Antiarrhythmic Properties of Acetaminophen in the Dog

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Mongrel dogs bred for research and weighing 25 ± 3 kg were used to test the hypothesis that acetaminophen has antiarrhythmic properties. Only ventricular arrhythmias defined by the Lambeth Conventions were investigated. Dogs were exposed either to 60 mins of regional myocardial ischemia followed by 180 mins of reperfusion (n = 14) or were administered a high dose of ouabain (n = 14). Both groups of 14 dogs were further divided into vehicle and acetaminophen treatment groups (n = 7 in each). During selected 10-min intervals, we recorded the numbers of ventricular premature beats, ventricular salvos, ventricular bigeminy, ventricular tachycardia (nonsustained and sustained), and we recorded the heart rate, systemic arterial blood pressure, and left ventricular function. Neither heart rate nor the number of ventricular arrhythmias differed significantly under baseline conditions. Conversely, the combined average number of ventricular ectopic beats during ischemia and reperfusion was significantly less in the presence of acetaminophen (28 ± 4 vs. 6 ± 1; $P < 0.05$). Similarly, percent ectopy during reperfusion in vehicle- and acetaminophen-treated dogs was 1.4 ± 0.4 and 0.4 ± 0.2, respectively ($P < 0.05$). The number of all ventricular ectopic beats except ventricular salvos was also significantly reduced in the presence of acetaminophen. Similar results were obtained with ouabain. Our results reveal that systemic administration of a therapeutic dose of acetaminophen has previously unreported antiarrhythmic effects in the dog. Exp Biol Med 232:1245–1252, 2007

Key words: ouabain; arrhythmogenesis; canine myocardium; ischemia/reperfusion injury

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Introduction

For more than a century, clinicians and scientists have focused on the analgesic and antipyretic properties of acetaminophen (paracetamol), yet little or nothing is known about the drug's effects in the human myocardium or other major organs. Investigators of the 19th and 20th centuries were so focused on the analgesic and antipyretic actions of acetaminophen that they probably lacked time to consider a rigorous physiological investigation of other potential effects of the drug. Interest in acetaminophen's properties in the mammalian cardiovascular system appears to be changing as we enter the 21st century. For example, Boutaud *et al.,* (1) reported concentration-dependent decrements in the production of prostacyclin when acetaminophen was used to block the synthesis of prostaglandin. H. Chou and Greenspan (2) found that by attenuating the activity of myeloperoxidase, acetaminophen significantly reduced the oxidation of low-density lipoprotein (LDL) in macrophages. Vascular oxidation of LDL is intimately connected to atherogenesis (3), and myeloperoxidase is an important marker of ischemic heart disease in humans (4). In the guinea pig heart, acetaminophen appears to possess cardioprotective properties that are seen at the functional, histological, and metabolic levels (5–7). Golfetti *et al.,* (8, 9) reported that acetaminophen is efficacious after chronic, oral administration as well as at the onset of reperfusion in the postischemic, Langendorff-perfused guinea pig heart. In addition, we (10) observed that acetaminophen reduced the size of an infarct in dogs, but we did not study other indicators of *in vivo* efficacy. Using rats, Zhu *et al.* (11) found both an acetaminophen-mediated reduction in infarct size and a diminution in mortality 2 days after experimentally induced myocardial infarction.

The purpose of this investigation was to determine if disturbances in rhythmicity in the dog heart can be attenuated by acetaminophen. We chose to use regional myocardial ischemia and reperfusion, as well as administered, toxic levels of ouabain, because these interventions

have caused similar kinds of ventricular arrhythmias in the anesthetized, instrumented dog heart (10, 13, 32–34). Our results are reported herein.

Methods

Animals. After institutional review and approval, we performed experiments in male dogs of mixed lineage (bred for research), weighing 25 ± 3 kg and averaging 14 ± 4 months of age. Dogs were housed in American Association for Accreditation of Laboratory Animal Care–accredited facilities where room temperature, humidity, and lighting were controlled, and they were fed a daily ration of Purina Dog Chow, with water provided *ad libitum*. Dogs were allowed several days to acclimate to their new housing conditions before they were used in the experiment.

Anesthesia and Instrumentation. Dogs were transported to the laboratory and were anesthetized using an intravenous (iv) dose of 5 mg/kg propofol (Propoflo Anesthetic Injection; Abbott Laboratories, Chicago, IL). They were then intubated and placed on isoflurane anesthesia (Aerrane, Isoflurane, USP; Baxter, Deerfield, IL) administered in supplemental oxygen at a minimal alveolar concentration (MAC) of 2.0% ± 0.5% and a flow rate of 2.0 ± 0.5 l/min (Matrix Calibrated Vaporizer, model VIP 3000; Matrix, Orchard Park, NY; in-line with a Veterinary Anesthesia Ventilator, 2000-ml adult bellows, model 2002IE; Hallowell EMC, Pittsfield, MA).

The right femoral and brachiocephalic arteries and corresponding veins were cannulated to monitor systemic arterial blood pressure (femoral artery), to administer heparin and acetaminophen (femoral vein), to collect arterial blood samples (brachiocephalic artery), and to administer and infuse ouabain (brachiocephalic vein). A left-sided thoracotomy was performed in the fifth intercostal space, lobes of the left lung were retracted, and the heart was exposed and positioned in a pericardial sling as previously reported (12–14). The left anterior descending coronary artery (LAD) was isolated just distal to the third or fourth major lateral branches, and a short section of PE 90 tubing was passed beneath it. A 12–15-cm length of 2.0 silk suture was passed through the tubing, and they were used later to occlude the LAD.

A saline-filled, short, large-bore angiocatheter (14g, BD Angiocath Autoguard; Infusion Therapy Systems Inc., Sandy, UT) was then advanced into the left ventricular chamber (*via* the apical dimple) and was used to monitor left ventricular developed pressure (LVDP) and its differentiation ($\pm dP/dt_{max}$). Dogs were administered heparin (250 U/kg plus supplements, iv, < 10 ml), and a standard limb-lead electrocardiogram was attached for monitoring the heart rate (HR) and ventricular ectopic beats. Core body temperature (by rectal probe) and epicardial surface temperature (Physitemp, model BAT-12; Physitemp Instrument, Inc., Clifton, NJ) were monitored and maintained at physiological levels. Dogs were allowed 30 mins for monitored variables to achieve their steady-state levels before baseline (control) data were collected.

Monitored Variables and Data Acquisition. Monitored variables included core body and epicardial surface temperatures (°C), ventilatory frequency (Vf, cycles/min), tidal volume (Vt, ml), end tidal CO_2 (percent of expired gases; Nellcor Puritan Bennett Capnograph, model NPB-75; Nellcor Puritan Bennett, Pleasanton, CA), oxyhemoglobin saturation (percent, SaO_2; Capnograph, model NPB-75), blood gases (PO_2, PCO_2; mm Hg) and pH (units; model NPT-7 blood gases/pH analyzer; Radiometer America Inc., Westlake, OH), systemic mean arterial pressure (Pā, mm Hg), LVDP (mm Hg), $\pm dP/dt_{max}$ (mm Hg/sec), HR (cycles/min), and the electrocardiogram (ECG). These cardiovascular variables were recorded using a CB Sciences data acquisition system (iWorx model ETH-401 transducer interface, model 118, ECG isolation unit, model ETH-256, CB Sciences, Dover, NH) in series with a computer running Labscribe software (version 1.811; CB Sciences, Dover, NH).

Ventricular Arrhythmias and the Lambeth Convention Guidelines. The Lambeth Convention guidelines (15) were used to study ventricular arrhythmias in the dog as previously reported (13, 16). Briefly, we focused on ventricular premature beats (VPB), ventricular salvos (VS), ventricular bigeminy (VB), nonsustained ventricular tachycardia (VTn), and sustained ventricular tachycardia (VTs). We also used the formula of Lucchesi *et al.,* (17) to calculate percent ectopy.

Experimental Protocols. Twenty-eight dogs were studied. They were randomly divided into ischemia/reperfusion- ($n = 14$) and ouabain-treatment protocols ($n = 14$). Within these two protocols, dogs were further randomly subdivided into vehicle-treatment ($n = 7$) and acetaminophen-treatment ($n = 7$) groups. After instrumentation and achievement of the steady state, baseline (control) data were collected in all 28 dogs.

Ischemia/Reperfusion Subgroups. In the ischemia/reperfusion subgroups, and just after collection of baseline data, the LAD was occluded distal to the third or fourth major lateral branches for 60 mins and was then released for an additional 180 mins. In this group, HR, and ventricular arrhythmias were monitored continuously for 10 mins immediately before the onset of ischemia (during baseline), for the first 10 mins of ischemia, and for the first 10 mins of reperfusion. Only arrhythmias collected during these three 10-min intervals were compared in vehicle- versus acetaminophen-treatment groups.

Ouabain Subgroups. After collection of baseline data, ouabain was administered iv as bolus injections (25 μg/kg) at 15-min intervals for a total of 75 μg/kg *via* bolus injection. Upon completion of the first bolus injection, a continuous iv infusion of 0.2 μg/kg/min was initiated and sustained for 60 mins. Thus, each of these dogs received a total of approximately 2.18 mg (7–8 ml) of ouabain in a 1-hr period. This protocol was developed in consultation with

Dr. R.L. Hamlin, QTest Labs/Ohio State University, Columbus, OH. Ventricular arrhythmias were scrutinized during the last 10 mins immediately before administration of the first bolus of ouabain (during baseline) and again during the last 10 mins of infusion of ouabain in both the vehicle- and acetaminophen-treated dogs.

Acetaminophen was administered as an iv bolus injection at the onset of ischemia 15mg/kg iv, 5 ml) and again at the onset of reperfusion (15 mg/kg iv, 5 ml). An equal volume of 0.9% NaCl was administered in place of acetaminophen in the vehicle-treated group. In the ouabain protocol, acetaminophen (30 mg/kg iv total dose, 10 ml) was administered as a single bolus injection immediately before administration of the first bolus of ouabain. In all cases, acetaminophen was prepared fresh daily about 1 hr before its administration.

Statistics. All data are presented as means ± one standard error of the mean (SEM). The experiments were designed *a priori*, and the Student's *t* test for nonpaired replicates was used to identify statistically significant differences between treatment means. Significance was accepted at $P < 0.05$.

Results

Ischemia/Reperfusion-Induced Ventricular Arrhythmias and Acetaminophen. HRs did not vary significantly between vehicle- and acetaminophen-treated dogs under any conditions in this protocol. HRs ranged from 125 ± 6 to 129 ± 9 cycles/min in both subgroups during baseline, ischemia, and reperfusion conditions. The number of ventricular arrhythmias did not differ between the two subgroups under baseline conditions. Conversely, the number of ventricular arrhythmias during both ischemia and reperfusion was significantly reduced in the presence of acetaminophen ($P < 0.05$). For example, during the first 10 mins of reperfusion, the number of ventricular arrhythmias was 19 ± 6 versus 5 ± 2 ($P < 0.05$) in the vehicle and acetaminophen subgroups, respectively. Percent ectopy was also significantly reduced during both ischemia and reperfusion in the presence of acetaminophen (Tables 1 and 3).

A range of ventricular ectopic beats was evident in this investigation (Fig. 1), with VPBs being the most commonly seen during both ischemia and reperfusion in vehicle- and acetaminophen-treated dogs (Fig. 2). Their numbers did not differ significantly between the two subgroups under baseline conditions. However, VPBs were significantly more common during both ischemia and reperfusion in vehicle-treated dogs. For example, during reperfusion there were 9 ± 3 VPBs in the presence of the vehicle and only 1 ± 1 VPB in the presence of acetaminophen ($P < 0.05$; Fig. 2). The occurrence of life-threatening VTs was also significantly reduced by acetaminophen (Fig. 3), and the incidence of VB during reperfusion was 5 ± 2 versus 2 ± 1 ($P < 0.05$) in the presence of the vehicle and acetaminophen, respectively. The total number of all ventricular arrhythmias, as well as percent ectopy, recorded during each of the three 10-min periods (baseline, ischemia, reperfusion) were significantly reduced by acetaminophen. These data are summarized in Figure 4.

Ouabain-Induced Ventricular Arrhythmias and Acetaminophen. Ouabain, administered as consecutive bolus injections coupled with a continuous iv infusion, produced all the ventricular arrhythmias that were seen in the ischemia and reperfusion protocol. In vehicle-treated dogs, the order of occurrence starting with the most common arrhythmia was VPB > VS > VTn> VB > VTs. A slightly different pattern was observed in acetaminophen-treated dogs (VPB > VS > VB > VTn). There were no occurrences of VTs in the presence of acetaminophen in these seven dogs.

Acetaminophen administration significantly attenuated ouabain-induced ventricular arrhythmias (Fig. 5). For example, the sum of the five arrhythmias noted above during the last 10 mins of ouabain infusion in the seven vehicle-treated dogs was 311. During the same period of time, the corresponding number in the seven acetaminophen-treated dogs was 88, that is, a 72% reduction. In the presence of acetaminophen, the mean incidences for VS, VB, and VTn were also significantly reduced when compared with corresponding numbers in vehicle-treated dogs (Table 2). Moreover, the time from onset of ouabain infusion to occurrence of the first ventricular arrhythmias was also significantly increased by acetaminophen from 36 ± 4 (vehicle) to 48 ± 2 mins ($P < 0.05$).

Hemodynamic Conditions. In all dogs, we routinely monitored systemic mean arterial blood pressure, LVDP, and $\pm dP/dt_{max}$ as indicators of ventricular function and circulatory competence. These variables did not differ under baseline conditions or during the two experimental protocols. Nor did the HR vary between the two treatment groups at any time in vehicle- and acetaminophen-treated dogs (Table 3).

Discussion

Dose and Route of Administration of Acetaminophen. Acetaminophen is a monophenol. Its antioxidant properties are well established. When warmed and gently stirred, it is soluble in physiological salt solutions as well as in distilled, deionized water. Cardiovascular effects of doses of acetaminophen ranging from approximately 1–100 mg/kg have been studied recently in mice (1, 2, 18), rats (11, 19–21), guinea pigs (5–7), rabbits (22, 23), sheep (23), dogs (10), and humans (24, 25). None were toxic under the conditions of the experimental protocols. We selected a dose of 30 mg/kg acetaminophen, to be consistent with former studies in mammals and because we have experience investigating the effects of that dose of acetaminophen on infarct size in dogs during regional myocardial ischemia and reperfusion (10).

Table 1. Summary of Ventricular Arrhythmias Caused by Ischemia and Reperfusion in the Absence and the Presence of Acetaminophen[a]

	HR (cpm)		Total ventricular arrhythmias		% ectopy	
	V	A	V	A	V	A
Baseline	125 ± 10	125 ± 6	5 ± 3	3 ± 2	0.4 ± 0.1	0.2 ± 0.1
Ischemia	127 ± 8	127 ± 5	9 ± 3	1 ± 1*	0.7 ± 0.3	0.1 ± 0.07*
Reperfusion	129 ± 9	125 ± 5	19 ± 6	5 ± 2*	1.4 ± 0.4	0.4 ± 0.2*

[a] Data are mean ± one SEM. HR, heart rate; cpm, cycles per minute; V, vehicle-treated; A, acetaminophen-treated.
* $P < 0.05$ relative to the corresponding V value.

As vehicles for acetaminophen, we prefer physiological salt solutions to solvents such as alcohol, because saline lacks the confounding direct and indirect effects caused by the harsher solvents. For example, alcohol, recently used by Dai and Kloner (10), Hale and Kloner (20, 22), and Leshnower *et al*. (23) in their studies of the cardiac effects of acetaminophen, produces well-known, compromising influences on the mammalian myocardium, including negative inotropy, negative chronotropy, negative dromotropy, and coronary vasoconstriction (26, 27), as well as other metabolic effects. Such physiological influences might override or otherwise obscure the direct actions of acetaminophen.

The iv route of administration was selected to ensure rapid delivery of acetaminophen to the interstitium and the cells. Timing for monitoring ventricular arrhythmias was chosen to maximize chances of identifying drug efficacy. The times selected are those during which we have been most likely to see ventricular arrhythmias in dogs during ischemia, reperfusion, hypoxia, reoxygenation, and infarction (12–14, 16).

Open-chested, anesthetized dogs exposed to 60 mins of regional myocardial ischemia followed by 180 mins of reperfusion were significantly less arrhythmogenic in the presence of acetaminophen than in its absence. For the 10-min periods investigated, acetaminophen uniformly attenuated VPB, VS, VB, VTn, and VTs. These particular arrhythmias range from the innocuous (VPB) to the potentially life-threatening (VTs). Had we monitored the innocuous arrhythmias only (for example, VPBs), we would have erroneously concluded that acetaminophen abolishes ischemia/reperfusion-induced ventricular arrhythmias (Fig. 2). Fortunately, we chose to monitor several of the arrhythmias defined by the Lambeth Conventions (15) and therefore did not err on the side of acetaminophen.

The significant attenuation of ischemia/reperfusion-induced ventricular arrhythmias by acetaminophen cannot be explained on the basis of differences in HRs or peripheral hemodynamics in these dogs. There were no significant differences between the groups in any of these variables at the time ECG data were collected. Also, dogs were closely matched for age and weight, were obtained from the same vendor, and were exposed to the same diet and environmental housing conditions during the study. Additionally, they were all male, thus ruling out intergender differences as an explanation for the results. According to the veterinary staff of Laboratory Animal Services, Rutgers University, all dogs were healthy and in excellent condition at the time of anesthesia.

Potential Acetaminophen Mechanism. In the heart, one manifestation of ouabain overdose is the occurrence of ventricular arrhythmias (28–30). Ouabain blocks Na^+-K^+ pumps that are ubiquitously located in the sarcolemma of excitable myocytes in the mammalian myocardium (17, 30–34). This leads to transient elevations in intracellular sodium and extracellular potassium, both of which are stimuli for activating the pump (32–34). Other stimuli that activate Na^+-K^+ pumps include renal hypertension (35, 36), acute production of hypo- and hyperkalemia (37), and myocardial ischemia and reperfusion injury (38, 39). Ouabain has been particularly useful in the dog to study involvement of the Na^+-K^+ pump in experimental ventricular arrhythmias.

The cardiac glycosides in general have been valuable in helping to identify potential antiarrhythmic agents whose mechanisms include blockade of sodium channels (30).

Table 2. Ability of Ouabain to Produce Ventricular Arrhythmias in the Dog in the Absence and the Presence of Acetaminophen[a]

	VPB	VS	VB	VTn	VTs
Vehicle ($n = 7$)	18.0 ± 9.0	14.5 ± 5.4	5.7 ± 2.2	13.7 ± 7.2	0.2 ± 0.1
Acetaminophen ($n = 7$)	11.6 ± 3.2*	4.0 ± 1.8*	1.4 ± 0.7*	0.6 ± 0.3*	0.0 ± 0.0

[a] Data are mean ± one SEM. VPB, ventricular premature beat; VS, ventricular salvo; VB, ventricular bigeminy; VTn, nonsustained ventricular tachycardia; VTs, sustained ventricular tachycardia.
* $P < 0.05$ relative to the corresponding vehicle value.

Table 3. Systemic Circulatory Hemodynamics in Dogs During Experimentally-Induced Ventricular Arrhythmias in the Absence and the Presence of Acetaminophen[a]

	Ischemia		Reperfusion		Ouabain	
	V	A	V	A	V	A
Baseline (control)						
Pa (mm Hg)	98 ± 6	102 ± 4	100 ± 12	103 ± 10	102 ± 4	100 ± 6
LVDP (mm Hg)	104 ± 8	106 ± 5	102 ± 12	108 ± 8	100 ± 6	102 ± 6
+dP/dt (mm Hg/sec)	2650 ± 580	2795 ± 476	2850 ± 480	2925 ± 512	3565 ± 470	3750 ± 445
Experimental conditions						
Pa (mm Hg)	90 ± 10	95 ± 6	104 ± 8	108 ± 12	92 ± 8	98 ± 6
LVDP (mm Hg)	98 ± 6	96 ± 12	94 ± 8	96 ± 10	132 ± 12	138 ± 10
+dP/dt (mm Hg/sec)	2345 ± 460	2480 ± 512	2576 ± 390	2485 ± 468	3685 ± 650	3726 ± 515

[a] Data are mean ± one SEM ($n = 5–7$). V, vehicle in absence of acetaminophen; A, acetaminophen; Pa, systemic mean arterial blood pressure; LVDP, left ventricular developed pressure; +dP/dt, first derivative of developed left ventricular pressure.

Moreover, ouabain and myocardial ischemia/reperfusion injury are known to cause the same kinds of ventricular arrhythmias in the canine myocardium (10, 13, 32–34).

We previously observed acetaminophen-mediated membrane-stabilizing properties at the functional, biochemical, and morphological levels in an *in vitro* setting during myocardial ischemia/reperfusion injury (5–7). Similarities between ischemia/reperfusion-induced and ouabain-mediated ventricular arrhythmias suggest that the rhythm disturbances in the present study were due at least in part to impairment of the Na^+-K^+ pump. The Na^+-K^+ pump is an energy-dependent protein synthesized in the mitochondria. Our prior experience with acetaminophen demonstrates that one of its sites of cytoprotection is the mitochondrion (6, 7), although we have not confirmed this in the canine myocardium. In the present study, acetaminophen stabilized cardiomyocytes generally and cardiac rhythmicity specifically. Our observations suggest that acetaminophen might either protect the site of ATPase production (i.e., the mitochondria) or it might act directly on the sarcolemma to protect membrane function of the ATPases. Additional work is needed, however, to clarify this and to identify potential extra- versus intracellular Na^+-K^+ ATPase domains at which acetaminophen might operate.

Earlier studies revealed that potassium release from ischemic canine cardiomyocytes induced ventricular arrhythmias (38–40). Experimentally elevated extracellular potassium in the dog activates the Na^+-K^+ pump, causes ectopic beats, and can lead to ventricular fibrillation (41–45). The more serious and prolonged the disruption, the more severe the arrhythmias (46, 47). Transiently increasing basal coronary arterial concentrations of potassium more than 4-fold, that is, greater than approximately 16 mEq/l, in the dog can provoke ventricular fibrillation and cardiac

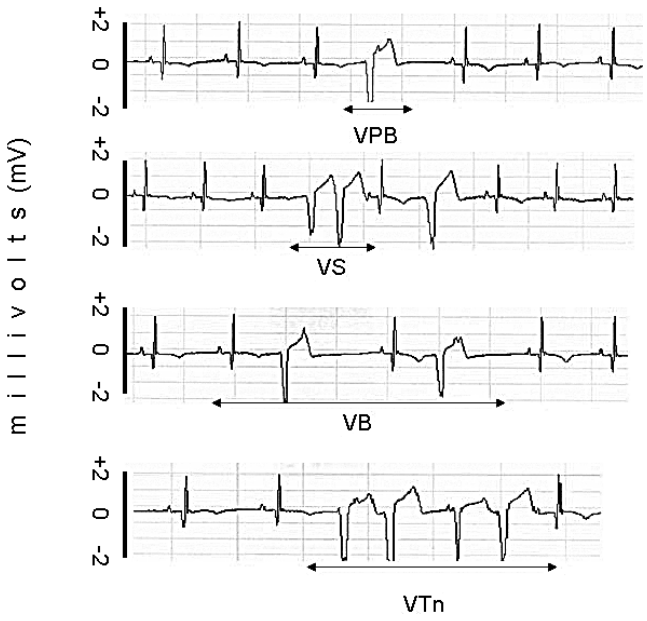

Figure 1. Sample tracing of the kinds of ventricular arrhythmias evoked by ischemia/reperfusion and ouabain in the current investigation. VPB, ventricular premature beat; VS, ventricular salvo; VB, ventricular bigeminy; VTn, nonsustained ventricular tachycardia. See reference 15 for further definitions.

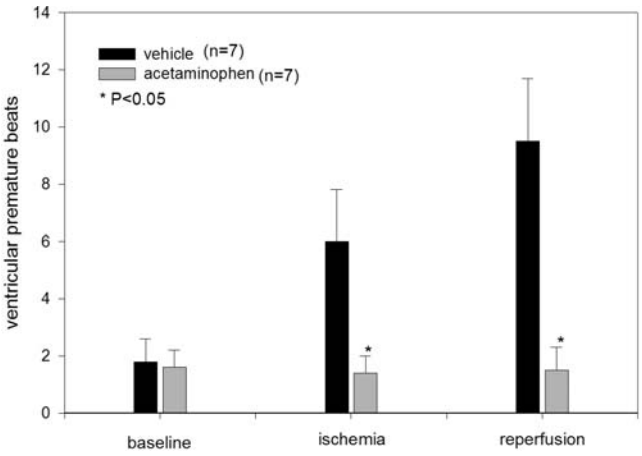

Figure 2. The number of VPBs recorded during 10-min periods at baseline and during ischemia and reperfusion in the presence of the vehicle (dark histograms) and of acetaminophen (light histograms). * $P < 0.05$ compared with the corresponding vehicle sample.

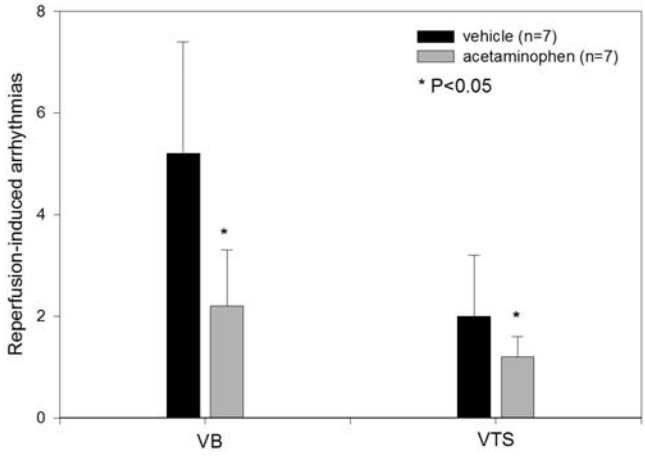

Figure 3. The number of reperfusion-induced bouts of VB and VTs in the presence of the vehicle and of acetaminophen. * $P < 0.05$ compared with the corresponding vehicle sample.

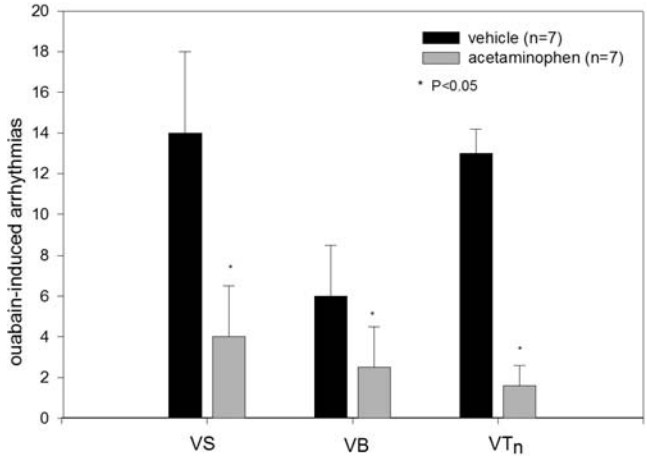

Figure 5. The number of ouabain-induced ventricular arrhythmias in the presence of the vehicle and of acetaminophen. VS, ventricular salvos; VB, ventricular bigeminy; VTn, nonsustained ventricular tachycardia. * $P < 0.05$ compared with the corresponding vehicle sample.

arrest in less than 20 secs (38, 39). Although we did not measure coronary arterial potassium concentrations in the present study, we assume that these increased during myocardial ischemia and might have contributed to the arrhythmias. Hyperkalemia-induced (7–8 mEq/l potassium) ventricular ectopy has also been reported in humans (48). The consistencies between ischemia/reperfusion-, ouabain-, and potassium-induced ventricular arrhythmias suggest a generalized, antiarrhythmic mechanism that involves acetaminophen-mediated stabilization of the homeostasis of sodium and potassium pumping.

In the current study, there were no cases of ventricular fibrillation. All dogs in both groups completed the study, and we did not have to use a defibrillator or cardioversion at any point. This was achieved in part by our choice of an LAD occlusion site that was distal to the second or third major epicardial branches of the LAD. We have had similar success in avoiding terminal ventricular fibrillation by choosing a similar LAD-occlusion site in previous dog experiments in our laboratory.

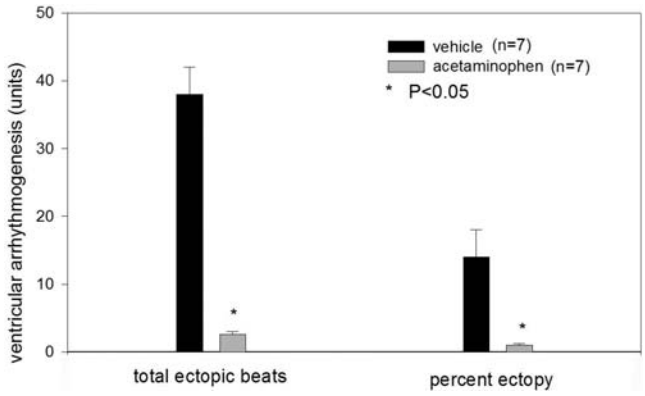

Figure 4. The total number of ventricular ectopic beats (left histograms) and percent ectopy (right histograms) seen during combined 10-min periods of baseline, ischemia, and reperfusion in the absence and presence of acetaminophen. * $P < 0.05$ compared with the corresponding vehicle sample.

Timing of Ventricular Arrhythmias. The time-dependent occurrence of ventricular arrhythmias during myocardial ischemia and reperfusion has been well studied. In our hands, ischemia-induced ventricular arrhythmias are generally seen shortly after interruption of blood flow (seconds to minutes) but thereafter occur less reliably than do reperfusion-induced arrhythmias. Of course, this is largely determined by the specific location of the flow disruption. Occlusions of the high, proximal LAD or of the circumflex branches of the left main coronary artery will often result in ventricular fibrillation in seconds to minutes. Such high occlusions are routinely avoided by investigators unless they are purposely studying ventricular fibrillation.

Also, many investigators have reported reperfusion-induced bursts of ventricular ectopy after short and long periods of ischemia. In dogs and guinea pigs, we have found such arrhythmogenecity to be closely associated with corresponding bursts of reactive oxygen species, including peroxynitrite and hydroxyl radicals (6, 7, 13). Acetaminophen attenuates production of both of these at the same time that it confers cardioprotection. Although there are other times during which ventricular arrhythmias occur in the reperfused canine myocardium, for example, between 15 and 20 mins of reflow (13), the 10-min periods that we studied were ample to test our hypothesis that acetaminophen has antiarrhythmic properties. Had we intended to compare early versus late arrhythmias in either ischemia or reperfusion, we would have altered the experimental design accordingly. However, the significance of the question of late versus early arrhythmias and the potential effects of acetaminophen on recovery from either or both require investigation in future experiments designed for those purposes.

Summary and Conclusions. Two new findings have emerged from the current investigation. First, acetaminophen has previously unreported antiarrhythmic properties in the canine myocardium. Secondly, the mechanism appears to involve either protection of the production of Na^+-K^+ pumps (in the mitochondria) or protection of function of the pumps at the sarcolemma and other locations. Acetaminophen is known to be protective in the isolated, perfused guinea pig heart (5–9) and against myocardial infarction in the dog (10). The drug also reduces infarct size and 48-hour mortality in rats, and these actions appear to involve a catalase/superoxide dismutase-mediated mechanism (11). This is the first report we are aware of that describes antiarrhythmic properties of acetaminophen in an experimental, *in vivo* setting.

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