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Arrhythmogenic potential of positive inotropic agents

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Abstract The clinical use of positive inotropic agents has been associated with increased mortality, with proarrhythmia speculated to be a contributing factor. This study compares the arrhythmogenic potentials of six positive inotropic agents representing different mechanistic classes: the β-adrenergic agonist dobutamine, the adenylyl cyclase activator forskolin, the phosphodiesterase-III inhibitor milrinone, the cardiac glycoside ouabain, and the sodium channel agonists DPI 201-106 and BDF 9148. These agents were studied in dogs with anterior myocardial infarction using lower and higher dose i.v. regimens targeted to elicit 20–40 % and 70–90 % increases in LV+dP/dt, respectively. Precipitation of new ventricular arrhythmia by programmed ventricular stimulation was observed in all treatment groups. Incidences of new arrhythmia were comparable in the lower dose regimens, ranging from 16.7 % (3/18 animals with BDF 9148) to 31.6 % (6/19 animals with DPI 201-106), and in the higher dose regimens, ranging from 10.0 % (1/10 animals with milrinone) to 27.7 % (5/18 animals with DPI 201-106). The overall incidence of new ventricular arrhythmia ranged from 27.3 % (3/11 animals with ouabain) to 47.4 % (9/19 animals with DPI 201-106). No differences were observed in underlying infarct size or time from infarction to electrophysiologic study between subgroups of animals in which new arrhythmias were precipitated vs. those remaining non-responsive in any treatment group. The positive inotropic agents tested displayed diverse total group effects on heart rate, electrocardiographic intervals including QTc and ventricular refractoriness. Within individual treatment comparisons revealed a general but not universal pattern of greater ventricular refractory period values in newly inducible vs. non-inducible subgroups in the DPI 201-106, BDF 9148 and ouabain (low and high dose); milrinone and dobutamine (high dose) treatment groups. These findings indicate that regardless of underlying cellular mechanism of action, the six positive inotropic agents tested all displayed comparable proarrhythmic potentials unrelated to underlying infarct size and time from infarction. This observation suggests the general shared property of increased myocardial contractility, potentially adversely affecting myocardial oxygen balance, myocardial perfusion and electrical stability in the setting of previous myocardial infarction, to be a common underlying cause for arrhythmogenesis. Additionally, alterations in ventricular refractoriness and repolarization may contribute significantly to proarrhythmia with some positive inotropic interventions.

Key words Positive inotropic agent – proarrhythmia – arrhythmia – myocardial infarction – programmed ventricular stimulation

Introduction

The concept of heart failure as a primary defect in cardiac contractility has led to the clinical study of positive inotropic agents to enhance myocardial performance. However, experience over the past 10–15 years with positive inotropic agents of varying mechanisms has been disappointing with respect to long-term survival in heart failure patients. Extended outpatient infusions of the β-adrenergic agonist dobutamine (11), and chronic oral administration of the partial β-adrenergic agonist xamoterol (44), the phosphodiesterase-III inhibitors milrinone (34) and enoximone (8), the vasodilator/inotrope flosequinan (35) and the ion channel blocker/inotrope vesnarinone (7) have all resulted in increased mortality. Pimobendan, a calcium sensitizer/inotrope with phosphodiesterase-III inhibitory activity, tended to increase mortality (43). The cardiac glycoside digoxin, the mainstay inotropic therapy for heart failure, has been shown to have no beneficial effect on survival (41). Proarrhythmia has been considered to be an important contributor to the detrimental effect of positive inotropic agents on survival. Increases in mortality with milrinone, flosequinan and vesnarinone were specifically attributed to increased incidences of sudden, presumably arrhythmic death (7, 34, 35). The incidence of sudden death also tended to be increased with xamoterol (44) and enoximone (8). Facilitation of arrhythmia in patients has been reported anecdotally with the administration of dobutamine, milrinone, and flosequinan (31, 45). Finally, a long-standing controversy persists regarding an adverse effect on mortality with digoxin in the setting of myocardial infarction, potentially through an increased incidence of sudden death, counterbalancing the salutary hemodynamic and neurohumoral effects of this agent (21, 29, 30, 42). Basic experimental studies have demonstrated elevations in intracellular cAMP, sodium and calcium concentrations, biochemical and ionic mechanisms which underlie the cardiostimulatory actions of most if not all currently available positive inotropic agents, to be inherently arrhythmogenic (22, 23, 40).

Preclinical animal studies have not been uniformly useful in characterizing either the absolute or relative arrhythmogenic potentials of positive inotropic agents. Most previous preclinical assessments of the arrhythmogenic risk of positive inotropic agents have been single agent assessments (16, 24, 25, 32, 46, 48) or limited comparisons of agents (2, 26, 33, 47). Experimental models and protocols have also varied considerably in preceding studies. The purpose of the present investigation was to assess the arrhythmogenic risk of a variety of mechanistically diverse positive inotropic agents in a standard experimental paradigm, i.e., precipitation of new ventricular tachyarrhythmia by programmed ventricular stimulation in dogs with previous anterior myocardial infarction. In this study, the positive inotropic agents were administered at doses targeted to elicit comparable increases in myocardial contractility. The agents assessed in this study were the β-adrenergic agonist dobutamine, the adenylyl cyclase activator forskolin, the phosphodiesterase-III inhibitor milrinone, the cardiac glycoside ouabain, and the sodium channel agonists DPI 201-106 and BDF 9148.

Methods

All procedures related to the use of animals in these studies were reviewed and approved by the Institutional Animal Care and Use Committee at Merck Research Laboratories at West Point. These procedures conform to the Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council, 1996).

Surgical preparation

The surgical preparation, instrumentation and methods for the measurement of cardiac electrophysiologic parameters and conduct of programmed ventricular stimulation (PVS) in postinfarction dogs have been described previously (27). Briefly, male or female purpose-bred mongrel dogs were preanesthetized with sodium thiamylal (5.0 mg/kg i.v.), and general anesthesia was induced with isoflurane. A left thoracotomy was performed in the fourth intercostal space, the pericardium incised and the heart suspended in a pericardial cradle. The left anterior descending coronary artery (LAD) was isolated near the tip of the left atrial appendage distal to the first major diagonal branch. Anterior myocardial infarction was produced by occlusion of the LAD for a period of 2 h followed by reperfusion. If the area of myocardial ischemic injury produced by the initial occlusion appeared insufficient by visual inspection of myocardial cyanosis, one or two epicardial collateral connections were ligated. After reperfusion, the surgical incisions were closed and the animals were allowed to recover.

Experimental protocol

At 10.5 ± 0.7 days after surgically induced anterior myocardial infarction, animals were re-anesthetized with alpha chloralose (80–100 mg/kg i.v.) and were ventilated with room air. The right femoral artery and vein were cannulated for measurement of systemic arterial pressure and for drug administration, respectively. The heart was re-exposed via a left thoracotomy at the fourth intercostal space and was suspended in a pericardial cradle. A bipolar plunge electrode was inserted into the interventricular septum near the right ventricular outflow tract (RVOT) adjacent to the site of coronary artery occlusion. This

electrode was used to introduce ventricular extrastimuli during PVS. One bipolar plunge electrode was sutured into each of the following regions: posterolateral left ventricle (non-infarct zone, NZ), and anterior left ventricle distal to the site of coronary artery occlusion (infarct zone, IZ). The latter electrodes were used to measure ventricular excitation thresholds and refractory periods. Lead II electrocardiogram was also monitored.

After stabilization, sinus heart rate, mean arterial pressure (diastolic plus 1/3 pulse pressure), left ventricular pressure (LVP) and the rate of development of LV pressure (LV+dP/dt), and electrocardiographic intervals were measured. The latter included a rate-corrected QTc interval [QTc = (QT ms) (R-R s)$^{-1/2}$]. Non-infarct and infarct zone ventricular relative and effective refractory periods (minimal coupling intervals achieving a propagated ventricular response with 2 ms square wave extrastimuli, 2x and 10x ventricular excitation threshold respectively) were determined during 2.5 Hz atrial pacing. PVS consisting of 1–3 ventricular extrastimuli during sinus rhythm and atrial pacing was then performed at the RVOT site. If ventricular extrastimuli could not be induced at the RVOT site, PVS was attempted at the infarct zone site. Ventricular extrastimuli were introduced using a 2x excitation threshold or, if extrastimuli were not introduced adequately, at 4x excitation threshold. Responses to PVS were categorized as non-inducible (less than five nonstimulated ventricular complexes); nonsustained ventricular tachycardia (five or more nonstimulated ventricular complexes terminating spontaneously with a duration less than 15 s); monomorphic or polymorphic sustained ventricular tachycardia (duration exceeding 15 s); and ventricular tachycardia degenerating into ventricular fibrillation. PVS was continued until the induction of either sustained ventricular tachycardia, tachycardia degenerating into fibrillation, or until the end of the pacing protocol with either nonsustained tachycardia or no response occurring. Sustained ventricular tachycardia was terminated by burst pacing; tachycardia degenerating into ventricular fibrillation was terminated by rapid cardioversion which was nearly universally successful with one shock. Any animals requiring more than two cardioversion shocks to terminate ventricular fibrillation following lower dose regimen treatment were not administered the higher dose regimen. Determination of hemodynamic, ECG intervals, cardiac electrophysiologic parameters and PVS testing was conducted at baseline and following two intravenous doses of test agents (see doses below). Following post-dose electrophysiologic and PVS testing after the second higher dose of test agent, animals were euthanized by anesthesia overdose. Anterior myocardial infarct size was determined by cutting the heart into 1 cm transverse sections which were incubated in 0.4 % triphenyltetrazolium chloride solution. Reaction with triphenyltetrazolium forms a red precipitate in viable tissue, whereas infarcted tissue remains pale (13, 50). Infarct size was quantitated gravimetrically and expressed as a percentage of total left ventricle. Only postinfarction preparations that were completely non-inducible, i.e., non-responsive, to baseline PVS testing were entered into the present study of inotropic agents.

A total of 98 postinfarction dogs were characterized as baseline non-inducible, i.e., non-responsive to baseline PVS testing, during a five-year consecutive time frame (overall PVS experience during time frame: 386 animals tested, 288 inducible, 98 non-inducible). These non-inducible animals were assigned to the following intravenous treatment groups: BDF 9148, 0.3 and 3.0 mg/kg (n = 18, 9.2 ± 0.3 kg, 14.1 ± 2.5 days postinfarction); dobutamine, 0.0003 and 0.003 mg/kg (n = 20, 8.2 ± 0.2 kg, 7.5 ± 0.5 days postinfarction); DPI 201-106, 0.3 and 3.0 mg/kg (n = 19, 8.9 ± 0.3 kg, 10.7 ± 1.7 days postinfarction); forskolin, 0.001 and 0.003 mg/kg (n = 20, 9.6 ± 0.3 kg, 9.9 ± 0.9 days postinfarction); milrinone, 0.003 and 0.01 mg/kg (n = 10, 9.2 ± 0.3 kg, 7.5 ± 0.3 days postinfarction); and ouabain, 0.01 and 0.02 mg/kg (n = 11, 8.7 ± 0.4 kg, 10.6 ± 2.0 days postinfarction). All doses of test agents represent cumulative intravenous doses. DPI 201-106, BDF 9148 and ouabain doses were administered as 15 min infusions, with post-dose electrocardiographic, electrophysiologic, and PVS testing conducted at 15 min after termination of dosing (i.e., 30 min after initiation of dose infusion). Dobutamine, forskolin and milrinone doses were administered as 30 min infusions, with post-dose electrocardiographic, electrophysiologic, and PVS testing conducted at termination of dosing (i.e., 30 min after initiation of dose infusion). Test agent doses, dosing regimens, and timing of dosing relative to testing were based on previous *in vivo* experimental studies with these agents (2, 14, 20, 32, 33, 47, 49) as well as preliminary in-house studies, and were tailored and targeted to elicit approximate 20–40 % and 70–90 % increases in LV+dP/dt. This goal was generally achieved with all test agents except ouabain, where intrinsic arrhythmogenicity, i.e., occurrence of spontaneous nonstimulated premature ventricular contractions, limited the higher dose tested.

Statistical analysis

Data are mean ± SEM. Among group comparisons of parameters such as underlying anterior myocardial infarct size, days postinfarction to study, and baseline hemodynamics were performed using a one-way analysis of variance and a Fisher's Protected Least Significant Difference post-hoc test. Within group baseline vs. test doses comparisons of hemodynamic, electrocardiographic and cardiac electrophysiologic parameters were performed using a repeated measures one-way analysis of variance and a Fisher's Protected Least Significant Difference post-hoc test. Within treatment group comparisons of newly inducible vs. non-inducible subgroups were performed using a two-tailed unpaired Student's t-test.

Results

Baseline characteristics

There were no significant differences among treatment groups with respect to underlying anterior infarct sizes or times from surgical production of anterior infarction to postinfarction cardiac electrophysiologic and PVS testing. Likewise, there were no significant differences in baseline heart rates and LV+dP/dt, two important determinants of myocardial oxygen consumption, among the six treatment groups.

Effects on hemodynamic, electrocardiographic and cardiac electrophysiologic parameters

Tables 1–6 summarize the total group effects of intravenous dobutamine, forskolin, milrinone, BDF 9148, DPI 201-106, and ouabain, respectively, on hemodynamics, electrocardiographic intervals, and cardiac refractoriness. All of the agents elicited dose-dependent increases in myocardial contractility measured as LV+dP/dt. The lower dose regimens of all positive inotropes tested elicited 18.6–45.0 % increases in LV+dP/dt. The higher dose regimens elicited 65.7–94.8 % increases in LV+dP/dt, with the exception of ouabain which

Table 1 Effect of dobutamine in chloralose-anesthetized dogs with previous anterior myocardial infarction

Parameter/Site	Base	Dobutamine (mg/kg i.v.) 0.0003	0.003
Sinus Heart Rate (bpm)	120 ± 3	132 ± 4*	153 ± 5**
Mean Arterial Pressure (mm Hg)	45 ± 3	53 ± 4	68 ± 5**
PR Interval (msec)	124 ± 5	119 ± 5	111 ± 4*
QRS Interval (msec)	54 ± 2	56 ± 2	56 ± 3
QTc Interval (msec)$(sec)^{-1/2}$	382 ± 11	384 ± 11	374 ± 12
LVP (mm Hg)	62 ± 3	72 ± 4	93 ± 7**
LV +dP/dt (mm Hg/sec)	930 ± 65	1151 ± 84	1690 ± 111**
Left Ventricle Non-Infarct Zone			
Relative Refractory Period (msec)	168 ± 3	168 ± 3	155 ± 5*
Effective Refractory Period (msec)	144 ± 2	144 ± 3	133 ± 5*
Left Ventricle Infarct Zone			
Relative Refractory Period (msec)	161 ± 4	154 ± 5	154 ± 6
Effective Refractory Period (msec)	132 ± 4	127 ± 5	128 ± 6

Data are mean ± SEM with n = 17–20. *p < 0.05; **p < 0.01 compared to base value by ANOVA followed by a Fisher's Protected Least Significant Difference post-hoc test.

Table 2 Effect of forskolin in chloralose-anesthetized dogs with previous anterior myocardial infarction

Parameter/Site	Base	Forskolin (mg/kg i.v.) 0.001	0.003
Sinus Heart Rate (bpm)	125 ± 2	182 ± 5**	202 ± 6**
Mean Arterial Pressure (mm Hg)	59 ± 4	54 ± 4	54 ± 4
PR Interval (msec)	123 ± 5	113 ± 4	109 ± 4*
QRS Interval (msec)	54 ± 2	56 ± 2	54 ± 2
QTc Interval (msec)$(sec)^{-1/2}$	367 ± 5	365 ± 7	346 ± 8*
LVP (mm Hg)	78 ± 7	81 ± 6	96 ± 9
LV +dP/dt (mm Hg/sec)	1057 ± 47	1457 ± 110**	2059 ± 136**
Left Ventricle Non-Infarct Zone			
Relative Refractory Period (msec)	175 ± 5	151 ± 7*	133 ± 7**
Effective Refractory Period (msec)	150 ± 6	127 ± 7*	107 ± 7**
Left Ventricle Infarct Zone			
Relative Refractory Period (msec)	160 ± 6	146 ± 8	134 ± 7**
Effective Refractory Period (msec)	139 ± 5	123 ± 7	106 ± 8**

Data are mean ± SEM with n = 18–22. *p < 0.05; **p < 0.01 compared to base value by ANOVA followed by a Fisher's Protected Least Significant Difference post-hoc test.

Table 3 Effect of milrinone in chloralose-anesthetized dogs with previous anterior myocardial infarction

Parameter/Site	Base	Milrinone (mg/kg i.v.) 0.003	0.010
Sinus Heart Rate (bpm)	122 ± 4	175 ± 6**	210 ± 6**
Mean Arterial Pressure (mm Hg)	51 ± 2	43 ± 2*	40 ± 3**
PR Interval (msec)	134 ± 4	126 ± 3	119 ± 3**
QRS Interval (msec)	61 ± 1	63 ± 2	60 ± 2
QTc Interval (msec)$(sec)^{-1/2}$	363 ± 7	346 ± 9	332 ± 12*
LVP (mm Hg)	67 ± 2	73 ± 11	104 ± 12**
LV +dP/dt (mm Hg/sec)	1017 ± 41	1473 ± 89**	1951 ± 124**
Left Ventricle Non-Infarct Zone			
Relative Refractory Period (msec)	164 ± 3	135 ± 3**	117 ± 4**
Effective Refractory Period (msec)	140 ± 5	112 ± 4**	93 ± 5**
Left Ventricle Infarct Zone			
Relative Refractory Period (msec)	153 ± 6	131 ± 9*	114 ± 8**
Effective Refractory Period (msec)	131 ± 3	106 ± 4**	89 ± 7**

Data are mean ± SEM with n = 10. *p < 0.05; **p < 0.01 compared to base value by ANOVA followed by a Fisher's Protected Least Significant Difference post-hoc test.

elicited a 31.7 % increase in LV+dP/dt with a higher dose regimen limited by intrinsic, spontaneous arrhythmogenicity.

Aside from expected increases in LV+dP/dt and LVP, the positive inotropic agents tested displayed diverse effects on heart rate, mean arterial pressure, electrocardiographic intervals, and ventricular refractoriness. The β-adrenergic agonist dobutamine significantly increased heart rate and elevated mean arterial pressure, shortened PR interval consistent with the increase in heart rate, and reduced ventricular refractoriness in the non-infarct zone. The adenylyl cyclase activator forskolin markedly increased heart rate with no change in mean arterial pressure, shortened PR interval consistent with the increase in heart rate, and markedly decreased QTc interval and ventricular refractoriness in both non-infarct and infarct zones. The phosphodiesterase-III inhibitor milrinone markedly elevated heart rate, decreased mean arterial pressure, shortened PR interval consistent with the increase in heart rate, and markedly decreased QTc interval and ventricular refractoriness in both non-infarct and infarct zones.

The sodium channel agonists DPI 201-106 and BDF 9148 displayed divergent total group cardiac electrophysiologic profiles. DPI 201-106 increased QTc interval and ventricular

Table 4 Effect of DPI 201-106 in chloralose-anesthetized dogs with previous anterior myocardial infarction

Parameter/Site	Base	DPI 201-106 (mg/kg i.v.) 0.3	3.0
Sinus Heart Rate (bpm)	121 ± 3	129 ± 3	127 ± 5
Mean Arterial Pressure (mm Hg)	62 ± 5	66 ± 4	74 ± 5
PR Interval (msec)	123 ± 5	120 ± 5	120 ± 5
QRS Interval (msec)	56 ± 1	57 ± 1	57 ± 1
QTc Interval (msec)$(sec)^{-1/2}$	381 ± 13	412 ± 12	421 ± 14*
LVP (mm Hg)	77 ± 5	82 ± 4	97 ± 6**
LV +dP/dt (mm Hg/sec)	1173 ± 65	1486 ± 76*	2280 ± 149**
Left Ventricle Non-Infarct Zone			
Relative Refractory Period (msec)	166 ± 3	176 ± 4	185 ± 4**
Effective Refractory Period (msec)	143 ± 2	150 ± 3	162 ± 5**
Left Ventricle Infarct Zone			
Relative Refractory Period (msec)	157 ± 4	164 ± 4	176 ± 5**
Effective Refractory Period (msec)	136 ± 4	144 ± 4	156 ± 5**

Data are mean ± SEM with n = 18–19. *p < 0.05; **p < 0.01 compared to base value by ANOVA followed by a Fisher's Protected Least Significant Difference post-hoc test.

Table 5 Effect of BDF9148 in chloralose-anesthetized dogs with previous anterior myocardial infarction

Parameter/Site	Base	BDF9148 (mg/kg i.v.) 0.3	3.0
Sinus Heart Rate (bpm)	129 ± 2	135 ± 4	147 ± 6**
Mean Arterial Pressure (mm Hg)	61 ± 5	65 ± 5	73 ± 6
PR Interval (msec)	116 ± 4	113 ± 4	105 ± 3
QRS Interval (msec)	54 ± 3	55 ± 3	55 ± 3
QTc Interval (msec)$(sec)^{-1/2}$	361 ± 14	367 ± 15	375 ± 17
LVP (mm Hg)	72 ± 4	81 ± 5	99 ± 7**
LV +dP/dt (mm Hg/sec)	1156 ± 81	1375 ± 95	1915 ± 166**
Left Ventricle Non-Infarct Zone			
Relative Refractory Period (msec)	163 ± 3	165 ± 4	163 ± 7
Effective Refractory Period (msec)	140 ± 3	142 ± 3	144 ± 7
Left Ventricle Infarct Zone			
Relative Refractory Period (msec)	156 ± 4	158 ± 4	157 ± 7
Effective Refractory Period (msec)	133 ± 4	133 ± 4	135 ± 7

Data are mean ± SEM with n = 15–18. *p < 0.05; **p < 0.01 compared to base value by ANOVA followed by a Fisher's Protected Least Significant Difference post-hoc test.

Table 6 Effect of ouabain in chloralose-anesthetized dogs with previous anterior myocardial infarction

Parameter/Site	Base	Ouabain (mg/kg i.v.) 0.010	0.020
Sinus Heart Rate (bpm)	120 ± 4	128 ± 3	129 ± 3
Mean Arterial Pressure (mm Hg)	52 ± 5	56 ± 5	59 ± 6
PR Interval (msec)	126 ± 5	122 ± 5	123 ± 4
QRS Interval (msec)	50 ± 1	51 ± 2	51 ± 2
QTc Interval (msec)$(sec)^{-1/2}$	330 ± 9	332 ± 8	336 ± 7
LVP (mm Hg)	67 ± 4	74 ± 5	80 ± 6
LV +dP/dt (mm Hg/sec)	1032 ± 71	1224 ± 103	1359 ± 116*
Left Ventricle Non-Infarct Zone			
Relative Refractory Period (msec)	157 ± 8	177 ± 15	166 ± 10
Effective Refractory Period (msec)	132 ± 8	148 ± 12	142 ± 8
Left Ventricle Infarct Zone			
Relative Refractory Period (msec)	153 ± 9	172 ± 20	158 ± 9
Effective Refractory Period (msec)	131 ± 8	143 ± 14	133 ± 8

Data are mean ± SEM with n = 10–11. *p < 0.05; **p < 0.01 compared to base value by ANOVA followed by a Fisher's Protected Least Significant Difference post-hoc test.

refractoriness in both non-infarct and infarct zones, whereas BDF 9148 moderately increased heart rate but was without effect on QTc or refractory periods. The cardiac glycoside ouabain, at the doses tested, was devoid of significant effect on heart rate, mean arterial pressure, and electrocardiographic intervals. The effect of ouabain on ventricular refractoriness appeared biphasic, with variable and non-significant increases in non-infarct and infarct zone refractory periods with low but not high dose.

Induction of ventricular tachyarrhythmia: relationship of inducibility to underlying infarct size, heart rate, LV+dP/dt and cardiac electrophysiologic effects

Table 7 summarizes the incidence of precipitation of new sustained ventricular tachyarrhythmias, primarily polymorphic sustained ventricular tachycardia or ventricular tachycardia degenerating rapidly into ventricular fibrillation, in baseline non-inducible dogs treated with positive inotropic agents.

Table 7 Incidence of ventricular tachyarrhythmia (VT) induction by programmed ventricular stimulation (PVS) in chloralose-anesthetized dogs with previous anterior myocardial infarction

Test Agent	Incidence of VT Induction[a] Base	Lower[b] Dose	Higher[b] Dose	Cumulative	Anterior Myocardial Infarct Size (% of Left Ventricle)
BDF 9148	0/18	3/18	4/16	6/18	11.7 ± 1.7
Dobutamine	0/20	5/20	3/18	6/20	12.9 ± 2.2
DPI 201-106	0/19	6/19	5/18	9/19	13.4 ± 1.9
Forskolin	0/20	4/20	3/20	4/20	14.4 ± 2.1
Milrinone	0/10	3/10	1/10	3/10	19.6 ± 2.6
Ouabain	0/11	3/11	2/11	3/11	13.0 ± 3.0

a: incidence of VT induction by PVS, including induction of uniform sustained VT, polymorphic sustained VT, and VT degenerating into ventricular fibrillation, expressed as number of animals with VT induced as a function of number of animals receiving lower and higher doses, as well as total cumulative number of animals with VT induced at any dose as a function of total number of animals entered into group.
b: lower and higher doses, respectively, for each intervention were: BDF 9148, 0.3 and 3.0 mg/kg; dobutamine, 0.0003 and 0.003 mg/kg; DPI 201-106, 0.3 and 3.0 mg/kg; forskolin, 0.001 and 0.003 mg/kg; milrinone, 0.003 and 0.01 mg/kg; ouabain, 0.01 and 0.020 mg/kg; all interventions administered as cumulative i.v. doses.

Precipitation of new ventricular arrhythmia occurred with all positive inotropes tested. The incidences of new ventricular arrhythmia with the lower dose inotropic regimens were comparable across treatment groups, ranging from 16.7 % (3/18 animals with BDF 9148) to 31.6 % (6/19 animals with DPI 201-106). Similarly, the incidences of new arrhythmia with the higher dose regimens were comparable across treatment groups, ranging from 10.0 % (1/10 animals with milrinone) to 27.7 % (5/18 animals with DPI 201-106). The overall incidence of new ventricular arrhythmia with any dose regimen ranged from 27.3 % (3/11 animals with ouabain) to 47.4 % (9/19 animals with DPI 201-106). No obvious dose-dependence for susceptibility to induction of new ventricular tachyarrhythmia was observed in any positive inotrope treatment group. Rather, there were examples in all groups of animals in which new ventricular arrhythmia was induced with the lower dose treatment regimen but not with the higher dose regimen.

Table 8 summarizes total cohort (all positive inotropic treatment groups combined) subgroup comparisons of underlying anterior myocardial infarct sizes, times from surgical production of anterior myocardial infarction to postinfarction cardiac electrophysiologic and PVS testing, and sinus heart rate and LV+dP/dt values with low and high dose positive inotrope treatment regimens for those postinfarction animals in which new ventricular arrhythmias were induced after treatment vs. those remaining non-inducible. No statistically significant differences in these parameters, most notably including underlying infarct size and time post myocardial infarction to electrophysiologic study, were observed across all positive inotropic treatments. Paradoxically, a modest albeit non-significant trend ($p = 0.07–0.12$) toward lower heart rates in the newly inducible vs. non-inducible group was present in this total cohort subgroup analysis.

Table 8 also summarizes within individual positive inotropic agent treatment subgroup comparisons of underlying anterior myocardial infarct sizes, time post myocardial infarction to electrophysiologic study, and sinus heart rate and LV+dP/dt values with low and high dose regimens for those postinfarction animals in which new ventricular arrhythmias were induced after treatment vs. those remaining non-inducible. While some random non-significant among treatment group variations in underlying infarct size and time post myocardial infarction to electrophysiologic study were present, directed within individual treatment group comparisons of newly inducible vs. non-inducible animals indicated no significant subgroup differences in these two parameters. Likewise, within treatment group comparisons of inducible vs. non-inducible animals indicated no systematic subgroup differences in heart rate or LV+dP/dt with both the lower and higher dose regimens of any of the positive inotropic agent treatment groups. The only statistically significant newly inducible vs. non-inducible subgroup differences that were detected were in LV+dP/dt for the higher dose regimen of DPI 201-106 and in heart rate for the higher dose regimen of milrinone. Paradoxically, in the two latter cases the values for LV+dP/dt for the higher dose DPI 201-106 regimen and for heart rate for the higher dose milrinone regimen were lower in the newly inducible vs. non-inducible subgroups.

Table 9 summarizes within individual positive inotropic agent treatment subgroup comparisons of non-infarct zone (NZ) and infarct zone (IZ) ventricular excitation threshold (VET) and relative refractory period (VRRP) values with low and high dose regimens for those postinfarction animals in which new ventricular arrhythmias were induced after treatment (inducible) vs. those remaining non-inducible. No significant subgroup differences in NZ VET or IZ VETs were

Table 8 Subgroup analysis: total cohort (top panel: all positive inotropic treatment groups combined) and within treatment group comparisons of underlying anterior myocardial infarct sizes, time from surgical production of anterior infarction to cardiac electrophysiologic study, sinus heart rate and LV +dP/dt in postinfarction dogs in which new ventricular tachyarrhythmias were induced (inducible) vs. those animals remaining non-inducible).

Treatment Group	Underlying Anterior Myocardial Infarct Size (% LV)	Time Post Infarction to Study (Days)	Sinus Heart Rate Low Dose (Beat/Min)	Sinus Heart Rate High Dose (Beat/Min)	LV +dP/dt Low Dose (mm Hg/sec)	LV +dP/dt High Dose (mm Hg/sec)
All Treatment Groups Combined						
Inducible	14.6 ± 1.3 (n=31)	11.5 ± 1.6 (n=31)	138 ± 4 (n=31)	150 ± 7 (n=26)	1354 ± 62 (n=31)	1881 ± 111 (n=26)
Non-inducible	13.4 ± 1.2 (n=67)	10.0 ± 0.8 (n=67)	150 ± 4 (n=67)	164 ± 5 (n=67)	1363 ± 52 (n=67)	1920 ± 77 (n=67)
P value[a]	0.55	0.29	0.07	0.12	0.92	0.78
Dobutamine						
Inducible	14.7 ± 2.6 (n=6)	9.0 ± 2.0 (n=6)	130 ± 5 (n=6)	155 ± 9 (n=4)	1052 ± 182 (n=6)	1641 ± 439 (n=4)
Non-inducible	12.1 ± 3.2 (n=14)	7.2 ± 0.4 (n=14)	133 ± 5 (n=14)	152 ± 6 (n=14)	1194 ± 94 (n=14)	1740 ± 89 (n=14)
P value[a]	0.61	0.16	0.76	0.80	0.45	0.82
Forskolin						
Inducible	17.2 ± 4.8 (n=4)	7.8 ± 0.5 (n=4)	183 ± 8 (n=4)	196 ± 9 (n=4)	1463 ± 166 (n=4)	2525 ± 278 (n=4)
Non-inducible	13.7 ± 2.4 (n=16)	10.4 ± 1.0 (n=16)	182 ± 6 (n=16)	203 ± 8 (n=16)	1456 ± 133 (n=16)	1972 ± 145 (n=16)
P value[a]	0.52	0.21	0.94	0.68	0.98	0.14
Milrinone						
Inducible	21.8 ± 4.6 (n=3)	7.0 ± 0.1 (n=3)	163 ± 9 (n=3)	188 ± 6 (n=3)	1438 ± 73 (n=3)	1925 ± 201 (n=3)
Non-inducible	20.1 ± 3.5 (n=7)	7.8 ± 0.5 (n=7)	180 ± 6 (n=7)	219 ± 5 (n=7)	1488 ± 127 (n=7)	1963 ± 165 (n=7)
P value[a]	0.78	0.27	0.19	0.01	0.81	0.90
DPI 201-106						
Inducible	13.3 ± 2.6 (n=9)	13.3 ± 3.3 (n=9)	124 ± 4 (n=9)	122 ± 7 (n=8)	1466 ± 99 (n=9)	1880 ± 103 (n=8)
Non-inducible	13.8 ± 3.2 (n=10)	8.2 ± 0.8 (n=10)	134 ± 4 (n=10)	131 ± 7 (n=10)	1504 ± 119 (n=10)	2600 ± 208 (n=10)
P value[a]	0.90	0.15	0.08	0.44	0.81	0.01
BDF 9148						
Inducible	15.2 ± 2.0 (n=6)	16.5 ± 4.3 (n=6)	133 ± 7 (n=6)	145 ± 12 (n=4)	1463 ± 86 (n=6)	2020 ± 253 (n=4)
Non-inducible	9.9 ± 2.3 (n=12)	12.9 ± 3.1 (n=12)	136 ± 5 (n=12)	148 ± 8 (n=12)	1327 ± 140 (n=12)	1877 ± 212 (n=12)
P value[a]	0.15	0.51	0.74	0.87	0.51	0.72
Ouabain						
Inducible	6.3 ± 3.2 (n=3)	8.0 ± 1.2 (n=3)	127 ± 10 (n=3)	127 ± 7 (n=3)	1179 ± 242 (n=3)	1329 ± 290 (n=3)
Non-inducible	14.1 ± 3.9 (n=8)	12.1 ± 3.0 (n=8)	129 ± 3 (n=8)	130 ± 4 (n=8)	1241 ± 120 (n=8)	1370 ± 131 (n=8)
P value[a]	0.26	0.42	0.79	0.67	0.81	0.88

Data are mean ± SEM. [a]P value of comparison of inducible vs. non-inducible preparations by two-tailed unpaired student's t-test.

apparent in any treatment group. A general pattern of either statistically significant or trend (p = 0.06–0.12) toward greater VRRP values in newly inducible vs. non-inducible subgroups was observed in the DPI 201-106, BDF 9148 and ouabain (NZ and IZ, both doses); milrinone (NZ and IZ high dose only); dobutamine (NZ high dose only) but not forskolin treatment groups. It is noteworthy that this pattern of greater refractory period values in newly inducible vs. non-inducible preparations was observed with treatments which effected total group increases in ventricular refractoriness (e.g., DPI 201-106), treatments which effected variable or no total group changes in ventricular refractoriness (e.g., BDF 9148, ouabain) as well as treatments which effected total group decreases in ventricular refractoriness (e.g., dobutamine, milrinone).

Discussion

Most previous preclinical assessments of the arrhythmogenic risk of positive inotropic agents have been single agent assessments (16, 24, 25, 32, 46, 48) or limited comparisons of agents

Table 9 Subgroup analysis: within treatment group comparisons of non-infarct zone ventricular excitation thresholds and relative refractory periods (NZ VET and NZ VRRP, respectively) and infarct zone ventricular excitation thresholds and relative refractory periods (IZ VET and IZ VRRP, respectively) in postinfarction dogs in which new ventricular tachyarrhythmias were induced (inducible) vs. those animals remaining non-inducible (non-inducible).

Treatment Group	NZ VET Low Dose (mA)	NZ VET High Dose (mA)	IZ VET Low Dose (mA)	IZ VET High Dose (mA)	NZ VRRP Low Dose (msec)	NZ VRRP High Dose (msec)	IZ VRRP Low Dose (msec)	IZ VRRP High Dose (msec)
Dobutamine								
Inducible	0.11 ± 0.02 (n = 6)	0.12 ± 0.02 (n = 4)	0.13 ± 0.03 (n= 6)	0.12 ± 0.02 (n = 4)	173 ± 5 (n = 6)	172 ± 16 (n = 4)	149 ± 8 (n = 6)	167 ± 21 (n = 4)
Non-inducible	0.12 ± 0.01 (n = 14)	0.13 ± 0.01 (n = 14)	0.22 ± 0.06 (n = 14)	0.21 ± 0.05 (n = 14)	166 ± 4 (n = 14)	150 ± 4 (n = 14)	156 ± 7 (n = 14)	150 ± 5 (n = 14)
P value[a]	0.80	0.62	0.37	0.33	0.24	0.07	0.56	0.26
Forskolin								
Inducible	0.12 ± 0.01 (n = 4)	0.13 ± 0.01 (n = 4)	0.19 ± 0.06 (n = 4)	0.18 ± 0.05 (n = 4)	149 ± 7 (n = 4)	133 ± 8 (n = 4)	145 ± 10 (n = 4)	131 ± 7 (n = 4)
Non-inducible	0.13 ± 0.01 (n = 16)	0.13 ± 0.01 (n = 16)	0.22 ± 0.03 (n = 16)	0.20 ± 0.03 (n = 16)	151 ± 8 (n = 16)	133 ± 8 (n = 16)	146 ± 10 (n = 16)	135 ± 9 (n = 16)
P value[a]	0.73	0.71	0.73	0.74	0.91	0.96	0.96	0.83
Milrinone								
Inducible	0.11 ± 0.02 (n = 3)	0.14 ± 0.04 (n = 3)	0.11 ± 0.03 (n = 3)	0.13 ± 0.03 (n = 3)	133 ± 5 (n = 3)	128 ± 3 (n = 3)	148 ± 19 (n = 3)	139 ± 9 (n = 3)
Non-inducible	0.10 ± 0.02 (n = 7)	0.11 ± 0.02 (n = 7)	0.11 ± 0.01 (n = 7)	0.12 ± 0.02 (n = 7)	136 ± 4 (n = 7)	112 ± 4 (n = 7)	123 ± 9 (n = 7)	103 ± 8 (n = 7)
P value[a]	0.83	0.41	0.97	0.89	0.73	0.05	0.21	0.03
DPI 201-106								
Inducible	0.12 ± 0.01 (n = 9)	0.14 ± 0.02 (n = 8)	0.12 ± 0.01 (n = 9)	0.14 ± 0.02 (n = 8)	182 ± 7 (n = 9)	193 ± 7 (n = 8)	172 ± 6 (n = 9)	186 ± 8 (n = 8)
Non-inducible	0.14 ± 0.01 (n = 10)	0.17 ± 0.02 (n = 10)	0.13 ± 0.01 (n = 10)	0.17 ± 0.03 (n = 10)	170 ± 2 (n = 10)	178 ± 5 (n = 10)	157 ± 5 (n = 10)	169 ± 6 (n = 10)
P value[a]	0.41	0.41	0.89	0.45	0.11	0.08	0.05	0.10
BDF 9148								
Inducible	0.12 ± 0.02 (n = 6)	0.14 ± 0.03 (n = 4)	0.17 ± 0.05 (n = 6)	0.15 ± 0.03 (n = 4)	173 ± 4 (n = 6)	194 ± 13 (n = 4)	171 ± 6 (n = 6)	182 ± 19 (n = 4)
Non-inducible	0.15 ± 0.02 (n = 12)	0.16 ± 0.02 (n = 12)	0.19 ± 0.04 (n = 12)	0.18 ± 0.02 (n = 12)	161 ± 5 (n = 12)	152 ± 6 (n = 12)	152 ± 3 (n = 12)	149 ± 5 (n = 12)
P value[a]	0.30	0.59	0.81	0.40	0.12	0.01	0.01	0.03
Ouabain								
Inducible	0.15 ± 0.03 (n = 3)	0.15 ± 0.04 (n = 3)	0.20 ± 0.02 (n = 3)	0.20 ± 0.04 (n = 3)	230 ± 41 (n = 3)	195 ± 15 (n = 3)	232 ± 67 (n = 3)	181 ± 23 (n = 3)
Non-inducible	0.12 ± 0.02 (n = 8)	0.12 ± 0.02 (n = 8)	0.33 ± 0.16 (n = 8)	0.33 ± 0.16 (n = 8)	157 ± 9 (n = 8)	155 ± 10 (n = 8)	149 ± 8 (n = 8)	149 ± 8 (n = 8)
P value[a]	0.36	0.51	0.62	0.64	0.03	0.06	0.07	0.12

Data are mean ± SEM. [a]P value of comparison of inducible vs. non-inducible preparations by two-tailed unpaired student's t-test.

(2, 26, 33, 47). Experimental models and protocols have varied considerably in the preceding studies. Assessments of pro-arrhythmic risk have been conducted in both anesthetized (2, 32, 33, 48) and conscious (16, 24–26,46–48) animal preparations, and have utilized i.v. boluses (2, 16, 24, 26, 32, 33, 46–48), i.v. infusions (26, 33, 47), and multiple day i.v. bolus dosing (25) regimens. While most preclinical assessments of the arrhythmogenic potential of positive inotropic agents have been conducted in the setting of myocardial ischemic injury, the timing of study protocols has ranged from minutes after coronary artery occlusion (2), 2 hours after coronary artery occlusion (48), 1–3 days after myocardial infarction, i.e., sub-acute phase myocardial infarction (16, 47, 48), and 3-21 days after myocardial infarction, i.e., chronic phase myocardial infarction (24–26, 33, 46, 47). Endpoint readouts for pro-arrhythmic potential have included increases in frequency of

spontaneous ventricular ectopy (2, 16, 47, 48), induction of ventricular tachyarrhythmia in response to programmed ventricular simulation (PVS) (24–26, 32, 33, 46), and development of lethal ischemic ventricular arrhythmia in response to the superimposition of ischemia in the setting of previous myocardial infarction (24, 26). Among the studies which have utilized PVS testing in the setting of chronic myocardial infarction in dog, some studies have assessed the propensity of positive inotropic agents to facilitate the induction of new ventricular tachyarrhythmia in baseline non-responsive animals with smaller underlying infarctions (25, 26), whereas other studies have assessed the effect of positive inotropic agents on pre-existing inducible ventricular tachyarrhythmias in animals with larger underlying infarctions (24, 33, 46). One study has utilized PVS in rabbits in the absence of myocardial ischemic injury to assess proarrhythmic risk with positive inotropic therapy (32). Not surprisingly, previous studies have reported conflicting results, including divergent conclusions for individual agents studied in different protocols, regarding the propensity of positive inotropic agents to facilitate arrhythmia.

Given the variations in the experimental design of the preceding studies, the present study sought to assess the proarrhythmic potential of a wider group of mechanistically diverse positive inotropic agents in one experimental paradigm. In the present study, PVS was used to assess the potential for positive inotropes to facilitate the induction of new ventricular tachyarrhythmias in baseline non-responsive dogs with previous myocardial infarction. Clinically, the value of PVS in identifying postinfarction patients at high risk of subsequent malignant arrhythmia has been addressed in numerous studies with varying pacing protocols, patient sizes, follow-up periods and timing of electrophysiologic study relative to infarction, with inconsistent findings. Some clinical studies have reported no predictive value for PVS after acute myocardial infarction (28, 38). In contrast, several clinical studies have reported response to PVS in postinfarction patients to be useful in identifying patients at high risk of subsequent occurrence of spontaneous ventricular arrhythmia or sudden death (4, 5, 10, 15, 17, 36, 52), although the predictive value of specifically induced arrhythmias (e.g., sustained monomorphic ventricular tachycardia vs. ventricular fibrillation) varies among studies. While response to PVS after acute myocardial infarction appears on balance clinically useful in predicting high risk for spontaneous arrhythmic events, the value of PVS in guiding antiarrhythmic therapy to prevent subsequent spontaneous arrhythmic events in postinfarction patients is highly uncertain e.g. (6). The approach of the present preclinical study was to consider the ability of a myocardial substrate to entertain and sustain reentrant rhythm indicative of high risk of subsequent arrhythmia. Hence, a treatment-related conversion from a myocardial substrate resistant to arrhythmia to one which entertains reentrant arrhythmia, including ventricular tachycardia degenerating into fibrillation was considered an adverse, proarrhythmic effect. This experimental approach has been used previously to demonstrate proarrhythmic risk with Class IC antiarrhythmic agents (18, 51) which also adversely affect survival in postinfarction patients through a facilitation or aggravation of arrhythmia (12).

In the present postinfarction canine preparation, lower and higher dose intravenous regimens were tailored and targeted to elicit approximate 20–40 % and 70–90 % increases in LV+dP/dt for each agent, such that arrhythmogenic risk might be compared among compounds at comparable inotropic dosages. This goal was generally achieved with the positive inotropic agents tested with the exception of the cardiac glycoside ouabain, the higher dose regimen for which was limited by the appearance of spontaneous ventricular ectopy. The major finding of this study was that all positive inotropic agents tested, regardless of underlying mechanism of inotropic activity, displayed generally comparable incidences of precipitation of new ventricular tachyarrhythmia. Comparable facilitation of arrhythmia was observed with all agents despite diverse total group effects on heart rate, electrocardiographic intervals including QTc interval, and ventricular refractoriness, the latter parameters having been implicated in arrhythmogenesis in settings of pathologic or iatrogenically-induced long QT syndrome (3, 37). The latter point is exemplified by the comparable precipitation of new arrhythmia with the two sodium channel agonists DPI 201-106 and BDF 9148, despite differential total group effects on QTc interval and ventricular refractoriness presumably by virtue of differing effects on cardiac potassium currents (1). Interestingly, within individual treatment subgroup comparisons indicated a general albeit not universal pattern of greater ventricular refractory period values in newly inducible vs. non-inducible. This pattern was observed in treatments which effected total group increases in ventricular refractoriness (e.g., DPI 201-106), treatments which effected variable or no total group changes in ventricular refractoriness (e.g., BDF 9148, ouabain) as well as treatments which effected total group decreases in ventricular refractoriness (e.g., dobutamine, milrinone). However, this pattern was not consistently observed with both low and high dose positive inotrope treatment regimens, was not always observed in both non-infarct and infarct zones, and was not observed at all with forskolin. Nonetheless, this observation suggests that alterations in ventricular refractoriness and repolarization may be an important mechanism of arrhythmogenesis for many of the positive inotropic agents tested.

Overall, the present findings suggest that no specific effect on heart rate or cardiac electrophysiologic parameters with these mechanistically diverse cardiotonic agents constituted a common determinant of arrhythmogenesis. Rather, the present findings are consistent with the general shared property of increased myocardial contractility, potentially adversely affecting myocardial oxygen balance, myocardial perfusion

and electrical stability in the setting of previous myocardial infarction, being a common underlying cause for arrhythmogenesis. Additionally, the present results suggest that alterations in ventricular repolarization and refractoriness may contribute significantly to proarrhythmia with some positive inotropic interventions. The present study does not attempt to address the mechanism of facilitated induction of new ventricular tachyarrhythmia by PVS with the six positive inotropic agents tested. Ventricular tachyarrhythmias induced by PVS in postinfarction dogs as well as patients have been demonstrated to be reentrant (9, 19), and hence it is logical to speculate that the ultimate proarrhythmic effect of the positive inotropic agents tested was to facilitate reentry. Alterations in ventricular repolarization and refractoriness such as observed in the present study may contribute to the initiation or maintenance of reentry. Additionally, alterations in myocardial conduction may facilitate reentry; however, no direct measurements of the effects of the present positive inotropic agents on ventricular conduction were obtained in this postinfarction model, and, therefore, no comment can be made on possible changes in conduction as an underlying arrhythmogenic mechanism of these agents. Cellular electrophysiologic studies would more appropriately address specific electrophysiologic changes which might promote reentry, and indeed it cannot be precluded that the six positive inotropic agents tested might exert diverse cellular electrophysiologic effects which might result in a similar incidence of newly induced reentrant arrhythmia.

No systematics within treatment differences in underlying myocardial infarct size, time from surgical myocardial infarction to electrophysiologic study, or in absolute values for heart rate or myocardial contractility were detected between subgroups of animals in which new ventricular arrhythmias were precipitated vs. those which remained non-responsive. Additionally, there was no clear dose-dependence for enhanced incidence of arrhythmia with the positive inotropic agents tested. An important caveat in the assessment of dose-response in this type of study relates to reproducibility in arrhythmia induction by PVS. In order to minimize the number of episodes of ventricular tachyarrhythmia/fibrillation with attendant cardioversions in each preparation, the reproducibility of induction of arrhythmia at each distinct dose was not proven. Therefore, variation in induction of arrhythmia by PVS may influence dose-response. Overall, however, the lack of apparent dose-response as well as the fact that arrhythmia facilitation was not universal in all dogs with previous myocardial infarction suggests that arrhythmia facilitation resulted from a critical interaction between inotropic or electrophysiologic effect and appropriately susceptible myocardial substrate. That is, arrhythmogenesis may have resulted in some but not all animals at certain dose levels due to a critical interplay between metabolic stress, alteration in cardiac electrophysiologic status and particular underlying myocardial substrate to permit genesis and maintenance of arrhythmia. Since myocardial infarctions will vary with respect to many characteristics including location, architecture, degree of disruption of cardiac innervation, and degree of electrical instability, given changes in contractility or electrophysiologic status will be differentially arrhythmogenic in different infarct settings. The latter concept has important implications with regard to the assessment of the arrhythmogenic potential of a positive inotropic agent. The latter concept also presents important complications in the assessment of susceptibility of patients with myocardial ischemic injury toward arrhythmia facilitation with positive inotropic interventions, given the recently advanced view that positive inotropic agents with demonstrated adverse survival impact may be considered for clinical use if they provide a meaningful improvement in quality of life and if patients most susceptible to adverse effects can be identified (7, 39). Finally, while the present results suggest that the mechanistically diverse positive inotropic agents assessed in the present study possess comparable arrhythmogenic risk in the postinfarction setting, these findings do not preclude the development of positive inotropic agents working either through novel cellular inotropic or electrophysiologic mechanisms or possessing salutary ancillary activities that would possess lower arrhythmogenic risk.

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