Cardiac Inotropic and Coronary Vascular Responses to Countershock

EVIDENCE FOR EXCITATION OF INTRACARDIAC NERVES

By Frederick R. Cobb, M.D., Andrew G. Wallace, M.D., and Galen S. Wagner, M.D.

ABSTRACT

These experiments were designed to examine the role of excitation of intracardiac nerves in the response to countershock with either alternating current (ac) or direct current (dc). Studies were performed on intact anesthetized dogs and on isolated perfused hearts. In intact dogs ac and dc countershock produced transient sinus arrest and an increase in myocardial contractile force. Sinus arrest could be prevented with atropine, and the positive inotropic response could be prevented with propranolol or prior surgical denervation of the heart. In isolated hearts, ac and dc countershock produced sinus arrest which could be prevented with atropine or hemicholinium-3. Alternating-, but not direct-, current countershock increased contractile force of the isolated heart. The inotropic response to ac could be blocked with propranolol and was absent in hearts removed from dogs which had undergone prior cardiac denervation. Both ac and dc countershock produced a decrease in coronary vascular resistance which could be prevented with atropine. Cholinergic responses to countershock persisted after surgical denervation of the heart. These observations provide evidence for excitation of intracardiac cholinergic and adrenergic nerves by countershock. Direct-current countershock excites cardiac sympathetic nerves in intact dogs, but not in isolated hearts. Intracardiac cholinergic nerves persist after surgical denervation of the heart.

ADDITIONAL KEY WORDS

Alternating current  direct current
autonomic nervous system  cardiac denervation  myocardium
hemicholinium-3  coronary arteries

Alternating current (ac) and direct current (dc) have been used successfully to terminate ventricular fibrillation and other cardiac arrhythmias. Although countershock has found widespread clinical acceptance, arrhythmias apparently produced by countershock represent a significant problem especially with ac, or with either form of countershock in digitalized patients (1, 2). Recent studies have provided evidence that dc countershock results in excitation of the intrathoracic autonomic nerves and that arrhythmias observed immediately after countershock are the consequence, at least in part, of released norepinephrine (3, 4). Although the mechanism of excitation of intrathoracic nerves by countershock has not been established, other forms of electrical energy such as suprathreshold stimulation (5), field stimulation (6), and high frequency threshold (7, 8) or subthreshold stimulation (9) have been shown to release autonomic transmitters from isolated atrial and ventricular myocardium. The experiments described in this report were designed to compare cardiac responses to countershock in intact dogs and in isolated perfused hearts. The observations indicate that ac and dc countershocks produce excitation of intracardiac autonomic nerves. Certain of the differences in the cardiac response to ac and dc countershocks are attributable to qualitative and quantitative

From the Department of Medicine, Duke University Medical Center, Durham, North Carolina 27706.

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differences in the type of autonomic nerve stimulation. These studies also provide evidence for the functional integrity of postganglionic cardiac cholinergic nerves after "total cardiac denervation."

**Methods**

Preliminary studies were performed on ten intact mongrel dogs weighing 15 to 20 kg. The animals were anesthetized with 7 to 10 ml of 2% sodium pentothal and ventilated with a Harvard respirator. A median sternotomy was performed to expose the heart, and a Walton Brodie strain-gauge arch was sutured to the wall of the right ventricle to monitor changes in contraction force. The output of the gauge was a linear function of force over the range of forces observed in these experiments. Because it was often necessary to adjust diastolic tension in the course of an experiment, the tracings of contraction force were not calibrated in units of force. Instead, percent change of force was used to evaluate the effects of any given intervention. A polyethylene catheter was placed in the femoral artery and connected to a Statham P23Db strain gauge to measure arterial blood pressure. The electrocardiogram was monitored continuously. Each signal was amplified with Sanborn 350 series amplifiers and recorded on a direct-writing oscillograph at paper speeds of 0.25 to 25 mm/sec. Alternating- and direct-current discharges were delivered to the chest wall through a standard set of external paddles. Alternating-current countershocks (150 msec of 60 Hz) were delivered with a Medtronics defibrillator at energies of 120, 240, and 360 v. Direct-current countershocks were delivered with an American Optical synchronized defibrillator at energies from 1 to 400 watt-sec. A recovery period of 5 minutes was allowed between countershocks. After control observations, either cholinergic or adrenergic blockade or both was produced. Cholinergic blockade was accomplished with atropine, 2.0 mg, iv. Beta-receptor blockade was accomplished with propranolol (Inderal), 0.2 mg/kg, iv. The response to countershock was also examined in two dogs which had undergone total cardiac denervation (10) 4 weeks prior to the studies. Cardiac denervation was evaluated at the time of the experiments and considered adequate if vagal nerve stimulation failed to produce bradycardia and if stellate ganglion stimulation or the administration of tyramine, 60 µg/kg, iv, failed to increase myocardial contraction force.

Responses to countershock were also examined in 11 isolated, supported heart preparations (Fig. 1). Mongrel dogs weighing 13 to 29 kg were donors. These dogs were anesthetized with 7 to 10 ml of 2% sodium pentothal. The chest was opened, and umbilical tapes were placed around the brachiocephalic and left subclavian arteries and around the descending thoracic aorta. A no. 10 Iaria catheter was inserted into the left subclavian artery and advanced into the aortic arch. After anticoagulation with heparin, 10 mg/kg, iv, the subclavian catheter was opened, and the dog was exsanguinated rapidly. The aorta and brachiocephalic arteries were then ligated. The beating heart was removed and transferred to a bath which had been filled with blood from the donor dog. The bath contained a heat exchanger to maintain temperature at 37°C. Electrodes on each side of the bath were used for recording an electrocardiogram.

Dogs weighing at least 20 kg were used as support animals. The support animal was anesthetized with 10 to 12 ml of 2% sodium pentothal and ventilated with a Harvard respirator. A catheter was placed in the left femoral artery for measuring arterial blood pressure. The right femoral artery and vein were then cannulated. The arterial and venous lines were led through opposite sides of a variable-speed peristaltic pump to the inlet and outlet ports of the bath. Perfusion of the isolated heart was established by connecting the cannula in the subclavian artery of the donor heart to the inlet port of the bath and starting the pump. Coronary venous return and arterial blood pressure were monitored.
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spilled into the bath and was returned to the support dog's femoral vein. Coronary flow was maintained constant in each heart and ranged from 70 to 90 ml/min in different studies. Competence of the aortic valve was checked frequently by direct visualization through the left atrium. Coronary perfusion pressure was monitored through a catheter placed in the aortic arch, and changes in coronary pressure were used as an index of changes in coronary vascular resistance. A Walton Brodie strain-gauge arch was sutured to the wall of either the right or left ventricle to record changes in contraction force.

The responsiveness of the coronary circulation and of myocardial contraction force was examined initially by injecting either acetylcholine, 0.01 to 0.50 \( \mu \)g, or norepinephrine, 0.01 to 0.50 \( \mu \)g, into the coronary arterial input line. Responses to a-c and d-c countershock were determined in each heart. Countershocks were delivered to the heart through a set of internal paddles held in the bath at least 4 cm from the heart. Alternating-current countershocks of 120 v were used, and d-c countershocks ranged in energy from 1 to 80 watt-sec. After these control studies, autonomic blockade was accomplished by giving atropine, 2.0 mg, or propranolol, 0.2 mg/kg, or both intravenously to the support dog and allowing time for these agents to circulate to the isolated heart. Blockade was confirmed by demonstrating the absence of a response to the appropriate agent administered through the coronary input line. After autonomic blockade, responses to a-c and d-c countershock were examined again.

In two additional experiments depletion of cardiac acetylcholine was accomplished prior to removal of the heart from the donor dog. Acetylcholine depletion was produced by giving the donor dog 2 mg/kg of hemicholinium-3, and then stimulating the distal ends of the cut cervical vagi, for 30 seconds each, until no change in heart rate occurred. Hemicholinium-3 is a competitive inhibitor of the uptake of choline in parasympathetic nerves (11). It required approximately 1 hour of intermittent vagal stimulation, after the administration of hemicholinium-3, to abolish the responses to vagal stimulation. In two studies utilizing the isolated supported heart preparation, hearts were removed from dogs which had undergone total cardiac denervation 1 month before the studies.

Results

Transcutaneous d-c countershock in intact dogs produced an increase in blood pressure and myocardial contraction force and a transient period of sinus arrest. These effects on blood pressure and contraction force were not observed at energies of less than 20 watt-sec.

1Hemicholinium-3 kindly supplied by Aldrich Chemical Company.
Effect of 80 watt-sec d-c countershock before (A) and after (B) controlled aortic pressure. Abbreviations same as Figure 2. Paper speed 2.5 mm/sec (heavy vertical time lines = 2 seconds).

Although the inhibitory influence of countershock on sinus rate was evident even at the lowest energies of stimulation (1 watt-sec). Tracings from one representative experiment are shown in Figure 2, A-C. Results with d-c countershock in all ten dogs were comparable.

Alternating-current countershock also produced a pressor response and a positive inotropic effect. Tracings from one such experiment are shown in Figure 2, D. The increase in contraction force produced by ac (120 or 360 v) was always greater (5-15%) than that which followed dc, even at the highest energies (400 watt-sec) used. The positive inotropic responses to d-c and a-c countershock were not dependent on an increase in arterial blood pressure. Inotropic responses similar to those described above were observed in these animals in which the increase in blood pressure was attenuated or prevented (Fig. 3). Attenuation of the pressor response to countershock was accomplished by connecting the femoral arteries to a bottle filled with blood and raised to a height equivalent to 100 mm Hg. Positive inotropic responses to countershock were also observed in three dogs in which heart rate was controlled by ventricular pacing. The period of asystole following d-c countershock could be abolished completely by prior administration of atropine. Positive inotropic response to either d-c or a-c countershock could be abolished by prior administration of propranolol and was markedly delayed in two dogs which had undergone prior surgical denervation of the heart (Fig. 4). These results are summarized in Table 1.

Studies on the Isolated Heart

In studies on 11 hearts, contraction force increased by 70 to 120% above control after a-c countershock (120 v) and coronary perfusion pressure decreased by 30 to 50%. After d-c countershock (40 to 60 watt-sec) coronary perfusion pressure decreased by 20 to 30% with little or no change in contraction force (0 to -10%). Tracings in Figure 5 are from an experiment illustrating the effects of a-c and d-c countershocks applied to an isolated heart. Alternating-current countershock (panel A) produced a marked increase in contraction force and a decrease in coronary perfusion pressure at a constant coronary...
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Effects of d-c (A) and a-c (B) countershock in an intact chronically denervated dog. Abbreviations same as Figure 2. Paper speed 1.0 mm/sec (heavy vertical time lines = 5 seconds).

TABLE 1

Effects of Propranolol, Atropine, Hemicholinium-3, and Surgical Denervation on Responses Produced by A-C and D-C Countershock on Intact and Isolated Hearts

<table>
<thead>
<tr>
<th>Response</th>
<th>Propranolol</th>
<th>Atropine</th>
<th>Hemicholinium-3</th>
<th>Surgical denervation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased blood pressure</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Increased contraction force</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Multiple ventricular extrasystoles</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Increased blood pressure</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Increased contraction force</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Sinus arrest</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Increased contraction force</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Decreased coronary resistance</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Multiple ventricular extrasystoles</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>yes</td>
</tr>
</tbody>
</table>

blood flow. Direct-current countershock had a positive inotropic effect on intact dogs, but in isolated hearts it produced either no change or a slight decrease in contraction force and a substantial decrease in coronary perfusion pressure (Fig. 5, B).

The effects of d-c countershock on myocardial contraction force and coronary vascular resistance were qualitatively similar to the effects of an intracoronary injection of acetylcholine (Fig. 6, A). Acetylcholine produced a decrease in coronary perfusion pressure and little change in contraction force. The effects of a-c countershock were qualitatively similar to the response to an intracoronary injection of norepinephrine (Fig. 6, B). Norepinephrine produced a marked increase in myocardial contraction force accompanied by a decrease in coronary perfusion pressure.

The tracings in Figure 7 illustrate the response of an isolated heart to d-c countershock at energies ranging from 1 to 40 watt-sec. It should be noted that, even at the...
FIGURE 5
Effects of a-c (A) and d-c (B) countershock in an isolated heart preparation. SD = aortic pressure of the support dog; CF = contraction force; CPP = coronary perfusion pressure; ECG = electrocardiogram of the isolated heart. Coronary flow was constant at 80 ml/min.
Ventricles were paced at 90/min. Paper speed 3.5 mm/sec (heavy vertical time lines = 2 seconds).

FIGURE 6
Effects of 0.01 µg of acetylcholine (A) and 0.01 µg of norepinephrine (B). Each drug was injected in 0.5-ml volumes into the coronary perfusion line. Illustrations were taken from different experiments. Coronary blood flow was 75 ml/min. Abbreviations same as Figure 5.
Paper speed 1.0 mm/sec (heavy vertical lines = 5 seconds).
Effects of d-c countershock at varying energies on an isolated heart preparation. Coronary flow constant at 80 ml/min. Abbreviations same as Figure 5. Paper speed 1.0 mm/sec (heavy vertical lines = 5 seconds).

Effects of d-c countershock in an isolated heart before (A) and after (B) cholinergic blockade by atropine. Atropine, 2.0 mg, i.v., was injected into the support dog. Abbreviations same as Figure 5. Paper speed 2.5 mm/sec (heavy vertical time lines = 2 seconds).

The lowest energy used (1 watt-sec), d-c countershock caused transient sinus arrest and a decrease in coronary perfusion pressure. The magnitude of these responses was only slightly greater with 60 watt-sec than with 1 watt-sec.
FIGURE 9
Effects of a-c countershock in an isolated heart before (A), after 2 mg of atropine (B), and after 2 mg of atropine and 2 mg of propranolol (C) were injected intravenously into the support dog. Abbreviations same as Figure 5. Paper speed 2.5 mm/sec (heavy vertical time lines = 2 seconds).

FIGURE 10
Effect of a-c and a-c countershock in an isolated heart after cholinergic blockade by hemicholinium-3. A and B show the response to 20 watt-sec dc and 120 v ac, respectively. Small panel following B shows the return to control by 60 seconds. C shows that, in the presence of cholinergic blockade, propranolol, 0.2 mg/kg, blocked the decrease in coronary resistance and increase in contraction force produced by ac. Abbreviations same as Figure 5. Paper speed 2.5 mm/sec (heavy vertical time lines = 2 seconds).
Atropine was given in 6 of the 11 isolated heart experiments. In each experiment it abolished the coronary vascular response to d-c countershock. Figure 8 shows tracings from one such experiment in which the ventricle was paced to maintain a constant heart rate. In A (control), d-c countershock produced a decrease of 30 mm Hg in coronary perfusion pressure. In B, after 2 mg of atropine had been given to the support dog, d-c countershock had no effect on coronary perfusion pressure.

The positive inotropic response to a-c countershock could be abolished by propranolol. Tracings from one such experiment are shown in Figure 9. In A (control), a-c countershock produced a marked increase in contraction force and a decrease in coronary vascular resistance. Atropine did not influence the inotropic response to a-c countershock (B), but after the subsequent administration of propranolol, a-c countershock had no effect on contraction force (C).

When hearts were removed from the two dogs that had been given hemicholinium-3, d-c countershock failed to produce a drop in coronary perfusion pressure (Fig. 10, A). Alternating-current countershock still produced a marked increase in contraction force and a drop in coronary perfusion pressure (B). Both responses were abolished by propranolol (C).

Responses to a-c and d-c countershock were examined in two isolated hearts removed from dogs that had total cardiac denervation 4 weeks prior to the studies (Fig. 11). Direct-current countershock produced a transient period of sinus arrest, a decrease in coronary perfusion pressure, and no major change in contraction force (A). The influence of d-c countershock on sinus rate and coronary resistance was abolished by atropine (B). In marked contrast to its effect on hearts removed from normal dogs, a-c countershock had no inotropic effect on the denervated heart (C). Thus cardiac denervation abolished the adrenergic response to a-c
countershock, but did not abolish the cholinergic response to d-c countershock. These results are summarized in Table 1.

Discussion

The most common arrhythmias encountered after countershock include sinus bradycardia or sinus arrest, prolonged A-V conduction, atrial or ventricular extrasystoles, ventricular tachycardia and, rarely, ventricular fibrillation. Several investigators have shown that arrhythmias such as those noted above can be produced experimentally by appropriate activation of the nervous system even in animals with presumably normal hearts (12, 13). That certain of the above arrhythmias might be related to excitation of the vagi during countershock has long been suspected, and this has prompted clinicians to treat such events with atropine. Recent studies have suggested that countershock can stimulate intrathoracic sympathetic nerves and that such stimulation may contribute to ectopic rhythms seen after cardioversion (3, 4).

In 1963, Vincenzi and West (9) showed that stimulation of the sinus node with a train of pulses of insufficient strength to excite the muscle produced hyperpolarization of the nodal cells, initial slowing of the atrial rate, and a secondary acceleration of atrial rate. The negative chronotropic effect could be prevented with atropine, and the delayed positive chronotropic response could be prevented by adrenergic antagonists. In 1966, Blinks (6) described a method for producing graded release of autonomic neurotransmitters from isolated heart muscle by means of field stimulation. In 1967, Ten Eick et al. (3) examined the duration of arrhythmias after d-c countershock in untreated and digitalized dogs. In both groups, adrenergic antagonists or cardiac denervation reduced the incidence and duration of arrhythmias after countershock. Childers et al. (4) demonstrated that d-c countershock shortened the atrial refractory period and prolonged A-V conduction and that these effects could be blocked by propranolol.

Certain arrhythmias after countershock can be reduced or abolished by beta-receptor blocking agents, but these agents appear to have antiarrhythmic properties that are independent of their blocking effect on adrenergic receptors (14, 15). We thought that monitoring the contraction force of ventricular muscle might provide a more sensitive and specific index of the release of catecholamines during countershock. We are not aware that anyone has monitored changes of contraction force during countershock, although several investigators (16, 17) have described ventricular function before and after countershock. Furthermore, to our knowledge no one has studied the effects of countershock on the coronary circulation and no one has systematically compared a-c and d-c countershocks with respect to activation of the autonomic nervous system. Thus, these studies were designed to test two hypotheses: (1) that a-c and d-c countershocks produce stimulation of intracardiac nerves, and (2) that differences in the cardiac response to a-c and d-c countershock are a function, at least in part, of qualitative and quantitative differences in adrenergic and cholinergic nerve stimulation.

Alternating- and direct-current countershocks produced brief periods of sinus arrest. Sinus arrest was observed even with the lowest energies of stimulation (1 watt-sec) and could be prevented by prior administration of atropine. Alternating- and direct-current countershocks produced an increase in myocardial contractile force and blood pressure in intact dogs. The positive inotropic responses to a-c and d-c countershock were not dependent on changes in blood pressure, however, since comparable changes in contractile force were observed when the blood pressure was maintained essentially constant. The inotropic responses to a-c and d-c countershock could be prevented by prior administration of propranolol and were not evident in dogs that had had surgical denervation of the heart. Although these studies utilized indirect methods of examining autonomic nerve activity, they support the view proposed by others that countershock produces...
excitation of cardiac adrenergic and cholinergic nerves in the intact dog.

Although studies of countershock in the intact animal are relevant to the clinical use of this technique, certain variables of potential interest could not be measured easily in the intact preparation. Thus, the studies of the isolated heart provided an opportunity to examine the effects of countershock on intracardiac nerves and on coronary vascular resistance. Although these studies do not exclude a role for stimulation of afferent nerves or the spinal cord in the responses observed in intact dogs, they do provide evidence that a substantial component of the response to countershock can be attributed to excitation of the intracardiac nerves. In the isolated heart, a-c countershock produced changes similar to those observed in the intact animal. These included transient sinus arrest which could be prevented with atropine, and a positive inotropic response which could be prevented with propranolol or cardiac denervation. Even after propranolol had been given to block the inotropic response, a-c countershock still elicited a decrease in coronary vascular resistance which could be prevented by atropine. These observations indicate that a-c countershock can excite both intracardiac adrenergic and cholinergic nerves.

Direct-current countershock decreased coronary vascular resistance even with energies as low as 1 watt-sec. There was no significant change in contraction force even at the highest energies of stimulation. Injection of small amounts of acetylcholine into the coronary circulation produced responses comparable to those observed with d-c countershock. These observations provide additional evidence for cholinergic innervation of the coronary circulation. In hearts removed from dogs that had been treated with hemicholinium-3, d-c countershock failed to cause sinus arrest or a decrease in coronary vascular resistance. These hearts still responded to injections of acetylcholine, and a-c countershock elicited a profound positive inotropic response which could be prevented with propranolol. Thus the studies using hemicholinium-3 complement those in which atropine was used and provide additional evidence that the decrease in coronary resistance induced by countershock was mediated by release of acetylcholine from intracardiac cholinergic nerves.

Both a-c and d-c counter-shocks increased contraction force in the intact animal, but only a-c countershock had a positive inotropic effect on the isolated heart. It was demonstrated that the isolated heart was responsive to injections of small quantities of norepinephrine and that a-c countershock caused an increase in contraction force which could be prevented by beta-receptor blockade. Failure of d-c countershock to cause an increase in contraction force in the isolated heart came as a surprise to us. Conceivably, the single d-c discharge could stimulate preganglionic fibers or ganglion cells in the intact dog, but was insufficient to excite intracardiac postganglionic fibers.

Finally, it was of considerable interest to us that hearts removed from dogs with "total" cardiac denervation failed to reveal adrenergic responses to countershock, but that the effects of countershock on sinus rate and on coronary vascular resistance were still present. These changes could be prevented with atropine. Napolitano et al. (18) have reported previously that after autotransplantation of the heart the sympathetic innervation undergoes degeneration, but that ganglion cells and their axons persist in the heart. These neural elements which persist were assumed to be cholinergic. The procedure of cardiac denervation, or of autotransplantation, divides the postganglionic sympathetic nerves, and it is not surprising that sympathetic fibers undergo degeneration. However, these procedures divide the preganglionic vagal fibers since postganglionic vagal fibers originate within the heart. The observations described in this report support the view that the terminal vagal innervation is intact in the "denervated heart" and that cholinergic responses can be elicited by countershock. This was an important observation since we...
had concluded incorrectly, on the basis of previous data, that there was no physiologic evidence of cholinergic innervation after denervation (12).

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References
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FREDERICK R. COBB, ANDREW G. WALLACE and GALEN S. WAGNER

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