ESC HEART FAILURE
ESC Heart Failure (2024)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14655

ORIGINAL ARTICLE

Novel electrocardiographic criteria may render possible the more accurate recognition of cardiac amyloidosis

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Abstract

Aims The early diagnosis of cardiac amyloidosis (CA) is paramount, since there are effective therapies that improve patient survival. The diagnostic accuracy of classical electrocardiographic (ECG) signs, such as low voltage, pseudoinfarct pattern, and conduction disturbances in the diagnosis of CA, is inferior to that of the echocardiographic myocardial deformation criteria; therefore, our aim was to find more accurate novel ECG criteria for this purpose.

Methods We tested the diagnostic value of five novel ECG criteria, two of them devised by us, in 34 patients with confirmed CA (20 transthyretin amyloidosis and 14 AL amyloidosis) and 45 control patients with left ventricular hypertrophy on echocardiography due to hypertension, valvular aortic stenosis and hypertrophic cardiomyopathy. The following novel ECG criteria, that suggested CA, were tested: QRS amplitude in lead I $<$ 0.55 mV (I $<$ 0.55); QRS amplitude in lead aVR $<$ 0.5 mV (aVR $<$ 0.5); average QRS amplitude of leads I + aVR $<$ 0.575 mV [(I + aVR) $<$ 0.575]; average QRS amplitude of leads I + aVR/average QRS amplitude of leads $V_{1–4}$ $<$ 0.375 [(I + aVR)/($V_{1–4}$) $<$ 0.375]; average QRS amplitude of leads I + aVR/longest intrinsicoid deflection in leads I,aVL,$V_{1–6}$ $<$ 0.0115 [(I + aVR)/I,aVL,$V_{1–6}$ID $<$ 0.0115].

Results The I $<$ 0.55, aVR $<$ 0.5, (I + aVR) $<$ 0.575, (I + aVR)/($V_{1–4}$) $<$ 0.375, (I + aVR)/I,aVL,$V_{1–6}$ID $<$ 0.0115 test accuracy (TA) were 81%, 84.8%, 82.3%, 84.8%, and 83.3%, respectively; the sensitivity (SE): 76.5%, 82.4%, 85.3%, 82.4%, and 76.9%; specificity (SP): 84.4%, 86.7%, 80%, 86.7%, and 87.5%; positive predictive values (PPV): 78.8%, 82.4%, 76.3%, 82.4%, and 80%; negative predictive values (NPV): 82.6%, 86.7%, 87.8%, 86.7%, and 85.4%; area under curve (AUC) values: 0.8922, 0.8794, 09016, 0.8824, and 0.8462 were respectively. These parameters of the novel ECG criteria were at least as good as those reported by other authors in the literature of the qualitative (TA: 67%, SE: 80%, SP: 34%, PPV: 75%, NPV: 42%, AUC: 0.57) and quantitative apical sparing (TA: 64–80%, SE: 66–81.3%, SP: 55–78.3%, PPV: 33–83.9%, NPV: 41–75%, AUC: 0.62–0.68) and left ventricular ejection fraction/global longitudinal strain $>$4.1 (TA: 77%, SE: 93%, SP: 38%, PPV: 79%, NPV: 69%, AUC: 0.65) echocardiographic criteria. Among the classical criteria, the low voltage in limb leads criterion was present most frequently (in 73.5%) in patients with CA, with slightly worse diagnostic value than the novel ECG criteria (TA: 78.5%, SE: 73.5%, SP: 82.2%, PPV: 75.8%, NPV: 80.4%).

Conclusions The novel ECG criteria [mostly the aVR $<$ 0.5, (I + aVR)/($V_{1–4}$) $<$ 0.375] seem at least as reliable in the diagnosis of CA as the best echocardiographic myocardial deformation criteria and might be used either together with the echocardiographic criteria or as stand-alone criteria to diagnose CA in the future.

Keywords Cardiac amyloidosis; Electrocardiography; Echocardiography; Myocardial deformation

Received: 22 July 2023; Revised: 4 October 2023; Accepted: 12 December 2023
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Introduction

Cardiac amyloidosis (CA) is an infiltrative, restrictive cardiomyopathy, which is still underdiagnosed and misdiagnosed and now increasingly recognized as an underlying cause of increased left ventricular (LV) wall thickness, therefore may be mistaken with hypertensive cardiomyopathy, aortic stenosis, hypertrophic cardiomyopathy, and Fabry disease. CA has been found in 13% of patients with heart failure with preserved ejection fraction (HFpEF), in 16% of patients with degenerative valvular aortic stenosis and in 9% of patients initially diagnosed as hypertrophic cardiomyopathy. As there are effective therapies that improve survival both in patients with light chain (AL) or transthyretin (ATTR) amyloidosis, the two main subtypes of CA, the early diagnosis of CA is critical to prevent irreversible alterations and to prolong patient survival.[1,2]

The classical electrocardiographic (ECG) signs, such as low QRS voltage, pseudoinfarct pattern, conduction disturbances (atrioventricular block, intraventricular conduction disturbances), although useful in the diagnosis of CA, reportedly have inferior diagnostic accuracy to that of the newer echocardiographic myocardial deformation criteria. The prevalence of ECG signs in CA patients were: low voltage (11–46%), pseudoinfarct pattern (29–50%), atrioventricular (AV) block (22–24%), and intraventricular conduction disturbance (21.7–30.5%).[3–7] The echocardiographic myocardial deformation criteria are present more commonly than the classical ECG signs in patients with CA; therefore, the non-invasive presumptive diagnosis of CA is currently rather based on the presence of these echocardiographic criteria. The visual apical sparing criterion was present in 80.3%, the average apical strain/average basal strain + average mid strain ratio >1.0 criterion in 55–66.2%, the average apical strain/average basal strain ratio >2.1 criterion in 80.3%, and the left ventricular ejection fraction (LVEF)/global longitudinal strain (GLS) > 4.1 criterion in 93% of CA patients.[5,8] Our aim was to test and devise novel ECG criteria that have as good diagnostic accuracy as the echocardiographic myocardial deformation criteria in the non-invasive, presumptive diagnosis of CA.

Methods

Patients

We tested the diagnostic value of five novel ECG criteria in the standard 12-lead ECGs of 34 patients with confirmed CA (20 transthyretin amyloidosis and 14 AL amyloidosis) managed at the Division of Non-Invasive Cardiology Department of Internal Medicine, University of Szeged and 45 control patients with left ventricular hypertrophy on echocardiography (defined as the average septum and left ventricular posterior wall thickness $\geq$12 mm) due to hypertension, valvular aortic stenosis, and hypertrophic cardiomyopathy. CA cases were diagnosed, and CA was ruled out in the control patients, when it was necessary, according to the recent position statement of the ESC Working Group on Myocardial and Pericardial Diseases.[9] This study was a retrospective cohort study, in which we used only the 12-lead ECGs of the patients recorded during routine work-up retrospectively. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the University of Szeged (protocol code: 165/2016). The requirement for written informed consent was waived due to the retrospective nature of the analyses.

Electrocardiogram methods

We tested the following five novel ECG criteria, which suggested the diagnosis of CA: (1) QRS amplitude in lead I $<$ 0.55 mV (I $<$ 0.55), (2) QRS amplitude in lead aVR $<$ 0.5 mV (aVR $<$ 0.5), (3) average QRS amplitude of leads I + aVR $<$ 0.575 mV [(I + aVR) $<$ 0.575], (4) average QRS amplitude of leads I + aVR/average QRS amplitude of leads $V_{1–4}$ $<$ 0.375 [(I + aVR)/$V_{1–4}$ $<$ 0.375], (5) average QRS amplitude of leads I + aVR/longest time to the onset of intrinsicoid deflection (ID) in leads I, aVL,$V_{1–6}$ $<$ 0.0115 [(I + aVR)/I,aVL,$V_{1–6}$ longest ID $<$ 0.0115]. Among the tested five novel ECG criteria the QRS amplitude in lead I and aVR criteria were published by Huang et al.[6] and the idea to devise the average QRS amplitude in leads I + aVR criterion came also from the results of Huang et al.[6]

The idea to devise the (I + aVR)/$V_{1–4}$ $<$ 0.375 criterion came from our observation that although low voltage despite ventricular hypertrophy is characteristic to CA, the QRS voltage in leads $V_{1–4}$ is relatively more preserved compared with other leads, while the low voltage is most conspicuous in the limb leads, and among the limb leads in leads aVR and I. A potential explanation for the relatively preserved QRS voltage in leads $V_{1–4}$ might be that amyloid infiltration usually involves not only the left ventricle, but also the right ventricle. If the right ventricle is not involved by amyloidosis, its normal activation results in an opposite vector to the resultant ventricular activation vector mainly influenced by left ventricular activation and causing the S wave in leads $V_{1–4}$, thereby the right ventricular activation vector diminishing the S wave in these leads. However, if the right ventricle is also involved by amyloid infiltration, the opposite vector of right ventricular activation will be much smaller; therefore, the S waves in leads $V_{1–4}$ will be more preserved. The bottom line idea behind the (I + aVR)/I, aVL,$V_{1–6}$ longest ID $<$ 0.0115 criterion was that the time to the onset of ID (briefly ID) in the anterolateral leads is expected to be prolonged in patients with left ventricular hypertrophy; thus, we used the ID as an indirect electrocardiographic marker of left ventricular hypertrophy, and there is a

low voltage in leads I and aVR despite left ventricular hypertrophy. Since the ID in anterior leads can also be prolonged in bundle branch blocks or nonspecific intraventricular conduction disturbance, the (I + aVR)/I,aVL,$V_{1–6}$ longest ID $<$ 0.0115 criterion could not be applied in patients with these intraventricular conduction disturbance patterns; therefore, we could apply this criterion only in 66 of our 79 patients. The first two authors (A.V. and K.G.) analysed the ECGs blinded to the group the patient belonged to. The following exclusion criteria were applied: patients with a greater than mild amount ($>$5 mm) pericardial effusion, severe chronic obstructive lung disease (COPD) and overt hypothyroidism during the recording of the ECG were excluded from the study, because these conditions can be associated with low voltage and can influence the tested ECG criteria. Initially, 83 patients were enrolled to the study, but four patients were excluded from the study (one patient had both overt hypothyroidism and more than mild pericardial effusion, two patients had overt hypothyroidism, and one patient had more than mild pericardial effusion), because they met the exclusion criteria.

Practical application of the new electrocardiogram criteria

When we measured the QRS amplitude in the limb leads, we measured the sum of the maximum positive (R wave) and negative amplitudes (Q wave or S wave) of the QRS complex and among the QRS complexes in each lead we chose the highest amplitude QRS complex for the analysis.

To measure the time to the onset of ID we used the interval from the onset of the QRS to the peak of the R wave. When QS complex was present in a lead, we used the interval from the QRS onset to S nadir, which should be only negligibly ($\leq$10 ms) longer than the QRS onset to R peak interval. When there were multiple R waves within the QRS complex we chose the R wave preceding the final QRS downstroke.

Both the QRS amplitudes and the times to the onset of ID were measured manually; the QRS amplitude could be estimated with an approximately 0.025 mV and the time to the onset of ID with an approximately 10 ms accuracy.

Statistical analysis

Test accuracy, sensitivity, specificity, positive, and negative predictive values, likelihood ratios as well as receiver-operator characteristic (ROC) curves were calculated by GraphPadPrism version 8 for Windows (GraphPad Software Inc., San Diego, CA, USA) or Excel (Microsoft Office Professional Plus 2016). The number of patients above and below the cut-off values in the ROC curves in the two patient groups was compared using Fisher's exact test. Statistical comparisons of patient characteristics were performed using unpaired *t*-test and Mann–Whitney *U* test for continuous variables, and Fisher's exact test for categorical variables. A *P*-value of $<$0.05 was considered statistically significant. Significant difference between the likelihood ratio values was indicated by disjoint (non-overlapping) 95% confidence intervals (95% CI). The kappa statistic was performed to quantify overall interobserver agreement using the IBM SPSS Statistics 25 for Windows software package (IBM Corp. Armonk, NY, USA). Overall interobserver agreement was defined as near complete if $\kappa > 0.8$, good if κ = 0.61 to 0.8, moderate if κ = 0.41 to 0.6, fair if κ = 0.21 to 0.4 and poor if $\kappa < 0.2$.[10]

Results

Among the demographic and clinical patient characteristics a lower LVEF and BMI, a greater LV mean wall thickness were present in patients with CA and more patients with aortic valve stenosis were present among control patients. There were no between-group differences in other investigated patient characteristics (*Table 1*).

Table 2 demonstrates the clinical stage and disease severity at the time of ECG recording of patients with CA. The staging of ATTR-CA was done according to the Gillmore staging system[11], and the staging of AL-CA was done by applying the European 2015 modification of the Mayo 2004 staging system[12]. Patients with AL-CA were at a more advanced stage than patients with ATTR-CA. When it was possible, we used the ECGs recorded at a date closest to the establishment of CA diagnosis for analysis. The ECGs used for the analysis were recorded either shortly before, or on the day of the diagnosis or $\leq$30 days after the diagnosis in 10/14 (71%) of AL-CA patients and 8/20 (40%) of ATTR-CA patients and $>$30 days after the diagnosis in 4/14 (29%) of AL-CA patients and 12/20 (60%) ATTR-CA patients (not shown). The great majority of control patients were out-patients in a stable and good or relatively good condition, who came in for cardiology consultation on their own feet and 40/45 (89%) of them had a preserved LVEF of $\geq$50%.

After the initial evaluation the two observers using the (I $<$ 0.55), (aVR $<$ 0.5), [(I + aVR) $<$ 0.575] criteria disagreed in the diagnosis of one ECG for each criterion and using the [(I + aVR)/$V_{1–4}$ $<$ 0.375] and [(I + aVR)/I,aVL,$V_{1–6}$ longest ID $<$ 0.0115] criteria disagreed in the diagnosis of 4–4 ECGs; thus, the concordance rate was 78/79 (99%) for the (I $<$ 0.55), (aVR $<$ 0.5), [(I + aVR) $<$ 0.575] criteria and 75/79 (95%) for the [(I + aVR)/$V_{1–4}$ $<$ 0.375] criterion, and 62/66 (94%) for the [(I + aVR)/I,aVL,$V_{1–6}$ longest ID $<$ 0.0115] criterion, but after re-evaluation of these cases, they could resolve the disagreement by consensus. Data based on the consensus of the two observers are presented. Thus, the percentage of agreement between the two observers was $\geq$94% in the case of each criterion and the κ value was

Table 1 Some baseline demographic and clinical characteristics of patients

	CA	C	*P* value
	n = 34	*n* = 45	
Age, years	73.4 ± 9.4	69.5 ± 14.3	NS
Female, *n* (%)	8 (35)	19 (42)	NS
BMI (kg/m^2)	23 ± 2.1	29.6 ± 5.23	0.0001
LVEF (%)	51.5 ± 13.7	57 ± 8.7	0.0326
LV mean wall thickness (mm)	17.5 ± 3.46	14 ± 1.7	0.0001
Baseline rhythm			
Sinus rhythm	23 (68)	39 (87)	NS
Atrial fibrillation	6 (18)	4 (9)	NS
Atrial flutter	0 (0)	1 (2)	NS
Atrial tachycardia	5 (15)	1 (2)	NS
Co-morbidities or underlying diseases that can be associated with LVH			
Hypertension	14 (41)	35 (78)	NS
Aortic valve stenosis	0 (0)	12 (27)	0.003
Hypertrophic cardiomyopathy	0 (0)	3 (7)	NS

BMI, body mass index; C, control; CA, cardiac amyloidosis; LV, left ventricle; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy.

Table 2 Clinical stage and disease severity of our patients with cardiac amyloidosis at the time of ECG recording

Type of amyloidosis	Clinical stage	NYHA stage	eGFR (mL/min/1.73 m2)	NT-pro-BNP (pg/mL)	hs-cTnT (ng/L)
ATTR-CA (*n* = 20)	Gillmore[10] stage: 3 pts. Stage I 11 pts. Stage II 6 pts. Stage III	1 pt. Stage 0 3 pts. Stage I 7 pts. Stage II 8 pts. Stage III 1 pt. Stage III-IV	53.9 ± 22.8	9344 ± 11 068	209.5 ± 265
AL-CA (*n* = 14)	European 2015 modification of the Mayo 2004 staging system[11] 3 pts. Stage II 4 pts. Stage IIIA 7 pts. Stage IIIB	7 pts. NYHA II 7 pts. NYHA III	53.8 ± 20.9	28 248 ± 26 194	192 ± 238

AL-CA, AL-cardiac amyloidosis; ATTR-CA, transthyretin cardiac amyloidosis; eGFR, estimated glomerular filtration rate; hs-cTNT, high-sensitive cardiac troponin T; NT-pro-BNP, N-terminal prohormone of brain natriuretic peptide; pt(s)., patient(s).

Table 3 The occurrence of novel and classical ECG criteria in CA and C patients

ECG criterion	CA *n* = 34	C *n* = 45	*P* value
I < 0.55	26/34 (76%)	7/45 (16%)	<0.001
aVR<0.5	28/34 (82%)	6/45 (13%)	<0.001
(I + aVR) < 0.575	29/34 (85%)	9/45 (20%)	<0.001
(I + aVR)/V_{1-4} < 0.375	28/34 (82%)	6/45 (13%)	<0.001
(I + aVR)/I,aVL,V_{1-6} longest ID<0.0115	20/26 (77%)	5/40 (20%)	<0.001
Low voltage all leads	10/34 (29%)	1/45 (2%)	<0.001
Low voltage limb leads	25/34 (73.5%)	8/45 (18%)	<0.001
Infarct pattern	13/34 (38%)	3/45 (7%)	<0.01
AV conduction disturbance	3/24 (12.5%)	6/39 (15%)	NS
Intraventricular conduction disturbance	12/33 (36%)	10/45 (22%)	NS

AV, atrioventricular; C, control; CA, cardiac amyloidosis; ID, intrinsicoid deflection.

≥0.895 for each criterion, indicating a near complete interobserver agreement.

All five novel ECG criteria were present significantly more commonly in patients with CA than in control patients and were much more commonly present in patients with CA than most classical ECG criteria with the exception of the low voltage in limb leads criterion (*Table 3*). Among the classical ECG criteria, the low voltage in limb leads criterion had the greatest diagnostic value, it was present in 73.5% of patients with CA and in only 18% of control patients (*Table 3*).

The five novel ECG criteria proved to have a great diagnostic value in the diagnosis of CA, which is convincingly demonstrated by their ROC curves with AUCs between 0.8462–0.9016 (*Figure 1*).

All novel ECG criteria with cut-off values determined by the analysis of the ROC curves had high (≥80%) test accuracy (TA),

Figure 1 The ROC curves of the novel ECG criteria. QRSa I = I < 0.55 criterion, QRSa aVR = aVR < 0.5 criterion, QRSa (I + aVR) = (I + aVR) < 0.575 criterion.

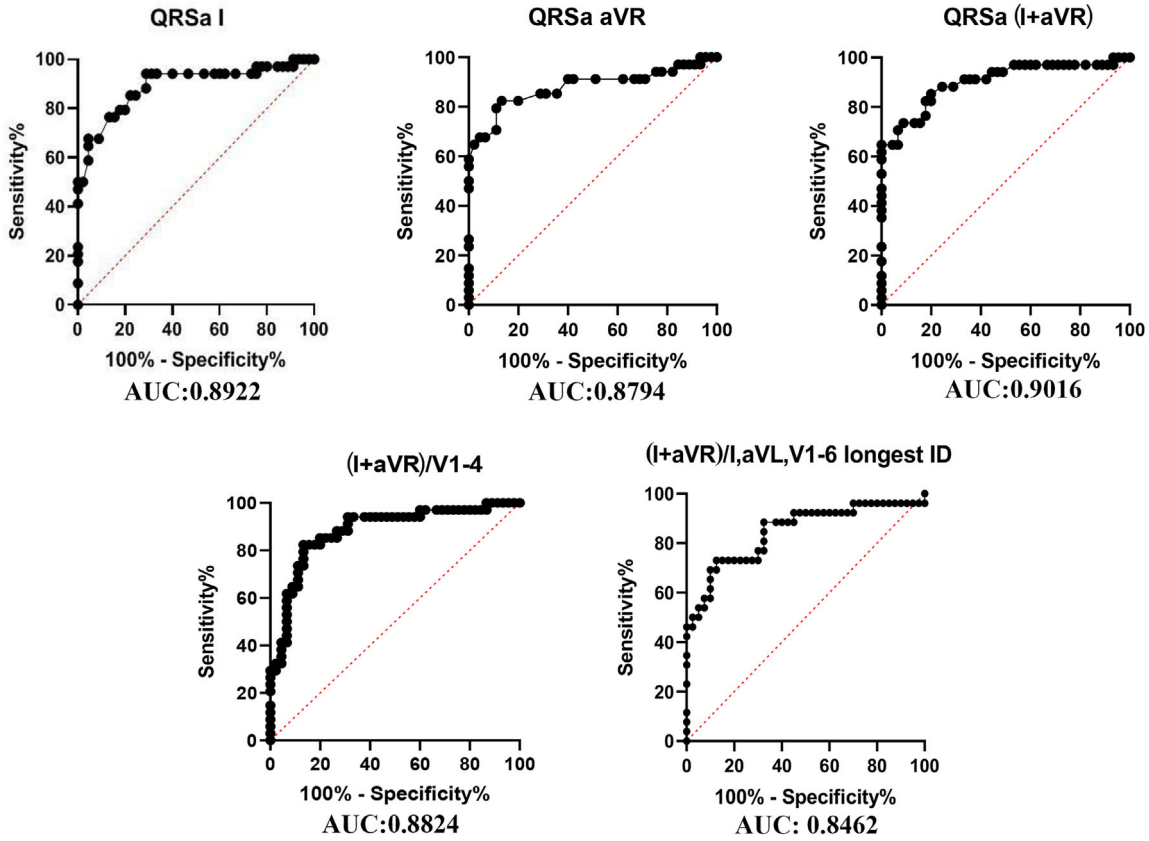
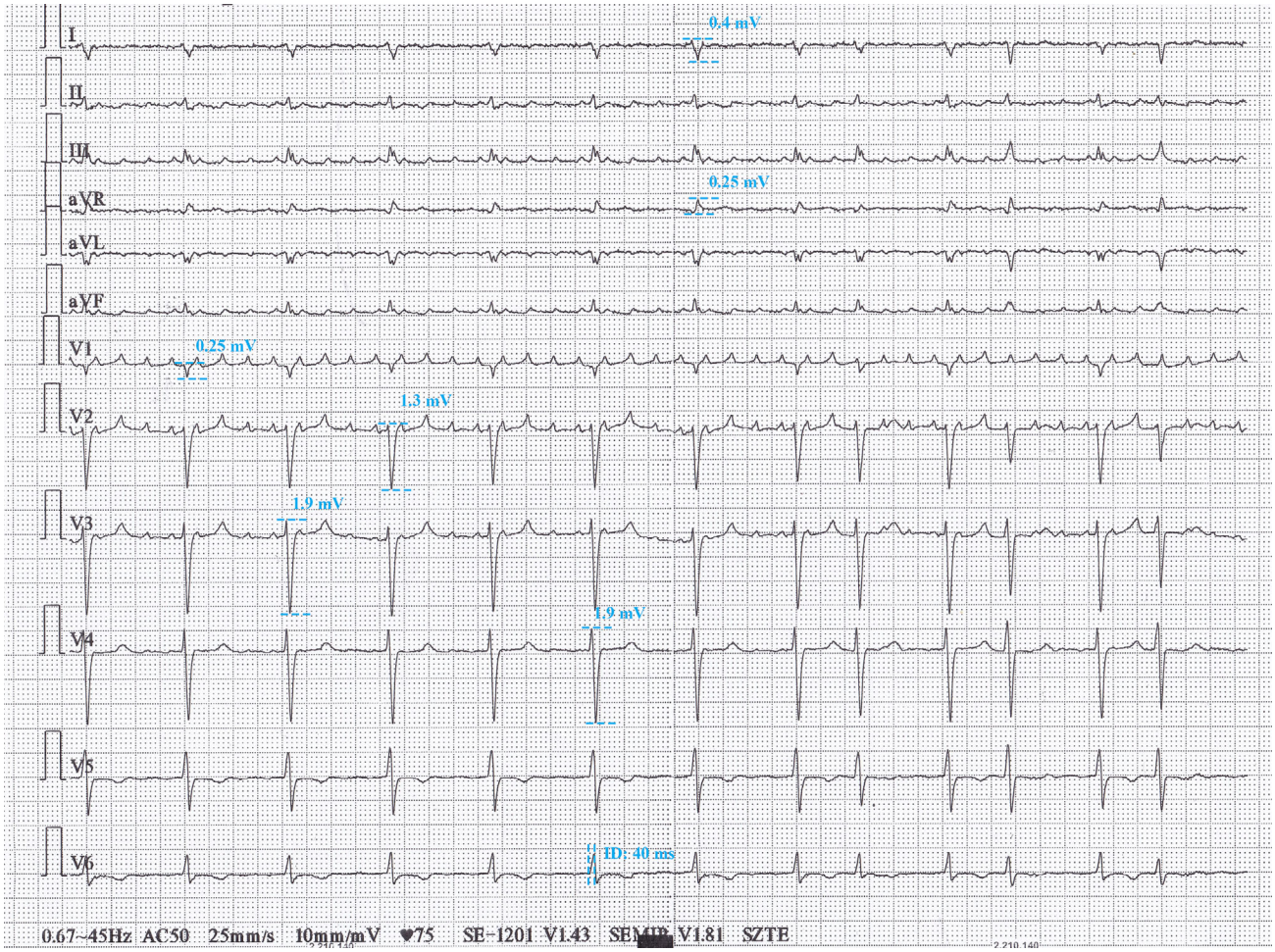


Table 4 The sensitivity, specificity, predictive values, test accuracy, and likelihood ratios of the novel and classical ECG criteria

ECG criteria	SE	SP	PPV	NPV	TA	+LR	−LR
	%	%	%	%	%		
	95% CI	95% CI	95% CI	95% CI	95% CI	95% CI	95% CI
I < 0.55	76.5	84.4	78.8	82.6	81	4.916	0.279
	62.2–90.7	73.9–95	64.8–92.7	71.7–93.6	72.4–89.7	2.427–9.957	0.15–0.517
aVR < 0.5	82.4	86.7	82.4	86.7	84.8	6.176	0.204
	69.5–95.2	76.7–96.6	69.5–95.2	76.7–96.6	76.9–92.7	2.886–13.22	0.098–0.425
(I + aVR) < 0.575	85.3	80	76.3	87.8	82.3	4.265	0.184
	73.4–97.2	68.3–91.7	62.8–89.8	77.8–97.8	73.9–90.7	2.339–7.777	0.081–0.418
(I + aVR)/V_{1-4} < 0.375	82.4	86.7	82.4	86.7	84.8	6.176	0.204
	69.5–95.2	76.7–96.6	69.5–95.2	76.7–96.6	76.9–92.7	2.886–13.22	0.098–0.425
(I + aVR)/I,aVL,V_{1-6} longest ID < 0.0115	76.9	87.5	80	85.4	83.3	6.154	0.264
	60.7–93.1	77.3–97.7	64.3–95.7	74.5–96.2	74.3–92.3	2.639–14.349	0.129–0.537
Low voltage in limb leads	73.5	82.2	75.8	80.4	78.5	4.136	0.322
	58.7–88.4	71.1–93.4	61.1–90.4	69–91.9	60.4–87.5	2.138–8.002	0.181–0.573
Low voltage in all leads	29.4	97.8	90.9	64.7	68.4	13.235	0.722
	14.1–44.7	93.5–102.1	73.9–107.9	53.3–76.1	58.1–78.6	1.779–98.467	0.579–0.901
Infarct pattern	38.2	93.3	81.3	66.7	69.6	5.735	0.662
	21.9–54.6	86–100.6	62.1–100.4	55–78.3	59.5–79.8	1.773–18.548	0.502–0.872
AV conduction disturbance	12.5	84.6	33.3	61.1	57.1	0.813	1.034
	0–25.7	73.3–95.9	2.5–64.1	48.1–74.1	44.9–69.4	0.224–2.95	0.845–1.265
Intraventricular conduction disturbance	36.4	77.8	54.5	62.5	60.3	1.636	0.818
	20–52.8	65.6–89.9	33.7–75.4	49.8–75.2	49.4–71.1	0.805–3.325	0.605–1.106

AV, atrioventricular; CI, confidence interval; ID, intrinsicoid deflection; −LR, negative likelihood ratio; +LR, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; SE, sensitivity; SP, specificity; TA, test accuracy.

Figure 2 The 12-lead ECG of a patient with transthyretin CA. All novel ECG criteria suggest the diagnosis of CA. The QRS amplitudes in leads I, aVR are 0.4 and 0.25 mV respectively, the average of these amplitudes is 0.325 mV; therefore, the I < 0.55, aVR < 0.5, (I + aVR) < 0.575 criteria suggest the presumptive diagnosis of CA. The average QRS amplitude in leads $V_{1–4}$ is (0.25 + 1.3 + 1.9 + 1.9)/4 = 1.3375 mV; therefore, the (I + aVR)/$V_{1–4}$ criterion = 0.325/1.3375 = 0.243; thus, the (I + aVR)/$V_{1–4}$ < 0.375 criterion is positive and suggests CA. The longest ID in leads I, aVL, $V_{1–6}$ is 40 ms in lead V_6; thus, the (I + aVR)/I,aVL,$V_{1–6}$ longest ID criterion = 0.325/40 = 0.0081; therefore, the (I + aVR)/I,aVL,$V_{1–6}$ longest ID < 0.0115 criterion is positive and suggests CA. Among the classical criteria the low voltage in limb leads criterion was present. Short, blue, horizontal, dashed lines mark the QRS amplitudes and short, blue, vertical, dashed lines mark the ID, and blue letters and numbers denote the obtained values, which are necessary for the determination of novel ECG criteria.



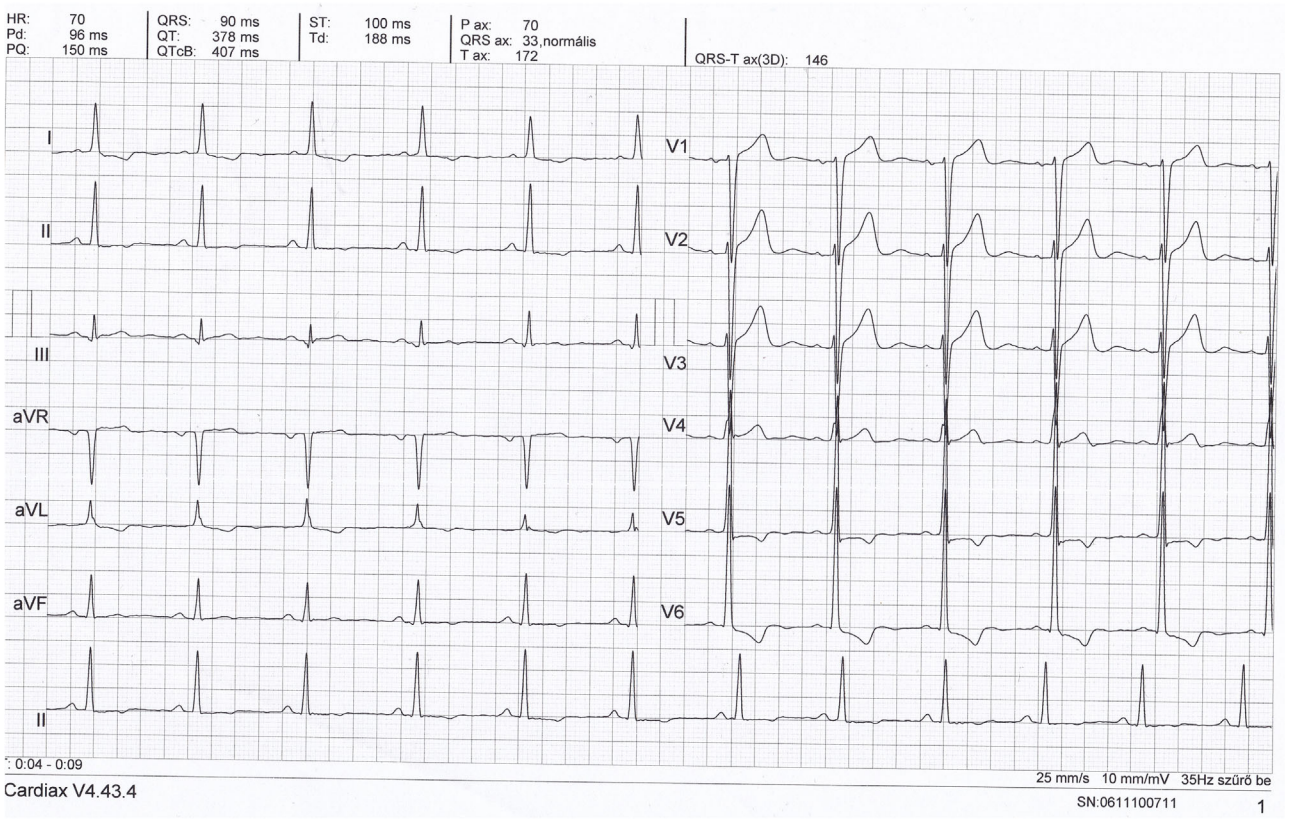
negative predictive value (NPV), and specificity (SP) (*Table 4*). Taking into consideration the sensitivity (SE), SP, positive predictive value (PPV), NPV and TA values, the aVR < 0.5 and the (I + aVR)/$V_{1–4}$ < 0.375 criteria showed the greatest diagnostic accuracy among the five novel ECG criteria in the diagnosis of CA (*Table 4*). *Table 4* demonstrates that the diagnostic value of the novel ECG criteria is much greater than that of the classical ECG criteria, with the only exception of low voltage in limb leads classical ECG criterion, which has only a slightly worse diagnostic accuracy than the novel ECG criteria in the diagnosis of CA. The diagnostic accuracy of the novel ECG criteria was at least as good for the diagnosis of CA as that of the recommended echocardiographic myocardial deformation criteria, such as the visual (qualitative) apical sparing, the average apical strain/average basal strain + average mid strain >1.0, the average apical strain/average basal strain >2.1, the left ventricular ejection fraction (LVEF)/global longitudinal strain (GLS) > 4.1, published by other authors.[5,8,13] The practical application of the novel ECG criteria is demonstrated in *Figures 2* and *3*.

Discussion

Major observations

We tested five newer ECG criteria devised for the diagnosis of CA, three of which are based on the publication of Huang

Figure 3 The 12-lead ECG of a control patient with hypertension and aortic valve stenosis. The novel limb leads ECG criteria are not present, the QRS amplitudes in leads I and aVR were 1.15 and 1.075 mV respectively, the average (I + aVR) QRS amplitude was 1.1 mV. The average QRS amplitude in leads $V_{1–4}$ was 2.306 mV; thus, the (I + aVR)/$V_{1–4}$ criterion = 1.1/2.306 = 0.477; therefore, the (I + aVR)/$V_{1–4}$ < 0.375 criterion is also not met. The longest ID in leads I, aVL, V1–6 was 55 ms in lead aVL; thus, the (I + aVR)/I,aVL,$V_{1–6}$ longest ID criterion = 1.1/55 = 0.02; therefore, the (I + aVR)/I, aVL,$V_{1–6}$ longest ID < 0.0115 criterion is not met. None of the classical ECG criteria of CA is present.



et al.[6] and two of which are novel ECG criteria devised by us. These five novel ECG criteria proved to have a much greater diagnostic accuracy than the classical ECG criteria recommended for the diagnosis of CA (with the exception of low QRS voltage in limb leads criterion, which had only a slightly lower diagnostic accuracy) and at least as good diagnostic accuracy as that published for the recommended echocardiographic myocardial deformation criteria by other authors, which are currently most frequently used to set up the presumptive, non-invasive diagnosis of CA. The greatest importance of our results is that the combination of novel ECG criteria with the best echocardiographic myocardial deformation criteria, or the novel ECG criteria as stand-alone criteria can improve the establishment of an accurate, quick, non-invasive, presumptive CA diagnosis in the future. It was not surprising that the best classical ECG criterion was the low QRS voltage in limb leads criterion, because it is related to three out of the five new ECG criteria, which are also based on low voltage in one or two limb leads.

The diagnostic value of the echocardiographic myocardial deformation criteria reported in the literature

Löfbacka et al.[13] reported 80% TA, 81.3% SE, 78.3% SP, 83.9% PPV, and 75% NPV of the relative apical sparing (average apical strain/average basal strain + average mid strain >1.0) criterion. For the same criterion, Nakao et al.[5] reported a TA of 87.5%, and Kyrouac et al.[8] reported a 64% TA, 66% SE, 59% SP, 80% PPV, 41% NPV and an AUC of 0.62. The TA, SE, SP, PPV, NPV, AUC of the LVEF/GLS > 4.1, the average apical strain/average basal strain >2.1, and the visual (qualitative) apical sparing criteria were 77%, 93%, 38%, 79%, 69%, and 0.65; 73%, 80%, 55%, 81%, 53%, 0.68; 67%, 80%, 34%, 75%,

42%, and 0.57, respectively.[8] Bavishi et al.[14] reported a PPV of 38.6% of relative apical sparing of longitudinal strain with a strain ratio ≥2.0 (although they did not define it accurately, it was probably a ratio of average apical strain/average basal strain) for patients with confirmed or suspicious CA. Wali et al.[15] reported very similar results, among patients with the relative apical sparing (average apical strain/average basal strain + average mid strain >1.0) criterion only 33% of patients had confirmed or highly probable CA; thus, the PPV of this criterion was only 33%. These data support our statement that the diagnostic value of the novel ECG criteria is at least as good as that of the best myocardial deformation criteria, which are most commonly used to establish the non-invasive, presumptive diagnosis of CA.

There are some data in the literature that the diagnostic accuracy of apical sparing for CA is reduced due to false positive results in certain diseases. The relative apical sparing criterion had a reduced TA of 78% for CA in patients with chronic kidney disease.[16] The presence of relative apical sparing was also reported in patients with primary hyperoxaluria type 1, a hereditary cause of progressive nephrocalcinosis, that commonly leads to end-stage renal failure due to relatively lower accumulation of oxalate crystals in the apex compared with the basal and mid segments.[17] The relative apical sparing criterion was present in 15.3% of patients with severe, symptomatic valvular aortic stenosis in whom CA was ruled out by histological examination, and proved to be mostly (in 91% of cases) reversible after aortic valve replacement surgery.[18] In another study the relative apical sparing criterion was present in much more (88%) patients with severe aortic valve stenosis before transcatheter aortic valve implantation (TAVI) and after TAVI it was found in only 77% of the patients.[15] The latter two studies[18,19] showed that the presence of relative apical sparing was associated with more severe aortic valve disease, left ventricular dysfunction and hypertrophy, which was in some or most cases reversible after aortic valve replacement.

Löfbacka et al.[13] reported a somewhat better diagnostic value of R in aVR ECG criterion than that of the relative apical sparing echocardiographic criterion based on their SE, SP, PPV, NPV, TA values, and AUCs. Moreover, these authors[13] suggested that the best non-invasive method to set up the presumptive diagnosis of CA may be the combination (a ratio) of an echocardiographic parameter of left ventricular mass or myocardial deformation criterion in the numerator and an ECG voltage criterion in the denominator of the ratio. They found the best diagnostic accuracy with the following combination ratios: relative wall thickness (RWT)/R wave amplitude in lead aVR (AUC: 0.99), relative apical sparing/R wave amplitude in lead aVR (AUC: 0.96) and posterior wall thickness (PWT)/R wave amplitude in lead aVR (AUC: 0.96). The RWT was calculated in the following way: 2× posterior wall thickness (PWT)/left ventricular diastolic diameter (LVDd).

Limitations

The retrospective and single-centre nature of our study are important limitations. Another limitation, which is due to the retrospective nature of the study, that we did not perform a systematic prospective comparison of the diagnostic value of the novel ECG criteria with that of the echocardiographic myocardial deformation criteria in our patients during the study. The relatively low number of controls and patients with CA is also a limitation.

Conclusions

In conclusion, the five novel ECG criteria tested in our study had a better diagnostic accuracy in the diagnosis of CA than the classical ECG criteria and at least as good diagnostic accuracy as that of the echocardiographic myocardial deformation criteria reported by other authors in the literature. Among the classical ECG criteria, the low voltage in limb leads criterion had the best diagnostic value. Due to the important limitations, our results can be considered preliminary. In the future, the combined application of the novel ECG criteria with the echocardiographic myocardial deformation (or left ventricular mass) criteria may render possible a more accurate and faster establishment of the non-invasive, presumptive diagnosis of CA.

Author contributions

András Vereckei designed the study, devised some of the novel ECG criteria, analysed the ECGs, and participated in the preparation of the manuscript. Gábor Katona analysed the ECGs, participated in patient recruitment, and data analysis. Viktória Nagy, Hedvig Takács, and László Dániel Vidács participated in data acquirement, patient recruitment and management, and interpretation of some data. Gábor Szénási performed the statistical analysis and contributed to the preparation of the manuscript. Róbert Sepp supervised the data acquirement, contributed to the preparation of the manuscript, and the interpretation of data and to the study design.

Funding sources

None.

Conflict of interest

None declared.

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