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Induction of ventricular arrhythmia by high and low osmolarity ionic and nonionic contrast media

Studies that used prolonged contrast media infusion in canine arteries have generated controversy regarding the arrhythmogenic potential of low osmolarity, nonionic contrast agents. In order to establish the relative safety of these agents in the more typical setting of bolus injections, 4 ml intracoronary bolus injections of Hypaque-76 (n = 54), Iohexol-350 (n = 51), and Iohexol-140 (n = 51) were given in random order to 10 anesthetized, open-chest dogs undergoing programmed cardiac stimulation. Hemodynamics and electrocardiogram were monitored during stimulation, both during and for 2 minutes after the end of contrast infusion. Occurrence of evoked single and coupled premature ventricular contractions and nonsustained ventricular tachycardia did not differ statistically among agents. Sustained ventricular tachycardia (five episodes) and ventricular fibrillation (seven episodes) occurred only after Hypaque-76 injections ($p < 0.002$). These results differ from those in studies that use continuous contrast infusion and suggest that low osmolarity nonionic contrast agents are as safe as high osmolarity nonionic contrast media. Both appear safer than ionic contrast material. (*AM HEART J* 1989;117:1283.)

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Many studies¹⁻⁶ document the hemodynamic and electrocardiographic effects of ionic and nonionic contrast agents, and report fewer adverse effects with nonionic contrast media. Hyperosmolarity has been implicated as a major determinant of toxicity, but studies that used prolonged infusions of nonionic isoosmolar agents have contested the safety of such agents with respect to induction of ventricular

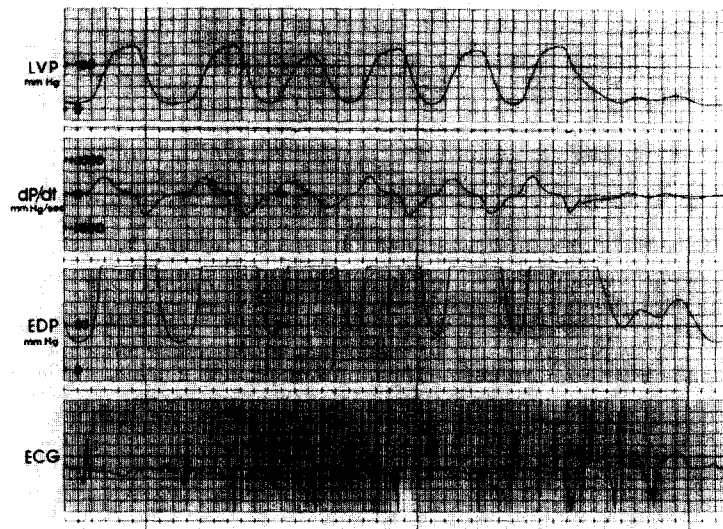


Fig. 1. Tracings recorded during observations. From top to bottom are shown left ventricular pressure, its first derivative dP/dt , and end-diastolic pressure. The electrocardiogram and stimulation protocol are recorded in the fourth tracing.

Table I. Physical properties of contrast media

	<i>Hypaque-76</i>	<i>Iohexol-350</i>	<i>Iohexol-140</i>
Osmolality (mosm/kg)	2100.0	862.0	322
Viscosity (at 25° C)	13.3	18.5	2.0
[Iodine] (mg/ml)	370.0	350.0	140
Ion	Sodium (3.7 mg/ml)	Calcium (0.1 mg/ml)	Calcium (0.1 mg/ml)

arrhythmia.⁷⁻¹⁰ The clinical relevance of such studies is questionable, however, since intracoronary contrast infusion for diagnostic and intervention purposes is usually performed with rapid bolus injections rather than with prolonged infusions. The present study compares the arrhythmogenicity of bolus injections of high and low osmolality nonionic agents and ionic contrast media.

METHODS

Ten mongrel dogs (mean weight 21.9 kg) were anesthetized with 35 mg/kg of sodium pentobarbital and ventilated with a Harvard pump (15 ml/kg) (Harvard Apparatus Inc., S. Natick, Mass.). The left carotid artery and the left jugular vein were dissected for vascular access. A left thoracotomy was performed in the fifth intercostal space, the pericardium was incised, and the heart was exposed. Needle electrodes were inserted subcutaneously to monitor the electrocardiogram. A 5F micromanometer (Millar Instruments, Inc., Houston, Texas) was inserted into the left ventricle, via apical puncture, to monitor left ventricular pressure and its first derivative (dP/dt).

Two leads were clipped onto the surface of the right

atrium and two leads were sutured to the left ventricle. These leads were connected to a cardiac stimulator (Model DTU-110, Bloom Associates, Narberth, Pa.) for programmed pacing. All animals were pretreated with propranolol (1 mg/kg) and atropine (1 mg) to reduce effects of sympathetic and parasympathetic tone on heart rate and function.

Programmed stimulation consisted of atrial pacing followed by three ventricular extrastimuli. The atrial pacing rate was selected at 5 to 10 beats faster than the intrinsic heart rate and a stable 1:1 atrioventricular (AV) conduction was maintained. At the end of a four-beat train of atrial pacing, diastole was scanned with a single extrastimulus (S_2). The S_2 was started late in diastole and moved toward the basic drive train at 10 msec intervals until the S_2 repeatedly failed to stimulate the ventricle. The interval between the last QRS (S_1) complex of the basic train and S_2 was defined as the ventricular effective refractory period (ERP) and S_2 was delivered 10 msec beyond it. A second extrastimulus (S_3) interval followed S_2 , and the initial coupling interval was equal to S_1 - S_2 . The S_2 - S_3 interval was reduced to 10 msec steps until S_3 failed to provoke a ventricular response. The S_2 - S_3 interval was defined as the S_2 ERP, and S_3 was delivered 10 msec after S_2 ERP. Diastole was scanned with a third extrastimulus (S_4). S_4 was first introduced with a coupling interval equal to S_2 - S_3 and subsequently reduced in 10 msec steps until S_4 failed to provoke a ventricular response. The S_3 - S_4 interval was defined as the S_3 ERP, and S_4 was delivered 10 msec after this. A 2-second interval separated delivery of each train of atrial and ventricular extrastimuli.

The left coronary artery was catheterized with a 5F or 6F catheter, and a bolus injection of 4 ml of either Hypaque-76, Iohexol-350, or Iohexol-140 was given in random order during a 2-minute repetitive stimulation of the protocol established above (Table I). The limb lead II of the electrocardiogram, left ventricular pressure, and

Table II. QT interval and hemodynamic parameters

	<i>Iohexol-140</i>	<i>Iohexol-350</i>	<i>Hypaque-76</i>
QT interval 0 min	225 ± 20	222 ± 21	223 ± 21
QT interval 1 min	222 ± 22	221 ± 23	229 ± 24
QT interval 2 min	219 ± 20	218 ± 20	225 ± 18
SBP	143 ± 17	146 ± 15	141 ± 19
EDP	9 ± 2	9 ± 3	9 ± 3
Peak + dP/dt	2405 ± 559	2379 ± 525	2485 ± 702
Peak - dP/dt	2011 ± 258	2077 ± 253	2062 ± 355

SBP, Systolic blood pressure; EDP, end-diastolic pressure; +, positive; -, negative.

dP/dt were recorded (Model 2800S, Gould Electronics, Cleveland, Ohio) (Fig. 1), before and for 2 minutes after injection of each agent. Tracings at 100 mm/sec paper speed were recorded before injection and at 1 and 2 minutes after injection for QT interval measurements. Each agent was injected three times, and the period of injection was precisely recorded. A 4-minute resting period separated each test.

When sustained ventricular tachycardia or ventricular fibrillation occurred, defibrillation was attempted with a cardiac defibrillator (Mennen-Greatbatch Electronics, Clarence, N.Y.), set at 50 joules and applied directly to the heart. When defibrillation was required, further testing of the agents was suspended for at least 20 minutes. In eight dogs, the entire sequence of drug testing was repeated a second time. In two dogs, the sequence could not be completed due to unsuccessful defibrillation.

Tracings were analyzed for systolic blood pressure, left ventricular end-diastolic pressure, dP/dt, heart rate, QT interval, occurrence of single premature ventricular contractions, ventricular couplets, nonsustained ventricular tachycardia (defined as a sequence of at least three premature ventricular contractions that lasted no more than 30 seconds and spontaneously resolved), sustained ventricular tachycardia (defined as ventricular tachycardia lasting longer than 30 seconds or requiring treatment for resolution), and ventricular fibrillation (defined as gross irregularity of the QRS complex and hemodynamic deterioration).

Hypothesis testing of frequency data was carried out by means of a chi square statistic.¹¹ Continuous variables were analyzed with BMDP3V statistical software (Biomedical Data Package, UC Press, Berkeley, Calif.) for mixed model unbalanced designs.¹² A modified *t* test (Bonferroni) was used to assess specific differences from control values.¹³ Data not normally distributed were analyzed with a Kruskal Wallis test. Results were considered significant when *p* < 0.05.

RESULTS

Hypaque-76 was injected 54 times, and Iohexol-350 and Iohexol-140 were injected 51 times. The numbers differ because two dogs died during Hypaque-induced arrhythmia. Boluses were injected by

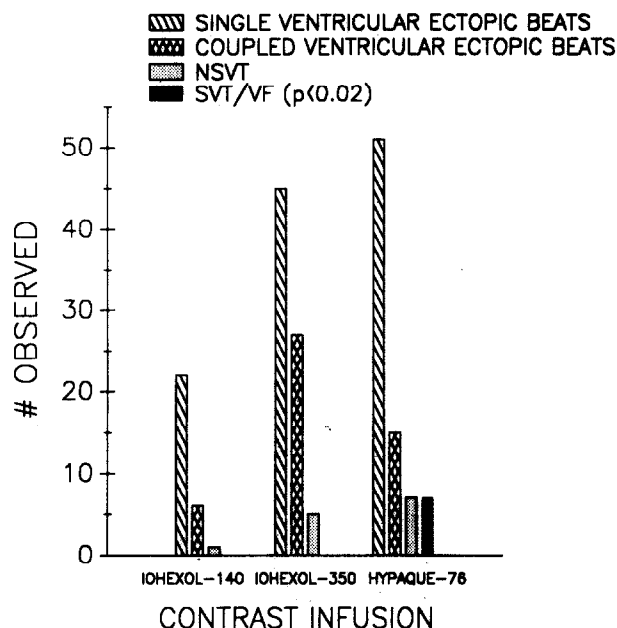


Fig. 2. Incidence of single and coupled ectopic beats, nonsustained (NSVT) and sustained (SVT) ventricular tachycardia for total observations of Iohexol-140, Iohexol-350, and Hypaque-76 injections. The five episodes of SVT after Hypaque-76 injections degenerated into ventricular fibrillation and are shown in the same graph.

hand as rapidly as possible, but because of viscosity differences, the injection duration differed for each agent. Mean infusion duration for Hypaque-76 was 3.2 ± 1.3 seconds (±SD), for Iohexol-350 it was 3.2 ± 1.3 seconds, and for Iohexol-140 it was 1.5 ± 0.5 seconds (*p* = NS). QT interval differences were not significant at 1 and 2 minutes after injection. Hemodynamics parameters (systolic and end-diastolic pressure, dP/dt) were similar among all groups (Table II). Temporal stability of each preparation was confirmed with a paired *t* test of pre- and post-protocol basal pressures, dP/dt, and heart rate; no statistically significant changes were noted.

The incidence of evoked single and coupled premature ventricular contractions was not statistically different after infusion of any agent (Fig. 2). Similarly, the incidence of nonsustained ventricular tachycardia was not significantly different—7 in 54 Hypaque-76 observations, 5 in 51 Iohexol-350 observations, and 1 in 51 Iohexol-140 observations, *p* = NS. Sustained ventricular tachycardia occurred only after Hypaque-76 injections (5 episodes in 54 injections, *p* = 0.02), and degenerated into ventricular fibrillation each time.

Ventricular fibrillation occurred only after Hypaque-76 injections. While five episodes were a consequence of sustained ventricular tachycardia, two were primary events. Thus there were seven episodes of ventricular fibrillation after 54 Hypaque-76

injections (12.9%), and this was significantly greater than with the other agents ($p = 0.02$). Cardioversion was successful in five of seven episodes.

DISCUSSION

Harmful effects of contrast agents are extensively described.^{1,3,14-19} Suggested mechanisms that may induce these reactions include protein binding and inactivation of enzymatic function, deformation of erythrocyte morphology, complement activation, and direct cardiotoxicity.^{1,14-17,20} In addition, the presence of ethylenediamine tetraacetic acid (EDTA) and sodium citrate in some formulations may facilitate induction of arrhythmia.^{21,22} Nonionic contrast media may alleviate some of these adverse reactions.²³⁻²⁶ They stimulate inducing mechanisms to a lesser degree, and several studies suggest that they induce fewer undesirable hemodynamic and electrocardiographic changes.²⁷⁻³⁴

Another long recognized potential inducer of adverse effects is hyperosmolarity. Several reports^{5,23,27} have shown that low osmolarity contrast agents induce even less significant hemodynamic changes than standard media. Although their arrhythmogenicity has seldom been tested, some evidence³⁴ suggests that nonionic, low osmolarity contrast media induce fewer arrhythmias than conventional agents. However, some studies^{7,8,10,35} created controversy by suggesting that ionic and high osmolarity contrast media are safer. These conflicting studies differ predominantly in the method of contrast injection. Studies that showed adverse effects of low osmolarity contrast agents^{9,10,35} have routinely used high doses and prolonged infusions of contrast agents.

The current study is an attempt to simulate a more typical clinical situation by assessing the effects of rapid bolus hand injections. To potentiate the arrhythmogenicity of the contrast agents and to mimic a high-risk state,³⁶ the heart was subjected to repeated ventricular stimulation. Thus sustained ventricular tachycardia and ventricular fibrillation occurred only after Hypaque-76 injections. Previous reports^{14,22-24,34} show a smaller arrhythmogenic propensity of Iohexol-350 compared to standard ionic agents, but this is the first time that the arrhythmogenicity of Iohexol-140 has been compared to that of Iohexol-350 and Hypaque-76. The results show that the arrhythmogenicity of Iohexol-140 is comparable to that of Iohexol-350 and that both are significantly less arrhythmogenic than Hypaque-76.

These data confirm that nonionic contrast media are an attractive option for high-risk situations. The comparable results of Iohexol-140 to Iohexol-350 in

this study offers an impetus for further evaluation of low osmolarity nonionic media in the setting of cardiac catheterization. While some such agents are currently being used in Europe with reports of improved patient tolerance,³⁷ studies addressing the quality of coronary and ventricular images when low osmolarity agents are used will be required.

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