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Effects of Gadolinium on Regionally Stunned Myocardium: Temporal Considerations

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Objectives. **The lanthanide cation, gadolinium (Gd^{3+}), accelerates recovery of stunned myocardium when given prior to ischemia. This study sought to determine whether giving Gd^{3+} during ischemia or during reperfusion also ameliorates stunning, as these temporal relationships could help determine the clinical utility of this novel agent.**

Methods. **Regional myocardial stunning was induced in anesthetized dogs by coronary occlusion for 15 min followed by reperfusion for 3 h. Gd^{3+} (500 μmol) was given intravenously in three treatment groups: [1] pre-ischemia; [2] during ischemia; [3] after reperfusion. No Gd^{3+} was given to controls (Group 4). Measures of global and regional myocardial function were assessed serially.**

Results. **Treatment with Gd^{3+} prior to ischemia (Group 1) had no effects on hemodynamics or regional contraction. Coronary occlusion resulted in diastolic lengthening and paradoxical systolic bulging equally in all groups. After 3 h of reperfusion, regional systolic shortening (%) in the stunned segment was greater in Groups 1 (10.9 ± 3.4; $P = 0.02$) and 2 (6.6 ± 1.3; $P = 0.047$) compared with controls (−0.6 ± 0.03). Recovery of systolic function (% of baseline shortening) after 3 h of reperfusion was similarly improved in Groups 1 (56.1 ± 16.8; $P = 0.02$) and 2 (43.3 ± 8.1; $P = 0.04$) compared with controls (−11.5 ± 4.7).**

Conclusions. **Gadolinium has no inherent inotropic effects but enhances recovery of stunned myocardium. This effect appears maximal if Gd^{3+} is given prior to ischemia, indicating potential utility in elective cardiac surgical procedures or percutaneous coronary interventions. Gadolinium also enhances recovery if given during ischemia but prior to reperfusion, and may thus be useful in acute coronary syndromes as well.**

Key Words: **myocardial ischemia; ischemia-reperfusion; reperfusion; gadolinium; myocardial stunning; myocardial stretch; stretch-activated ion channels.**

INTRODUCTION

The lanthanide cation, gadolinium (Gd^{3+}), modulates pathophysiology associated with a variety of cardiac problems, including arrhythmias, dilated cardiomyopathy and myocardial stunning [1–6]. The authors have previously demonstrated that Gd^{3+} abolishes stretch-induced contractile dysfunction in both normal and post-ischemic myocardium *in vitro*, without effects on voltage-gated (L-type) calcium channels [7]. They have also demonstrated that Gd^{3+} attenuates regional myocardial stunning associated with ischemia-reperfusion (IR) in an *in vivo* canine model [8]. While Gd^{3+} is known to inhibit stretch-activated ion channels in a variety of tissues, including myocardium [9–13], the relationship of this action to its effect on cardiac pathophysiology remains speculative.

Although the mechanism(s) underlying the effects of Gd^{3+} on the heart remain undetermined, this novel agent may have important clinical applications. However, its utility in different clinical scenarios of myocardial IR (elective coronary surgery, acute coronary syndromes, postinfarct contractile dysfunction) could vary if its effects vary with the timing of administration. To date, its effects have only been assessed by giving it prior to ischemia; the effects of administering it either during ischemia or during reperfusion remain unknown. Accordingly, the purpose of the present study was to determine how the timing of Gd^{3+} administration with respect to IR impacts its effects on contractile function in an *in vivo* canine model of regional

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stunning. Results of this study may have important implications regarding the use of this agent in particular clinical settings.

MATERIALS AND METHODS

Instrumentation

Mongrel dogs (approximately 25 kg) were anesthetized with the intravenous combination of pentobarbital (200 mg/kg) and barbital (26 mg/kg). They were intubated and ventilated with supplemental oxygen. Normothermia was maintained with a heating blanket. Catheters were placed into the femoral artery to measure blood pressure and into the femoral vein for infusion of both drugs and crystalloid solution. The heart was exposed by left thoracotomy. The left anterior descending coronary artery (LAD) was encircled with a silk thread immediately distal to the first diagonal branch. Epicardial collateral arteries to the distal LAD territory were meticulously suture ligated. A micromanometer-tipped catheter (Millar Instruments, Inc., Houston, TX) was inserted into the carotid artery and advanced retrograde across the aortic valve to measure left ventricular (LV) pressure. Two cylindrical, ultrasonic dimension crystals were imbedded into the anterior LV free wall, approximately 1 cm apart, to measure instantaneous free wall segment length (FWSL) in the distal LAD territory (IR segment). A second crystal pair was imbedded into the lateral LV free wall to measure FWSL in the circumflex coronary artery territory (remote segment). The crystals were connected to an ultrasonic dimension system (Sonometrics Corp., London, Ontario, Canada). An ultrasonic flow probe (Transonics Systems, Inc., Ithaca, NY) was placed around the pulmonary artery to measure cardiac output. A snare was placed around the inferior vena cava (IVC) to intermittently vary preload. Supplemental barbiturate anesthesia was given as indicated by corneal and hemodynamic reflexes.

Protocol

Animals were stabilized for at least 15 min after instrumentation. Intravenous heparin (100 units/kg) and lidocaine (30 mg) were administered prior to collecting baseline (preischemic) data. Regional ischemia was then induced by tightening the LAD snare. Data were collected again after 10 min of ischemia. The snare was released after 15 min of ischemia and the segment was reperfused for 180 min. Data were collected prior to ischemia, after 10 min of ischemia, and after 180 min of reperfusion. Gadolinium chloride hexahydrate (500 μmol dissolved in 10 mL of 0.9% NaCl solution; Sigma, Milwaukee, WI) was injected intravenously in three treatment groups: [1] Preischemia ($n = 7$) − Gd^{3+} given 5 min prior to induction of ischemia; [2] Ischemia ($n = 7$) − Gd^{3+} given after 10 min of ischemia (immediately *after* collecting ischemia data); [3] Post-ischemia ($n = 6$) − Gd^{3+} given 5 min after reperfusion. A fourth group ($n = 7$) that received no Gd^{3+} served as controls. All animals were sacrificed at the end of the protocol by inducing ventricular fibrillation in the presence of deep general anesthesia. All animals received humane care in compliance with the Guide for the Care and Use of Laboratory Animals.

Data Collection and Analysis

Data were digitized at 250 Hz per channel and stored directly to computer disk using commercial software (Sonometrics Corp.). Heart rate (HR), left ventricular end-diastolic pressure (LVEDP), mean arterial pressure (MAP), and stroke volume (SV) were measured in triplicate during a steady state and averaged. Cardiac output was calculated as the product of SV and HR. Steady-state regional systolic shortening (rSS; %) was defined by the formula: rSS = (EDD − ESD)/EDD, where EDD is end-diastolic dimension and ESD is end-systolic dimension. Instantaneous pressure-dimension relations were analyzed using commercial software (Sonometrics Corp.). Regional preload recruitable stroke work (rPRSW), as described by Glower *et al*. [14] was used to assess the inotropic response of normal myocardium to Gd^{3+}. Briefly, a family of pressure-dimension loops was generated for each region during transient IVC occlusion. Regional stroke work (rSW; mmHg·mm) was defined by the area of the loop. Stroke work was then plotted on a beat-to-beat basis as a function of EDD and fitted to the linear formula:

$$rSW = M_w(EDD - D_w)$$

where D_W is the dimension-axis intercept and the slope (M_w; mmHg) of the relation varies directly with contractile state in a load-independent fashion. Prior studies by the authors [8, 15] have demonstrated inherent difficulties in using this index to assess serial changes in contractility during ischemia and reperfusion, and it was therefore not used for this purpose in the current study.

Statistical Analysis

Mean profile plots of hemodynamic data and steady-state values for regional function were analyzed over time within each group using analysis of variance (ANOVA) for repeated measures. Differences among the four groups were assessed at different points in time using the Kruskal-Wallis nonparametric test. Significance was determined using the Wilcoxon test. A probability less than 0.05 was used to define significance.

RESULTS

Hemodynamics

Mean hemodynamic data are presented in Table 1. There were no baseline differences among the groups with respect to HR, MAP, SV, or CO. Administration of intravenous Gd^{3+} after baseline data but prior to ischemia (Group 1 animals) caused no changes in hemodynamics or regional contractile function (Table 2). Occlusion of the LAD was associated with a mild decrease in MAP in all groups, although the change was statistically significant in Groups 1 and 4. Ischemia also resulted in small decreases in both SV and CO in all groups, with a significant difference in Group 3. Hemodynamics returned to baseline after 180 min of reperfusion except for MAP in Group 1 and both SV and CO in Group 3.

Regional Function

There were no differences among groups at baseline with respect to either EDD or rSS, in either the IR or remote segments. Occlusion of the LAD resulted in abrupt paradoxical systolic bulging in the IR segment (Fig. 1); the change in rSS from baseline to ischemia was significant ($P < 0.05$) in all groups. Contractile dysfunction in the IR segment was accompanied by increased EDD (Fig. 2) that was also significant ($P < 0.05$) in all groups. There were no changes in either rSS or EDD in the remote segment during ischemia.

After 180 min reperfusion, both rSS and EDD in the remote segment were equivalent among groups and did not differ from baseline values in any group. This was not the case, however, in the IR segment. End-diastolic