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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

TABLE 1

Mean Hemodynamic Values at Baseline (t_{-10}), During Ischemia (t_0), and After 180 Minutes of Reperfusion (t_{180})

	t_{-10}	t_0	t_{180}
HR			
Group 1	120 ± 5	119 ± 5	118 ± 6
Group 2	127 ± 9	121 ± 6	103 ± 16
Group 3	119 ± 8	121 ± 9	122 ± 9
Group 4	137 ± 9	142 ± 12	139 ± 9
MAP			
Group 1	127 ± 3	109 ± 4*	119 ± 6*†
Group 2	109 ± 5	102 ± 6	104 ± 7
Group 3	128 ± 6	123 ± 6	128 ± 7
Group 4	130 ± 8	112 ± 6*	127 ± 5
SV			
Group 1	21.2 ± 1.4	18.1 ± 1.2	21.8 ± 1.8
Group 2	19.7 ± 1.5	18.7 ± 1.7	19.9 ± 2.2
Group 3	21.9 ± 2.3	18.7 ± 2.1*	17.6 ± 2.3*
Group 4	22.3 ± 1.5	19.8 ± 1.9	18.4 ± 2.3
CO			
Group 1	2.54 ± 0.22	2.16 ± 0.24	2.53 ± 0.17
Group 2	2.49 ± 0.24	2.28 ± 0.21	1.83 ± .025
Group 3	2.53 ± 0.18	2.18 ± 0.11	2.04 ± .012*
Group 4	3.06 ± 0.26	2.73 ± 0.20	2.51 ± 0.26

HR = heart rate; MAP = mean arterial pressure (mm Hg); SV = stroke volume (mL); CO = cardiac output (L/min). See text for group designations.

* $P < 0.05$ *versus* baseline.

† $P < 0.05$ *versus* ischemia.

dimension (Fig. 2), when compared within each group, had returned to baseline in the three groups treated with Gd^{3+}, but remained increased in controls (12.35 ± 0.57 *versus* 11.64 ± 0.38; $P < 0.05$). End-diastolic dimension in controls was increased compared with both Groups 1 (9.96 ± 0.51 mm; $P = 0.01$) and 2 (10.53 ± 0.58 mm; $P = 0.04$), but did not differ from Group 3 (10.25 ± 0.65 mm). Regional systolic shortening at 180 min (Fig. 1) remained decreased compared with baseline values within each groups, but was improved from ischemia in the three groups treated with Gd^{3+}. In controls, rSS remained unchanged from ischemia (−0.6 ± 2.3% *versus* −4.5 ± 0.6%). Compared with controls, mean rSS at 180 min was greater in Group 1 (10.9 ± 3.4%; $P = 0.02$) and Group 2 (6.6 ± 1.3%; $P = 0.047$), but was not statistically different in Group 3 (6.45 ± 3.19%). The percent recovery of systolic shortening at 180 min, which compares the value at 180 min to baseline and thus adjusts for any minor differences in baseline values, was also greater in both Groups 1 (56 ± 17%; $P = 0.02$) and 2 (43% ± 8%; $P = 0.04$) compared with controls (−11% ± 4%).

DISCUSSION

The results of the current study suggest potential applications of the lanthanide cation, gadolinium (Gd^{3+}), in certain clinical settings involving myocardial IR. The data indicate that if Gd^{3+} can be given before an ischemic event, then IR-induced contractile dysfunction is significantly ameliorated. Gadolinium might thus be useful in cardiac surgery, including any operation in which aortic cross-clamping is used and, in such cases, one might consider systemic administration of Gd^{3+} (as was used in the current study) or perhaps adding Gd^{3+} to cardioplegia solutions. Gadolinium may also be useful in off-pump coronary bypass surgery in which the surgeon elects not to employ shunting of the coronary vessel during distal anastomoses and exposes the downstream territory to ischemia for up to 15 min. Gadolinium may also be useful in elective percutaneous coronary interventions (PCI) in which prolonged coronary occlusions might be anticipated.

The current data also indicate that administration of Gd^{3+} during ischemia, but before reperfusion, has a significant effect on IR-induced contractile dysfunction. Thus, Gd^{3+} might be useful in acute coronary syndromes, administering the drug before reperfusion is established, either by thrombolysis, PCI, or operation. The effect of administering Gd^{3+} during ischemia in the current study seems to be less than preischemic administration, but is still significant compared with controls. Administration of Gd^{3+} after reperfusion has occurred may improve contractile function after ischemia, but in the present study, did not offer benefit compared with controls. The effects of postreperfusion administration appeared to be similar to the effects of administration during ischemia, but did not reach statistical significance, likely due to larger standard errors in Group 3.

The mechanism underlying gadolinium's effects on regionally stunned myocardium remains speculative,

TABLE 2

Mean Hemodynamics and Regional Contractile Function Before and After Administration of Intravenous Gadolinium (Gd^{3+}) in Group 1 Animals ($n = 7$)

	Pre-Gd	Post-Gd
HR	120 ± 5	118 ± 5
MAP	127 ± 3	120 ± 5
SV	21.2 ± 1.4	21.2 ± 1.3
LAD-EDD	9.83 ± 0.53	9.69 ± 0.54
LAD-SS	16.7 ± 2.0	16.7 ± 1.9
LAD-M_w	85.3 ± 24.2	79.3 ± 17.5
LAD-D_w	7.41 ± 0.92	7.41 ± 0.95
LCX-EDD	10.76 ± 1.07	10.67 ± 1.10
LCX-SS	12.8 ± 1.3	12.5 ± 1.3
LCX-M_w	80.9 ± 12.89	79.9 ± 13.63
LCX-D_w	9.05 ± 0.71	8.98 ± 0.82

LAD = territory supplied by left anterior descending coronary artery; LCX = territory supplied by left circumflex coronary artery; EDD = end-diastolic dimension (mm); SS = systolic shortening (%); Mw and Dw = slope and x-axis intercept, respectively, of the regional preload recruitable stroke work relation.

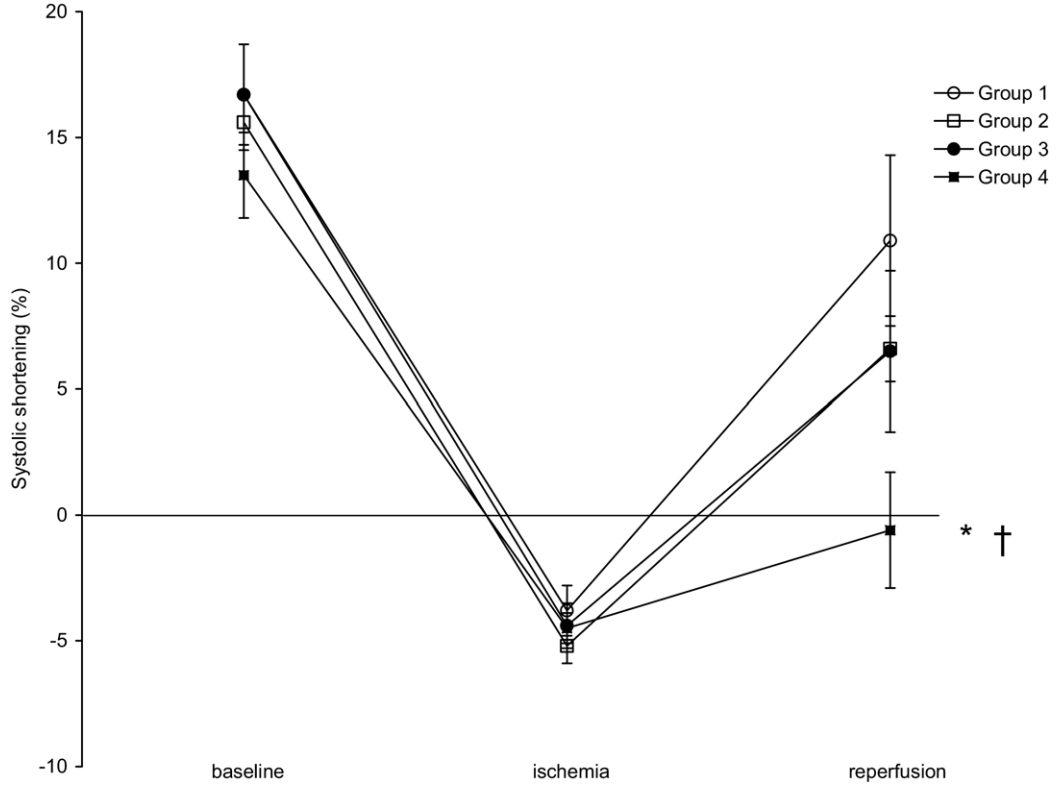

FIG. 1. Systolic shortening in regionally stunned myocardium (see text for group designations). Paradoxical systolic bulging occurs equally in all groups during ischemia and resolves after 180 min reperfusion in the three groups treated with Gd^{3+}. Shortening at 180 min remains less than baseline within each group, however, Groups 1 (*) and 2 (†) are both improved compared with Group 4 ($P < 0.05$) after 180 min reperfusion.

and was not the focus of the present investigation. It is clear that Gd^{3+} does not have inherent positive inotropic effects in normal myocardium, as evidenced by the lack of effect on contractile function when administered prior to ischemia (Group 1; Table 2). There is ample evidence in the literature that stretch-activated ion channels play a key role in cardiac physiology [16–20] and pathophysiology [2–8], and Gd^{3+} is the most widely known and widely used antagonist of these channels. Furthermore, abnormal tissue stretch is a characteristic feature of myocardial IR, both in paradoxical systolic bulging, (first described by Tennant and Wiggers) [21], and in diastolic lengthening, or "creep" [22]. Data from the current experiment (Figs. 1 and 2) and from our previous studies [8, 15] certainly demonstrate abnormal stretch resulting from IR. We thus contend that the effects of gadolinium observed in this and our previous studies reflect its antagonism of stretch-activated ion channels, which are activated by IR. We acknowledge, however, that Gd^{3+} also has potential actions on other ion channels [23–25] and perhaps on macrophage production of oxygen free radicals [26–29], and it may thus ameliorate IR-induced contractile dysfunction through actions unrelated to stretch-activated ion channels. The dose of gadolinium used in the current study was the same dose that we had used in prior studies [8], and was originally adapted from a previous *in vivo* canine study by Ovize and colleagues [30]. While it is possible that other doses may result in greater efficacy, we have not conducted dose-response testing in the *in vivo* model. Dose-response testing in our *in vitro* experiments [7] suggests that a gadolinium concentration of 20 μmol is ideal.

The results of the present study confirm those of our previous studies [6–8] using Gd^{3+}, in that we could not demonstrate any inherent positive or negative inotropic effects of the agent on normal myocardium. Animals in Group 1 that were treated with Gd^{3+} prior to ischemia had no changes in hemodynamics or measures of regional contractile function (Table 2).

One weakness of the current study is the lack of consistent load-independent measures of regional contractile function throughout the experiment. As noted, ischemia resulted in marked distortion of regional pressure-dimension loops, yielding poor linear regressions for the regional rPRSW relation. There were frequent instances in which the slope of the relation remained positive despite the fact that systolic paradox resulted in mainly negative values for rSW. We did not feel that the relation accurately reflected the contractile state of the myocardium in these situations. Simi-

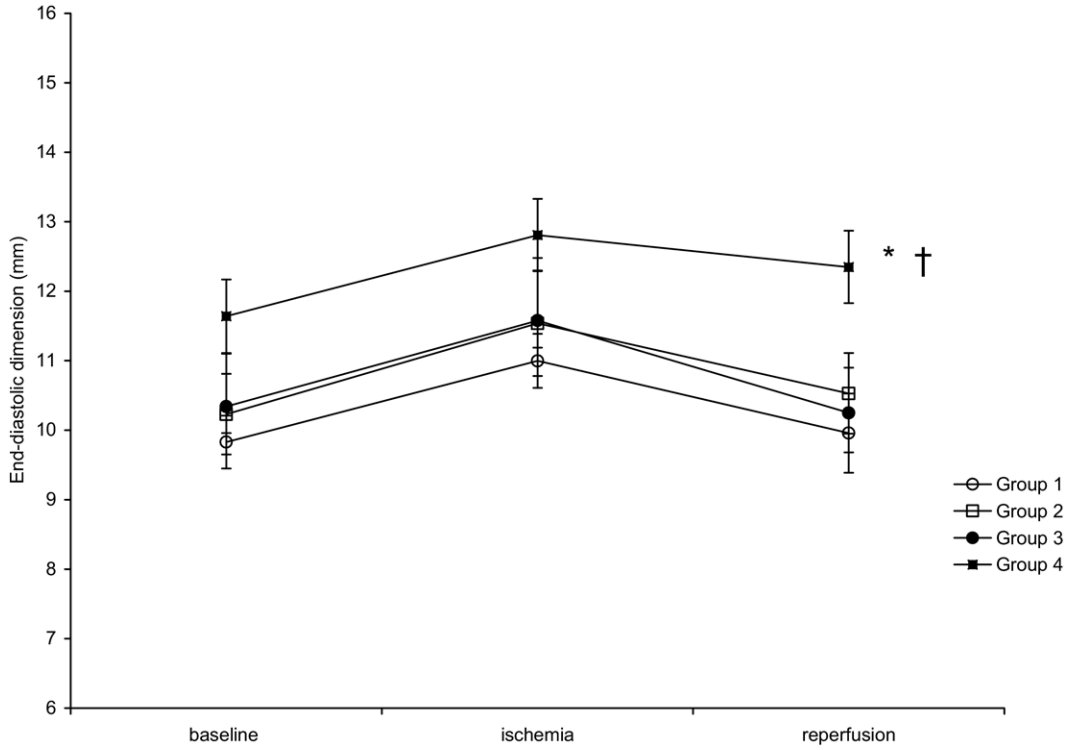

FIG. 2. End-diastolic dimension in regionally stunned myocardium (see text for group designations). Ischemia induces an increase from baseline ($P < 0.05$) within each group. After 180 min reperfusion, end-diastolic dimension equals baseline values in the three groups treated with gadolinium. End-diastolic dimension at 180 min is less in both Groups 1 (*) and 2 (†) compared with Group 4 ($P < 0.05$).

larly, we observed marked distortion of loops late into reperfusion and did not feel that analysis of pressure-dimension relations was valid. Another minor weakness of the present study is the apparent difference in baseline values among groups in certain measured parameters. This is particularly evident with EDD in the LAD territory (Fig. 2), where EDD for Group 4 appears greater than the other three groups. Measured EDD however, is highly dependent on the distance at which the investigator places the two ultrasonic dimension crystals in a given experiment, and the differences in placement can account for the baseline differences in EDD. Furthermore, the differences at baseline were not statistically significant (in any measured parameter). Finally, we tracked changes within each group over time to account for possible minor differences in baseline means.

In summary, this study demonstrates that systemic administration Gd has varying effects on contractile dysfunction of stunned myocardium, depending on the time of administration. The data indicate that preischemic administration is optimal and thus suggests that gadolinium might be useful clinically in elective cardiac surgery. They also indicate that there is some benefit to administration of Gd^{3+} during ischemia, prior to reperfusion, and thus also suggest a role for this novel agent in acute coronary syndromes, where Gd^{3+} can be given prior to reperfusion. Further studies are necessary to define the mechanism underlying gadolinium's effects on stunned myocardium and to determine the effects of Gd^{3+}-enhanced cardioplegia.

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