Anesthesiology
62:610–614, 1985

Postcountershock Myocardial Damage after Pretreatment with Adrenergic and Calcium Channel Antagonists in Halothane-anesthetized Dogs

David M. Gaba, M.D., Samuel Metz, M.D.,† Mervyn Maze, M.B., Ch.B.**

Transthoracic electric countershock can cause necrotic myocardial lesions in humans as well as experimental animals. The authors investigated the effect on postcountershock myocardial damage of pretreatment with prazosin (0.1 mg/kg), an alpha-1 antagonist; L-metoprolol (0.5 mg/kg), a beta-1 antagonist, and verapamil (0.5 mg/kg), a calcium channel-blocking agent. Twenty dogs were anesthetized with halothane and given two transthoracic countershocks of 295 delivered joules each after drug or vehicle treatment. Myocardial injury was quantitated 24 h following countershock by measuring the uptake of technetium-99m pyrophosphate in the myocardium. Elevated technetium-99m pyrophosphate uptake occurred in visible lesions in most dogs regardless of drug treatment. For each of four parameters of myocardial damage there was no statistically significant difference between control animals and those treated with prazosin, metoprolol, or verapamil. These data suggest that adrenergic or calcium channel-mediated mechanisms are not involved in the pathogenesis of postcountershock myocardial damage. (Key words: Anesthesia: cardiovascular. Heart: defibrillation. Surgery: Cardiovascular.)

ELECTRIC COUNTERSHOCK can cause necrotic myocardial lesions in humans, as evidenced by ST segment changes in the electrocardiogram.[1,2] by elevations of myocardial specific isoenzymes of CPK,[3] and by myocardial scintigrams after injection of technetium-99m pyrophosphate (Tc-PYP).[4] In experimental animals both internal and external countershock have been found to produce myocardial lesions, albeit at different energy doses. The amount of damage is related inversely to paddle size and time between shocks[5] and directly related to the administered energy dose.[6–8] Histologic examination of the lesions by light and electron microscopy reveals pathologic changes that are consistent with the entity known as myofibrillar degeneration.[9,10] The administration of high doses of catecholamines can result in a similar pathologic pattern.

The pathogenesis of the postcountershock myocardial lesion is not known. A number of hypotheses have been advanced, including thermal injury[7] and direct injury of myocyte cellular and subcellular membranes by electric shock.[11,12] The similarity of the postcountershock lesion to that observed following administration of high doses of catecholamines has led to the hypothesis that release of systemic or myocardial catecholamines mediates the formation of myocardial lesions.[9,10] Alternatively, disruption of local calcium homeostasis has been proposed as a mechanism for myocardial injury because the cellular damage is associated with calcium deposition in mitochondria.[7,11] This view is supported by the finding that verapamil, an agent that blocks calcium channels, can attenuate postcountershock myocardial damage in dogs.[13] We investigated the effect of pretreatment with either adrenergic antagonists, or verapamil, on myocardial damage resulting from transthoracic direct current countershock in anesthetized dogs. Myocardial damage was quantitated by measuring myocardial uptake of technetium-99m pyrophosphate, a radionuclide that binds to irreversibly damaged myocardial tissue.[14–16] Quantitation of myocardial damage using this technique has been confirmed as a valid assessment of the effects of countershock on the heart.[6,7,12]

Methods

With approval from the Animal Care Committee, 20 mongrel dogs of either sex (weight 17–27 kg) were anesthetized using halothane in oxygen through a specially designed face mask. After induction of anesthesia, lead II of the ECG was monitored and a 16-gauge intravenous cannula placed in the forelimb. A maintenance fluid infusion of normal saline or lactated Ringer's solution was started at a rate of 4 $ml \cdot kg^{-1} \cdot h^{-1}$. The trachea was intubated with a cuffed endotracheal tube without muscle relaxation, and controlled ventilation was adjusted to maintain an end-tidal CO_2 concentration (Beckman LB-2® gas analyzer) of 4%. A 20-gauge cannula was placed percutaneously in the femoral artery for continuous monitoring of arterial blood pressure and blood sampling. The ECG, arterial pressure, and end-tidal CO_2 and halothane (Beckman LB-2® gas analyzer) concentrations were recorded continuously with a Beckman Polygraph (R-511A)®. An arterial blood gas was obtained for correlation with the end-tidal CO_2 and to confirm adequate oxygenation. The inspired halothane

* Assistant Professor of Anesthesiology.
† Research Fellow in Anesthesiology.
Received from the Department of Anesthesiology, Stanford University School of Medicine, Anesthesia Service, Palo Alto Veterans Administration Medical Center, Palo Alto, California. Accepted for publication December 10, 1984. Supported in part by the Veterans Administration and National Institutes of Health Grant #R23 GM30232. Presented at the 6th Annual Meeting, Society of Cardiovascular Anesthesiologists, Boston, Massachusetts, May 6–9.
Address reprint requests to Dr. Gaba: Anesthesia Service 112A, PAVAMC, Palo Alto, California 94304.

concentration was adjusted to maintain the end-tidal concentration between 1.25% and 1.5%. If the mean arterial pressure (MAP) was below 60 mmHg, an infusion of normal saline or lactated Ringer's solution was given and the halothane concentration decreased to a minimum of 1.25% until the MAP was >60 mmHg.

Each animal then received one of four drug treatments over a 5–10 min period: continuation of maintenance fluid (control); prazosin (an alpha-1 antagonist), 0.1 mg/kg; L-metoprolol (a beta-1 antagonist), 0.5 mg/kg; verapamil (a calcium channel antagonist) 0.5 mg/kg. We have shown that these doses of prazosin and L-metoprolol completely block the hemodynamic responses to phenylephrine 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and isoproterenol 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively.[17]

The animal was placed with the right chest down and the thorax tilted 30 degrees above the table. Five minutes following the end of drug infusion, two 8-cm electrode paddles, well coated with conducting paste (Redux® paste, Hewlett Packard), were applied to the shaved chest. One paddle was placed on the right chest over the point of maximal cardiac impulse, and the other paddle was placed directly opposite on the left chest. Two damped sine-wave countershocks of 295 delivered joules each were administered at 1-min intervals using a Hewlett Packard 780D® defibrillator. Postcountershock bradycardia was treated with atropine 0.2 mg iv, and ventricular arrhythmias (frequent premature ventricular complexes and short runs of ventricular tachycardia) were treated with lidocaine, 1–2 mg/kg iv. When the animal was stable, anesthesia was discontinued and the animal recovered from anesthesia.

Twenty-four hours after countershock, 10–12 mCi of technetium-99m stannous pyrophosphate (Pyrolite, New England Nuclear) was injected intravenously. One hour later the animal was killed by an intravenous injection of T61 (Taylor Pharmacal, Decatur, Illinois). A median sternotomy was performed and the heart removed at the level of the great vessels. The atria and vessels were excised and the right and left ventricular free walls each were dissected away from the septum. Any visible lesion was removed *en bloc* and subdivided into multiple specimens. An adjacent border zone of tissue also was taken and subdivided. All other ventricular tissue and the septum were sampled for technetium activity measurement. Each tissue sample was identified as being from a lesion, from a border zone, or from normal tissue. Selected tissue specimens from the center of lesions were placed in formyl alcohol solution for fixation. These were sectioned and stained with hematoxylin and eosin and examined by light microscopy for evidence of myofibrillar degeneration. Scoring of histologic severity of damage was not performed.

Each myocardial specimen was weighed and counted for technetium activity in a Searle 1185® automatic gamma scintillation counter using a window of 120–160 kev. The specific activity of each specimen was expressed as counts per minute per gram of tissue, corrected for background activity and for decay of the isotope (6.0 h). A sample to normal ratio (SNR) was computed for each specimen by dividing its specific activity by the activity of normal tissue. The normal activity was computed by averaging the specific activity of samples from the posterior left ventricular free wall, which always were free of myocardial lesions. Each animal thus acted as its own control.

As in prior studies,[6,8,12] any sample with a SNR > 3.0 was considered damaged. The mean SNR of these specimens was computed for each animal using a mass-weighted average formula:

$$\text{Weighted average SNR} = \frac{\Sigma\,(\text{mass}_i \times \text{SNR}_i)}{\Sigma\,(\text{mass}_i)}$$

This measure of myocardial damage is relatively insensitive to specimen volume. The total weight of damaged specimens also was computed, both in absolute terms (Σ mass_i for samples with a SNR > 3.0) and as a percentage of the total ventricular weight. For each animal an index of damage (INDEX) reflecting both intensity and extent of injury was defined as the product of the weight of damaged tissue and the weighted average SNR of damaged tissue.

Each of these four parameters of myocardial necrosis was compared statistically between groups receiving different drug pretreatment using one-way analysis of variance followed by Dunnet's test for comparison of multiple groups with a control group.[18] Comparison of lidocaine use was carried out using the chi-square statistic. Comparison of myocardial to blood uptake of Tc-PYP in the different drug groups used one-way analysis of variance. Correlation of myocardial to blood uptake with parameters of myocardial damage was accomplished with linear correlation and regression. Statistical significance was considered at a P value of less than 0.05.

Results

Hemodynamic changes occurred following drug pretreatment. Alpha-adrenergic blockade with prazosin and beta blockade with metoprolol caused a small drop in mean arterial pressure (6 ± 3 mmHg). Verapamil treatment caused a pronounced drop in mean arterial pressure (33 ± 16 mmHg). This difference was statistically significant ($P < 0.02$). Treatment with metoprolol consistently caused a slowing of heart rate (2–15 beats/min).

Lidocaine was administered in 9 of 20 animals for postcountershock ventricular arrhythmias. There was no significant difference in the use of lidocaine in

TABLE 1. Effect of Drug Pretreatment on the Uptake of Technetium-99m Pyrophosphate by Normal Myocardium

Drug Group	Ratio of Tc-PYP Specific Activity of Whole Blood to Normal Myocardium
Control	2.50 ± 0.32
Prazosin	3.05 ± 0.14
Metoprolol	3.55 ± 0.83
Verapamil	2.99 ± 0.30

Comparison of myocardial *versus* whole blood specific activity of Tc-PYP for different drug pretreatment groups (mean ± standard error). There is no significant difference in this ratio between any groups.

different pretreatment groups. Atropine was administered in three of four verapamil treated dogs for hemodynamically significant sinus and nodal bradycardias after countershock.

The two transthoracic countershocks produced visually apparent myocardial damage in four of five control animals. The lesions were pale and well demarcated from normal myocardium. These occurred most frequently in the midportion of the right ventricular free-wall, just adjacent to the left anterior descending coronary artery. Some lesions were found in an analogous position in the left ventricular free-wall. All obvious lesions were found to have elevated Tc-PYP uptake (SNR greater than 3.0), which was confined to the lesion or its immediately adjacent border zone. No samples from normal myocardium had elevated Tc-PYP uptake. Animals receiving drug pretreatment with adrenergic or calcium channel blockers had a high incidence of visible myocardial lesions. The gross appearance and location of lesions in these animals were not different from those in control animals. One animal in the metoprolol group and one animal in the verapamil group had no visible myocardial lesions and no increased uptake of Tc-PYP.

The possibility that receptor blockade itself might alter myocardial uptake of Tc-PYP was assessed by computing the ratio of Tc-PYP specific activity in whole blood to that of normal myocardium in each animal. These data are shown in table 1. There is no significant difference in this ratio between groups suggesting that drug treatment did not alter the tracer uptake. Furthermore, there was no correlation between this ratio and any parameter of myocardial damage.

The parameters of myocardial damage derived from Tc-PYP uptake data are presented in table 2. Control groups showed substantial uptake of Tc-PYP, as did all drug treatment groups. Using analysis of variance, there was no significant difference between treatment groups for any parameter of myocardial damage. Using Dunnett's test, no treatment group was shown to be significantly different from control.

Discussion

Transthoracic countershocks caused grossly visible myocardial lesions in most animals, regardless of drug treatment. The size, shape, appearance, and Tc-PYP uptake of the lesions were similar to those previously reported.[6,8,12,13]

Our results indicate that, during halothane anesthesia, blockade of either adrenergic receptors or calcium channels cannot protect the myocardium from the deleterious effects of a fixed dose of electric countershock. We have shown previously that the doses of adrenergic antagonists used in this study produce profound blockade of each adrenoceptor in dogs anesthetized with halothane.[17] Thus, adrenergic mechanisms do not seem to play an important role in the mediation of postcountershock myocardial damage at this energy dose. The similarity of the histologic appearance of the postcountershock lesion to that seen after catecholamine administration may reflect an identical final common pathway of cell injury rather than a similar initiating mechanism.

While halothane itself has calcium entry blocking properties[19,20] that could have effects on the production

TABLE 2. Effect of Drug Pretreatment on Parameters of Myocardial Damage Following Transthoracic Countershock

Drug Group	Weighted Average SNR	Weight of Damaged Tissue (SNR > 3.0)		
		Grams	Per Cent of Ventricle	INDEX
Control (n = 5)	14.1 ± 3.9	1.58 ± 0.58	1.48 ± 0.50	27.0 ± 10.2
Prazosin (n = 6)	13.9 ± 3.9	2.99 ± 0.63	2.69 ± 0.68	46.0 ± 13.7
Metoprolol (n = 5)	10.6 ± 3.1	1.71 ± 0.68	1.23 ± 0.46	25.2 ± 13.0
Verapamil (N = 4)	21.5 ± 12.5	1.56 ± 0.68	1.16 ± 0.54	49.8 ± 32.6

SNR = sample to normal ratio. For each animal INDEX = weighted average SNR × weight of damaged tissue (g). Values above are mean ± SEM for each treatment group. No drug group differs significantly from control or from any other group.

of postcountershock myocardial damage, the hemodynamic effects of verapamil observed in our study demonstrated that more intense calcium blocking activity could be superimposed on halothane anesthesia. In addition, any such calcium-blocking actions of halothane would be expected to protect the myocardium from damage. Indeed, halothane has been shown in some studies[21] to delay the onset and intensity of ischemic contracture in rat hearts. Our finding that control animals anesthetized with halothane had obvious and substantial (1.5% of ventricle) myocardial lesions suggests that halothane itself could not prevent postcountershock myocardial damage. Furthermore, halothane offered the benefit of a single anesthetic agent that reliably produces profound analgesia.

Verapamil has been found to protect the heart from calcium-mediated myocardial damage during cardiopulmonary bypass[22,23] and Patton *et al.*[13] found that verapamil (1 mg/kg), but not propranolol (0.4 mg/kg), decreased the amount of damaged myocardium in dogs subjected to intense countershock (10 shocks of 400 J each). We have confirmed their observation of a lack of protective effect for beta-adrenergic blockade and also have demonstrated the lack of protective effect for alpha-1 adrenergic blockade. We could not confirm their findings for verapamil. However, the dose of verapamil used in their study is quite high and is probably high enough[24] to invoke other pharmacologic effects of verapamil.[25] Furthermore, the level of countershock they used is exceptionally high and is unlikely to be used in clinical circumstances. Our data suggest that verapamil does not have any protective effect when used at a dose of 0.5 mg/kg in the setting of moderate countershock energy (2 shocks of 295 J each).

Electric shock has been shown to directly injure myocardial cells in culture,[9] and ultrastructural studies of myocardium show disruption of subcellular components, especially mitochondria, immediately after countershock.[11] It seems likely that these direct effects of electrical current on myocytes, combined with a small temperature-related injury,[7] are the major causes of lesion formation.

We conclude the following: 1) postcountershock myocardial damage does occur in halothane-anesthetized dogs administered clinically relevant energy doses of electric countershock (2 shocks of 295 J each); 2) profound blockade of alpha-1 or beta-1 adrenergic receptors, or substantial doses of verapamil, a calcium-channel antagonist, do not protect the myocardium from such myocardial damage; 3) alpha-1 and beta-1 adrenergic receptors are unlikely to play a major role in the development of postcountershock myocardial damage. The exact pathophysiology of the formation of the lesions remains unexplained.

The authors thank Chris M. Smith, M.Sc., for his technical assistance, Suzanne M. Matsui, M.D., for her insightful consultation, and Kelly Clark for manuscript preparation.

References

1. Turner JEB, Towers JRH: Complications of cardioversion. Lancet 2:612–614, 1965
2. Aberg H, Cullhed I: Direct current countershock complications. Acta Med Scand 183:415–421, 1968
3. Ehsani A, Ewy GA, Sobel BE: Effects of electrical countershock on serum creatine phosphokinase (CPK) isoenzyme activity. Am J Cardiol 37:12–18, 1976
4. Pugh BR, Buja LM, Parkey RW, Bonte FJ, Poliner L, Willerson JT: Cardioversion and "false positive" technetium-99m stannous pyrophosphate myocardial scintigrams. Circulation 54: 399–402, 1976
5. Dahl CF, Ewy GA, Warner ED, Thomas ED: Myocardial necrosis from direct current countershock: Effect of paddle electrode size and time interval between discharges. Circulation 50: 956–961, 1974
6. DiCola VC, Freedman GS, Downing SE, Zaret BL: Myocardial uptake of technetium-99m stannous pyrophosphate following direct current transthoracic countershock. Circulation 54: 980–986, 1976
7. Doherty PW, McLaughlin PR, Billingham M, Hernoff R, Goris ML, Harrison DC: Cardiac damage produced by direct current countershock applied to the heart. Am J Cardiol 43: 225–232, 1979
8. Gaba DM, Tainer NS: Myocardial damage following transthoracic direct current countershock in newborn piglets. Pediatr Cardiol 2:281–288, 1982
9. Reichenbach DD, Benditt EP: Catecholamines and cardiomyopathy: The pathogenesis and potential importance of myofibrillar degeration. Hum Pathol 1:125–150, 1970
10. Reichenbach DD, Benditt EP: Myofibrillar degeneration: A response of the myocardial cell to injury. Arch Pathol 85: 189–199, 1968
11. Van Vleet JF, Taker WA, Geddes LA, Ferrans VJ: Acute cardiac damage in dogs given multiple transthoracic shocks with a trapezoidal waveform defibrillator. Am J Vet Res 38:617–626, 1977
12. Schneider RM, Hayslett JP, Downing SE, Berger HJ, Donabedian RK, Zaret BL: Effect of methylprednisolone upon technetium-99m pyrophosphate assessment of myocardial necrosis in the canine countershock model. Circulation 56:1029–1034, 1976
13. Patton JN, Allen JD, Pantridge JF: The effects of shock energy, propranolol, and verapamil on cardiac damage caused by transthoracic countershock. Circulation 69:357–368, 1984
14. Parkey RW, Bonte FJ, Meyer SL, Atkins JM, Curry GC, Stokely EM, Willerson JT: A new method for radionuclide imaging of myocardial infarcts. Radiology 110:473–474, 1974
15. Dewanjee MK, Kahn PC: Mechanism of localization 99mTc-labeled pyrophosphate and tetracycline in infarcted myocardium. J Nucl Med 17:639–646, 1976
16. Buja LM, Tofe AJ, Kulkarni PV, Mukherjee A, Parkey RW, Francis MD, Bonte FJ, Willerson JT: Sites and mechanisms of localization of technetium-99m phosphorus radiopharma-

ceuticals in acute myocardial infarcts and other tissues. J Clin Invest 60:724–740, 1977
17. Maze M, Smith CM: Identification of receptor mechanism mediating epinephrine-induced arrhythmias during halothane anesthesia in the dog. ANESTHESIOLOGY 59:322–326, 1983
18. Zar JH: Biostatistical Analysis. Englewood Cliffs, Prentice-Hall, 1974, p 158
19. Price HL, Ohnishi ST: Effects of anesthetics on the heart. Fed Proc 39:1575–1579, 1980
20. Lynch C III, Vogel S, Sperelakis N: Halothane depression of myocardial slow action potentials. ANESTHESIOLOGY 55:360–368, 1981
21. Norfleet EA, Carter LS, Mueller RA, Kates RA, Saltzman LS: Halothane cardioplegia (abstract). ANESTHESIOLOGY 61:A82, 1984
22. Starnes VA, Hammon JW Jr, Lupinetti FM, Olson RD, Boucek JRJ Jr, Bender HW: Functional and metabolic preservation of immature myocardium with verapamil following global ischemia. Ann Thorac Surg 34:58–65, 1982
23. Pinsky WW, Lewis RM, McMillan-Wood JB, Hara H, Hartley CJ, Gillette PC, Entman ML: Myocardial protection from ischemic arrest: Potassium and verapamil cardioplegia. Am J Physiol 240:H326–H335, 1981
24. Mangiardi LM, Hariman RJ, McAllister RG Jr., Bhargava V, Surawicz B, Shabetai R: Electrophysiologic and hemodynamic effects of verapamil. Correlation with plasma drug concentrations. Circulation 57:366–372, 1978
25. Bayer R, Kalusche D, Kaufmann R, Mannhold R: Intropic and electrophysiological actions of verapamil and D-600 in mammalian myocardium. III. Effects of the optical isomers on transmembrane action potentials. Naunyn Schmiedebergs Arch Pharmacol 290:81–97, 1975