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Transendocardial CD34$^+$ Cell Therapy Improves Local Mechanical Dyssynchrony in Patients With Nonischemic Dilated Cardiomyopathy

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Abstract

We investigated the effects of cell therapy on local mechanical dyssynchrony (LMD) in patients with nonischemic dilated cardiomyopathy (NICM). We analyzed electromechanical data of 30 NICM patients undergoing CD34$^+$ cell transplantation. All patients underwent bone marrow stimulation; CD34$^+$ cells were collected by apheresis and injected transendocardially. At baseline and at 6 months after therapy, we performed electromechanical mapping and measured unipolar voltage (UV) and LMD at cell injection sites. LMD was defined as a temporal difference between global and segmental peak systolic displacement normalized to the average duration of the RR interval. Favorable clinical response was defined as increase in the left ventricular ejection fraction (LVEF) ≥5% between baseline and 6 months. Using paired electromechanical point-by-point analysis, we were able to identify 233 sites of CD34$^+$ cell injections in 30 patients. We found no overall differences in local UV between baseline and 6 months (10.7 ± 4.1 mV vs 10.0 ± 3.6 mV, $P = 0.42$). In contrast, LMD decreased significantly (17 ± 17% at baseline vs 13 ± 12% at 6 months, $P = 0.00007$). Favorable clinical response at 6 months was found in 19 (63%) patients (group A), and 11 (37%) patients did not respond to cell therapy (group B). At baseline, the two groups did not differ in age, gender, LVEF, or N terminal-pro brain natriuretic peptide (NT-proBNP) levels. Similarly, we found no differences in baseline UV (9.5 ± 2.9 mV in group A vs 8.6 ± 2.4 mV in group B, $P = 0.41$) or LMD at cell injection sites (17 ± 19% vs 16 ± 14%, $P = 0.64$). In contrast, at 6 months, we found higher UV in group A (10.0 ± 3.1 mV vs 7.4 ± 1.9 mV in group B, $P = 0.04$). Furthermore, when compared with group B, patients in group A displayed a significantly lower LMD (11 ± 12% vs 16 ± 10%, $P = 0.002$). Thus, it appears that favorable clinical effects of cell therapy in NICM patients may be associated with a decrease of LMD at cell injection sites.

Keywords

stem cells, mechanical dyssynchrony, dilated cardiomyopathy

Introduction

Nonischemic dilated cardiomyopathy (NICM) is a *heterogeneous disorder that* can be attributed to a complex interplay of various genetic and environmental causes[1]. Regardless of the underlying etiology, the hallmark of NICM is the development and progression of myocardial remodeling, affecting the myocardium at molecular, cellular, and tissue levels and resulting in the dilatation of all four cardiac chambers, with the left ventricle being predominantly affected[2]. One of the key consequences of myocardial remodeling in the setting of NICM is intraventricular mechanical dyssynchrony, which refers to increased temporal dispersion of regional contraction[3]. In NICM, mechanical dyssynchrony often develops due to abnormal electrical conduction in the failing left ventricle in the presence of left bundle branch block. However, mechanical dyssynchrony may also occur in the

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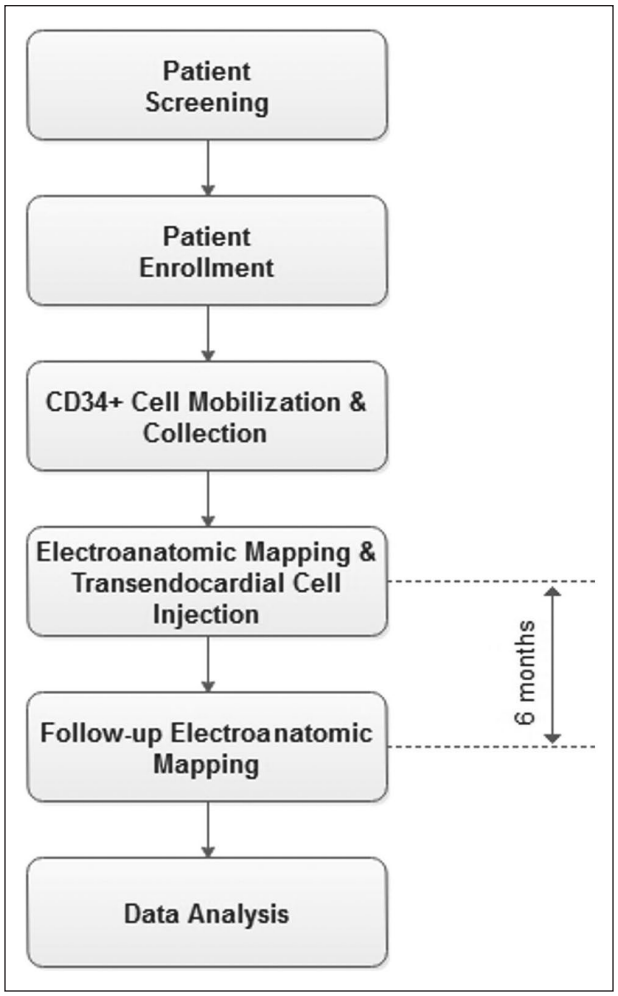


Figure 1. Flowchart of the study design.

absence of conduction system abnormalities; it may be present in up to 30% of heart failure patients with significantly impaired left ventricular systolic function and normal duration of the QRS complex[4].

Although intraventricular mechanical dyssynchrony has been shown to represent an independent predictor of adverse cardiac events in NICM patients[5], the underlying mechanisms are not yet fully understood. Current data suggest that intraventricular mechanical dyssynchrony may occur as a result of perivascular and intersitital replacement fibrosis. Studies have shown that NICM patients with higher burden of myocardial fibrosis have more pronounced intraventricular dyssynchrony and that regional variations in left ventricular interstitial fibrosis are closely related to the mechanical dyssynchrony, irrespective of the global function of the ventricle[6,7]. Currently, there are no specific pharmacological or device-based therapies available to mitigate intraventricular mechanical dyssynchrony in the absence of conduction system abnormalities in NICM patient population. Since an improvement of intraventricular mechanical dyssynchrony is likely to promote reverse remodeling of the failing myocardium, identification of these therapeutic options should be further explored.

Cell therapy represents an emerging therapeutic option in NICM patients and may be associated with improved myocardial performance, better exercise capacity, and decreased neurohumoral activation[8–13]. It is currently believed that these beneficial clinical effects are mediated through paracrine effects on the failing myocardium where cell-secreted cytokines likely act in a cytoprotective, proangiogenic, and antifibrotic manner[14]. As intraventricular mechanical dyssynchrony is likely closely related to the myocardial fibrosis, cell therapy might hypothetically reduce local mechanical dyssynchrony (LMD) through its antifibrotic effects. In accordance with this hypothesis, Yamada et al showed that in a preclinical model of dilated cardiomyopathy, intramyocardial administration of induced pluripotent stem cells was associated with reduced fibrosis and an improved synchronization of left ventricular systolic and diastolic wall motion[15]. To validate this hypothesis in a clinical setting, the aim of this study was to investigate the effects of $CD34^+$ cell therapy on LMD in patients with NICM.

Materials and Methods

Patient Population

We performed a prospective nonrandomized single-center study conducted at the Advanced Heart Failure and Transplantation Center, University Medical Center Ljubljana, Slovenia. Inclusion criteria consisted of the following: age 18–70 years, diagnosis of NICM according to the European Society of Cardiology position statement[16], optimal medical management for ≥3 months, left ventricular ejection fraction (LVEF) <40%, and New York Heart Association (NYHA) functional class III for ≥3 months before referral. Patients with acute multiorgan failure, a history of hematologic neoplasms, or inadequate response to granulocyte colony-stimulating factor (G-CSF) stimulation (defined as <80 million $CD34^+$ cells) were not considered for the participation in the study. The study was registered with Clinicaltrials.gov (NCT02248532).

Study Design

After enrolment, patients underwent bone marrow stimulation and apheresis, and cell suspension was injected transendocardially using electroanatomic mapping-guided approach. Patients were followed up for 6 months. The study design and timeline are outlined in Fig. 1. At the time of enrolment, and again at 6-month follow-up, clinical evaluation, echocardiography, and biochemical blood analysis were performed. In addition, at 6-month follow-up, electroanatomic mapping was repeated.

Study Endpoints

The *primary* endpoint was a change in LMD at the cell injection sites between baseline and 6-month follow-up. The *secondary* endpoint was a change in unipolar voltage (UV) between baseline and 6 months.

Exploratory Analysis

In an *exploratory* analysis, we sought to compare changes in LMD and UV in patients with a favorable clinical response to cell therapy (group A) and the remaining cohort (group B). Favorable clinical response to cell therapy was defined as an increase in LVEF ≥5% measured by echocardiography between baseline and 6-month follow-up[17].

Peripheral Blood Stem Cell Mobilization and Collection

All patients underwent $CD34^+$ cell mobilization and collection as previously described[18]. In short, all patients underwent stem cell mobilization by daily subcutaneous injections of G-CSF (10 μg/kg daily). On the fifth day, a peripheral blood $CD34^+$ cell was performed. Bone marrow-derived cells were collected by cytapheresis using the Amicus cell separator (Baxter Healthcare, Chicago, IL, USA). Positive immunomagnetic selection of $CD34^+$ cells was performed with the CliniMACS System (Miltenyi Biotech, Bergisch Gladbach, Germany). A total of 80 million collected $CD34^+$ cells were then concentrated to a final volume of 6-ml cell suspension.

Electroanatomic Mapping Procedure and Transendocardial $CD34^+$ Cell Delivery

After stem cell collection, all patients underwent transendocardial injection of collected $CD34^+$ cells. The procedure was performed using the Biosense NOGA system (Biosense Webster®, Diamond Bar, CA, USA). First, electroanatomic mapping of the left ventricle was performed. Points were acquired when the catheter tip was stable on the endocardium (defined as simultaneous stability of local activation time (LAT), location stability, loop stability, and cycle length stability). A map of the left ventricle was reconstructed with all endocardial regions adequately represented. For each patient, color-coded UV, local linear shortening (LLS), and their corresponding bull's-eye maps, consisting of at least 200 sampling points, were generated. The target area for cell delivery was defined as areas with UV ≥8.3 mV and LLS <6%[19]. Transendocardial delivery of cell suspension was performed with the MyoStar (Biosense Webster®) injection catheter. After acquiring a stable mapping point with the tip of the injection catheter perpendicular to the endocardial surface, the needle was advanced into the myocardium, and injections of cell suspension were performed. In the follow-up NOGA maps, any sampling points within the 3-mm radius of cell injection sites were defined as congruent points and were considered for the analysis.

LMD Evaluation

LMD was defined as a mechanical parameter describing local contraction dyssynchrony for a given segment of the left ventricle compared with global left ventricular contraction. At each stem cell injection point, it was measured as a temporal difference between global and segmental peak systolic displacement normalized to the average duration of the RR interval. Using a digital caliper, we measured the time interval in milliseconds between the peak global and peak segmental systolic displacement (Fig. 2).

Echocardiography

Echocardiography was performed at baseline and at 6-month follow-up in accordance with American Society of Echocardiography (ASE)/ European Association of Cardiovascular Imaging (EACVI) current guidelines and recommendations[20]. Using 2D echocardiography, LV end-systolic dimension (LVESD) and LV end-diastolic dimension (LVEDD) were measured in the parasternal long-axis view. LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV), and LVEF were estimated using the Simpson biplane method. All echocardiographic measurements were averaged over five cycles. Echocardiography was analyzed at the end of the follow-up by an independent investigator, blinded to the patients' clinical, biochemical, or imaging data.

Biochemical Analysis

At the time of enrolment and 6 months thereafter, we obtained venous blood sample via cubital vein for laboratory analysis. Biochemical parameters such as electrolytes, renal and liver function tests, complete blood count, and NT-proBNP serum levels were determined in each blood sample. All NT-proBNP assays were performed at a central independent laboratory, blinded to the patients' clinical data using a commercially available kit (Roche Diagnostics, Mannheim, Germany).

Statistical Methods and Analysis

Continuous variables were expressed as mean ± SD. Continuous variables were explored for normal distribution with the Shapiro–Wilk test. Differences within the baseline and follow-up values were analyzed using *t* test for continuous variables with correction for unequal variance when appropriate and with χ^2 or Fisher exact test when appropriate. Differences between responders (group A) and nonresponders (group B) to cell therapy were analyzed with repeated measures one-way analysis of variance (ANOVA). A value of $P < 0.05$ was considered significant. All statistical analyses were performed with IBM SPSS Statistics® software (version 26.0, Armonk, NY, USA).

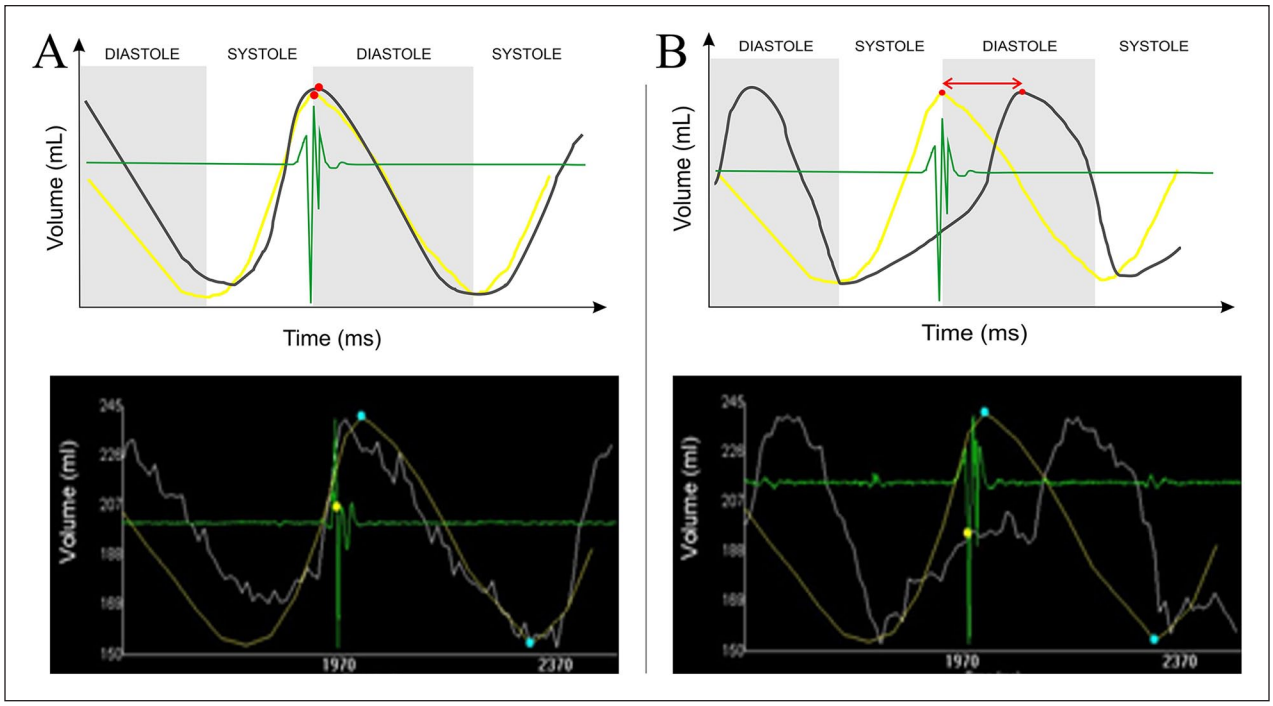


Figure 2. Local mechanical dyssynchrony measurement. The figure represents electromechanical tracings measured at a specific mapping point (lower panel), and their schematic representation (upper panel). Yellow line depicts global ventricular movement and black line (upper panels) or white line (bottom panels) depicts movement of a selected myocardial segment. In synchronous segmental movement (panel A), the two lines are synchronized. In panel B, the two lines are discordant, demonstrating a mechanical dyssynchrony of a given segment of the left ventricle.

Results

Patient Clinical Characteristics

Patient characteristics at baseline and 6 months after cell therapy are outlined in Table 1. Of 44 patients we screened for the participation in the study, six patients did not meet the inclusion criteria or were found to have at least one exclusion criterion, three patients refused to participate in the study, and five patients presented with an inadequate response to G-CSF bone marrow stimulation. Ultimately, we included 30 NICM patients in the analysis. The patients were predominantly male with a mean age of 55 years, moderately reduced LVEF, and significantly elevated baseline serum levels of NT-proBNP. At 6-month follow-up, we observed a significant increase in LVEF, a decrease in LVESV, and a trend of a decrease in LVEDV. Furthermore, we noted a significant decrease in NT-proBNP serum levels. All patients received standard-of-care heart failure medical management as per relevant heart failure guidelines at the time of enrolment[1], which remained unchanged throughout the study period.

Effects of Cell Therapy on Electromechanical Parameters

During the transendocardial $CD34^+$ cell injection, a total of 600 injection points (20 injection sites per patient) were sampled in electroanatomical left ventricular maps. During the second procedure at 6-month follow-up, we were able to identify 233 congruent points, amenable to further analysis.

When compared with baseline, we observed a significant decrease in LMD at the cell injection sites at 6-month follow-up (17 ± 17% at baseline vs 13 ± 12% at 6 months, $P = 0.00007$) (Fig. 3). In contrast, we found no significant differences in local UV at the cell injection sites (10.7 ± 4.1 mV vs 10.0 ± 3.6 mV, $P = 0.42$).

Changes in LMD and Clinical Response to Cell Therapy

When stratifying patients according to the clinical response to $CD34^+$ cell therapy, 19 patients (63%, group A) were found to respond favorably (increase in LVEF ≥5%), and 11 patients (37%, group B) did not show a positive clinical response to cell therapy. At baseline, the two groups did not differ in clinical, echocardiographic, or biochemical parameters (Table 2). Similarly, we found no baseline differences in electromechanical properties of the target myocardium: The mean LMD at cell injection sites was 17 ± 19% in group A vs 16 ± 14 in group B ($P = 0.64$) and mean UV at cell injection sites was 9.5 ± 2.9 mV in group A vs 8.6 ± 2.4 mV in group B, ($P = 0.41$) (Fig. 4).

Table 1. Patient Characteristics at Baseline and 6 Months After Cell Therapy.

	Baseline, $N = 30$	6 months, $N = 30$	*P* value
Demographics			
Age, years		54.8 ± 9.3	/
Male, %		90%	/
Echocardiography			
LVEF, %	32.7 ± 9.5	38.9 ± 10.2	0.001
LVEDD, cm	6.3 ± 1.5	6.4 ± 0.9	0.71
LVEDV, ml	227 ± 91	197 ± 76	0.06
LVESV, ml	159 ± 80	146 ± 87	0.05
Biochemical analysis			
Glucose, mmol/L	6.1 ± 2.6	5.6 ± 1.4	0.48
Sodium, mmol/L	141 ± 2	140 ± 3	0.78
Potassium, mmol/L	4.6 ± 0.4	4.7 ± 0.4	0.88
Creatinine, µmol/L	79 ± 24	84 ± 17	0.15
gGT, µkat/L	1.3 ± 1.5	1.0 ± 1.1	0.53
Bilirubine, µmol/L	15 ± 7	14 ± 5	0.20
Hemoglobin, g/L	142 ± 11	141 ± 13	0.87
WBC count, $\times 10^9$/L	7.4 ± 1.5	7.0 ± 1.8	0.65
NT-proBNP, µg/ml	1,381 ± 1,177	885 ± 778	0.05
Medical management			
ACEI/ARB/ARNI, %		100	/
Beta blockers, %		96.7	/
MRA, %		100	/
Loop diuretics, %		36.7	/

ACEI: ACE inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; gGT: gamma-glutamyltransferase; LVEDD: left ventricular end-diastolic diameter; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; WBC: white blood cell; MRA, mineralocorticoid receptor antagonist; NT-proBNP: N terminal-pro brain natriuretic peptide.

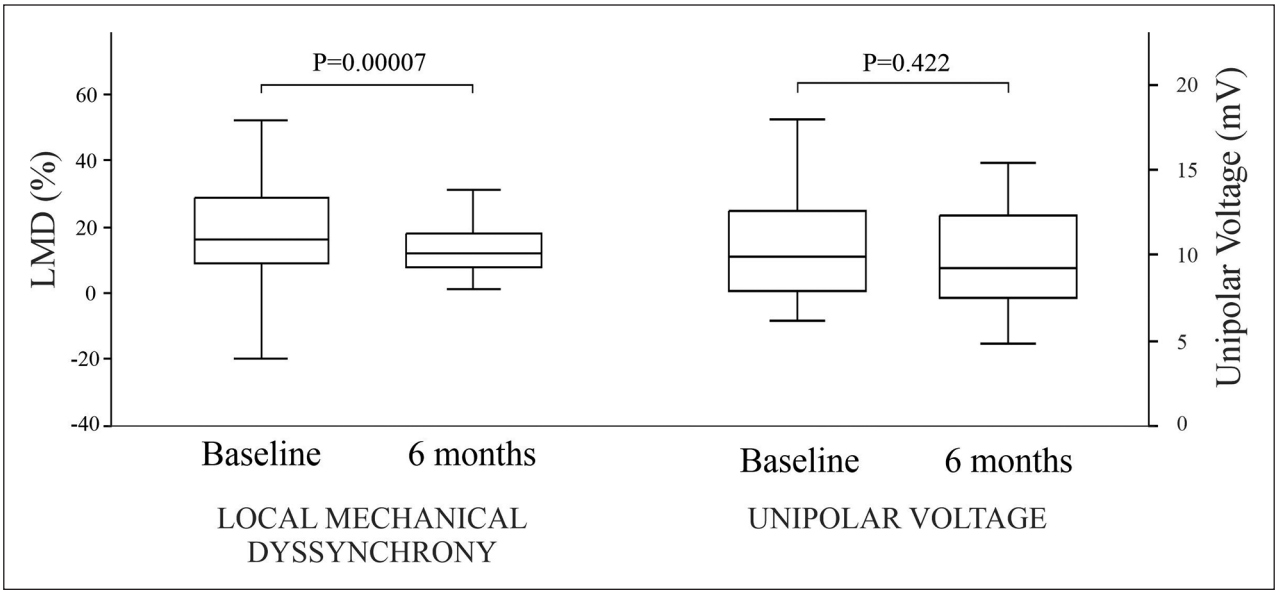


Figure 3. Changes in local mechanical dyssynchrony and unipolar voltage after cell therapy. Using paired electromechanical point-by point analysis, we found a significant decrease in LMD at cell injected sites between baseline and 6-month follow-up. However, we did not observe any significant changes in local UV. Data are presented as median (IQR). IQR: interquartile range; LMD: local mechanical dyssynchrony; UV: unipolar voltage.

Table 2. Baseline Characteristics of Responders (Group A) and Nonresponders (Group B) to Cell Therapy.

	Group A, $N = 19$	Group B, $N = 11$	P value
Demographics			
Age, years	55 ± 8	55 ± 9	0.86
Male, %	95	82	0.27
Echocardiography			
LVEF, %	33.1 ± 9.3	31.9 ± 9.5	0.73
LVEDD, cm	6.1 ± 1.6	6.7 ± 0.9	0.33
LVEDV, ml	216 ± 79	252 ± 109	0.39
LVESV, ml	147 ± 65	188 ± 103	0.32
Biochemical blood analysis			
Glucose, mmol/L	6.1 ± 3.1	5.9 ± 1.4	0.85
Sodium, mmol/L	140 ± 2	140 ± 2	0.35
Potassium, mmol/L	4.6 ± 0.4	4.5 ± 0.3	0.36
Creatinine, µmol/L	77 ± 17	83 ± 31	0.54
gGT, µkat/L	1.3 ± 1.5	1.2 ± 1.2	0.80
Bilirubine, µmol/L	15 ± 8	14 ± 2	0.64
Hemoglobin, g/L	141 ± 10	142 ± 12	0.81
WBC count, $\times 10^9$/L	7.5 ± 1.4	7.0 ± 1.5	0.30
NT-proBNP, µg/ml	1,162 ± 1,031	1,828 ± 1,210	0.10
Medical management			
ACEI/ARB/ARNI, %	100	100	/
Beta blockers, %	100	91	0.18
MRA, %	100	100	/
Loop diuretics, %	26.3	55%	0.12
Electromechanical properties			
UV, mV	9.5 ± 2.9	8.6 ± 2.4	0.41
LMD, %	17 ± 19	16 ± 14	0.64

ACEI: ACE inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; gGT: gamma-glutamyltransferase; LMD: local mechanical dyssynchrony; LVEDD: left ventricular end-diastolic diameter; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; MRA, mineralocorticoid receptor antagonist; UV, unipolar voltage; WBC: white blood cell; NT-proBNP: N terminal-pro brain natriuretic peptide.

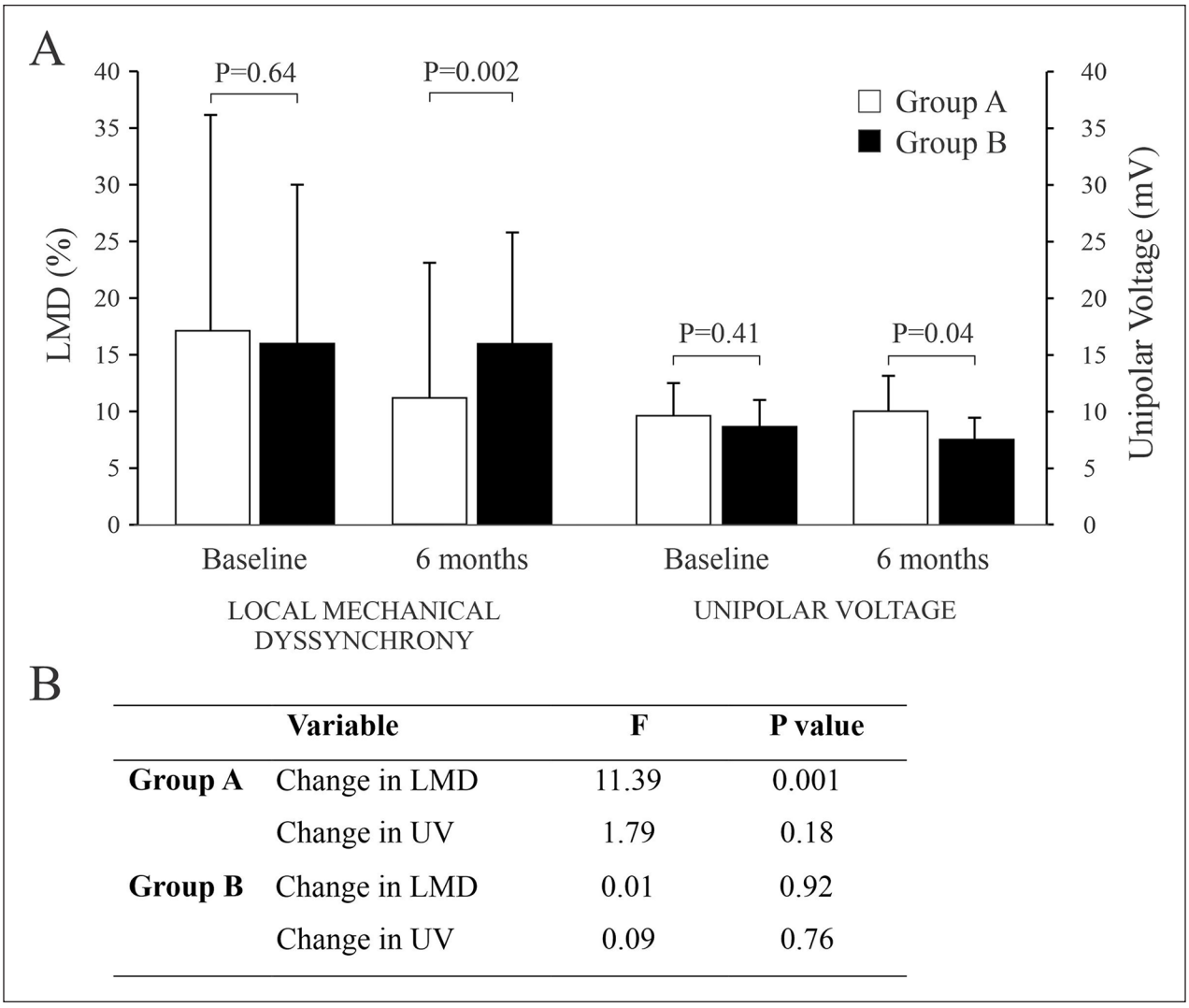
At 6-month follow-up, we found a significantly lower local LMD in group A than in group B (11 ± 12% vs 16 ± 10%, $P = 0.002$). Moreover, when compared with group B, patients in group A displayed a significantly higher UV (10.0 ± 3.1 mV vs 7.4 ± 1.9 mV, $P = 0.04$) (Fig. 4).

Discussion

This is the first clinical trial investigating the effects of transendocardial $CD34^+$ cell therapy on local dyssynchrony in patients with NICM. Our results suggest that $CD34^+$ cell therapy may significantly improve electromechanical properties of the target myocardium by decreasing LMD, which may subsequently translate to the favorable clinical response to cell therapy in this patient population.

In our study, we proposed LMD as a novel parameter for the evaluation of local contraction dyssynchrony, which was derived from the data, obtained by electroanatomical mapping. Current literature supports the feasibility of this approach as Yadczyk et al used similar methodology to evaluate the rotational mechanics of the left ventricle in heart failure patient population with concomitant left bundle branch block. In addition to unipolar and bipolar voltage, the authors also evaluated the LAT, local electromechanical delay (LEMD), and total electromechanical delay (TEMD)[21]. They were able to establish an association between the LAT, LEMD, and TEMD and the electromechanical coupling properties and scar tissue burden of the failing myocardium[21]. Furthermore, Maffesanti et al used electroanatomical parameters to define areas of latest electrical and mechanical activation of the left ventricle in heart failure patients, eligible for either cardiac resynchronization therapy (CRT) device therapy or intramyocardial biological therapy[22]. The authors were able to demonstrate that the presence of myocardial scar adversely affects the spatiotemporal relationship between electrical and mechanical activation of the myocardium[22]. These data collectively show that electroanatomical mapping represents a relevant methodological approach for the evaluation and understanding of electromechanical properties of the myocardium and may therefore represent an essential tool in upcoming mechanistic heart failure studies.

Recently, in a preclinical (mouse) model of adult-onset NICM with mechanical dyssynchrony and a narrow QRS complex, Yamada et al were able to show, using speckle



B

	Variable	F	P value
Group A	Change in LMD	11.39	0.001
	Change in UV	1.79	0.18
Group B	Change in LMD	0.01	0.92
	Change in UV	0.09	0.76

Figure 4. Changes in local mechanical dyssynchrony and unipolar voltage in clinical responders and nonresponders. At baseline, no differences were found comparing LMD or UV at cell injection sites between responders (group A) and nonresponders (group B). At 6 months, a significant decrease in LMD and a significant increase in UV were observed in responders, but not in nonresponders (panel A; data presented as mean ± SD). Panel B represents repeated-measures one-way ANOVA of LMD and UV at baseline and 6-month follow-up in group A and group B. ANOVA: analysis of variance; LMD: local mechanical dyssynchrony; UV: unipolar voltage.

tracking echocardiographic analysis, a significant improvement of discordant wall motion after induced pluripotent stem cell therapy. Epicardial delivery of induced pluripotent stem cells resulted in a significantly shortened intraventricular delay in time-to-peak strain, stabilization of disparity in timing of tissue contraction, and correction in discoordination and stretch-to-shortening ratio, respectively, in cell-treated hearts. In addition, they observed a significant reverse remodeling of the failing myocardium and improved clinical status of the animals receiving cell therapy[15].

Our data are in accordance with these preclinical observations as we have showed a significant improvement in left ventricular mechanical dyssynchrony after transendocardial cell therapy. Using repeated left ventricular electroanatomical mapping, our data demonstrate a significant improvement in LMD at cell injection sites at 6-month follow-up. Furthermore, our data suggest a significant correlation between an improvement in LMD and myocardial viability at cell injection sites in patients who responded favorably to cell therapy. The same association was, however, not observed in the nonresponder group, which may suggest that cell therapy-associated improvement of electromechanical properties of the failing myocardium may translate into the observed clinical benefits of this treatment modality.

Although the pathophysiologic mechanisms underlying the beneficial effects of cell therapy on mechanical dyssynchrony of the failing myocardium remain poorly defined, several explanations may be proposed. First, histological examination of the myocardium in patients with NICM typically shows areas of myocyte necrosis[23] and predominantly

reactive (interstitial and perivascular) fibrosis[24]. These functional and structural changes in extracellular matrix may adversely affect cardiomyocyte function and cardiomyocyte excitability, cell-to-cell coupling, and impaired calcium handling and may thus lead to the development of intraventricular dyssynchrony[6]. Second, myocardial fibrosis is also associated with the development of conduction blocks[25], which may represent a significant contributor for the development of intraventricular dyssynchrony in NICM patients, even in the absence of overt conduction abnormalities, such as the left bundle branch block. Third, microvascular dysfunction is being increasingly recognized as one of the central pathophysiologic mechanisms in NICM. In these patients, decreased capillary density has been shown to be inversely related with myocardial contractility and to significantly contribute to the progression of myocardial fibrosis, which may in turn promote the occurrence of intraventricular mechanical dyssynchrony[26,27]. In a placebo-controlled study, Kawamoto et al evaluated the effect of different stem cell types and doses (purified $CD34^+$ endothelial progenitor cells and unfractionated bone marrow mononuclear cells—BMMC) on neovascularization, inhibition of left ventricular remodeling, and preservation of left ventricular function in an animal model of acute myocardial infarction. The authors were able to show that purified $CD34^+$ endothelial progenitor cells were associated with the largest increase in myocardial capillary density when compared with placebo, low-dose, or high-dose BMMCs[28]. In addition, left ventricular remodeling, as assessed by the ratio of percent fibrosis area to entire left ventricle area, was significantly reduced in the $CD34^+$ cell group compared with all other study groups. $CD34^+$ therapy was also associated with the highest degree of myocardial functional recovery as $CD34^+$ cell group demonstrated the highest left ventricular fractional shortening at 4-week follow-up[28].

Taken together, available data in the literature and the results of our study suggest that the proangiogenic and antifibrotic effects of $CD34^+$ cell therapy may translate into significant improvements of the electromechanical properties of the failing myocardium and improved myocardial contractile performance. In our study, this relationship was especially pronounced in patients in whom cell therapy was associated with an increase in LVEF of at least 5%. Since, in chronic heart failure, an improvement of LVEF $\geq$5% has been associated with improved survival[17], cell therapy may also hypothetically lead to better long-term clinical outcomes in this patient population.

Study Limitations

The results of our study are subject to several limitations. Our study sample was small, and the study was performed in a nonrandomized manner. Also, it was not possible, due to technical constraints, to match all injection points on baseline electroanatomical maps to the points on the follow-up maps. However, as the distribution of responders and nonresponders to cell therapy was similar to our previous stem cell trials[29,30], we believe that current results do not reflect a selection bias or a chance finding but provide a meaningful initial insight into the effects of cell therapy on the electromechanical properties of the failing myocardium.

Conclusions

The results of our study suggest that in NICM patients, transendocardial $CD34^+$ cell therapy may improve LMD at the cell injection sites. Furthermore, our data implicate that the improvements of local mechanical dyssynchrony may also translate into favorable clinical effects of $CD34^+$ cell therapy. As the underlying pathophysiological mechanisms remain incompletely understood, further preclinical and clinical studies are warranted to confirm our preliminary data.

Ethical Approval

Study protocol was approved by the National Medical Ethics Committee of Slovenia (# 121/91/14).

Statement of Human and Animal Rights

All procedures in this study were conducted in accordance with the National Medical Ethics Committee of Slovenia (# 121/91/14) -approved protocols.

Statement of Informed Consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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