiac arrhythmias. However, despite its widespread use, the electrophysiological effects of direct current countershock on the heart have only recently received attention (1). This is particularly important in understanding why some patients taking digitalis develop serious postshock arrhythmias (2-5). Although it has been demonstrated experimentally that digitalis administration greatly increases the sensitivity to postshock arrhythmias (6), the electrophysiological mechanism for this sensitivity phenomenon remains unknown.

In addition, a recent experimental study in our laboratory demonstrated that diphenylhydantoin greatly increases the amount of electrical energy required to produce an arrhythmia by countershock after digitalis sensitization (7). The electrophysiological effects of these interventions were explored in the present study by ascertaining the effects of direct current countershock on ventricular automaticity, intraventricular conduction and atrioventricular conduction before and after ouabain sensitization and after diphenylhydantoin desensitization.

Method

Twenty-three adult mongrel dogs were anesthetized with intravenous sodium pentobarbital (30 mg/kg) after an overnight fast. A polyethylene catheter was inserted into the femoral
artery and attached to a Statham pressure transducer for continuous monitoring of arterial pressure.

GROUP A

In 16 experiments, the right cervical vagus nerve was sectioned and stimulating electrodes were applied to its distal end; the left vagus nerve was left intact. The time for a ventricular escape beat to terminate the cardiac arrest produced by the stimulation of the distal end of the sectioned nerve was taken as an index of ventricular automaticity. The stimuli, 9 to 15 volts, were applied at a frequency of 20/sec; the duration of each impulse was 2.5 milliseconds. The ventricular escape time, determined during three separate control runs, was reproducible for each animal within 2 to 3 seconds. After control records were taken, two electrode paddles, 9 cm in diameter, were covered with conductive jelly and manually placed and held on either side of the shaved chest at the level of the cardiac apex beat. Using a direct current defibrillator, discharges synchronized to occur during the QRS complex were applied at 30-second intervals. Beginning at 10 watt-seconds, the level of electrical energy was progressively increased to 25, 50, 100, 200, 300 and 400 watt-seconds or until ventricular tachycardia (defined as four or more consecutive ventricular premature beats) was produced. The discharge was repeated twice at each level of electrical energy. At each level the electrophysiological effects were reproducible, indicating that there was no cumulative effect. At the level of electrical energy which produced an arrhythmia, the effects of vagal stimulation were recorded immediately after return to regular sinus rhythm. At each level of electrical energy, shock was also applied during the asystole produced by vagal stimulation.

Ouabain (7.5 \( \mu \)g/kg) was then injected; this was followed by infusion of 2.5 \( \mu \)g/kg per min, until ventricular tachycardia was produced. The level for ventricular escape was determined at 5-minute intervals throughout. Within 15 seconds after the ouabain-induced ventricular tachycardia returned to regular sinus rhythm, the time for ventricular escape was recorded and the level of electrical energy required to produce ventricular tachycardia was again determined. At this time, diphenylhydantoin (5 mg/kg) was administered intravenously, and its effect on ventricular automaticity was determined. The threshold of electrical energy necessary to cause

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**Figure 1**

The effect of direct current countershock during asystole. In A, vagal stimulation (arrow) causes asystole for 24 seconds before a ventricular escape beat occurs. In B, three seconds after vagal stimulation (arrow) induced asystole, a 200 watt-second (WS) discharge across the precordium causes a short run of ventricular beats which spontaneously subsides after 10 seconds; 1-second time lines.
ventricular tachycardia and its effects on automaticity were again ascertained.

GROUP B

In seven dogs an electrogram of the His bundle was obtained by passing a bipolar catheter into the right atrium via the femoral vein and stabilizing its position at the atrioventricular junction. Intraventricular conduction time was measured as the interval between the electrogram of the bundle of His and the end of the QRS complex. Atrioventricular conduction time was taken as the interval between the beginning of atrial activity on the electrogram of the His bundle and the His bundle spike. Records of intraventricular and atrioventricular conduction times were taken at a paper speed of 200 mm/sec.

After control records were taken, synchronized direct current discharges were administered as described above and conduction times were recorded after each discharge until the level of electrical energy required to produce an arrhythmia was determined. Conduction times were measured after each discharge and repeated 30 seconds, 2 minutes, and 5 minutes after the arrhythmic energy level was reached. Diphenylhydantoin was then administered and its effects on conduction studied. The amount of electrical energy to produce an arrhythmia was again determined, and its effects on conduction were measured immediately and after 30 seconds, 2 minutes, and 5 minutes.

**Results**

GROUP A

Before ouabain, an average of $159 \pm 78$ (SD) watt-seconds was required to produce ventricular tachycardia. Immediately following return to regular sinus rhythm, the time for ventricular escape was unchanged from the control level. However, discharge at the level of energy required to produce an arrhythmia

![Figure 2](http://circres.ahajournals.org/)

*The effects of ouabain and diphenylhydantoin (DPH) on ventricular automaticity. Control: vagal stimulation causes asystole lasting 10 seconds before the occurrence of a ventricular escape beat. Ouabain: see text for description; vagal stimulation at arrow. Diphenylhydantoin: see text; 1-second time lines.*

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Effects of Countershock on Atrioventricular and Intraventricular Conduction

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**AVERAGE ± SD**

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**Abbreviations:** WS = watt-seconds; SR = sinus rate, beats/min; AVC = atrioventricular conduction time (msec); IVC = intraventricular conduction time (msec); DPH = diphenylhydantoin; *P values represent comparison of atrioventricular and intraventricular conduction times before shock and immediately after shock under each of the three experimental conditions (before ouabain, just prior to ouabain-induced ventricular tachycardia and after diphenylhydantoin). An analysis of variance was performed among three different experimental conditions. Then a t-test for paired differences was applied to these three groups. The t value derived from the data was compared with the t table values multiplied by the square root of 2 to obtain an appropriate P value.
during the cardiac asystole produced by vagal stimulation consistently caused a short run of ventricular beats. This indicates a transient increase in ventricular automaticity (Fig. 1). Discharges at energy levels less than that required to produce an arrhythmia had no effect during asystole.

During the infusion of ouabain, the time for ventricular escape was progressively shortened. Shortly before an overt arrhythmia became manifest, a different and faster ventricular focus was unmasked by vagal stimulation. This new focus increased in rate until it became faster than the sinus rate and thus

![Figure 3](https://example.com/figure3.png)

**Figure 3**
The effects of countershock, ouabain, and diphenylhydantoin (DPH) on atrioventricular and intraventricular conduction. Lead II, ECC; H.B.E. = the His bundle electrogram showing the P wave, spike due to excitation of His bundle (arrows) and QRS complex. Before ouabain, control atrioventricular conduction time equals 60 milliseconds (P-H = 60); intraventricular conduction time equals 47 milliseconds (H-S = 47). Immediately following 25 watt-seconds (WS), P-H = 60 milliseconds and H-S = 47 milliseconds. After 100 watt-seconds, P-H is prolonged to 75 milliseconds and H-S to 52 milliseconds. After ouabain (return to regular sinus rhythm from ouabain-induced ventricular tachycardia): P-H = 75 milliseconds; H-S = 55 milliseconds. In this state, 25 watt-seconds increases P-H to 90 milliseconds, H-S to 60 milliseconds. After diphenylhydantoin, P-H decreases to 58 milliseconds and H-S to 47 milliseconds. After 25 watt-seconds, P-H remains 58 milliseconds and H-S = 47 milliseconds; 100 watt-seconds prolong P-H slightly to 60 milliseconds and H-S to 50 milliseconds; 400 watt-seconds prolong P-H to 75 milliseconds and H-S to 55 milliseconds. Paper speed 200 mm/sec.

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established an overt ventricular tachycardia. Immediately after return to regular sinus rhythm, the time for ventricular escape after vagal stimulation was markedly shortened and the same ventricular focus that had dominated the rhythm was immediately uncovered (Fig. 2). An average of $23 \pm 13.1$ watt-seconds produced overt ventricular tachycardia.

The administration of diphenylhydantoin at this time immediately prolonged the ventricular escape time to 15 seconds (Fig. 2).

**FIGURE 4**
Production of complete heart block after 100 watt-seconds for 11 seconds; 1-second time lines.

**FIGURE 5**
A continuous record demonstrating the production of bigeminal rhythm after 200-watt-second countershock which disappears during vagal stimulation (arrow), indicating that this arrhythmia is not caused by enhanced ventricular automaticity. (See discussion.)
and increased the threshold required to produce ventricular tachycardia to an average of 355 ± 67.1 watt-seconds. The ventricular arrhythmias produced by countershock were transient, and the discharge at energy levels required to produce arrhythmias during vagally induced cardiac asystole caused a run of ventricular beats lasting several seconds.

GROUP B
The effects of countershock on atrioventricular and intraventricular conduction in the undigitalized state are summarized in Table 1. Immediately after the arrhythmia caused by the electrical discharge returned to regular sinus rhythm, atrioventricular conduction time was prolonged an average of 12 milliseconds; intraventricular conduction was increased an average of 8 milliseconds. However, these effects were transient; records taken 30 seconds after countershock returned to control values.

Ouabain infusion prolonged both atrioventricular and intraventricular conduction. Just prior to overt toxicity, (average 20 to 40 minutes), ouabain increased atrioventricular conduction time an average of 29 ± 9.5 milliseconds. The average intraventricular conduction time was also increased by 11 ± 6.8 milliseconds. After return to regular sinus rhythm, atrioventricular and intraventricular conduction times remained elevated. Countershock at this time further increased atrioventricular conduction time an average of 19 milliseconds at arrhythmogenic levels of 23 watt-seconds. An example is seen in Figure 3. Transient complete heart block occurred in two experiments (Fig. 4).

Intraventricular conduction times were also increased an average of 11 milliseconds above that just prior to the electrical discharge (Table 1). These changes in atrioventricular and intraventricular conduction persisted 30 seconds to 5 minutes. In this connection, shock frequently induced bigeminal rhythms which appeared to be due to a re-entry mechanism and not to ventricular automaticity. These arrhythmias were not associated with the initial transient automaticity and were abolished during vagal stimulation coincident with abolition of supraventricular activity (Fig. 5).

Diphenylhydantoin speeded atrioventricular and intraventricular conduction. The average decrease in atrioventricular conduction was 26 ± 6.8 milliseconds; average intraventricular conduction time decreased 7 ± 5.8 milliseconds. Countershock at an average arrhythmogenic level of 355 watt-seconds increased atrioventricular conduction time an average of 7 ± 6.8 milliseconds and intraventricular conduction an average of 4 ± 7.6 milliseconds. These changes however were transient, lasting less than 30 seconds in all cases (Table 1).

Discussion
In the present study, the nature of the ventricular arrhythmogenic effects of direct current countershock appeared to be related to two distinct electrophysiological phenomena. There was a transient increase in ventricular automaticity, indicated by the fact that shocks applied during cardiac asystole caused a short repetitive run of ectopic ventricular beats lasting several seconds (Fig. 1). In addition, the shock frequently produced bigeminal rhythms which appeared to be due to a re-entry mechanism and not due to underlying ventricular automaticity, since the ventricular ectopic beats had a constant coupling time and were completely abolished when the sinus rhythm was inhibited by vagal stimulation (Fig. 5). Furthermore, at arrhythmogenic levels, shock prolonged both intraventricular and atrioventricular conduction. Although these effects also were transient, lasting less than 30 seconds, they were temporally related to the occurrence of the bigeminal rhythms. Hoffman and Cranefield postulated that extrasystoles of the re-entry type may be caused by depression of intraventricular conduction (8).

Ouabain infusion resulted in a progressive increase in ventricular automaticity and prolongation of intraventricular and atrioventricular conduction before toxicity was reached.
After return to regular sinus rhythm, underlying ventricular automaticity remained elevated (Fig. 2) and both atrioventricular and intraventricular conduction also remained prolonged (Fig. 3). Countershock at this time consistently brought out an overt, ventricular tachycardia at very low electrical energy levels, and this persisted for an average of 4 minutes. After regular sinus rhythm was again restored, ventricular automaticity and atrioventricular and intraventricular conduction times remained elevated. The electrophysiological effects of both ouabain and direct current countershock were therefore similar, since both increased ventricular automaticity and prolonged intraventricular and atrioventricular conduction times.

It has been shown that ouabain can cause ventricular arrhythmias of a re-entry type in addition to those caused by enhanced automaticity (9). Therefore, in addition to potentiating ouabain's arrhythmogenic effect by enhancing ventricular automaticity, countershock can also promote a re-entry type of arrhythmia by prolonging conduction in the presence of ouabain.

Diphenylhydantoin is an antiarrhythmic agent which seems to have particular value in the treatment of digitalis-induced arrhythmias (10-13). Experimental studies indicate that in the treatment of digitalis toxicity, diphenylhydantoin may be superior to agents such as procaine amide, since diphenylhydantoin decreases ventricular automaticity without affecting intraventricular conduction, thus minimizing the possibility of causing re-entry (14). In addition, diphenylhydantoin antagonizes the effect of digitalis on atrioventricular conduction, thus improving atrioventricular conduction in the digitalized heart (14-16). Prophylactic diphenylhydantoin increases the dose of digitalis necessary to produce arrhythmias an average of 122% (17).

In a recent experimental study we demonstrated that diphenylhydantoin administration greatly increases the amount of electrical energy required to produce an arrhythmia by countershock (7). This study appeared to indicate that diphenylhydantoin desensitized the heart to the arrhythmogenic effects of countershock after it had been sensitized by digitalis. In the present study, diphenylhydantoin administration consistently caused a marked depression of ventricular automaticity (Fig. 2) which persisted in most experiments even after 400-watt-second shocks. In addition, both atrioventricular and intraventricular conduction times were speeded by diphenylhydantoin (Fig. 3). Arrhythmic direct current shocks at much greater electrical energy levels than control caused only minor and transient effects on cardiac conductivity (Table 1). Thus it appears that the desensitizing effect of diphenylhydantoin on the arrhythmogenic effects of direct current countershock can be explained by its depressant effect on ventricular automaticity and speeding of cardiac conduction.

The explanation for the electrophysiological relationship between ouabain and countershock, as well as for the antagonism of diphenylhydantoin, remains unclear. Recent work indicates that the arrhythmic effects of countershock and digitalis may be related at least partly to catecholamine release, since catecholamine-blocking agents can inhibit countershock arrhythmias (18). In addition, studies in our laboratory have shown that the dose of epinephrine necessary to produce ventricular tachycardia is markedly reduced after digitalis administration and elevated above the control level by diphenylhydantoin treatment (19). It is also possible that the electrophysiological relationship of these interventions are related to their common effects on myocardial potassium balance. Consistent with this possibility is the finding that diphenylhydantoin reverses the myocardial potassium efflux caused by toxic doses of digitalis (20), while simultaneously reversing the effects of the glycoside on automaticity and conduction (21).

References

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