Intracoronary Artery Deployment of a Bioabsorbable Cardiac Matrix (BCM) Alginate Device Improves Mechanics of the Infarct Region in Pigs

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Introduction

Mechanical dysfunction in the infarct region is an important determinant for the development of left ventricular (LV) remodeling after myocardial infarction (MI) (1). In-situ gelling biomaterials that modify the abnormal structure and mechanics of the infarct region have shown promise in preventing LV remodeling in animal models (2). These biomaterials provide extracellular matrix-like mechanical reinforcement and physical substrate for cells involved in angiogenesis and scar formation (3-5).

BCM is a sterile solution of 1% sodium alginate and 0.3% calcium gluconate that is injected as a 4 mL volume into the infarct-related coronary artery after restoration of flow. BCM infiltrates into the interstitium where it reacts with the abnormally high extracellular calcium following MI (6,7) to form a hydrogel that acts as a flexible scaffold reinforcing the LV wall during healing (Fig 1, 2) . BCM is resorbed and excreted in the urine after the infarct heals and is undetectable in pig tissues 3-6 months post-deployment.

BCM is in clinical development for prevention of LV remodeling after ST-elevation MI and was evaluated in a first-in-man study of moderate-to-large STEMI and demonstrated that BCM was well-tolerated without device-related adverse events, serious arrhythmias, or impairing coronary blood flow. Serial echocardiographic studies showed preservation of ejection fraction and LV volume at 6 mo post-STEMI (8). A 300-patient clinical trial of BCM has completed enrollment (ClinTrials.gov NCT01226563).

Figure 1. Crosslinking of alginate by calcium ions producing hydrogel

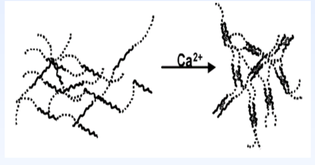
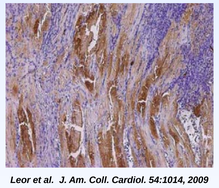


Figure 2. Photomicrograph of pig heart 2 hr after intracoronary injection of biotinylated alginate solution. Peroxidase-avidin staining. 100-X magnification.



Leor et al. J. Am. Coll. Cardiol. 54:1014, 2009

Purpose

Deposition studies using a liquid chromatography-mass spectrometry assay show that alginate deposits primarily in the infarct region. A mouse model of MI with another in-situ gelling biomaterial showed improved wall motion in the infarct region (9).

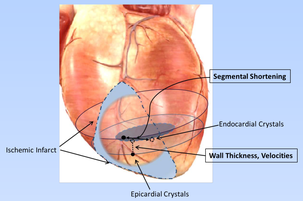
The purpose of this study was to evaluate the effect of BCM on the mechanical properties of the infarct, LV remodeling, and global cardiac function in a pig model of MI.

Methods

Surgical Procedure

Castrate male miniature Yucatan pigs, ~12 months of age, 46 – 54 kg BW, had a thoracotomy under isoflurane anesthesia to implant four 3 mm sonomicrometry crystals (Sonometrics) and a 4 mm Konigsberg pressure transducer on Study Day 0. Sonomicrometry crystals were placed on the endocardial and epicardial surfaces of the anterio-apical region of the LV to measure wall dimensions along the transmural and circumferential axes (Fig 3). Skin buttons were used to exteriorize the connecting cables for future signal recordings. A polyurethane vascular loop was placed around the LAD artery immediately distal to the first diagonal branch and constricted to produce total occlusion of blood flow for 90 min before releasing the snare allowing reperfusion of the heart (TIMI flow grade 3). A titanium bead marked the site of the occlusion.

Figure 3. Microsonography crystal placement relative to infarct



BCM Deployment

On Study Day 4, pigs were anticoagulated with heparin to ACT≥ 250 sec. A 4 French diagnostic catheter was advanced to the left main coronary bifurcation and an angiogram confirmed TIMI flow grade 3 in the LAD artery. The catheter was advanced to the titanium bead marker and BCM or saline control (4 mL) was deployed by slow bolus injection followed by a saline flush.

Hemodynamic Data

LV pressure and lead-II ECG were recorded using a PowerLab data acquisition system (AD Instruments). LV developed pressure and end diastolic pressures were determined at the peak of the pressure waveform and at the peak of R wave, respectively.

Echocardiographic Data

Cardiac dimensions were acquired and analyzed using a HP Sonos 4500 ultrasound machine. B-mode parasternal long axis view images of the LV were selected for systolic and diastolic volume determination. Images of M-mode short axis view at mid-papillary level were selected for LV diameter determination. Endocardial distance between ventricular septum and posterior wall were determined at end of systole and diastole.

Microsonography Data

The distance between microsonographic crystal pairs was measured at 250 Hz using SonoSoft software (Sonometrics).

Data Analysis

14 pigs were enrolled in the study (7/group). Treatment assignments were randomized and blinded to all study personnel. 3 pigs died before deployment (consistent with historical mortality in this animal model) resulting in analyzable data for N=5 in the BCM group and N=6 in the saline group. Data were analyzed as change in parameters after Day 4 with a mixed-effects model with repeated measures.

Results

BCM Reduces LV Remodeling and Improves Ejection Fraction

Figure 5. BCM reduces LV dilation after MI compared to saline control. LVESVI and LVEDVI steadily increased after MI in saline control pigs. BCM deployment on Day 4 significantly reduced the rise in LVESVI and LVEDVI.*

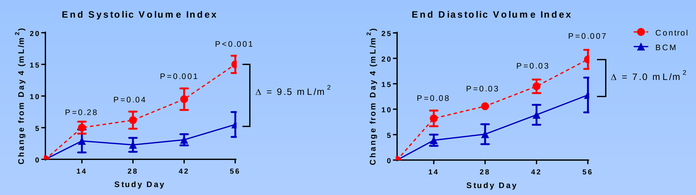
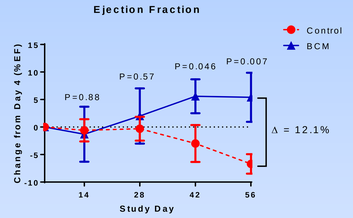


Figure 6. BCM improves ejection fraction after MI compared to saline control. Ejection Fraction steadily declined after MI in saline control pigs. BCM deployment on Day 4 significantly improved Ejection Fraction achieving a nearly normal value by 6 weeks.



BCM Improves the Mechanical Performance of the Infarct Zone

Figure 7. BCM improves the systolic function of the infarct zone compared to saline control. Circumferential segmental shortening and systolic wall thickening velocity were markedly reduced in the infarct zone of saline control pigs with no functional recovery over time. BCM increased systolic function in the infarct zone ≥ 6 weeks after deployment indicating partial recovery of function.

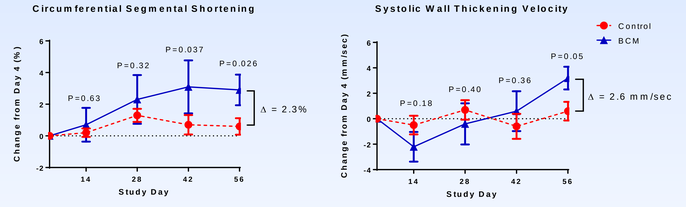
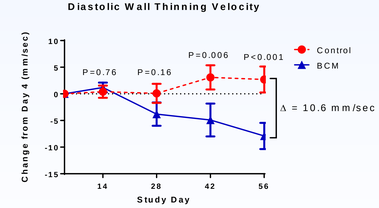


Figure 8. BCM improves the diastolic function of the infarct zone compared to saline control. Diastolic wall thinning velocity was markedly reduced in the infarct zone of saline control pigs with no functional recovery over time. BCM increased diastolic function in the infarct zone ≥ 6 weeks after deployment indicating partial recovery of function.



*** Reference Information**: Historical data for the pig model. Data are shown as mean ± S.D.

	Global Performance			Regional Mechanics (Infarct)		
	ESVI (mL/m²)	EDVI (mL/m²)	Ejection Fraction (EF) (%)	Segmental Shortening (%)	Sys. Wall Thickening Velocity (mm/sec)	Dias. Wall Thinning Velocity (mm/sec)
Baseline Day 0	17.0 ± 4.0	35.0 ± 7.3	51.3 ± 7.8	5.38 ± 5.49	9.26 ± 4.85	-22.0 ± 12.2
Day 4 Post-MI	20.2 ± 8.2	34.7 ± 9.03	43.4 ± 11.6	1.32 ± 1.34	6.93 ± 2.77	-8.45 ± 4.45

Conclusion

- **Administration of BCM 4 days after MI reduced LV dilation as measured by LVESVI and LVEDVI**
- **BCM increased ejection fraction after MI by +6% relative to immediately after MI and by +12% compared to saline control. At end-of-study, EF in BCM treated pigs was not significantly lower than the pre-MI level**
- **BCM increased segmental shortening % and systolic wall thickening velocity in the infarct zone relative to the depressed levels observed after MI and the low levels that persisted in saline control animals**
- **BCM increased the velocity of diastolic wall thinning in the infarct zone compared to both the depressed level after MI or the persistently impaired level in saline control animals**
- **BCM improved contractile performance of surviving myocardium in the infarct zone**
- **BCM was well tolerated when administered by intracoronary artery injection as a 4 mL volume after MI**

➢ **This study demonstrates that administration of an in-situ gelling alginate solution by intracoronary injection after MI results in reduced ventricular remodeling, improved global cardiac performance, and the partial restoration of contractility to the infarct zone**

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