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Dermal Filler Injection: A Novel Approach for Limiting Infarct Expansion

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Abstract

Background—Early infarct expansion after coronary occlusion compromises contractile function in perfused myocardial regions and promotes adverse long-term left ventricular (LV) remodeling. We hypothesized that injection of a tissue-expanding dermal filler material into a myocardial infarction (MI) would attenuate infarct expansion and limit LV remodeling.

Methods—Fifteen sheep were subjected to an anteroapical MI involving approximately 20% of the LV followed by the injection of 1.3 mL of a calcium hydroxyapatite-based dermal filler into the infarct. Real-time three-dimensional echocardiography was performed at baseline, 30 minutes after MI, and 15 minutes after injection to assess infarct expansion. Sixteen additional sheep were subjected to the same infarction and followed echocardiographically and hemodynamically for 4 weeks after MI to assess chronic remodeling. Eight animals had injection with dermal filler as described above immediately after MI, and 8 animals were injected with an equal amount of saline solution.

Results—All animals exhibited infarct expansion soon after coronary occlusion. The regional ejection fraction of the apex became negative after infarction, consistent with systolic dyskinesia. Injection of the dermal filler converted the apical wall motion from dyskinetic to akinetic and resulted immediately in significant decreases in global, regional, and segmental LV volumes. Chronically, relative to saline control, dermal filler injection significantly reduced LV end-systolic volume (62.2 ± 3.6 mL versus 44.5 ± 3.9 mL; $p < 0.05$) and improved global ejection fraction (0.295 ± 0.016 versus 0.373 ± 0.017 ; $p < 0.05$) at 4 weeks after infarction.

Conclusions—Injection of an acellular dermal filler into an MI immediately after coronary occlusion reduces early infarct expansion and limits chronic LV remodeling.

Left ventricular (LV) remodeling caused by a myocardial infarction (MI) is now responsible for almost 70% of 5 million cases of heart failure in the United States [1]. Early infarct expansion, or stretching, has been associated with adverse remodeling and a poor long-term prognosis [2–4]. In previous experimental studies using sonomicrometry [5], echocardiography [6,7], and magnetic resonance imaging [8–10], infarct expansion has been shown to result in stretching and decreased contractile function in the adjacent normally perfused borderzone myocardium. Additionally, although the perfused but hypocontractile myocardium is initially limited to the region immediately adjacent to the infarct, the process

extends with time to involve myocardium progressively more remote from the infarcted region [5,11].

We have demonstrated that ventricular restraint early after MI limits long-term global ventricular remodeling in animal infarction models [10,12–17]. Although these studies have established the prevention of early infarct expansion as a potentially important therapeutic goal, it is unlikely that the surgical placement of restraining devices early after MI will gain widespread acceptance and application. We hypothesized that a similar therapeutic benefit could be achieved by less invasive means. Therefore, as an initial step, we tested the hypothesis that intramyocardial injection of an acellular dermal filler material currently available for cosmetic facial procedures can reduce infarct expansion, limit global remodeling, and improve contractile function within nonischemic territories when injected early after MI. The material used in this study is a viscous suspension that could potentially be delivered by existing percutaneous catheter-based technologies [18].

Material and Methods

Biocompatible Dermal Filler

Radiesse (Bioform Medical Inc, San Mateo, CA) is a viscous (gel-like consistency) biocompatible dermal and soft tissue filler of calcium hydroxyapatite microspheres suspended in an aqueous gel carrier of water, glycerin, and carboxymethylcellulose. Once injected, fibroblasts grow on and around the microspheres, replacing the carrier over time [19]. Radiesse has been studied in diverse applications including radiopaque tumor marking, bladder neck augmentation, vocal cord injection, and cosmetic facial-volume augmentation [20–24].

Assessment of Early Infarct Expansion

SURGICAL PROTOCOL—The study protocol was reviewed and approved by the University of Pennsylvania School of Medicine Institutional Animal Care and Use Committee. In compliance with guidelines for humane care (National Institutes of Health Publication No. 85-23, revised 1996), 15 adult male sheep (35–40 kg) were anesthetized; the electrocardiogram, arterial blood pressure, LV pressure, and pulmonary artery pressure were monitored throughout the procedure. A left thoracotomy was performed, and baseline echocardiographic data were acquired. Suture ligatures were placed around the left anterior descending artery and its second diagonal branch 40% of the distance from the apex to the base of the heart. Occlusion of these arteries at these locations reproducibly results in a moderately sized infarction involving slightly more than 20% of the LV mass at the anteroapex [25]. Echocardiographic image acquisition was then repeated 30 minutes after infarction.

Forty-five minutes after infarction, 1.3 mL of Radiesse was injected at 20 uniformly spaced points within the ischemic territory, in each case to a depth of approximately 2 mm (Fig 1). Echocardiographic image acquisition was again repeated 15 minutes after injection.

ECHOCARDIOGRAPHIC PROTOCOL—Transapical epicardial real-time three-dimensional echocardiography was performed through a left thoracotomy immediately before MI, 30 minutes after MI, and 15 minutes after Radiesse injection in all subjects. In each case, electrocardiogram-gated full-volume images were acquired by a single, experienced operator using a Sonos 7500 (Philips Medical Systems, Andover, MA) platform equipped with a 2- to 4-MHz phased-array probe and an X4 matrix-array handheld transducer. Each full-volume data set was exported to a dedicated workstation (Dell Optiplex GX 270, Dell Inc, Round Rock, TX) for image manipulation and analysis.

IMAGE ANALYSIS—Image analysis was performed using QLab 3D Advanced Quantification Software (Philips Medical Systems, Andover, MA). For each data set, LV endocardial contours were manually traced in both end-diastolic and end-systolic frames. The endocardial contours of the remaining frames were traced in sequence by means of automated contour detection. The resulting four-dimensional LV model was then automatically segmented in accordance with the American Society of Echocardiography 17-segment model (Fig 2). The global and segmental volume-time curves were then exported as Excel CSV (Microsoft Corp, Redmond, WA) files for further analysis.

DATA ANALYSIS—Global end-diastolic and end-systolic volumes (EDV, ESV), which were defined as the maximum and minimum LV cavity volumes, were extracted from the global volume-time curve for each data set at each observation interval. Global ejection fraction (EF) was defined as $[(EDV - ESV) / EDV]$.

For each data set, the cardiac cycle was normalized to a length of 800 ms (systole = 500 ms, diastole = 300 ms), where end-diastole and end-systole were defined as the time points corresponding to the maximum and minimum global LV volumes, respectively. A shape-preserving interpolant was then fit to the time-normalized global time-volume curve and to each of the 17 time-normalized segmental volume-time curves within a given data set, after which interpolated volumes were extracted at 1-ms intervals from the global curve and from each segmental curve. For each data set, interpolated volumes from segments 1 through 6 were merged into a single basal regional volume-time curve. Interpolated volumes from segments 7 through 12 were merged into a single midventricular regional volume-time curve, whereas those from segments 13 through 17 were merged into a single apical regional volume-time curve. Basal, midventricular, and apical regional EDV, ESV, and EF were then calculated for each data set from these regional volume-time curves. Fifteen subject hybrid volume-time curves were then constructed for the LV cavity and for each of the three defined LV regions at baseline, after infarction, and after injection.

To clearly characterize the effect of Radiesse injection on infarct expansion, EDV, ESV, and EF were also calculated for each of the five segments comprising the apical region—apical anterior (segment 13), apical septal (segment 14), apical inferior (segment 15), apical lateral (segment 16), and the apical cap (segment 17). In all animals segment 17 was contained entirely within the infarct whereas the other segments (13–16) that contributed to the apical region contained both infarcted and perfused myocardium to variable degrees. Fifteen subject hybrid volume-time curves were then constructed for each of the five apical segments at baseline, after infarction, and after injection.

Statistical comparison among individual values at baseline, 30 minutes after infarction, and 15 minutes after Radiesse injection were made with a Student's *t* test for paired observations. All statistical analysis was performed using SPSS (Statistical Package for the Social Sciences, SPSS Inc, Chicago, Ill). The level of significance selected for all variables was $p < 0.05$. Probability values were computed with reference to baseline values after infarction and with reference to postinfarction values after injection. All data are reported as mean $\pm$ standard error of the mean.

Assessment of Late Left Ventricular Remodeling

A separate cohort of 16 sheep was used to assess the effect of Radiesse injection on longer-term LV remodeling. All animals were subjected to the anteroapical infarction described above. In 8 animals 1.3 mL of Radiesse was injected into the infarct region as described above 1 hour after infarction. Eight additional animals were injected with 1.3 mL of physiologic saline solution and acted as a control group. Three-dimensional echocardiography was performed before infarction, 1 hour after infarction (just before

injection), 1 hour after injection, and again at 4 weeks after infarction. Global LV end-diastolic and end-systolic volumes as well as EF were measured to assess the extent of LV remodeling. A pulmonary artery catheter was placed to allow for the measurement of cardiac output by means of thermodilution as well as central venous pressure. A high-fidelity pressure transducer was also placed in the LV to assess LV end-diastolic pressure. Hemodynamic data were recorded immediately before the echocardiographic studies.

Animals were sacrificed after the 4-week follow-up data was obtained. The infarct thickness was measured with a digital micrometer. The infarct tissue was fixed and stained with Mason trichrome.

STATISTICS—Measurements of long-term remodeling and hemodynamic function are reported as the mean $\pm$ standard error of the mean. Analysis of variance was used for all comparisons between groups, and repeated measures analysis of variance was used for all comparisons within groups. Individual post-hoc comparisons were performed using the Tukey HSD test. All analyses were completed using SPSS Version 11.0 (SPSS, Inc, Chicago, IL). Statistically significant differences were established at $p < 0.05$.

Results

Assessment of Early Infarct Expansion

GLOBAL REMODELING—Global EDV and ESV increased from 47.1 ± 3.0 mL and 23.7 ± 1.6 mL at baseline to 64.8 ± 3.0 mL ($p < 0.001$) and 39.9 ± 1.8 mL ($p < 0.001$) after infarction and then decreased to 58.6 ± 2.8 mL ($p < 0.001$, relative to post-MI) and 33.4 ± 1.7 mL ($p < 0.001$, relative to post-MI) after injection (Fig 3A). Ejection fraction decreased from 0.498 ± 0.015 at baseline to 0.382 ± 0.011 after infarction ($p < 0.001$) and then increased to 0.427 ± 0.018 after injection ($p \pm 0.05$, relative to post-MI; Fig 3B).

REGIONAL REMODELING—Apical regional EDV and ESV increased from 8.5 ± 0.6 mL and 3.6 ± 0.3 mL at baseline to 12.4 ± 0.6 mL ($p < 0.001$) and 12.5 ± 0.5 mL ($p < 0.001$) after MI and then decreased to 10.6 ± 0.5 mL ($p < 0.05$) and 9.9 ± 0.5 mL ($p < 0.001$) after injection. Apical regional EF decreased from 0.573 ± 0.031 to -0.028 ± 0.042 ($p < 0.001$) and then increased to 0.053 ± 0.043 ($p = 0.12$) after injection.

Midventricular EDV and ESV increased from 16.6 ± 1.1 mL and 7.0 ± 0.6 mL at baseline to 22.9 ± 1.4 mL ($p < 0.001$) and 11.8 ± 0.8 mL ($p < 0.001$) after MI and then decreased to 21.8 ± 1.2 mL ($p > 0.334$) and 10.1 ± 0.7 mL ($p < 0.05$) after injection, whereas midventricular EF decreased from 0.585 ± 0.020 to 0.471 ± 0.040 ($p < 0.05$) and then increased to 0.537 ± 0.022 ($p = 0.11$) after injection.

Basal EDV and ESV increased from 21.5 ± 1.3 mL and 11.8 ± 0.7 mL at baseline to 27.0 ± 1.7 mL ($p < 0.001$) and 14.7 ± 0.9 mL ($p < 0.001$) after MI and then decreased to 25.5 ± 1.3 mL ($p > 0.206$) and 12.8 ± 0.9 mL ($p < 0.05$) after injection, whereas basal EF increased from 0.439 ± 0.026 to 0.447 ± 0.027 ($p > 0.06$) and then to 0.497 ± 0.027 ($p < 0.05$). These volume and EF data are summarized in Figure 4.

APICAL SEGMENTAL REMODELING—Apical anterior EDV and ESV increased from 1.6 ± 0.1 mL and 0.5 ± 0.1 mL at baseline to 2.2 ± 0.2 mL ($p < 0.05$) and 1.8 ± 0.2 mL ($p < 0.001$) after MI and then decreased to 1.9 ± 0.1 mL ($p = 0.14$) and 1.5 ± 0.1 mL ($p = 0.13$) after injection, whereas EF decreased from 0.631 ± 0.040 to 0.028 ± 0.193 ($p < 0.05$) and then increased to 0.202 ± 0.049 ($p = 0.37$). Apical septal EDV and ESV increased from 1.7 ± 0.1 mL and 0.8 ± 0.1 mL at baseline to 2.3 ± 0.2 mL ($p < 0.05$) and 2.3 ± 0.2 mL ($p < 0.001$) after MI and then decreased to 2.2 ± 0.1 mL ($p = 0.56$) and 2.0 ± 0.1 mL ($p = 0.11$)

after injection, whereas EF decreased from 0.557 ± 0.031 to -0.110 ± 0.134 ($p < 0.001$) and then increased to 0.035 ± 0.062 ($p = 0.30$). Apical inferior EDV and ESV increased from 1.8 ± 0.1 mL and 0.7 ± 0.1 mL at baseline to 2.7 ± 0.2 mL ($p < 0.05$) and 2.6 ± 0.1 mL ($p < 0.001$) after MI and then decreased to 2.2 ± 0.2 mL ($p < 0.05$) and 1.9 ± 0.1 mL ($p < 0.05$) after injection, whereas EF decreased from 0.593 ± 0.051 to -0.046 ± 0.084 ($p < 0.001$) and then increased to 0.058 ± 0.076 ($p = 0.21$). Apical lateral EDV and ESV increased from 1.3 ± 0.2 mL and 0.5 ± 0.1 mL at baseline to 2.2 ± 0.3 mL ($p < 0.05$) and 2.2 ± 0.1 mL ($p < 0.001$) after MI and then decreased to 1.7 ± 0.1 mL ($p = 0.07$) and 1.6 ± 0.2 mL ($p < 0.001$) after injection, whereas EF decreased from 0.599 ± 0.060 to -0.158 ± 0.157 ($p < 0.001$) and then increased to 0.070 ± 0.088 ($p = 0.12$). Apical cap (segment 17) EDV and ESV increased from 2.1 ± 0.2 mL and 1.1 ± 0.1 mL at baseline to 3.0 ± 0.2 mL ($p < 0.001$) and 3.6 ± 0.2 mL ($p < 0.001$) after MI and then decreased to 2.7 ± 0.1 mL ($p < 0.08$) and 2.8 ± 0.1 mL ($p < 0.001$) after Radiesse injection, whereas EF decreased from 0.465 ± 0.047 to -0.608 ± 0.488 ($p < 0.05$) and then increased to -0.092 ± 0.048 ($p = 0.31$). These volume and EF data are summarized in Figure 5.

APICAL SEGMENTAL VOLUME-TIME PLOTS—Each of the five apical segmental volume-time curves (Fig 6) is plotted for each observation interval on common axes. All volumes are plotted as the mean $\pm$ standard error of the mean for the 15-animal cohort. Regional volumes increased throughout the cardiac cycle for each of the five apical segments after infarction; paradoxical systolic bulging was most pronounced within the apical cap segment. Segmental volumes decreased throughout the cardiac cycle for each of the five apical segments after injection. Additionally, paradoxical systolic bulging was greatly reduced within the apical cap segment after injection, indicating a transition from apical dyskinesia to akinesia.

Assessment of Late Remodeling

GLOBAL REMODELING—In the control group, global LV ESV increased from 23.5 ± 2.2 mL at baseline to 60.7 ± 3.6 mL 4 weeks after infarction. In the Radiesse-treated group, ESV increased from 23.6 ± 1.6 mL at baseline to 47.0 ± 3.9 mL 4 weeks after infarction ($p < 0.05$ versus control). Global LV EDV increased from 48.1 ± 3.7 mL at baseline to 85.8 ± 3.7 mL 4 weeks after infarction in the control group. In the Radiesse-treated group, LV EDV increased from 47.1 ± 3.0 mL at baseline to 74.9 ± 2.9 mL 4 weeks after infarction ($p = 0.05$ versus control). Ejection fraction 4 weeks after MI in the Radiesse-treated group (0.373 ± 0.027) was significantly higher than in the control group (0.295 ± 0.016 ; $p = 0.05$). Remodeling and hemodynamic data are presented in Table 1.

POSTMORTEM MEASUREMENTS—Infarct thickness in Radiesse-treated animals was significantly greater than in control animals (4.5 ± 0.2 mm versus 2.7 ± 0.3 mm; $p = 0.001$). Histologically the untreated infarcts demonstrated acellular collagenous scar formation. Radiesse-treated infarcts contained hydroxyapatite microspheres surrounded by a dense cellular infiltrate. The increased thickness of the treated infarcts seemed to be related to the hydroxyapatite microspheres and associated cellular response as well as to an increase in collagen production within the scar (Fig 7).

Comment

All animals in this study were subjected to a moderately sized transmural anteroapical MI that resulted in immediate expansion of the infarct region, global LV dilatation, and impaired global LV function. A regional analysis of remodeling using real-time three-dimensional echocardiography demonstrated that all regions (apical, midventricular, and basilar) contributed to the global increase in LV volume early after MI. The regional EF at

the LV apex became highly negative immediately after infarction, indicating systolic dyskinesia. The EF of the normally perfused midventricular region was also significantly decreased relative to baseline, whereas the basilar regional EF remained unchanged after infarction. These early global and regional responses to MI are similar to those that we have previously documented with sonomicrometry and two-dimensional echocardiography in this infarct model [5].

Injection of 1.3 mL of Radiesse immediately stabilized the infarcted LV territory, effectively converted apical dyskinesia to apical akinesia, and resulted in significant decreases in global, regional, and segmental LV volumes. Injection of the filler material was also associated with a significant improvement in global EF. It is important to note that the observed improvement in global EF was attributable to improved regional EF in both the midventricular and basilar portions of the ventricle as well as attenuation of apical dyskinesia.

The longer-term arm of this experiment demonstrated that early limitation of infarct expansion by Radiesse injection significantly attenuated LV remodeling at 4 weeks after MI and improved global function when compared with saline-treated control animals. These beneficial effects on remodeling likely resulted from thickening or stiffening of the infarct, which acted to normalize regional myocardial stress distribution both in the infarcted and normally perfused regions of the LV. Increased stress in the normally perfused border zone myocardium has been proposed as a likely mechanism for the myopathic process that is inherent to the postinfarction remodeling process [5,11].

Our group has studied the impact of early postinfarction LV restraint on subsequent LV remodeling for nearly a decade [13]. We have extensively explored the use of surgical meshes of varying sizes and mechanical properties to effect this therapeutic goal [10,12–14]. Most recently we have reported the ability of the CorCap Cardiac Support Device (Acorn Cardiovascular, St. Paul, MN) to limit early infarct expansion [10,26,27]. These experiments have consistently demonstrated that mechanical restraint applied early after MI preserves LV function and substantially attenuates long-term LV remodeling. Although our previous work with external restraining devices has been encouraging, the clinical utility of this approach seems limited given the requirement for early post-MI general anesthesia and thoracic surgery. This study represents our initial effort to develop a technique for attenuating postinfarction remodeling that may be implemented by means of existing catheter-based technology.

Preclinical studies reporting dramatic effects of gene therapy, growth factor administration, and cell therapy in the context of ischemic heart disease have stimulated the rapid development of sophisticated catheter-based delivery systems [18]. In fact, the development of these percutaneous technologies has outpaced the refinement and regulatory approval of most, if not all, “biologic” therapies for heart disease. It is likely that these same catheter technologies could be applied to the transendocardial delivery of acellular, biologically inert materials designed primarily to affect regional mechanical (not biologic) changes within the damaged heart early after MI.

The number of patients who could benefit from this type of intervention is potentially quite large. Although reperfusion therapy for acute MI is likely the best method to limit infarct expansion [28,29], only about 50% to 60% of the 1.1 million MIs that occur annually in the United States receive this treatment [30] and it is ineffective in restoring microvascular perfusion in nearly one third [31,32] of patients. A catheter-based technique that could effectively limit infarct expansion early after MI would be beneficial to the large number of patients who are not offered or do not respond to reperfusion therapy.

The current study demonstrates the efficacy of a clinically available, acellular dermal filler in limiting infarct expansion when injected directly into the infarct region immediately after MI. Although these early results are encouraging, the durability of this approach and its effect on long-term remodeling both remain to be demonstrated. Furthermore, both optimal dosing and the delivery technique require further refinement. These caveats notwithstanding, it seems likely that a material can be engineered with the optimal mechanical, rheologic, and degradation variables to provide long-term protection from prolonged infarct expansion and associated adverse LV remodeling.

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Fig 1. Sheep heart as seen through a left thoracotomy. (A) Immediately after coronary ligation. Note the discolored apical region in the area of the infarct. (B) Immediately after dermal filler injection.

Fig 2.
American Society of Echocardiography 17-segment left ventricle model.

Fig 3.

Left ventricular global end-diastolic volumes (EDV) and end-systolic volumes (ESV) at baseline (medium gray bars), 30 minutes after infarction (Post-MI; dark gray bars), and 15 minutes after injection (Post-Injection; light gray bars) are plotted on common axes (A). The corresponding ejection fractions are illustrated in B. Data are presented as mean $\pm$ standard error of the mean. * $p < 0.05$ with respect to the corresponding value at baseline; † $p < 0.05$ with respect to the corresponding value after infarction.

Fig 4.

Regional end-diastolic volume (EDV; A), end-systolic volume (ESV; B), and ejection fraction (C) for each of the three left ventricular regions are presented at baseline (medium gray bars), 30 minutes after infarction (Post-MI; dark gray bars), and 15 minutes after injection (Post-Injection; light gray bars). Data are presented as mean $\pm$ standard error of the mean. * $p < 0.05$ with respect to the corresponding value at baseline; † $p < 0.05$ with respect to the corresponding value after infarction.

Fig 5.

Apical segmental end-diastolic volume (EDV; A), end-systolic volume (ESV; B), and ejection fraction (C) for each of the five left ventricular segments comprising the apical region are presented at baseline (medium gray bars), 30 minutes after infarction (Post-MI; dark gray bars), and 15 minutes after Radiesse injection (Post-Injection; light gray bars). Data are presented as mean $\pm$ standard error of the mean. * $p < 0.05$ with respect to the corresponding value at baseline; † $p < 0.05$ with respect to the corresponding value after infarction.

Fig 6.

Apical anterior (A), apical septal (B), apical inferior (C), apical lateral (D), and apical cap (E) segmental volumes have been plotted as functions of normalized time at baseline (black lines), 30 minutes after infarction (Post-MI; red lines), and 15 minutes after Radiesse injection (Post-Injection; blue lines) for the 15-subject cohort on common axes. Data are presented as mean (solid line) $\pm$ standard error of the mean (dotted lines). End-diastole occurs at 0 ms and 800 ms, whereas end-systole occurs at 500 ms. Note in E that the apical cap segment is profoundly dyskinetic after infarction but becomes virtually akinetic after injection.

Fig 7. Mason trichrome stain of infarct tissue at $\times 2$ and $\times 20$ from untreated (A, C) 4-week-old ovine infarcts and infarcts of the same age injected with 1.3 mL of Radiesse (B, D). Untreated infarcts are thin and relatively acellular with occasional islands of residual vacuolated myocytes. Radiesse-treated infarcts are thicker with more extensive collagen deposition. The calcium hydroxyapatite microspheres are apparent. The carrier agent has been replaced by a dense cellular infiltrate.

Table 1

Chronic Remodeling and Hemodynamic Data

Variable	Pre-MI			Post-MI			After Injection			4 Weeks Post-MI		
	Control	Radlesse		Control	Radlesse		Control	Radlesse		Control	Radlesse	
L VESV (mL)	23.5 ± 2.2	23.7 ± 1.6		38.9 ± 2.4 ^a	39.9 ± 1.8 ^a		39.3 ± 2.6 ^a	33.4 ± 1.7 ^{a,b}		61.2 ± 3.6 ^a	44.5 ± 3.9 ^{a,b}	
L VEDV (mL)	48.1 ± 3.7	47.1 ± 3.0		66.1 ± 3.4 ^a	64.8 ± 3.0 ^a		65.9 ± 3.5 ^a	58.6 ± 2.8 ^a		85.7 ± 3.7 ^a	70.7 ± 3.9 ^a	
Ejection fraction	0.517 ± 0.017	0.498 ± 0.015		0.410 ± 0.019 ^a	0.382 ± 0.011 ^a		0.403 ± 0.019 ^a	0.427 ± 0.018 ^a		0.295 ± 0.016 ^a	0.373 ± 0.017 ^{a,b}	
Cardiac output (L/min)	4.6 ± 0.2	4.9 ± 0.4		2.7 ± 0.5 ^a	2.6 ± 0.5 ^a		2.6 ± 0.4 ^a	3.1 ± 0.2 ^a		2.8 ± 0.3 ^a	3.9 ± 0.3 ^{a,b}	
L VEDP (mm Hg)	5 ± 2	4 ± 1.5		19 ± 6	20 ± 7		19 ± 6	16 ± 5		12 ± 4	9 ± 3	
CVP (mm Hg)	13 ± 3	12 ± 2		14 ± 2	13 ± 4		15 ± 3	12 ± 2		11 ± 2	10 ± 1	

^a $p < 0.05$ versus Pre-MI.

^b $p < 0.05$ versus Control.

CVP = central venous pressure; LVEDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; MI = myocardial infarction.