ORIGINAL ARTICLE

Diagnostic and Prognostic Value of Low QRS Voltages in Cardiac AL Amyloidosis

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Background: In cardiac AL amyloidosis, myocardial infiltration is typically associated with “low QRS voltages” at the 12-lead electrocardiogram (ECG). Although considered as one of the hallmarks of the disease, its reported prevalence varies from 45% to 70%, mainly because of nonhomogeneous definitions.

Methods: To identify the “low QRS voltage” parameter having the best diagnostic value in identifying cardiac amyloidosis, and to assess its possible prognostic role, ECG and echocardiographic data were collected at diagnosis in 337 consecutive never-treated AL patients (233 with, 104 without cardiac involvement). Prognosis was assessed after a median follow-up of 14.5 months.

Results: “Low QRS voltage” prevalence varied from 84.12% when using Sokolow-Lyon index ≤ 15 mm to 27.04% with the definition of low total voltages (QRS amplitude ≤ 5 mm in each peripheral and ≤ 10 mm in each precordial lead), the widely used definition of low peripheral voltages (≤ 5 mm in each peripheral lead) being able to identify 66.52% cardiac AL patients. The presence of “low peripheral voltages” was associated with a more severe cardiac involvement, and was able to differentiate Mayo stage II patients’ survival (i.e., AL patients with intermediate prognosis). According to receiver operator characteristic (ROC) curve analysis, sensitivity and specificity were 58.72% and 80.00%, for a peripheral QRS amplitude ≤ 24.5 mm (the sum of QRS in all the 6 peripheral leads), and 76.26% and 65.00% for a Sokolow-Lyon index ≤ 11 mm.

Conclusions: In cardiac AL amyloidosis the prevalence of low QRS voltages is highly dependent on the method used for defining this ECG alteration.

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In AL amyloidosis, aggregates of insoluble toxic proteins mainly derived by the N-terminus of a monoclonal immunoglobulin light-chain are deposited in forms of fibrils in several tissues.^{1,2} In western countries, the incidence of AL amyloidosis is approximately 1 case per 100,000 person-years, and in such patients cardiac involvement is not only frequent but it is also the most common cause of death.^{3,4} Beyond being one of the main determinants of survival, cardiac involvement also

limits the feasibility of intensive and effective therapy.^{5–7}

The 12-lead electrocardiogram (ECG) reflects the generalized infiltrative nature of this disease with low voltages in the limb leads, pseudoinfarction patterns in the anterior precordial and/or inferior limb leads,⁸ and conduction abnormalities such as fascicular block or atrioventricular block of varying degree.^{4,9–11} Moreover, it is not unusual to see “aspecific” abnormalities of the QRS complexes,

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such as notches and RsR' pattern in the absence of QRS prolongation, leading to alterations in QRS morphology defined as a fragmentation of QRS complexes (fQRS),¹² probably representing intramyocardial conduction abnormalities,¹³ that has been shown to be prognostically valuable in AL amyloidosis.¹⁴

In literature, the prevalence of low QRS voltages varies from 45%¹⁵ to 70%.⁴ A possible contributing factor to this variability may be due to the existence of several definitions of "low voltages," leading to some discrepancy in the evaluation of this ECG feature. The most diffuse definition is QRS amplitude in each peripheral lead ≤ 5 mm (0.5 mV)^{7,15,16}, although sometimes this definition is associated with or is alternative to QRS amplitude in each precordial lead ≤ 10 mm (1 mV).^{17,18} Another definition is derived from the Sokolow-Lyon index,¹⁹ as the sum of the S wave amplitude in lead V₁ and of the R wave in V₅ or V₆ ≤ 15 mm (1.5 mV).²⁰ Some Authors also used the combined definition of QRS amplitude in each peripheral lead ≤ 5 mm (0.5 mV) or a Sokolow-Lyon index ≤ 15 mm.²⁰⁻²² The latter combined definition was the only one that was shown as prognostically valuable by Kristen et al., in a relatively small group of cardiac AL patients (n = 43).²³

Given the nonhomogeneous definition of this ECG feature in the available literature, aim of the present study was to identify the "low peripheral voltage" index having the best diagnostic value in identifying the presence of cardiac involvement in AL amyloidosis. Since QRS voltage is a numerical parameter, we also identified a cutoff value. As a secondary aim, we verified the possible correlation of the finding of low peripheral voltages with other electrocardiographic and echocardiographic parameters, to better understand the involved physiopathologic mechanism(s). Moreover, the prognostic value of low QRS voltages in AL amyloidosis was assessed in a large case series.

METHODS

We enrolled all consecutive untreated subjects in whom first diagnosis of primary AL amyloidosis was concluded between 2008 and 2010. Diagnosis was made according to the International Society of Amyloidosis criteria, as well as assessment of organ involvement at baseline.^{24,25} The presence of heart involvement was defined according to either the

demonstration of amyloid deposits on the endomyocardial biopsy or by echocardiographic evidence of cardiac amyloidosis in the setting of a defined systemic disease combined with elevation of the N-terminal probrain natriuretic peptide (NT-proBNP) according to the recently updated criteria of the International Society of Amyloidosis.²⁶⁻³¹ Patients were also divided according to the Mayo staging system as proposed by Dispenzieri et al.³² Patients with other potential causes of low QRS voltages (large pericardial effusions, obesity, i.e., body mass index > 30 kg/m², chronic obstructive lung disease with emphysema, and severe peripheral edema, i.e., pitting edema above the knees) were excluded. Patients with paced rhythm, altering ECG voltage measurements, were also excluded. At presentation, all patients provided informed consent for the use of clinical data for research purposes and anonymous publication of scientific data.

Echocardiography

Echocardiographic data were collected with the patient in a supine left lateral decubitus position. Two-dimensionally targeted M-mode echocardiography (ACUSON Sequoia 512, Siemens Medical Solutions, Mountain View, CA, USA) was performed after the longitudinal parasternal view had been checked to avoid angulation of the ultrasonic beam and consequent changes in the LV shape. LV internal dimensions, posterior wall thickness, and interventricular septum thickness were analyzed by a single reader (F.M.) according to the standards of the American Society of Echocardiography.³³ LV mass was indexed to body surface area (g/m²). Mitral (MAPSE) and tricuspid (TAPSE) longitudinal annulus excursion was measured. Endocardial shortening fraction (SFendo) was calculated as the difference between the end-diastolic and the end-systolic diameter divided by the end-diastolic diameter and then multiplied by 100. Transmitral flow velocity in early (E) and late (A) diastole was measured by conventional pulsed Doppler in the apical 4-chamber view. Moreover, pulsed TDI derived early diastolic peak velocity at lateral (E' lateral) mitral annulus was evaluated as an index of LV relaxation. The E to E' ratio was also assessed.

12-Lead ECG

Analysis of the standard 12-lead electrocardiogram (Esaote P8000 Power 1e30, filter range

Figure 1. Representative examples of the measure of QRS score, that is, the sum of Q, R, and S height, each taken as absolute value in mm (blue color) and of QRS amplitude, that is, the total amplitude of the whole QRS complex, from its nadir to its zenith (red color).

0.05 to 50 Hz, 25 mm/s, 10 mm/mV; Esaote Italia, Genova, Italy) was performed by a single reader (R.M.) blinded to the organ involvement, echocardiographic data and levels of cardiac biomarkers as well as clinical data. Beyond the usual electrocardiographic parameters (PQ, QRS, QT intervals), QRS voltages were measured in each lead by two different methods: (1) QRS score, that is, the sum of Q, R, and S height, each taken as absolute value in mm (1 mm = 0.1 mV); (2) QRS amplitude, that is, the total amplitude of the whole QRS complex, from its nadir to its zenith (Figure 1). Peripheral, precordial, and total QRS scores and amplitudes, were calculated as the sum of QRS scores and amplitudes in all the 6 peripheral leads, in the 6 precordial leads, and in all the 12 leads, respectively. Also Sokolow-Lyon index was derived, as the sum of the S wave amplitude in lead V₁ and of the R wave in V₅ or V₆.¹⁹ For each of these quantitative QRS voltage measures, the best cutoff value able to identify patients with cardiac AL amyloidosis was derived by Receiver Operator Characteristic (ROC) curve analysis.

Patients were also classified according to the following categorical definitions of "low QRS voltages" reported in cardiac AL literature:

- (1) "low peripheral voltages," i.e., QRS amplitude ≤ 5 mm (0.5 mV) in each peripheral lead.^{7, 15, 16}
- (2) "low precordial voltages," i.e., QRS amplitude ≤ 10 mm (1 mV) in each precordial lead.
- (3) "low total voltages," i.e., QRS amplitude ≤ 5 mm (0.5 mV) in each peripheral lead and QRS amplitude ≤ 10 mm (1 mV) in each precordial lead.¹⁸
- (4) "low peripheral voltages" or "low precordial voltages."¹⁷
- (5) Sokolow-Lyon index ≤ 15 mm.^{20, 22}

(6) "low peripheral voltages" or Sokolow-Lyon index ≤ 15 mm.²³

(7) "low peripheral voltages" and Sokolow-Lyon index ≤ 15 mm.

Statistics

Continuous variables are expressed as median values and interquartile ranges, and categorical variables as frequencies and percentages. Comparisons of continuous variables were based on ANOVA followed by 2-tailed Mann-Whitney U test, and comparisons of proportions were based on chi-square tests. The capability of the different electrocardiographic indices to correctly identify patients with cardiac involvement was assessed by evaluating sensitivity (%), specificity (%), positive (PPV) and negative (NPV) predictive value, positive (+LR) and negative (-LR) likelihood ratio. For each quantitative QRS index, the best threshold diagnostic value was identified by ROC curve analysis and the area under the curve (AUC). Results were compared by c-statistics.³⁴ Survival curves were plotted according to Kaplan-Meier and differences in survival were tested for significance by the log-rank test. P values <0.05 were considered significant. All statistical analyses were performed using MedCalc version 12.2.1.0 (MedCalc Software, Mariakerke, Belgium).

RESULTS

Study Population

The study population included 337 consecutive patients, diagnosed between 2008 and 2010 (age 64 [range: 36–87] years; 203 males). The cohort was divided into two groups depending on the presence ($n = 233$) or absence ($n = 104$) of heart involvement by amyloidosis. Anthropometric, electrocardiographic, echocardiographic, and cardiac biomarker data are summarized in Table 1. As expected, cardiac amyloidosis was associated with left ventricular concentric hypertrophy with preserved ejection fraction, depressed longitudinal function and evident diastolic dysfunction. This was associated with a marked increase in NT-proBNP and TnI serum levels.

ECG Presentation

The presence of cardiac involvement was associated with a peculiar electrocardiographic pattern,

Table 1. Anthropometric, electrocardiographic, echocardiographic, cardiac biomarker data, and values of peripheral, precordial and total QRS scores, the corresponding QRS amplitudes, and Sokolow-Lyon index in AL patients with and without cardiac involvement.

	Cardiac AL (n = 233)	Noncardiac AL (n = 104)	P
Age (years)	65 [58–72]	64 [56–70]	0.483
Body surface area (m ²)	1.75 [1.62–1.87]	1.79 [1.67–1.94]	0.154
Systolic blood pressure (mmHg)	120 [105–135]	137 [125–150]	<0.001
Diastolic blood pressure (mmHg)	77 [70–84]	80 [75–90]	<0.001
Heart rate (b/min)	79 [69–88]	71 [63–82]	<0.001
Electrocardiographic parameters			
PQ Interval (ms)	175 [160–200]	160 [150–190]	0.031
QRS Interval (ms)	80 [80–100]	80 [80–90]	0.035
QT Interval (ms)	400 [378–420]	390 [360–410]	0.010
QTc Interval (ms)	455.7 [432–476]	423.4 [404–445]	<0.001
Echocardiographic parameters			
IVS (mm)	14.9 [13.6–16.2]	11.0 [10.0–11.2]	<0.001
PW (mm)	14.2 [13–15.6]	10.5 [9.2–11.6]	<0.001
EDVLD (mm)	42 [40–46]	46 [42–50]	<0.001
ESVLD (mm)	28 [24–32]	26 [22–30]	0.075
EF (%)	60.9 [52.6–66.2]	62.6 [59.4–66.4]	0.042
LVMI (g/m ²)	173 [139–197]	112 [90–136]	<0.001
E/A ratio	1.27 [0.76–2.28]	0.76 [0.68–1]	<0.001
E/E' ratio	10.01 [6.46–13.76]	4.73 [3.66–6.43]	<0.001
MAPSE (mm)	8.2 [5.8–11.1]	14.9 [12.7–16.6]	<0.001
TAPSE (mm)	15.0 [11.1–19.0]	22.1 [19.7–25.2]	<0.001
Cardiac biomarkers			
NT pro-BNP (pg/ml)	5449 [2002–13154]	290 [127–387]	<0.001
BNP (pg/ml)	454 [232–1082]	48.9 [28–87]	<0.001
cTnI (ng/ml)	0.130 [0.045–0.270]	0.011 [0.005–0.028]	<0.001
Different “low QRS voltage” indices			
Peripheral QRS score (mm)	23.5 [18.5–31.0]	33.5 [26.5–42.0]	<0.001
Peripheral QRS amplitude (mm)	24.0 [18.9–31.3]	33.7 [26.1–42.5]	<0.001
Precordial QRS score (mm)	59.0 [47.2–72.2]	64.5 [53.6–77.2]	0.029
Precordial QRS amplitude (mm)	58.5 [47.5–72.0]	65.0 [53.0–76.5]	0.023
Total QRS score (mm)	83.2 [68.0–101.0]	98.5 [83.2–116.4]	<0.001
Total QRS amplitude (mm)	82.5 [68.1–102.0]	98.0 [82.6–115.9]	<0.001
Sokolow-Lyon index (mm)	7.0 [4.0–11.0]	14.5 [10.0–18.4]	<0.001

IVS = septal end-diastolic thickness; PW = posterior wall end-diastolic thickness; EDVLD = end-diastolic left ventricular chamber diameter; ESVLD = end-systolic left ventricular chamber diameter; EF = ejection fraction; LVMI = left ventricular mass index; E/A ratio = early-to-atrial transmitral flow velocity ratio; E/E' ratio = TDI early velocity (E') to early transmitral flow velocity (E) ratio. Data are expressed as median (interquartile range). ANOVA followed by 2-tailed Mann-Whitney U test. No significant difference was observed when comparing peripheral QRS score and amplitude, precordial QRS score and amplitude, and total QRS score and amplitude, respectively.

with a 52.2% proportion of pseudoinfarction, as defined by the presence of a pathological Q wave in two or more contiguous leads in the absence of history of ischemic heart disease and/or evidence of akynetic/dyskinetic wall segments.⁴ Moreover, when compared with patients without cardiac amyloidosis, the presence of myocardial involvement was associated with prolonged PQ, QRS and QT intervals. As reported in Table 1, quantitative measurements of QRS voltages (measured as score

or as amplitude) showed that all indices were depressed in patients with cardiac involvement, confirming the higher prevalence of “low QRS voltages” in cardiac AL amyloidosis. However, when comparing the diagnostic performance in identifying the presence of cardiac involvement, peripheral QRS score, peripheral QRS amplitude and Sokolow-Lyon index were much better than the other measurements, that is, precordial or total QRS scores and amplitude, according to ROC

Table 2. Comparison between the Different Quantitative QRS Voltage Measures in Identifying Cardiac AL Patients

	c-statistics (95% CI)	P value *	Cutoff value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Peripheral QRS score (mm)	0.762 (0.711–0.808)	–	≤26	62.84	76.00	85.1491	85.1491
Peripheral QRS amplitude (mm)	0.763 (0.712–0.808)	0.5420	≤24.5	58.72	80.00	86.5397	46.9498
Precordial QRS score (mm)	0.586 (0.529–0.640)	<0.0001	≤53	38.99	76.00	78.0581	36.2597
Precordial QRS amplitude (mm)	0.586 (0.530–0.641)	<0.0001	≤63.5	62.10	52.00	73.9111	38.5205
Total QRS score (mm)	0.672 (0.617–0.723)	<0.0001	≤92	65.75	64.00	79.9977	46.0430
Total QRS amplitude (mm)	0.674 (0.620–0.726)	<0.0001	≤88.5	60.55	69.00	81.0504	44.4052
Sokolow-Lyon index (mm)	0.762 (0.711–0.808)	0.9703	≤11	76.26	65.00	82.6727	55.5624

Note: Comparison between peripheral, precordial and total QRS scores, the corresponding QRS amplitudes, and Sokolow-Lyon index in terms of their capability to identify patients with cardiac AL amyloidosis, according to ROC curve analysis.

*Difference in c-statistics is compared with peripheral QRS score. PPV = positive predictive value; NPV = negative predictive value.

Figure 2. Comparison between the different quantitative QRS voltage measures in identifying cardiac AL patients. ROC curve analysis for peripheral, precordial and total QRS scores, the corresponding QRS amplitudes, and Sokolow-Lyon index.

curve comparison. In detail, a peripheral QRS score ≤ 26 mm had a 62.84% sensitivity and a 76.00% specificity in identifying the presence of cardiac involvement (Table 2). Corresponding values of sensitivity and specificity were 58.72%

and 80.00%, for a peripheral QRS amplitude ≤ 24.5 mm, and 76.26% and 65.00% for a Sokolow-Lyon index ≤ 11 mm, respectively. As shown in Figure 2, no difference was observed when comparing QRS score or QRS amplitude in calculating peripheral, precordial and total QRS voltage indices, respectively.

The prevalence of the different categorical definitions of "low QRS voltages" reported in cardiac AL literature is summarized in Table 3. In cardiac AL patients, prevalence of "low QRS voltages" ranges from 27.04% when defined as "low total voltages" (i.e., QRS amplitude ≤ 5 mm [0.5 mV] in each peripheral lead and QRS amplitude ≤ 10 mm [1 mV] in each precordial lead)¹⁸ to 90.13% when defined as "low peripheral voltages or Sokolow-Lyon index ≤ 15 mm."²³

Similar results for both quantitative measurements and different categorical definitions of QRS voltages were obtained after excluding patients with complete right ($n = 18$) or left ($n = 15$) bundle branch block.

Correlation with Anthropometric, ECG, Echocardiographic Parameters and Cardiac Biomarkers in Cardiac AL Patients

No correlation was found between presence of low QRS voltages according to the different

Table 3. Comparison between the Different Qualitative QRS Voltage Measures in Identifying Cardiac AL Patients

	Prevalence (n,%)		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	+LR (%)	-LR (%)
	Noncardiac AL	Cardiac AL						
Low peripheral voltages	20 / 104 (19.23%)	155 / 233 (66.52%)	66.36	80.81	88.48	51.95	3.46	0.42
Low precordial voltages	55 / 104 (52.88%)	90 / 233 (38.63%)	38.81	47.47	62.04	25.97	0.74	1.29
Low total voltages	11 / 104 (10.58%)	63 / 233 (27.04%)	26.94	89.90	85.51	35.74	2.67	0.81
Low peripheral voltages or low precordial voltages	64 / 104 (61.54%)	182 / 233 (78.11%)	78.08	38.38	73.71	44.19	1.27	0.57
Sokolow-Lyon index $\leq$ 15 mm	54 / 104 (51.92%)	196 / 233 (84.12%)	84.02	48.48	78.30	57.83	1.63	0.33
Low peripheral voltages or Sokolow-Lyon index $\leq$ 15 mm	57 / 104 (54.81%)	210 / 233 (90.13%)	89.95	45.45	78.49	67.16	1.65	0.22
Low peripheral voltages and Sokolow-Lyon index $\leq$ 15 mm	17 / 104 (16.35%)	140 / 233 (60.09%)	60.27	83.84	89.19	48.82	3.73	0.47

Note: Comparison between “low peripheral voltages” (i.e., QRS amplitude $\leq$ 5 mm (0.5 mV) in each peripheral lead),^{7,15,16} “low precordial voltages” (i.e., QRS amplitude $\leq$ 10 mm (1 mV) in each precordial lead), “low total voltages” (i.e., QRS amplitude $\leq$ 5 mm (0.5 mV) in each peripheral lead and QRS amplitude $\leq$ 10 mm (1 mV) in each precordial lead),¹⁸ “low peripheral voltages” or “low precordial voltages,”¹⁷ Sokolow-Lyon index $\leq$ 15 mm,^{20,22} “low peripheral voltages” or Sokolow-Lyon index $\leq$ 15 mm,²² and “low peripheral voltages” and Sokolow-Lyon index $\leq$ 15 mm in terms of their capability to identify patients with cardiac AL amyloidosis. PPV = positive predictive value; NPV = negative predictive value; +LR = positive likelihood ratio; -LR = negative likelihood ratio.

quantitative and categorical definitions and body weight or surface area. In cardiac AL, the presence of low peripheral QRS voltages was associated with higher heart rate ($P < 0.001$), prolonged PQ interval ($P = 0.012$), and shorter QT interval ($P = 0.025$), although the corrected QT interval was comparable in patients with or without low QRS voltages. No correlation was found between the presence of low QRS voltages and of fQRS. As to the echocardiographic parameters, patients with low QRS voltages presented higher septal thickness ($P = 0.043$), larger end-diastolic left ventricular chamber diameters ($P = 0.027$), more severely depressed longitudinal systolic function (as assessed by both MAPSE and TAPSE, both $P < 0.001$) and larger extent of diastolic dysfunction (E/A ratio and E/E' ratio, both $P < 0.001$). Moreover, the presence of low QRS voltages was associated with higher BNP and NT pro-BNP ($P = 0.001$ for both) serum concentrations, whereas Troponin I concentrations were comparable in patients with or without low QRS voltages.

Prognostic Value of “Low QRS Voltages” in Cardiac AL Amyloidosis

As expected, in the whole population of AL amyloidosis patients survival (median follow-up: 14.5 months) was influenced by the presence or absence of “low QRS voltages,” defined as peripheral QRS amplitude $\leq$ 24.5 mm, Sokolow-Lyon index $\leq$ 11 mm or as “low peripheral voltages” ($P = 0.0457$, $P = 0.0028$, and $P = 0.0016$, respectively). In contrast, none of the different quantitative measurements of QRS voltages or of the different categorical definitions of “low QRS voltages” was able to stratify prognosis of the whole cohort of cardiac AL patients. However, when added to the Mayo staging system,³² the presence of “low QRS voltages” (either as peripheral QRS amplitude $\leq$ 24.5 mm or as “low peripheral voltages”) was able to differentiate stage II patients' survival ($P = 0.0344$ and $P = 0.0355$, respectively), whereas it did not affect stage I or stage III mortality (Figure 3). In detail, 6-month and 1-year survival

Figure 3. Kaplan-Meier survival curves according to the Mayo stage and to the presence or absence of low QRS voltages.

was 92% and 88% in stage II patients without "low QRS voltages," as opposed to 85% and 75% in stage II patients with "low QRS voltages."

DISCUSSION

The main result of the present study is that in cardiac AL amyloidosis the prevalence of low QRS voltages is highly dependent on the method used for the definition of this ECG alteration. In a single-center cohort of 233 patients, the prevalence varied from 84.02% when using the definition of Sokolow-Lyon index ≤ 15 mm to 26.94% when defining the presence of low QRS voltages as "low total voltages," that is, QRS amplitude ≤ 5 mm (0.5 mV) in each peripheral lead and QRS amplitude ≤ 10 mm (1 mV) in each precordial lead. The widely used definition of "low peripheral voltages," that is, QRS amplitude ≤ 5 mm (0.5 mV) in each peripheral lead identified 66.36% patients with cardiac AL amyloidosis. Therefore, it is extremely important to clarify the method used to define the presence of low QRS voltages when assessing the prevalence of this feature in a given patient population. As a second point, the present study aimed at defining whether there are differences in

computing QRS voltages either as by adding Q, R, and S respective heights, each taken as absolute value in mV (defined as QRS score in the Methods) or by measuring the total amplitude of the whole QRS complex, from its nadir to its zenith (defined as QRS amplitude in the Methods). Since these two methods were completely superimposable, we elected to use the simpler one, that is, the measurement of QRS amplitude. By this method, a cutoff of ≤ 24.5 mm in the peripheral QRS amplitude had a 80.00% specificity and a 58.72% sensitivity in identifying the 233 patients with cardiac involvement in a consecutive series of 337 AL amyloidosis patients. According to ROC curve analysis, the diagnostic performance of precordial and total QRS amplitudes or scores was significantly worse, whereas a Sokolow-Lyon index ≤ 11 mm was comparable with peripheral QRS amplitude, yielding a 76.26% specificity and a 65.00% sensitivity. Therefore, either low peripheral QRS amplitude or low Sokolow-Lyon index represent an useful electrocardiographic clue in the diagnosis of cardiac involvement in a population of patients with AL amyloidosis. It has to be noted that the cutoff of the Sokolow-Lyon index is lower than the one indicated in the literature for defining low QRS voltages, that is, 15 mm.^{20,22,23}

In the present analysis, the 15 mm cutoff value had higher specificity (84.93%) but much lower sensitivity (45.00%) than the 11 mm cutoff. Moreover, it has to be noted that the presence of pseudoinfarction in a sizeable number of cardiac AL patients (52.2% in the present series) makes the use of this index somewhat questionable, since in its original definition, Sokolow and Lyon excluded patients with previous necrosis.¹⁹ Under this perspective, peripheral QRS amplitude appears more practical, either by using a cutoff of ≤ 24.5 mm in the quantitative measure or by applying the categorical definition of "low peripheral voltages," that is, QRS amplitude ≤ 5 mm (0.5 mV) in each peripheral lead.

Obviously, the diagnosis of cardiac AL amyloidosis cannot be based on the presence of low QRS voltages, NT-proBNP having a much higher diagnostic sensitivity.^{26,31} Moreover, low QRS voltages may be present in other conditions, and in a larger series, we found a 19% (23/119) prevalence of low voltages in patients with non-cardiac AL and a 16% (76/478) prevalence of hypertensive subjects with left ventricular hypertrophy.³⁵ It has also to be noted that the prevalence of low QRS voltage varies in the different amyloidosis types, being particularly low (25%) in the ATTR subset.^{7,36-38} However, a careful look at the simple and widely available 12-lead ECG may be a powerful clue in prompting further analyses, particularly when associated with an unexplained increase in LV mass. In fact, it has to be remembered that in the setting of hypertensive heart disease or hypertrophic cardiomyopathy, echo-derived LV hypertrophy is associated with increased rather than decreased QRS voltages, in contrast with cardiac AL amyloidosis, as shown in a seminal paper by Carroll and coworkers.³⁹

In the present article, the presence of low QRS voltages according to the different quantitative and categorical definitions was associated with a more severe cardiac involvement, as can be derived from the evidence of higher septal thickness, more severely depressed systolic and diastolic function, higher BNP and NT pro-BNP serum concentrations, and higher heart rate. Although these associations did not confer a negative prognostic value to the presence of low QRS voltages in the whole cohort of cardiac AL patients, this ECG feature was able to differentiate Mayo stage II³² patients' survival ($P = 0.0344$), that is, patients with

intermediate survival among the whole population of cardiac AL amyloidosis. Also Kristen and coworkers reported a prognostic value of low QRS voltages in 43 cardiac AL patients,²³ although the lack of cardiac biomarkers does not allow a proper comparison between these two studies. Indeed, cardiac dysfunction as assessed by biomarker concentrations and their changes and hematologic response to treatment are the main prognostic determinants.²⁸

Study Limitations

When considering the diagnosis of cardiac AL amyloidosis, we cannot rely on the presence of low QRS voltages, NT-proBNP having a much higher diagnostic sensitivity.^{26,31} Moreover, low QRS voltages may be present in other conditions as well as in patients without biopsy-proven cardiac involvement. However, from the clinician's standpoint it is important to note that a simple and widely available 12-lead ECG showing low peripheral QRS voltages may be a powerful clue towards the diagnosis of cardiac AL amyloidosis, particularly when associated with an unexplained increase in LV mass.

CONCLUSIONS

In conclusion, in cardiac AL amyloidosis the prevalence of low QRS voltages is highly dependent on the method used for the definition of this ECG alteration. The widely used definition of "low peripheral voltages," that is, QRS amplitude ≤ 5 mm (0.5 mV) in each peripheral lead indentified 66.52% patients with cardiac AL amyloidosis, with a 66.36% sensitivity and a 80.81% specificity. Since in the computation of QRS voltages in each lead no difference is observed between QRS score (obtained by adding Q, R, and S respective mV absolute value) and QRS amplitude (obtained by measuring the total amplitude of the whole QRS complex, from its nadir to its zenith), the latter method may be preferred for its simplicity. A cutoff of ≤ 24.5 mm in the peripheral QRS amplitude had a 80.00% specificity and a 58.72% sensitivity in identifying AL amyloidosis patients with cardiac involvement. Moreover, both these indexes ("low peripheral voltages" and a peripheral

QRS amplitude ≤ 24.5 mm) were able to further stratify Mayo clinic³² stage II patients' survival.

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