Clinical Investigation

Association between High Endocardial Unipolar Voltage and Improved Left Ventricular Function

in Patients with Ischemic Cardiomyopathy

Ki Park, MD
Dejian Lai, PhD
Eileen M. Handberg, PhD
Lem Moyé, MD, PhD
Emerson C. Perin, MD
Carl J. Pepine, MD
R. David Anderson, MD
for the Cardiovascular Cell Therapy Research Network (CCTRN)

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From: *Division of Cardiovascular Medicine (Drs. Anderson, Handberg, Park, and Pepine), Department of Medicine, University of Florida College of Medicine, Gainesville, Florida 32610; Coordinating Center for Clinical Trials (Drs. Lai and Moyé), School of Public Health, University of Texas Health Science Center at Houston; and Stem Cell Center (Dr. Perin), Texas Heart Institute; Houston, Texas 77030*

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Address for reprints: *Lem Moyé, MD, PhD, 1200 Pressler, E-1009, Houston, TX 77030*

E-mail: *lemmoye@msn.com*

We know that endocardial mapping reports left ventricular electrical activity (voltage) and that these data can predict outcomes in patients undergoing traditional revascularization. Because the mapping data from experimental models have also been linked with myocardial viability, we hypothesized an association between increased unipolar voltage in patients undergoing intramyocardial injections and their subsequent improvement in left ventricular performance.

For this exploratory analysis, we evaluated 86 patients with left ventricular dysfunction, heart-failure symptoms, possible angina, and no revascularization options, who were undergoing endocardial mapping. Fifty-seven patients received bone marrow mononuclear cell (BMC) injections and 29 patients received cell-free injections of a placebo.

The average mapping site voltage was 9.7 ± 2 mV, and sites with voltage of ≥6.9 mV were engaged by needle and injected (with BMC or placebo). For all patients, at 6 months, left ventricular ejection fraction (LVEF) improved, and after covariate adjustment this improvement was best predicted by injection-site voltage. For every 2-mV increase in baseline voltage, we detected a 1.3 increase in absolute LVEF units for all patients (P=0.038). Multiple linear regression analyses confirmed that voltage and the CD34+ count present in bone marrow (but not treatment assignment) were associated with improved LVEF (P=0.03 and P=0.014, respectively).

In an exploratory analysis, higher endocardial voltage and bone marrow CD34+ levels were associated with improved left ventricular function among ischemic cardiomyopathy patients. Intramyocardial needle injections, possibly through stimulation of angiogenesis, might serve as a future therapy in patients with reduced left ventricular function and warrants investigation. ***(Tex Heart Inst J 2016;43(4):291-6)***

Bone marrow cell therapy for chronic ischemic heart failure has resulted in some evidence of left ventricular (LV) functional improvement upon meta-analysis. However, the magnitude of this effect is small and might not, in application, improve patient outcomes.[1,2] Consistent with this notion, we found—in the Cardiovascular Cell Therapy Research Network's (CCTRN's) trial of First Mononuclear Cells injected in the United States (FOCUS)[3]—no detectable improvement in maximal oxygen consumption (VO_2max) or New York Heart Association (NYHA) functional class, despite a 2.7% increase in LV ejection fraction (LVEF) (difference between bone marrow mononuclear cell [BMC] and placebo groups [95% confidence interval (CI), 0.3–5.1, P=0.03]). Although there is promise, it is clear that a better un-

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derstanding of the approach to cell-based treatments—one that includes patient characteristics, cell delivery, and functional outcomes—is needed to determine if these effects can be sufficiently augmented to be of real benefit to the patient.

Upon analysis, multiple factors might serve to explain the mixed responses that we observed in our data on these clinical trials, including the heterogeneity of the myocardial treatment sites, the method of delivery, the heterogeneity of the BMC product delivered, and other patient characteristics. Clinical trials and specific protocols are designed to control for many of these factors. This includes attempts to reduce variability in patient cohorts by strict selection criteria, rigid control of cell harvesting and processing, and detailed analysis of the BMC cell composition and functions.

However, no one has yet evaluated in detail the characteristics of myocardial delivery sites that have the potential to provide optimal recovery of functioning myocardium. Identification of the delivery-site characteristics associated with these improved outcomes might lead to a more personalized approach that would strengthen the therapeutic effect of delivered cells. Moreover, this information would certainly enrich our understanding of the mechanisms involved in myocardial regeneration, repair, or both.

Direct electromechanical mapping (EMM), developed for the detection of left ventricular endocardial functional viability, has been validated in multiple experimental models. This technique offers a patient-specific approach to the detection of myocardial sites capable of recovery, for the express purpose of delivering therapy. Direct EMM provides a direct evaluation of LV function that differs from traditional techniques, which merely estimate myocardial perfusion, wall-thickening, or motion. It has been used to identify areas of mechanical and electrical LV myocardial dysfunction, in order to help guide the intramyocardial delivery of gene- and cell-based treatments.[4] Electromechanical mapping collects electrical data (voltage) and functional data by means of linear local shortening (LLS). These data have been correlated with mechanical LV function as recorded via echocardiography.[5] In theory, EMM has the potential to provide an accurate estimate of myocardial viability, and already has been used in percutaneous coronary intervention, to evaluate viability.[6-9] In addition, voltage thresholds for differentiation between myocardial scar and normal tissue have been validated by means of magnetic resonance imaging.[10]

Although overviews of small studies[11] have associated the revascularization of viable (versus nonviable) myocardium with an improved prognosis, revascularization of viable myocardium was not associated with improved survival rates in the largest randomized trial to date.[12] Similar discrepant results have been found in large subgroups randomized in accordance with the presence of ischemia[13] or viability[14] (identified by means of perfusion imaging). Clearly, better techniques are needed for evaluating the recovery potential of damaged myocardium in patients with chronic heart failure caused by ischemic heart disease.

To this end, EMM might well be more sensitive in the identification of hibernating myocardium that has the ability to recover function over time, with the aid of medical therapy or revascularization.[15] Improvement in regional wall motion after revascularization has been associated with increased voltage and with reduced adverse cardiovascular outcomes.[6,7,15] Further, unipolar voltage by EMM has been shown to identify areas of myocardial fibrosis and possibly to help identify suitable targets for cell therapy[16] and therapeutic angiogenesis.[17] That EMM's identification of viable myocardial tissue as a target in ischemic cardiomyopathy patients can be used to maximize the effects of cell therapy is still hypothetical, however. To our knowledge, the ability of EMM findings to predict improvement in LV function, particularly in patients with ischemic cardiomyopathy and no revascularization, has not yet been investigated.

The aim of this present exploratory analysis was to determine whether EMM characteristics can accurately predict LV function over 6 months in a trial of therapeutic intramyocardial needle injections of BMCs versus placebo among patients with ischemic cardiomyopathy who were receiving guideline-recommended medical therapy. We hypothesized that patients with higher unipolar voltage (UpV) would manifest improvement in LVEF, because higher electrical potential should indicate more viable myocardium, and therefore the potential to recover contractile function.

Patients and Methods

FOCUS (the results of which were published in 2012)[3] was a phase 2 randomized, double-blinded trial that compared BMCs with placebo. The BMCs were in standard saline solution, containing 5% albumin adjusted to 100 $\times 10^6$ cells in 3 mL. The placebo group received a cell-free suspension in the same volume of saline and albumin. Both were given by intramyocardial injection to patients with ischemic cardiomyopathy, as described in detail.[3] Briefly, FOCUS enrolled symptomatic patients (NYHA class II/III or Canadian Cardiovascular Society class II–IV) with LVEF ≤0.45 who were receiving guideline-recommended medical therapy, had no revascularization options, and exhibited a perfusion defect upon single-photon-emission computed tomographic (SPECT) imaging. Demographic, functional, and EMM data were collected at baseline. Table I shows our more recent study's pertinent demographic data for this FOCUS cohort, and Table II shows our more recent study's data on baseline medical therapy by group. Patients were then randomized to re-

TABLE I. Baseline Characteristics in the 86 Patients

Variable	Value
Age (yr)	63.4 ± 10.07
Male (%)	89
UpV (mV) at injection site	9.74 ± 2
LVEF	0.34 ± 0.09
LVESV (mL)	129.39 ± 48.8
Vo_2max (mL/kg/min)	14.81 ± 4.05
Percentage reversible defect (SPECT)	19.7 ± 25.46

LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; SPECT = single-photon-emission computed tomography; UpV = unipolar voltage; Vo_2max = maximal oxygen consumption

Data are presented as mean ± SD unless otherwise stated.

TABLE II. Baseline Medical Therapy in the 2 Groups

Medication	**BMC** (n=57)	**Placebo** (n=29)	***P* Value**
ACE inhibitor	34 (60)	21 (72)	0.2438
Aldosterone antagonist	8 (14)	8 (28)	0.1268
β-blocker	53 (93)	28 (97)	0.5037

ACE = angiotensin-converting enzyme; BMC = bone marrow mononuclear cells

Data are expressed as number and percentage. P <0.05 was considered statistically significant.

ceive injections with either BMCs or a cell-free placebo, and functional data were collected again at 6 months. Although the specified co-primary outcome measures were not changed, improvement in LVEF was observed in the main FOCUS trial (2.7%, P <0.02).

Electromechanical Data Collection. We performed a retrospective analysis of a subgroup of the 92 patients from the FOCUS trial: those 86 patients had data adequate for analysis, in addition to their having undergone successful EMM, their having received intramyocardial treatment injections, and their having undergone follow-up evaluations at 6 months. To identify areas of viable myocardium, each patient had undergone EMM of the endocardial surface with the NOGA® XP Cardiovascular Mapping System (Biosense Webster, Inc.; Diamond Bar, Calif; distribution by Biologics Delivery Systems Group, Cordis Corporation; Miami Lakes, Fla; both Johnson & Johnson companies). The protocol had specified injections into areas of ischemic but viable LV myocardium of >8-mm thickness. Ischemia was evidenced by the presence of a perfusion defect on SPECT; then viability was defined as a unipolar voltage ≥6.9 mV. Of the 86 patients in our analysis, 57 had received BMC injections and the remaining 29 had received cell-free injections of placebo. Occasional deviations from injection protocol occurred when injections were followed by voltage measurements of <6.9 mV; however, these accounted for <4% of all injections.

From the EMM, we generated UpV and LLS segmental bullseye maps. Figures 1 and 2 show examples, respectively, of relatively high- and low-voltage maps. From the mapped segmental EMM data, potentially viable sites were chosen for intramyocardial needle injection, and those local UpV and LLS values were also recorded.

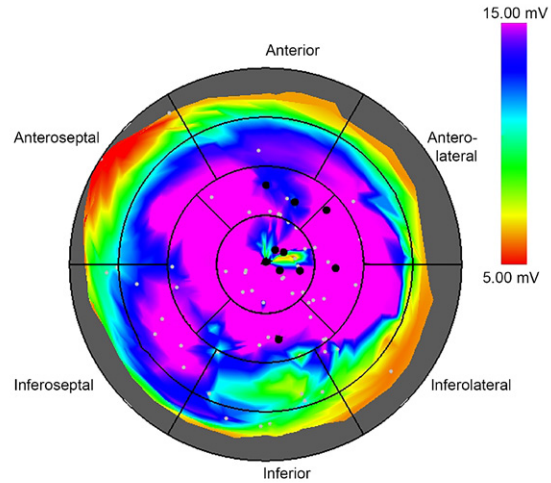

Fig. 1 *Magenta coloring on this segmental unipolar high-voltage map denotes areas of highest voltage in the left ventricle. The black dots are injection sites.*

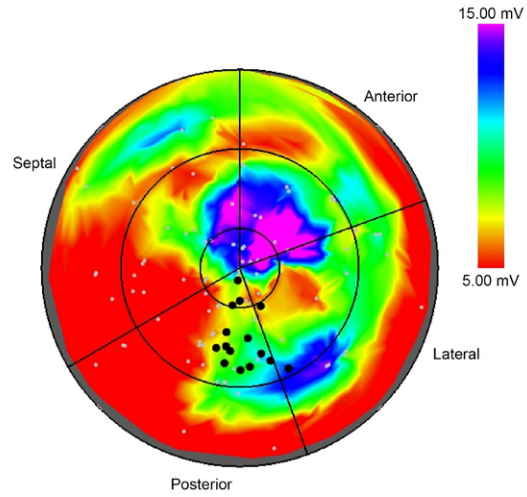

Fig. 2 *Dark orange coloring on this segmental unipolar low-voltage map denotes areas of low voltage in the left ventricle. The black dots are injection sites.*

Statistical Analysis

Pertinent demographic data were summarized as mean ± SD or as number and percentage when appropriate. Statistical analysis was performed with SAS version 9.3 (IBM Corporation; Endicott, NY). Left ventricular end-systolic volume (LVESV), percentage of reversible SPECT defect, VO_2max, and LVEF were summarized as changes from baseline to 6 months. For EMM data, we first analyzed the UpV values collected at sites of injection. We then averaged the UpV at all sites for each patient. These data were compared to the following outcomes at 6 months: change in LVESV, VO_2max, percentage of reversible SPECT defect, and LVEF. Clinical cardiovascular covariates included patients' age, cell treatment, and CD34+ and CD133+ counts. Simple linear regression modeling was used to identify significant covariates and to examine associations between outcomes and covariates. Multiple linear regression modeling was performed to evaluate clinically relevant covariates of age, treatment-site UpV, sex, percentage of reversible SPECT defect at baseline, baseline walking distance, cell treatment, and CD34+ count. *P* values <0.05 were considered statistically significant. Because these were exploratory analyses, no attempts at adjustment were made for multiple comparisons.

Results

Mean treatment-site UpV was 9.7 ± 2 mV (range, 5.5–18.6 mV). Side-by-side comparison of treatment groups and outcomes (Table III) was consistent with the overall findings of the FOCUS trial, in which BMC treatment was not associated with these same outcomes.[3] Table IV shows results of simple linear regression modeling for various outcomes, with only injection-site UpV as a predictor at 6 months. The UpV was not significantly associated with changes in VO_2max, LVESV, and percentage of reversible defect by SPECT. However, increases in LVEF and LVESV (at baseline and at 6 mo) were significantly associated with UpV. At baseline, higher voltages correlated to improvement in LVEF in such a manner that for every 2-mV increase in UpV, we observed a 1.3 increase in absolute LVEF units from baseline to 6 months (P=0.038) (Table IV). These associations remained significant after adjustments for age, for CD34+ and CD133+ counts, as well as for treatment assignment correlating with changes in LVEF (P=0.036; 95% CI, 0.04–1.2); in LVESV at baseline (P=0.0056; 95% CI, –13 to –2.31); and in LVESV final (P=0.0038; 95% CI, –13.11 to –2.63). By multiple linear regression modeling (including age, UpV, sex, percentage of reversible SPECT defect at baseline, baseline walking distance, and CD34+ count), UpV (P=0.03) and CD34+ count (P=0.014) remained significantly associated with improvement in LVEF. Treatment assignment was not associated with change in LVEF (P=0.503) in any analysis. Results by stratification of voltage values into tertiles also reveal the association between higher baseline UpV and change in LVEF (Fig. 3).

TABLE IV. Simple Linear Regression with Unipolar Voltage as Predictor for Stem-Cell and Placebo Patients (n=86)

Variable	Mean Change	*P* Value	95% Confidence Interval
Left ventricular ejection fraction	0.6	0.038	0.035 to 1.2
Left ventricular end-systolic volume	–0.9	0.51	–3.63 to 1.84
Maximal oxygen consumption	0.15	0.36	–0.16 to 0.46
Percentage of reversible defects	–0.28	0.82	–2.7 to 2.1
Walking distance	–10.8	0.65	–59.41 to 37.77

P <0.05 was considered statistically significant.

TABLE III. Analysis of Outcomes by Treatment Assignment

	BMC Group			Placebo Group		
Variable	Mean Change	*P* Value	95% CI	Mean Change	*P* Value	95% CI
LV ejection fraction	0.67	0.0415	(0.03 to 1.31)	0.44	0.4958	(–0.88 to 1.76)
LV end-systolic volume	–0.23	0.8791	(–3.28 to 2.82)	–0.38	0.328	(–9.43 to 3.28)
Maximal oxygen consumption	0.08	0.6413	(–0.26 to 0.41)	0.42	0.2839	(–0.37 to 1.2)
Percentage reversible defect	–1.1	0.4639	(–4.1 to 1.9)	2.37	0.3015	(–2.28 to 7.01)
Walking distance	2.82	0.9187	(–52.53 to 58.18)	–48.85	0.3604	(–157.51 to 59.81)

BMC = bone marrow mononuclear cells; CI = confidence interval; LV = left ventricular

P <0.05 was considered statistically significant

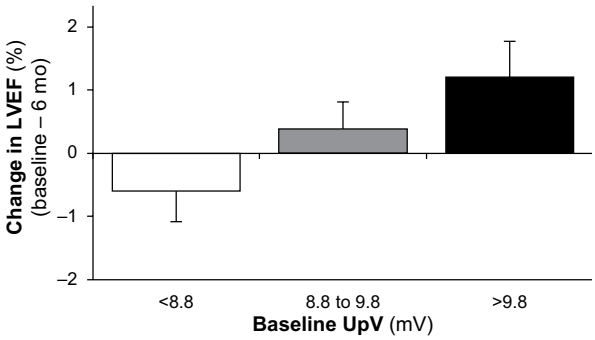

Fig. 3 *The x-axis of this graph shows the baseline unipolar voltage (UpV) stratified by tertiles, and the y-axis shows the concomitant change in left ventricular ejection fraction (LVEF) over the course of 6 months.*

Discussion

In this exploratory analysis, baseline endocardial UpV, as measured by EMM, was associated with improvement in LVEF among symptomatic patients who had ischemic cardiomyopathy and no revascularization option, but who had received intramyocardial needle injections. This association remained significant after accounting for age, CD34+/CD133+ cell counts, and treatment assignment, although it was comparatively less significant than cell count alone.

Results of our study support the suggestion that higher average endocardial voltage after intramyocardial needle injection is associated with greater increase in LVEF, regardless of whether BMCs or cell-free placebo was injected. These findings raise the possibility that the needle manipulations or the injection of placebo cell-free solution (or both) might be responsible for the LV functional improvement. In patients with preserved LVEF, comparison of EMM with perfusion defects identified by traditional perfusion imaging has shown that mean UpV potentials and LLS values were highest in myocardial segments with normal perfusion.[7] In patients with acute myocardial infarction, the EMM values of UpV and LLS both increased after intracoronary injection of autologous bone marrow mesenchymal cells.[18] Previous EMM data in patients with ischemic cardiomyopathy were limited to patients undergoing revascularization by either percutaneous or surgical coronary intervention.[6,19] However, none of our patients had recent revascularization, and after review all were determined not to have additional revascularization options. So our study is the first, to our knowledge, to find an association between baseline endocardial electrical values and outcomes in "no-revascularization-option" patients who have chronic LV dysfunction and are participating in a cell-therapy trial.

Although it is reasonable to expect that patients with higher UpV would have more potential to improve their LVEF (because the overall electrical potential of the myocardium is likely to correspond with viability), this association in our study was independent of treatment assignment. A possible explanation for this finding is that the intramyocardial injection (or the cell-free placebo solution itself) has a direct stimulatory effect. Preclinical data in the musculoskeletal rat model suggest that the degree of inflammation after needle injection alone is no different from that consequent to various injectates. This supports the idea that the needle alone might be all that is required to stimulate inflammation and perhaps to promote angiogenesis.[20] In addition, there is some evidence that direct manipulation of the myocardial surface, most notably with transmyocardial laser therapy, can lead to improvement in cases of angina,[21,22] possibly through the stimulation of angiogenesis. In a similar fashion, intramyocardial needle manipulations (for either mapping or injections) might stimulate the myocardial surface directly and thereby promote the release of stromal cell-derived factor-1[23] and the stimulation of growth factors, such as vascular endothelial growth factor and other signaling molecules.[24] These growth factors and signaling molecules could promote angiogenesis only in the more viable regions, leading to improvements in systolic function.

Study Limitations

The number of patients in this exploratory study was small. Moreover, the lack of follow-up EMM mapping rendered impossible our evaluation of changes in UpV and of the relationship of those changes to outcomes after the needle injections.

Conclusion

In this exploratory analysis, we provide the first evidence that endocardial UpV is associated with improvement in global systolic function over time, after intramyocardial needle injection in "no-revascularization-option" patients. This association was independent of treatment assignment and might be the direct effect of intramyocardial needle manipulations. Further study of the use of EMM values and stimulatory effects of direct myocardial injection warrants future investigation.

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