Spatial variance in the 12-lead ECG and mechanical dyssynchrony

María Paula Bonomini[1], Hugo Villarroel-Abrego[2], Raúl Garillo[3]

1.Instituto Argentino de Matemática (IAM), CONICET, Instituto de Investigaciones Biomédicas (IIBM), UBA, Argentina.
2. Hospital de Diagnóstico Escalón, Facultad de Medicina Universidad Salvadoreña Alberto Masferrer, San Salvador, El Salvador. https://orcid.org/0000-0003-1030-9717.
3. Facultad de Ciencias Médicas, Universidad Católica Argentina, Buenos Aires, Argentina.

E-mail: paula.bonomini@conicet.gov.ar

ABSTRACT.

Electrical transmission disorders have a deleterious effect on cardiac depolarization, resulting in a disorganized ventricular contraction that reduce global mechanical efficiency; this mechanical dyssynchrony can be corrected by cardiac resynchronization therapy. However, despite adjustments in the electrical criteria selection of QRS for the recognition of mechanical dyssynchrony, a significant proportion of patients do not currently respond to this therapy. Purpose: To find if a new predictor of dyssynchrony, the electrocardiogram spatial variance, is a better marker of mechanical dyssynchrony than QRS duration. Methods: 47 electrocardiograms and 47 strain (2-D speckle-tracking) echocardiograms were prospectively collected simultaneously in consecutive, non-selected patients; the left ventricular mechanical dispersion was measured in all the cases. The electrocardiographic analysis of variance was made with a digital superposition of the electrocardiographic leads and generate different indexes of variance of both QRS complex and repolarization phase. Results: ROC analysis probed that the best area under the curve (AUC) value correlated with left ventricular mechanical dispersion and was obtained combining several spatial variance markers (considering depolarization and repolarization spatial variance together; AUC=0.97); the same analysis using the QRS duration versus mechanical dispersion showed a significantly lower AUC value (AUC=0.64). Conclusion: Spatial variance combining depolarization and repolarization markers are a superior predictor of left ventricular mechanical dispersion than QRS duration.

Keywords: mechanical dyssynchrony – speckle tracking 2D – spatial variance
Declarations.

Funding: None of the authors received honoraria or financial support from third parties.

Conflicts of interest/Competing interest: None of the authors has any conflict or competing interests.

Availability of data and material: Data can be available by request at any time.

Code availability: Not applicable.

INTRODUCTION.

In recent years, cardiac electrical dyssynchrony has increasingly gained attention as an endpoint in cardiac resynchronization therapy (CRT). A growing body of evidence supports that intraventricular dyssynchrony, not always related with QRS duration, is the main cause for CRT application [1, 2] and, therefore, many studies have recently attempted to infer other cardiac dyssynchrony markers from the 12-lead ECG. Approaches has focused on temporal features mainly, covering diferences in intrinsecoid deflections [3], standard deviations of activation times in body surface isochronal maps [4] or index from ultra-high frequency ECG techniques [5].

Spatial variance (SV) of the 12-lead ECG represents the degree of electrical heterogeneity in the heart. When aberrant electrical circuits are generated in the specialized conduction circuit, the ECG lead morphologies get distorted. In this condition, electrical heterogeneity increases. Recently, some research groups reported electrical dyssynchrony markers based on ventricular depolarization dispersion, measured as the depolarization spatial variance [6] or based on correlation analysis [7, 8]. Although these are promising approaches, these markers never reported a relationship to a gold standard measurement such as left ventricular mechanical dyssynchrony (MD), measured by 2-D speckle-tracking strain echocardiography (STE).

The analysis of cardiac electrical dyssynchrony has been always limited to the depolarization phase. However, with the appearance of aberrant electrical paths and the consequent distortion of the depolarization front, it is natural to expect secondary alterations in repolarization. This work extends the analysis of spatial variance to both cardiac phases; depolarization and repolarization, measuring the ability of each marker to explain the MD measured by STE.

MATERIALS AND METHODS.

Patients who had an appointment for an STE between the months of August 2018 and July 2019 were studied at the Cardiovascular Center of Hospital de Diagnóstico Escalón, San Salvador, El Salvador.

1. *Inclusion criteria.*

- Patients older than 18 years
- Subjects whose longitudinal strain images by speckle tracking were technically satisfactory in at least 14 of 16 the segments into which the left ventricular myocardium is traditionally divided.

The STE studies were performed with Acuson SC2000 equipment (Siemens Healthcare GmbH), with 2-D speckle tracking technique. The standard deviation of time for maximum deformation of all left ventricular segments, the so-called mechanical dispersion (normal value less than 56 ms, severe dyssynchrony greater than 70 ms) was calculated. Once the STE was completed, having confirmed that the patient met the criteria detailed above, with prior informed consent, a standard 12-lead electrocardiogram (ECG) was performed, with speed of 25 mm/s and voltage 10 mm/1 mV, using Synchromax^{TM} (EXO, Buenos Aires, Argentina). The average QRS duration of the 12 standard leads was calculated. The cut-off value for diagnosing abnormal left ventricular mechanical dispersion was set at 56 milliseconds (ms).

2. Study population.

The group studied included 45 patients of both sexes, 25 men (55.6%) and 20 women (44.4%), of whom 47 electrocardiographic traces and 47 echocardiograms were obtained with evaluation of left ventricular MD by STE. The average age was 66.2 + 14.8 years. Table 1 summarizes the cardiac pathologies of the patients. Six of them had implanted electronic devices (13.3%: two resynchronizers, two single-chamber pacemakers with right ventricular pacing, one AAI-programmed left atrial unicameral pacemaker, and one dual-chamber pacemaker with DDD pacing).

3. Electrical dyssynchrony

Three different markers of electrical dyssynchrony were compared: Spatial Variance (SV), which measures morphological dispersion between groups of similar leads; correlation analysis, which measures similarity between pairs of leads; and the duration of the QRS complex.

3.1 Spatial variance (SV)

SV quantifies the maximum euclidean distance of every lead within an ensemble from the lead ensemble average. Therefore, SV can assign a numeric value to the different morphological ECG patterns involving two or more leads. In normal conduction patients, some inter-lead sets can produce high SV values while others can produce low SV values, depending on their similarity in morphology. Thus, two extreme scenarios for maximum (SV^{qrs}_{max}) and minimum (SV^{qrs}_{min}) SV in normal subjects were proposed. In [9] there is a detailed description of the method. In this piece of work, a particular set of 3 leads was proposed for either the maximal (aV_R - V_1 - V_6) or minimal (II - aV_F - V_5) scenarios of SV. The SV was computed for the mentioned leads on an 80 ms window centered on the QRS complex. To reduce parameters, the maximum and minimum SV values were combined into a ratio. The ratio between maximum and minimum variance was denoted as $SV^{qrs}_{r.}$ The repolarization counterparts were denoted consistently as SV^{T}_{max}, SV^{T}_{min} and $SV^{T}_{r.}$ Repolarization SV values were computed on the same set of leads as for depolarization. This time, variance was computed on a 200 ms window starting 50 ms apart from the QRS peak in order to span most of the T-wave morphology.

3.2 Correlation analysis

Correlation analysis between leads also contributes to spatial heterogeneity, restricted to pairs of leads. In this way, the cross-correlation between leads II and V_6, for example, can be informative about conduction alterations that occur mainly in the lower and left sides of the heart, such as left bundle branch blocks or left anterior hemiblock. In preserved conduction patients the intrinsic deflections of both leads are conserved, then the correlation signal will be centered at zero ms. On the contrary, if electrical ventricular conduction is not preserved, the maximum signal of the cross-correlation between the pair of leads will be broadened and with a latency (maximum at nonzero lag, in ms). The original correlation mark was presented on leads II and V6 [7,8]. From the original publication, only two parameters were analyzed, the shift of the peak of the cross-correlation signal ($Corr_S$, in ms) and the width of the cross-correlation signal ($Corr_W$, in ms) as measured at 0.7*peak amplitude.

4. Statistical analysis.

Continuous variables are presented as Mean (SD) and compared by a non-parametric test, the unpaired two-sample Wilcoxon test. Significance level was set to 0.05.
Logistic regression analysis was used to investigate relationship between electrical dyssynchrony markers and mechanical dyssynchrony. To avoid overfitting, a 5-fold cross validation scheme was used. Since the number of cases (n=47) was moderately low, no interaction terms were included in the models. Statistical calculations were performed using the Statistical Package for the Octave software.

RESULTS.

Table 1 shows the cardiac pathologies of the recruited patients. Figure 1 shows the distributions for the electrical dyssynchrony parameters analyzed in this study for dyssynchronic and non dyssynchronic patients (Group 1 and Group 2, respectively). Notice that in the dyssynchronic cases the depolarization variance for the set of leads aV_R-V_1-V_6, the set with the most heterogeneous morphologies, decreased its dispersion (SV^{qrs}_{max}; 27 vs 11 mV^2, p=5.9e-4), while the set of minimal variance II-aV_F-V_5 increased the dispersion, even though it failed to meet statistical significance.

On the contrary, the repolarization variance decreased its maximum dispersion and significantly increased its minimum dispersion (26 vs 31 mV^2, p=0.0013) in the dyssynchrony cases. This means that in the presence of conduction abnormalities, morphological variance goes further in the depolarization phase, growing even more in the maximum scenario and shrinking further in the minimum scenario. Exactly the opposite occurs with the repolarization phase. This means: the maximum SV gets lower and the minimum SV gets higher in the presence of dyssynchrony.

The Correlation Analysis presented broader peak shifts in the II-V_6 QRS peaks at Group 1, with a significant widening ($Corr_w$; 37 vs 24 ms, p=0.006). This widening is product of the QRS widenings in the actual leads II-V_6.

Based on the afore mentioned parameters, different logistic regression models were constructed to explain the MD measured by speckle tracking. Table 2 details separated models for the Depolarization and Repolarization Spatial Variance, the Correlation analysis and the traditional QRS duration criteria. Surprisingly, the most significant model for MD based on electrical dyssynchrony parameters was the repolarization spatial variance (p=3.52e-5), followed by the depolarization spatial variance (3.19e-4) and Correlation analysis (p=8.19e-4). The QRS_d model had the worst statistical significance (p=0.0345). ROC analysis for the former models is displayed in Figure 3. Note that the best area under the curve (AUC) values were obtained for the combined SV markers, depolarization and repolarization SV index, accounting in turn for both the maxima and minima scenarios in the following ratios: $SV^{qrs}_r = SV^{qrs}_{min} / SV^{qrs}_{max}$ and $SV^T_r = SV^T_{min}/SV^T_{max}$. From now on, the combined SV^{qrs}_r & SV^T_r marker will simply be denoted as “SV”.

The improvement in the combined SV marker (AUC=0.97) with respect to the Correlation analysis (AUC=0.78) and QRS duration (AUC=0.64) was also transferred to the classification performances of the combined SV markers, with an accuracy of 89.8% as depicted in Figure 2. Here, the confusion matrix for the combined SV marker is presented for a binary class (0: MD>56 ms (group 1), 1: MD<=56 ms (group 2)).

Finally, Figure 3 and 4 illustrates the Spatial Variance curves for the set of leads aV_R-V_1-V_6 and II-aV_F-V_5 for both the depolarization and repolarization phases (middle and lower panels) together with the Correlation analysis for leads II-V_6 (top panels) for a dyssynchronic representative patient and one with intact conduction, respectively. Notice the widening of the cross-correlation signal of the dyssynchronic case (Figure 3) with respect to preserved conduction case (Figure 4). Also, note the displacement of the cross-correlation peak from zero lag (0 ms) because of the shifts in the II-V_6 QRS peaks in the dyssynchronic case, while the native conduction case presents a cross-correlation signal centered around 0 ms. Regarding the spatial variance, the shifts in either multi lead set (aV_R-V_1-V_6 or II-aV_F-V_5) in the dyssynchronic case produce an increased spatial variance.

DISCUSSION.

A quarter of a century ago, Cazeau et al published a clinical case of refractory heart failure associated with prolonged QRS and mechanical dyssynchrony, treated with multichambered stimulation, laying the foundations for what was later called CRT [10]. Throughout these 25 years, several criteria employing the 12-lead ECG were used to identify subjects whose QRS alterations suggested the presence of MD, condition that could be corrected by CRT. Despite the adjustment in successive guidelines over time, a significant proportion of patients do not currently respond to this therapy.

Many studies aimed at quantifying depolarization dispersion. Turrini et al [10] reported QRS dispersion as a marker of cardiac risk in right ventricular cardiomyopathy. However, this method relied on temporal dispersion, the QT interval dispersion. Gage et al quantified depolarization dispersion by measuring the standard deviation of activation times (SDAT) on a 53-electrode body surface isochronal map [4].

The SV makes use of the spatially distributed information contained in the 12-lead ECG. Nearing et al applied SV to the QRS complex and to T-waves, to predict cardiac risk in a set of heart failure patients [11]. The first attempt to associate SV to electrical dyssynchrony was reported Bonomini et al [9], where the depolarization variance outperformed the QRS duration at explaining the left ventricular electrical activation (LVED) measured by electrophysiology study in a set of dyssynchronic patients. The Correlation analysis also achieved good correlation to the LVED in its original works [7-8]. However, both studies lacked the inclusion of mechanical dyssynchrony information.

In the present paper the prediction of MD by assessing the duration of the QRS complex, the spatial variance of QRS and the combined spatial variance of QRS and T wave were compared against a gold standard: MD measured with STE strain. The greatest predictive value was obtained with SV of the QRS depolarization combined with the T wave (repolarization) SV, offering a powerful tool to detect the presence of MD by measuring electrical dispersion. To date we have not found another publication using this evaluation method to predict MD.

CONCLUSIONS.

Analysis of SV on the 12-lead ECG, especially when dispersion during depolarization (QRS complex) and repolarization (T wave) are analyzed together, turned out to be a valuable predictor of MD, a condition that can be corrected by cardiac resynchronization therapy.

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FIGURE CAPTIONS.

Figure 1: Boxplots for the mechanical dyssynchrony (DM) and the electrical dyssynchrony markers analyzed. QRSdur: QRS duration, SV qrs max: maximal depolarization spatial variance, SV qrs min: minimal depolarization spatial variance, SV T max: maximal repolarization spatial variance, SV T min: minimal repolarization spatial variance, CorrS: shift in the aVF -V5 cross-correlation shift, Corrw: width in the aVF -V5 cross-correlation width at 0.7*Peak amplitude. *: $p<0.05$, †: $p<0.005$ against group 2, Wilcoxon test.

Figure 2: Performance for the MD model based on electrical dyssynchrony analysis. Left: ROC analysis for SV, Correl and QRSd markers. Right: Confusion matrix for the SV model accounting for depolarization and repolarization spatial variance.

Figure 3: Electrical and mechanical dyssynchrony. Representative analysis of Correlation (Top), Maxima spatial variance (middle) and minima spatial variance (Bottom) together with strain information for a dyssynchronic patient. Notice the widened cross-correlation signal and the high T-wave variance in the minima scenario and the high QRS variance in the maxima scenario. Lead variances were computed about the mean morphology (black line). A case of mechanical dyssynchrony, with a pathological MD (61 ms), the right panel shows strain curves of 4 chambers, 2 chambers and 3 chambers apical views (STE).

Figure 4: Electrical and mechanical dyssynchrony. Representative analysis of Correlation (Top), Maxima spatial variance (middle) and minima spatial variance (Bottom) together with strain information for a patient with preserved conduction. Lead variances were computed about the mean morphology (black line). A case of preserved mechanical synchrony, with a normal MD (28 ms), the right panel shows strain curves of 4 chambers, 2 chambers and 3 chambers apical views (STE).

TABLE CAPTIONS.

Table 1: Cardiac conditions in the 47 patients recruited for this study.

Table 2: Statistical performance for the different MD models based on electrical dyssynchrony parameters: Repolarization Variance, Depolarization Variance, Correlation analysis and QRSd. Notice the outperformance of the Repolarization model, producing the most significant of all of them.

Table 1.

Cardiac condition	n	%
Dyssynchrony index (Synchromax) > 0.4	29	61.7
Abnormal mechanical dispersion	22	46.8
QRS <120 ms	29	61.7
Non sinus rythm	5	10.6
Pacemaker rythm	5	10.6
Sick sinus syndrome	1	2.1
Structural heart disease		
Heart failure	20	42.5
Myocardial infarction	8	17.0
Hypertensive left ventricular hypertrophy	6	12.8
Hypertrophic cardiomyopathy	1	2.1
Non-compaction cardiomyopathy	1	2.1
Takotsubo cardiomyopathy	1	2.1
Mitral valve prolapse	1	2.1
Conduction abnormalities		
Advanced left bundle branch block	7	14.9
Bifascicular block	4	8.5
Right bundle branch block	3	6.4
Left anterior fascicular block	2	4.2
Left posterior fascicular block	1	2.1
Non-specific intraventricular conduction block	1	2.1
Bayés syndrome	1	2.1

Table 2

Depolarization spatial variance				
	Estimate	**SE**	**t stat**	**p**
Intercept	0.30947	0.33165	0.93311	0.35076
SV_r^{qrs}	1.8187	0.66964	2.7159	0.0066099
Chiˆ2-statistic vs. constant model: 13, p-value = 0.000319				
Repolarization spatial variance				
	Estimate	**SE**	**t stat**	**p**
Intercept	-0.52696	0.39783	-1.3246	0.18532
SV_r^T	-2.9966	0.97561	-3.0715	0.0021296
Chiˆ2-statistic vs. constant model: 17.1, p-value = 3.52e-05				
Correlation analysis				
	Estimate	**SE**	**t stat**	**p**
(Intercept)	-0.084067	0.30457	-0.27602	0.78254
$Corr_s$	0.1635	0.28939	0.56497	0.57209
$Corr_w$	-1.3001	0.44001	-2.9548	0.0031287
$\text{Chi}^2 - statisticvs.constantmodel : 14.2, p - value = 0.000819$				
QRS duration				
	Estimate	**SE**	**t stat**	**p**
Intercept	0.028235	0.27075	0.10428	0.91694
QRS_d	-0.57911	0.28572	-2.0269	0.042677
$\text{Chi}^2 - statisticvs.constantmodel : 4.47, p - value = 0.0345$				