

Original Article

# A Novel High-Resolution Surface Electrocardiographic Method to Identify and Characterize Myocardial Scar: A Proof-of-Concept Study

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## ABSTRACT

**Background:** The placement of the left ventricular (LV) lead in an area free of myocardial scar is an important determinant of cardiac resynchronization therapy response. We sought to develop and validate a simple, practical, and novel electrocardiographic (ECG)-based approach to intraoperatively identify the presence of LV scar. We hypothesized that there would be a reduction in the measured amplitude of the LV pacing stimulus on the skin surface using a high-resolution (HR) ECG when pacing from LV regions with scar compared with regions without scar. We term this the ECG Amplitude Signal Evaluation (EASE) method.

**Methods:** Consecutive patients with ischemic LV systolic dysfunction and standard criteria for de novo cardiac resynchronization therapy implantation were prospectively enrolled. All underwent a preimplant contrast-enhanced cardiac magnetic resonance study to assess for scar. The average amplitude of the LV pacing impulse was sampled on HR surface ECG intraprocedurally and then compared with the cardiac magnetic resonance results.

**Results:** A total of 38 LV pacing sites were assessed among 13 recipients. The median voltage measured on the surface HR ECG in regions

## RÉSUMÉ

**Contexte :** La mise en place de la sonde ventriculaire gauche dans une zone exempte de cicatrice myocardique est un facteur déterminant de la réponse au traitement de resynchronisation cardiaque. Nous avons cherché à développer et à valider une approche électrocardiographique (ECG) simple, concrète et novatrice afin de repérer de manière peropératoire la présence de tissu cicatriciel au ventricule gauche (VG). Nous avons émis l'hypothèse qu'il y aurait une diminution de l'amplitude du rythme de stimulation du ventricule gauche mesurée à la surface de la peau à l'ECG haute résolution (HR) lors de la stimulation de régions du VG présentant du tissu cicatriciel comparativement aux régions exemptes de cicatrices. Il s'agit de ce que nous appelons la méthode EASE (*ECG Amplitude Signal Evaluation*).

**Méthodologie :** Des patients vus de manière consécutive qui présentaient une dysfonction systolique ischémique du VG et répondaient aux critères standard pour l'implantation de novo d'un dispositif de resynchronisation cardiaque ont été recrutés de manière prospective. Tous ont fait l'objet d'une résonance magnétique cardiaque améliorée par injection d'un produit de contraste avant

Cardiac resynchronization therapy (CRT) is a standard therapy for select patients with heart failure (HF).<sup>1,2</sup> Yet, not all CRT recipients clearly benefit in terms of left ventricular (LV) remodeling,<sup>3</sup> such as those with ischemic LV systolic dysfunction.<sup>4</sup> The location and extent of LV scar is an important

determinant of subsequent response to CRT. Preferably, the LV lead is positioned near the latest activated area, commonly the lateral or posterolateral wall.<sup>5</sup> Positioning the LV lead in a basal region is associated with greater hemodynamic benefit and superior long-term outcome compared with an apical LV lead position.<sup>6,7</sup> However, even with an apparent optimal LV lead position, these beneficial effects are attenuated if pacing is within an area of extensive scar.<sup>5</sup> Placement of an LV lead in an area free of myocardial scar has been associated with optimal CRT response.<sup>8</sup>

Contrast-enhanced cardiac magnetic resonance (CMR) imaging reliably identifies the location and extent of scar, which can assist in guiding LV lead placement. That is, CMR-guided LV lead placement in areas without scar is associated with improved rates of reverse remodelling and reduced

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**Ethics Statement:** The study was approved by the Conjoint Health Research Ethics Board at the University of Calgary and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before participation in the study.

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with scar was reduced by 41% (interquartile range, 17% to 63%), whereas there was no measurable change in voltage (interquartile range, 0 to 0%) in regions without scar compared with the maximal amplitude (Wilcoxon  $P < 0.0001$ ).

**Conclusion:** The EASE method appears to be of potential value as a novel intraoperative tool to guide LV lead placement to regions free of scar. Future work is required to validate the utility of this method in a larger patient cohort.

risk of heart failure hospitalization, sudden cardiac death, and all-cause mortality.<sup>9-11</sup>

Although CMR is a valuable adjunct for optimizing CRT implantation, preimplant CMR is often not a practical option given the limitations in timely access and cost. Translating the results of a CMR to the intraprocedural fluoroscopic images may be challenging with additional complexity. Furthermore, a preimplantation CMR may be of limited use when planning a CRT upgrade in patients with an existing ICD or pacemaker due to imaging artifact.<sup>12</sup> Thus, other methods to identify areas of myocardial scar would be useful to help facilitate LV lead placement in real-time during CRT implantation.

We sought to develop and validate a simple, practical, and novel electrocardiogram (ECG)-based approach to identify the presence and extent of LV scar, the **ECG Amplitude Signal Evaluation (EASE)** method. We hypothesized that the amplitude of the LV lead pacing stimulus measured on the skin surface using a high-resolution (HR) ECG would be similar to the amplitude of the delivered pacing stimulus in areas without scar (ie, pacing impulse amplitude measured on the skin surface will mirror the amplitude of the stimulus delivered), whereas a reduced relative amplitude will be observed in LV regions with scar (ie, amplitude measured will be smaller than the amplitude delivered).

Specifically, the relationship between programmed device pulse amplitude and the surface recorded amplitude is directly associated with electrical impedance.<sup>13,14</sup> Because infarct scar is associated with a reduction in myocardial electrical impedance compared with healthy tissue,<sup>15-17</sup> pacing within a low impedance area would result in a lower recorded surface voltage.

In this proof-of-concept study, we aimed to correlate the voltage reduction in a given LV region with presence and extent (ie, transmural, nontransmural) of scar quantified by CMR. The aim of this was to provide a simple and practical method to identify more optimal LV pacing sites intraoperatively—those free of significant scar.

## Methods

### Patient enrollment

Patients with ischemic heart disease and conventional clinical criteria for de novo CRT implantation (ie, New York

implantation pour évaluer la présence de tissu cicatriciel. L'amplitude moyenne de l'impulsion de stimulation du VG a été échantillonnée sur l'ECG de surface HR réalisé pendant l'intervention, puis comparée aux résultats de la résonance magnétique cardiaque.

**Résultats :** En tout, 38 points de stimulation du VG ont été évalués chez 13 receveurs. Le voltage médian mesuré sur l'ECG de surface HR dans les régions présentant du tissu cicatriciel était réduit de 41 % (intervalle interquartile : 17 % à 63 %), tandis qu'il n'y avait pas de changement mesurable du voltage (intervalle interquartile : 0 à 0 %) dans les régions exemptes de cicatrices par rapport à l'amplitude maximale (test de Wilcoxon,  $p < 0,0001$ ).

**Conclusion :** La méthode EASE semble avoir une utilité potentielle en tant que nouvel outil peropératoire pour guider la mise en place de la sonde ventriculaire gauche dans les régions exemptes de cicatrices. Il faudra réaliser d'autres travaux pour valider l'utilité de cette méthode dans une cohorte de patients plus importante.

Heart Association functional class II or III symptoms, LV ejection fraction  $\leq 35\%$ , and left bundle branch block conduction delay with QRS duration of  $\geq 130$  ms) were prospectively enrolled.<sup>3</sup> A preimplant late gadolinium enhancement (LGE) CMR study was performed in the 3 months before enrolment. The study was approved by the Conjoint Health Research Ethics Board at the University of Calgary and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before participation in the study. Those unable or unwilling to provide informed consent or with a clinically significant event (eg, myocardial infarction) in the 3 months before the CRT procedure and those unable to lay supine for the procedure were excluded.

### Voltage assessment

While positioning the LV lead intraoperatively, different LV regions were paced. The voltage change was calculated as the relative difference in voltage amplitude of the LV pacing stimulus compared with maximal recorded voltage amplitude when measured on HR surface ECG for a given pacing electrode configuration, delivered voltage, and pulse width (Fig. 1). Because the surface ECG voltage recordings may vary between subjects, the measured voltage was standardized as a percentage of the maximum measured amplitude for a given LV lead pacing output and configuration in each patient individually. For example, if the measured maximal pacing impulse amplitude on the skin surface was 100 units in a given patient, a region with a measured pacing amplitude of 60 units would indicate a voltage reduction of 40% (100-60 units/100 units).

### High-resolution ECG data acquisition and analysis

HR 12-lead ECGs were performed during CRT implantation using a modified CAM-14 ECG acquisition module to acquire HR ECG data for the MAC 5500 electrocardiograph (GE Medical, Milwaukee, WI). The HR ECG measured surface voltage recordings at a frequency of 75,000 Hz compared with the standard ECG sampling of 2000 Hz. ECG sampling with the HR system was conducted on each study participant

during CRT implantation to compare the LV lead voltage output and surface voltage recording from the HR ECG.

During CRT implantation, ECG sampling was attempted in at least 3 different LV locations via LV lead pacing in either the main body of the coronary sinus, great cardiac vein, middle cardiac vein, and/or posterolateral vein. Each location was assessed sequentially where clinically relevant voltage inputs (2.0 or 5.0 volts) were used with a pacing duration of 0.4 or 0.8 milliseconds depending on the pacing capture threshold (ie, a minimal output of twice the pacing capture threshold at the site with the highest threshold was used to ensure reliable capture at all sites). With each LV pacing position, fluoroscopic images were taken in the left (40°–60°) and right (30°–40°) anterior oblique positions and used to localize LV lead tip position represented on a standard American Heart Association 17-segment model.<sup>18</sup> Specifically, the left anterior oblique view was used to classify the LV wall into anterior, lateral, and inferior segments, and the right anterior oblique view was used to identify a basal, mid-ventricular, or apical lead position.

### CNR image acquisition and scar quantification

Before CRT implantation, each patient underwent CMR imaging with LGE to determine the extent and location of myocardial scar. CMR studies were performed on a 1.5-T magnetic resonance image scanner (Avanto; Siemens Healthcare, Erlangen, Germany) equipped with a 32-channel cardiac coil using ECG gating.

Image analysis was performed by blinded core laboratory personnel using commercially available software (cvi42; Circle Cardiovascular Inc, Calgary, AB). Semiautomated contour tracing with manual adjustment was performed of the endocardial and epicardial borders from short-axis cine images to determine LV end-diastolic volume, left ventricular end-systolic volume, LV mass, and left ventricular ejection fraction. Sequential short-axis LGE images were analyzed to quantify scar burden. The absence of hyperenhancement indicated no scar, hyperenhancement of 1% to 50% of the LV wall thickness was considered nontransmural scar, and  $\geq 50\%$  hyperenhancement defined transmural scar. The location and number of segments of scarred myocardium were quantified based on the American Heart Association 17-segment model.<sup>18</sup> Correlation of LV lead position on fluoroscopy and scar location by CMR was performed blinded and before voltage assessment.

### Statistical analysis

Voltage recordings from the HR ECG were measured using MATLAB (MathWorks Inc, Natick, MA). The amplitude of the LV pacing spike was measured (in volts), and the average amplitude of pacing spike from all 12 leads of surface HR ECG were compared. Assessment of the measured surface HR voltage in areas of scarred and non-scarred myocardium was measured using the average of all surface ECG leads to minimize the confounding variable of voltage differences based on surface ECG lead location. Voltage reduction was assessed based on a fixed pulse width and amplitude at each pacing site. Because measured surface HR voltage may vary among subjects, analysis was restricted to intrapatient

comparison. Voltage analyses were performed blinded to the CMR data.

Continuous variables are presented as median and interquartile range, whereas categorical variables are expressed as frequencies and percent. The relationship between the ECG voltage and presence of scar at each pacing site was assessed using standard nonparametric statistical methods (Wilcoxon rank-sum test for pair-wise comparisons and the Kruskal-Wallis test for 3-way comparisons). Two-sided *P* values less than 0.05 were considered significant. All statistical analyses were performed using Stata/IC 15.0 (StataCorp, College Station, TX).

## Results

### Patient cohort

A total of 20 subjects were enrolled. Four were excluded from analysis because of protocol deviations: 1 did not receive a CRT device, as they were found to have only intermittent left bundle branch block conduction; 1 did not undergo a pre-implantation CMR that was protocolled for scar assessment; and in 2, the operator could not obtain at least 3 LV pacing sites. In addition to the protocol deviations, 3 subjects were excluded because of issues with calibrating the Grigori program during intraoperative recordings, resulting in loss of the HR ECG data. Table 1 summarizes the characteristics of the 13 subjects included in the analysis.

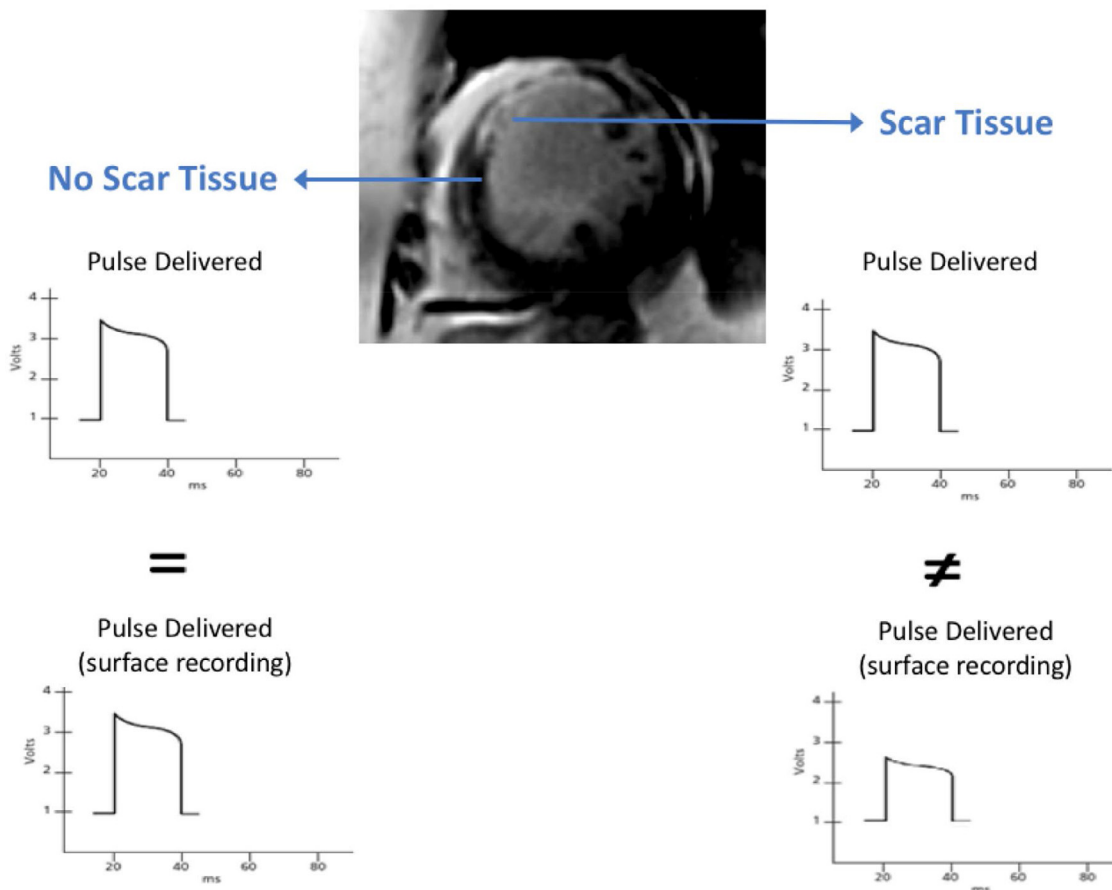
The mean age of the 13 subjects was 72 years, and most subjects were men. The majority had NYHA Class II symptoms (62%). All subjects had left bundle branch block on their baseline surface ECG with an average QRS duration of 175 ms. The average CMR-derived left ventricular ejection fraction was 23%. The average LV end-systolic and diastolic volumes were 276 mL and 353 mL, respectively.

Although this study was not designed to assess for differences in clinical outcomes based on scar volume, subjects were followed up for an average of  $4.2 \pm 1.4$  years post-study enrollment. During this follow-up period, 4 subjects died, and 5 were hospitalized. None of these deaths occurred within the first year of follow-up, and none were considered related to the study or the CRT procedure. Subjects with adverse clinical outcomes (ie, death or hospitalization) had a non-significantly higher total scar burden (15.7%) compared with those without adverse outcomes (12.3%; *P* = 0.2).

### Voltage assessment

Among the 13 subjects, 38 pacing sites were sampled for measurement of surface voltage. The voltages were measured from pacing in the lateral or posterolateral (25 sites; 63%), inferior (2 sites; 5%), anteroseptal (6 sites; 18%), or anterior wall (5 sites; 13%) (Supplemental Fig. S1 and Supplemental Table S1).

The median reduction in voltage for areas of myocardium with transmural scar, nontransmural scar, and no scar were 36% (interquartile range [IQR], 18% to 55%), 51% (IQR, 17% to 67%), and 0% (IQR, 0% to 0%), respectively (Kruskal-Wallis *P* = 0.0001) (Fig. 2). There was no significant difference in voltage reduction when comparing nontransmural and transmural scar (*t* test *P* = 0.6); however, there was a



**Figure 1.** Schematic of voltage change concept. Voltage is measured using high-resolution surface electrocardiogram. In concept, the electrical pulse measured on the skin surface will be similar to that delivered by the left ventricular pacing lead in regions without scar (ie, no change), whereas the electrical pulse measured on the skin surface will be diminished to that delivered by the left ventricular pacing lead in regions with scar (ie, voltage reduction).

**Table 1. Baseline characteristics**

Characteristic	Study cohort (N = 13)
Age, y	72 ± 9
Female, n %	1 (8)
Ischemic etiology, n (%)	13 (100)
Hypertension, n (%)	10 (77)
Diabetes, n (%)	5 (38)
CKD, n (%)	3 (23)
Paroxysmal AF, n (%)	4 (31)
NYHA Class II/III, n (%)	8 (62)/5 (38)
LBBB, n (%)	13 (100)
QRS duration, ms	175 ± 13
LVESV, mL	276 ± 83
LVEDV, mL	353 ± 86
LVEF, %	22.8 ± 5.7
LV lead types, n (%):	
St Jude Medical 1258T QuickFlex (20 mm)*	4 (31)
Guidant 4555 Acuity (8 mm)	3 (23)
Guidant 4549 Easytrack (11 mm)	1 (8)
Medtronic 3830 SelectSecure (9 mm)	2 (15)
Medtronic 4296 Attain Ability (21 mm)	3 (23)
Polarity: true bipolar/integrated bipolar, n (%)	14 (37%) / 24 (63%)

AF, atrial fibrillation; CKD, chronic kidney disease; LBBB, left bundle branch block; LV, left ventricular; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume; NYHA, New York Heart Association.

\*Electrode distance (mm) reported as per model specifications in brackets.

significant difference in voltage reduction comparing areas of no scar with either nontransmural (*t* test  $P < 0.0001$ ) or transmural scar (*t* test  $P < 0.0001$ ). When stratified by the presence of scar (ie, either transmural or nontransmural scar) vs no scar, the median voltage reductions were 41% (IQR, 17% to 63%) and 0% (IQR, 0% to 0%; Wilcoxon  $P < 0.0001$ ), respectively (Table 2).

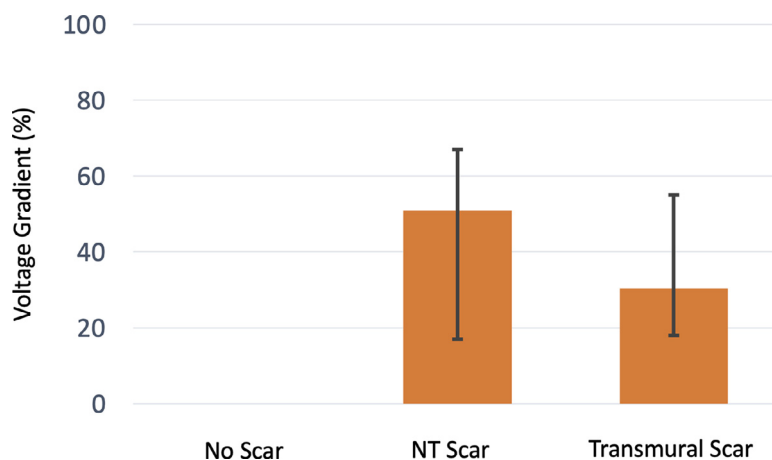
Figure 3 depicts the voltages measured in a single patient when pacing from sites with no scar, nontransmural scar, and transmural scar for a given pulse width and amplitude. When varying the input settings of the delivered pacing impulse, there are similar differences in voltage values observed between areas of scar and no scar.

**Table 2. Relationship of voltage reduction to myocardial scar**

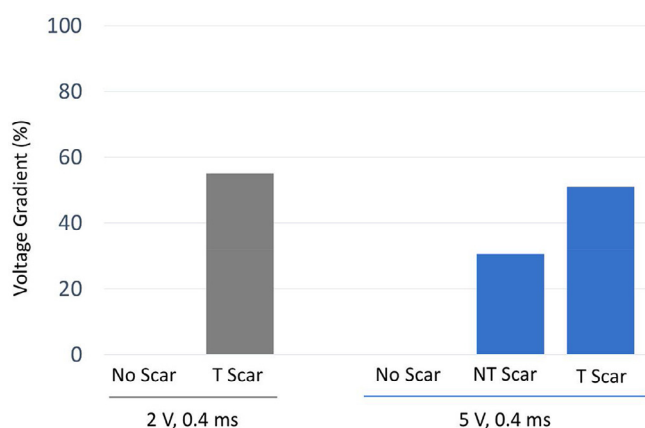
	Median (IQR) of voltage reduction (% of max amplitude)	Mean (95% CI)	Wilcoxon <i>P</i> value
Scar*	41 (17 to 63)	42 (30 to 54)%	< 0.0001
No scar	0 (0 to 0)	0 (0 to 0)%	

CI, confidence interval; IQR, interquartile range.

\*Scar refers to transmural or nontransmural.



**Figure 2.** Median voltage reductions. Median voltage reductions when pacing areas of transmural, nontransmural (NT), and no scar. **Error bars** represent the 25th and 75th percentiles. There is no significant difference comparing the voltage reduction between transmural and nontransmural scar ( $P = 0.6$ ). The voltage reductions significantly differ when pacing in areas of no scar compared with those of transmural scar ( $P < 0.0001$ ) or compared with those of nontransmural scar ( $P < 0.0001$ ).



**Figure 3.** Example of voltage differences in a single patient. Example of voltage differences when pacing from sites of no scar, non-transmural (NT) scar, and transmural (T) scar using 2 different input pacing impulse parameters.

## Discussion

The main finding of this proof-of-concept study is that voltage reduction is correlated with the presence of transmural or nontransmural myocardial scar as quantified by CMR. Voltage reduction was defined as the difference between the voltage amplitude of the delivered LV pacing stimulus vs the voltage amplitude of the pacing stimulus measured on HR surface ECG for a given pulse width. To our knowledge, this is the first description correlating the voltage change in pacing amplitude to localize myocardial scar in humans during CRT implantation. This work extends prior observations in animal models in which changes in myocardial electrical impedance during pacing was useful in identifying infarct scar regions.<sup>16</sup>

### Postulated mechanism for a reduced pacing stimulus amplitude

In prior work to improve 12-lead surface ECG detection of pacemakers, the relationship between the programmed

pacemaker pulse amplitude and the surface recorded amplitude was found to be directly influenced by myocardial electrical impedance.<sup>13,14</sup> That is, a lower myocardial impedance would decrease the surface recorded amplitude of a pacing stimulus.

Prior studies have also assessed the relationship between local electrical impedance and myocardial tissue, in which infarct tissue was associated with a decrease in impedance.<sup>15-17</sup> For example, in a porcine model of myocardial infarction, Amoros-Figueras et al.<sup>16</sup> assessed 137 endocardial pacing sites and found that areas of infarct scar demonstrated a 37.4% reduction in impedance magnitude compared with areas of healthy tissue ( $P < 0.001$ ). Schwartzman et al.<sup>15</sup> found that there was a gradient in impedance from healthy to infarct tissue, in which decreasing impedance correlated with a decrease in viable tissue myocyte content. Thus, because of lower myocardial electrical impedance, the surface voltage recorded on the HR surface ECG is dampened (from the delivered pacing voltage) to a greater degree in areas of nontransmural and transmural scar. Our findings are concordant with these findings where we observed that the surface voltage recorded on the HR is dampened (from the delivered pacing voltage) to a greater degree than nonscar regions.

### Clinical implications and future directions

In this proof-of-concept study, assessment of voltage reduction has the potential to be a useful intraoperative tool to help guide LV lead placement in areas that have minimal scar. The current study relies on readily available 12-lead surface ECG machines with an attached modified acquisition model for high frequency sampling. Upon validation and automation of voltage assessment, the potential advantages of this ECG-based technique include (1) intraoperative real-time scar assessment to guide LV lead position, (2) use in patients with CMR contraindications, and (3) more cost-efficient use of hospital resources, as real-time scar quantification can be obtained using existing ECG machines rather than emerging imaging techniques or hybrid imaging suites.<sup>19,20,21</sup>

There are several technical aspects that need to be addressed for the assessment of voltage reduction to be a useful, real-time intraoperative tool. In this study, voltage change was measured postoperatively using MATLAB software. For clinical use, assessment of voltage would need to be automated for use at point-of-care in the intraoperative setting. Nonetheless, this study was performed using standard ECG equipment with programming enhancements via the Grigori software. Future versions of the Grigori software could consider automated analysis of surface voltage assessment. Finally, further study is warranted to correlate voltage assessment with long-term lead parameters (including pacing thresholds and R wave amplitudes) as well as echocardiographic and clinical response to CRT.

### Limitations

Several study limitations need to be considered. The HR surface ECG system required a second electrode set (ie, 1 electrode set for each the standard and HR ECGs) to be placed on the patient's chest. The addition of a second electrode set reduced the visual field during fluoroscopy during CRT implant. This second set could be avoided in the future with ECG lead splitters to use 1 lead (instead of 2) per site to obtain standard and HR ECG recordings. Second, the current version of the Grigori program software was sensitive to noise or malfunction during the intraoperative data collection. The malfunction may be caused by interference by other devices in the operating room, although the aspects of technical optimization are beyond the scope of the report. Third, the patient cohort was small with limited enrollment of women. To validate the findings in this proof-of-concept study, the observed correlation of voltage reduction with scar burden warrants further study in a larger cohort with increased enrollment of more diverse groups. Finally, undersampling of some LV positions may confound results since voltage assessments are standardized within each patient as a percentage of the maximum measured amplitude for a given LV lead pacing configuration. As per the study protocol, pacing sites in at least 3 different myocardial locations would improve the likelihood of standardizing voltage assessments to a scar-free area.

### Conclusions

Voltage assessment using the EASE method is a novel marker derived from HR surface ECG, and is defined as the difference in pacing impulse measured on the surface ECG compared with the pacing impulse in an area without myocardial scar. For a given pulse amplitude and width, voltage reduction correlates linearly with myocardial scar burden. That is, the greatest voltage decline, or difference in measured pacing impulse amplitude, occurred when pacing was conducted in areas of transmural scar. Future work is required to validate the relationship of voltage reduction to myocardial scar in a larger cohort of patients. With automated measurement of voltage reduction, this readily derived surface ECG marker has the potential to be a valuable, real-time intraoperative tool to help facilitate LV lead positioning in areas without myocardial scar.

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### Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at <https://www.cjcoopen.ca/> and at doi:10.1016/j.cjco.2021.05.010.