ORIGINAL ARTICLE

The Findings of Electrocardiography in Patients with Cardiac Amyloidosis

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Objective: The electrocardiography (ECG) was the simplest and common adjunctive diagnostic tool for cardiac amyloidosis (CA). We sought to clarify the findings of ECG in patients with CA in order to early identification of CA according to the findings of ECG.

Methods: A total of 276 patients with diagnosis of systemic amyloidosis admitted to Peking Union Medical College Hospital from January 2000 to December 2011, were enrolled. Two groups were classified according to the cardiac involvement or not, namely CA (n = 189) and control (n = 87) groups. The low voltage on limb leads defined by the amplitude of the QRS complex in each limb leads ≤0.5 mV. The pseudo-infarct pattern defined by the presence of pathologic Q waves on at least two contiguous leads on ECG without obstructive coronary artery disease.

Results: The mean age was 55 ± 12 (15–88) years, 168 patients (61%) were male. Atrial arrhythmia (15.9% vs 3.4%, P = 0.003), low voltage on limb leads (54.5% vs 20.7%, P < 0.001), atrioventricular block (14.8% vs 1.1%, P = 0.001) and pseudo-infarct pattern (40.2% vs 4.6%, P < 0.001) were more prevalent in CA than control groups. The combination of low voltage on limb leads and pseudo-infarct pattern was more common (28.0% vs 2.3%, P < 0.001) in CA than control groups. The sensitivity, specificity, positive and negative predictive values of the presence of low voltage on limb leads and pseudo-infarct pattern for the diagnosis of CA were 28%, 98%, 96%, and 39%, respectively.

Conclusion: In CA patients, low voltage on limb leads and pseudo-infarct pattern were the most common ECG findings. Atrial arrhythmia and atrioventricular block were the most common arrhythmias in CA patients. The combination of low voltage on limb leads and pseudo-infarct pattern had high specificity and positive predictive value for the diagnosis of CA.

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electrocardiography; cardiac amyloidosis; low voltage on limb leads; pseudo-infarct pattern

Amyloidosis frequently involves the heart. Deposition of amyloid fibrils in myocardial tissue results in reduced ventricular compliance with impairment of relaxation and eventually contraction. Amyloid fibrils may also deposit in myocardial vessels and cause local ischemia. Amyloid deposition is associated with fibrosis of conduction tissue, resulting in conduction abnormalities and arrhythmias. Cardiac amyloidosis (CA) is associated with a variable but generally poor prognosis,[1–4] and early recognition may is the simplest and common adjunctive diagnostic tool for CA. However, the findings of ECG in patients with CA remain unclear. In this study, we aimed to determine the findings of ECG in patients with CA and thus as a clue for the early identification and diagnosis of CA.

METHODS

Study Population

This was a single center, retrospective study of 276 patients with systemic amyloidosis (at least

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one tissue or organ biopsy with positive Congo red staining and demonstration of apple-green birefringence under polarized light) who admitted to Peking Union Medical College Hospital from January 2000 to December 2011, were enrolled. A total of 189 patients diagnosed of CA (or systemic amyloidosis with cardiac involvement) who met one of the following criteria, were classified into CA group.

(1) Endomyocardial biopsy (EMB) confirmed the diagnosis of CA.
(2) The presence of clinical and laboratory evidence of amyloidosis and echocardiographic features of amyloidosis, include a mean left ventricular wall thickness (septum and posterior wall) greater than 12 mm in the absence of hypertension or other potential causes of left ventricular hypertrophy; right ventricular free wall thickening in the presence of left ventricular thickening and in the absence of pulmonary or systemic hypertension.[1]

The remaining 87 patients without cardiac involvement were classified into control group.

Data Collection

We performed a detailed examination of the medical records of the 276 patients after obtaining the approval from Institutional Review Board of Peking Union Medical College Hospital. A review of the medical records was performed by a team of physicians blinded to the grouping.

The ECG was analyzed for the following characteristics: rhythm, conduction abnormalities (such as right or left bundle branch block), a low voltage pattern (defined by the amplitude of the QRS complex in each limb leads ≤ 0.5 mV[5], a pseudo-infarct pattern (pathologic Q waves on at least two contiguous leads on ECG without obstructive coronary artery disease by coronary angiography or computed tomography angiography). In addition, we calculated the voltages of QRS complex in all 12 leads, and the QRS duration, QT as well as QTc interval. The QTc interval was QT interval corrected for the heart rate according to Bazett's formula ($QTc = QT/\sqrt{RR}$). The unit of ECG leads voltage is millivolt.

The ECHO was analyzed for the following characteristics: left atrial (LA) size, interventricular septal (IVS) thickness, left ventricular posterior wall (LVPW) thickness, left ventricular end of diastolic diameter (LVEDD), left ventricular end of systolic diameter (LVESD), pericardial effusion, left ventricular ejection fraction (LVEF), and E/A ratio. Transthoracic ECHO was performed using commercially available GE Vivid seven Ultrasound machines (Horten, Norway). IVS and LVPW thicknesses were measured in standard fashion according to American Society of Echocardiography guidelines.[6] Also, LA size and LVEDD as well as LVESD were measured in standard fashion. LVEF was assessed using the biplane Simpson's equation from apical two-chamber views. Mitral inflow peak velocities of E and A waves, were measured in patients in normal sinus rhythm, E/A-wave ratio was calculated in standard fashion.

Statistical Analysis

Data were reported as mean ± standard deviation (SD) for continuous variables or percentage for categorical variables. Differences in baseline characteristics between the two groups were evaluated with paired *t*-tests or Mann-Whitney U test for all continuous variable, all categorical variables were compared using chi-square test or Fisher's exact test. All P values were two-sided and the results were considered statistically significant at the level of $P < 0.05$. SPSS statistical software of version 13.0 for windows was used for all statistical analyses.

RESULTS

Patients

A total of 276 patients with systemic amyloidosis were enrolled. The mean age was 55 ± 12 (15–88) years, 168 patients (61%) were male. Twenty-eight patients (10%) died during the stay of hospitalization, including heart failure in 16 patients (5.8%), sudden death in six patients (2.2%), septic shock in four patients (1.4%) and pulmonary infection in two patients (0.7%). The concomitant diseases were diabetes mellitus in 19 patients (6.9%), ischemic stroke in eight patients (2.9%). The classification of amyloidosis were primary (immunoglobulin light chains) CA in 170 patients (61.6%), CA associated with multiple myeloma in 52 patients (18.8%), secondary CA in 16 patients (5.8%), hereditary CA in 6 patients (2.2%), and unclassified CA in 32 patients (11.6%).

Electrocardiographic Findings

Tables 1–3 summarized the ECG findings of the 276 patients. Atrial arrhythmia (15.9% vs 3.4%,

Table 1. Electrocardiographic Findings

Variables	All (n = 276)	CA (n = 189)	Control (n = 87)	P value
Rhythm				
Atrial arrhythmia[a]	33 (12.0%)	30 (15.9%)	3 (3.4%)	0.003
Low voltage on limb leads	121 (43.8%)	103 (54.5%)	18 (20.7%)	<0.001
Conduction abnormalities	42 (15.2%)	39 (20.6%)	3 (3.4%)	<0.001
Atrioventricular block	29 (10.5%)	28 (14.8%)	1 (1.1%)	0.001
Third degree	4 (1.4%)	3 (1.6%)	1 (1.1%)	1.000
First degree	25 (9.1%)	25 (13.2%)	0	<0.001
Left bundle branch block	4 (1.4%)	4 (2.1%)	0	0.312
Right bundle branch block	14 (5.1%)	13 (6.9%)	1 (1.1%)	0.072
Pseudo-infarct pattern	80 (29.0%)	76 (40.2%)	4 (4.6%)	<0.001
Combination of low voltage on limb leads and pseudo-infarct pattern	55 (19.9%)	53 (28.0%)	2 (2.3%)	<0.001

[a]Including atrial fibrillation, atrial flutter and atrial tachycardia.

Table 2. The Voltages of QRS Complex of the 12 Leads

Leads	All (n = 276)	CA (n = 189)	Control (n = 87)	P value
I (mV)	0.46 ± 0.30	0.40 ± 0.27	0.58 ± 0.34	<0.001
II (mV)	0.55 ± 0.31	0.48 ± 0.30	0.69 ± 0.28	<0.001
III (mV)	0.46 ± 0.31	0.48 ± 0.34	0.44 ± 0.23	0.918
aVR (mV)	0.44 ± 0.26	0.37 ± 0.24	0.59 ± 0.25	<0.001
aVF (mV)	0.47 ± 0.36	0.45 ± 0.39	0.50 ± 0.27	0.016
aVL (mV)	0.39 ± 0.25	0.38 ± 0.26	0.40 ± 0.22	0.120
V_1 (mV)	0.85 ± 0.52	0.81 ± 0.53	0.95 ± 0.49	0.009
V_2 (mV)	1.67 ± 1.96	1.68 ± 2.32	1.65 ± 0.73	0.150
V_3 (mV)	1.60 ± 0.84	1.58 ± 0.89	1.65 ± 0.73	0.290
V_4 (mV)	1.50 ± 0.76	1.42 ± 0.76	1.68 ± 0.72	0.003
V_5 (mV)	1.23 ± 0.75	1.14 ± 0.75	1.44 ± 0.70	<0.001
V_6 (mV)	0.91 ± 0.58	0.80 ± 0.54	1.13 ± 0.61	<0.001

Table 3. QRS Duration, QT, and QTc Intervals

Variables	All (n = 276)	CA (n = 189)	Control (n = 87)	P value
QRS duration (ms)	93 ± 28	95 ± 22	90 ± 38	0.002
QT interval (ms)	377 ± 48	382 ± 49	368 ± 44	0.019
QTc interval (ms)	444 ± 39	451 ± 40	428 ± 32	<0.001

P = 0.003), low voltage on limb leads (54.5% vs 20.7%, P < 0.001), atrioventricular block (14.8% vs 1.1%, P = 0.001) and pseudo-infarct pattern (40.2% vs 4.6%, P < 0.001) were more prevalent in CA than control groups. The combination of low voltage on limb leads and pseudo-infarct pattern was more common (28.0% vs 2.3%, P < 0.001) in CA than control groups. The sensitivity, specificity, positive and negative predictive values of the presence of low voltage on limb leads and pseudo-infarct pattern for the diagnosis of CA were 28%, 98%, 96%, and 39%, respectively. The voltages of leads I (0.40 ± 0.27 vs 0.58 ± 0.34 mV, P < 0.001), II (0.48 ± 0.30 vs 0.69 ± 0.28 mV, P < 0.001), aVR (0.37 ± 0.24 vs 0.59 ± 0.25 mV, P < 0.001), V_1 (0.81 ± 0.53 vs 0.95 ± 0.49 mV, P = 0.009), V_4 (1.42 ± 0.76 vs 1.68 ± 0.72 mV, P = 0.003), V_5 (1.14 ± 0.75 vs 1.44 ± 0.70 mV, P < 0.001) and V_6 (0.80 ± 0.54 vs 1.13 ± 0.61 mV, P < 0.001) were significantly lower in CA than control groups. QRS duration (95 ± 22 vs 90 ± 38 ms, P = 0.002), QT (382 ± 49 vs 368 ± 44 ms, P = 0.019) and QTc (451 ± 40 vs 428 ± 32 ms, P < 0.001) intervals were significantly longer in CA than control groups. Figure 1 showed the typical ECG findings of low voltage on limb leads and pathologic Q waves in one 46-year old male patient with primary CA.

Echocardiographic Findings

Table 4 summarized the ECHO findings of the 276 patients. The LVEDD was significantly smaller

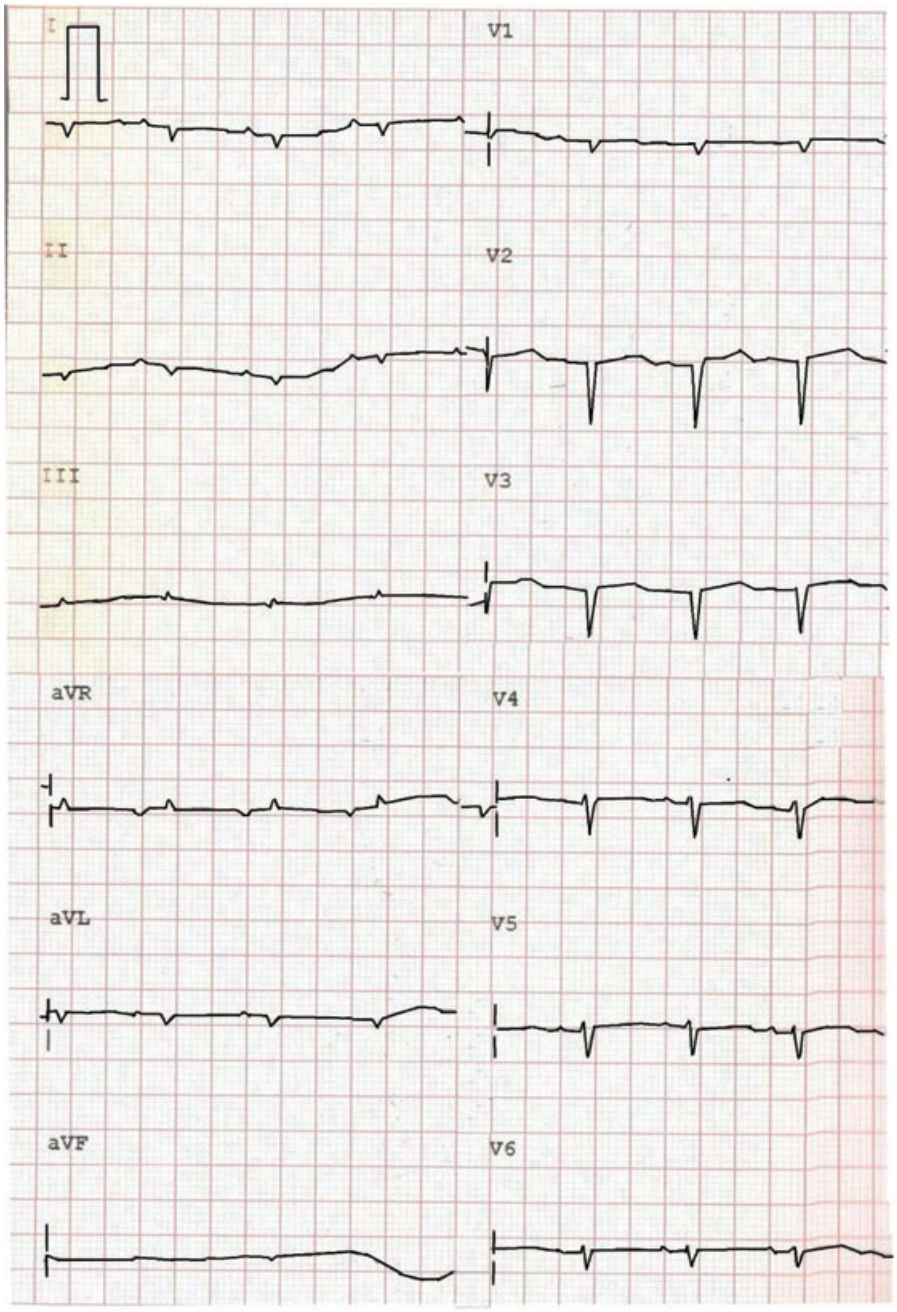

Figure 1. The ECG of one 46-year old male patient with primary cardiac amyloidosis revealed the low voltage on limb leads and pseudo-infarct pattern (pathologic Q waves on leads V_1 to V_3).

in CA than control groups (44 ± 6 vs 47 ± 6 mm, $P < 0.001$). The LVEF was significantly lower in CA than control groups (56 ± 14% vs 65 ± 7%, $P < 0.001$). The LA dimension was significantly larger in CA than control groups (41 ± 7 vs 36 ± 6 mm, $P < 0.001$). The thicknesses of IVS (14 ± 2 vs 9 ± 2 mm, $P < 0.001$) and LVPW (13 ± 1 vs 8 ± 1 mm, $P < 0.001$) were significantly thicker in CA than control groups. The incidence of LVEF ≤ 50% (32.3% vs 4.6%, $P < 0.001$) and pericardial effusion (65.1% vs 24.1%, $P < 0.001$) were significantly more common in CA than control groups.

Table 4. Echocardiographic Features

Variables	All (n = 276)	CA (n = 189)	Control (n = 87)	P value
LVEDD (mm)	45 ± 7	44 ± 6	47 ± 6	<0.001
LVESD (mm)	31 ± 6	31 ± 7	31 ± 6	0.764
LVEF (%)	59 ± 13	56 ± 14	65 ± 7	<0.001
LA (mm)	40 ± 7	41 ± 7	36 ± 6	<0.001
E/A ratio	1.4 ± 0.9	1.6 ± 0.9	0.9 ± 0.4	<0.001
IVS (mm)	12 ± 3	14 ± 2	9 ± 2	<0.001
LVPW (mm)	12 ± 3	13 ± 1	8 ± 1	<0.001
LVEF ≤ 50%	65(23.6%)	61(32.3%)	4(4.6%)	<0.001
Pericardial effusion	144(53.0%)	123(65.1%)	21(24.1%)	<0.001

CA = cardiac amyloidosis; LVEDD = left ventricular end of systolic dimension; LVESD = left ventricular end of systolic dimension; LVEF = left ventricular ejection fraction; LA = left atrial dimension; IVS = interventricular septum; LVPW = left ventricular posterior wall.

DISCUSSION

This was a large CA cohort. The prognosis of CA was poor once the occurrence of symptoms, therefore, the early diagnosis was important for the early treatment.[7] ECG was an important adjunctive diagnostic tool and clue for the identification of possible CA. This study revealed several classical and important findings of ECG in CA patients. The low voltage on limb leads was the most common finding, followed by pseudo-infarct pattern and atrioventricular block. The combination of low voltage on limb leads and pseudo-infarct pattern was more common in CA than control groups, it had high specificity and positive predictive value for the diagnosis of CA. Atrial arrhythmia was very common in CA patients. The results of the present study were similar with previous reports.[8–11] Murtagh et al.[8] from the Mayo Clinic reported that 127 patients with biopsy-proven primary CA and found that the low voltage was present in 46% of patients and a pseudo-infarct pattern was present in 47% of patients. The pseudo-infarct patterns were anterior (36%), inferior (12%), and lateral (14%). Both low voltage and pseudo-infarct pattern were present in 25% of patients. Atrial fibrillation and flutter was the most common arrhythmia. Rahman et al.[9] reported that the low voltage was in 56% and pseudo-infarct pattern was in 60% of patients. Austin et al.[10] reported that 45 patients with biopsy-proven CA, the low voltage was seen in 27% of patients. Another important finding was the increased thicknesses of IVS and LVPW, its reverse relationship with the voltages of limb leads, the similar finding with previous reports. The presence of above mentioned findings of ECG or the reverse relationship between the thickness of IVS/LVPW and voltages of limb leads strongly supported the possibility of CA after excluding other potential diseases. Rahman et al.[9] reported that the low voltage on limb leads associated with IVS thickness > 1.98 cm, the diagnosis of CA could be made with a sensitivity of 72% and a specificity of 91%, the positive and negative predictive values were 79% and 88%, respectively. Cheng et al.[11] studied the ECG and ECHO features of 11 patients with biopsy-proven CA, concluded the ratio of R(I) / LVPW < 0.4 for the diagnosis of CA had the sensitivity of 91% and specificity of 100%, the positive and negative predictive values of 100% and 91%, respectively; the ratios of R(V5/6) /LVPW < 0.7 had the sensitivity of 91% and specificity of 89%, the positive and negative predictive values of 91% and 89%, respectively.

Limitations

This study had several limitations. First, the diagnosis of CA wasn't all based on EMB, the majority of patients in CA group diagnosed from typical ECHO features of CA and pathological evidence of extra-cardiac tissue or organ. Second, the ECG features of different type of CA would be variable. Rapezzi et al.[12] reported that hereditary CA patients less often displayed low voltage than primary CA patients (25% vs 60%; P < 0.0001). This study didn't classify all the CA patients and determine the different ECG findings of different type of CA. Third, the ECG findings of CA was the clue for identification of possible CA, couldn't substitute the EMB of the golden standard for the diagnosis of CA. Although the above-mentioned limitations, combination of low voltage

on limb leads and pseudo-infarct pattern had high specificity and positive predictive value for the identification and early diagnosis of CA.

CONCLUSION

In the large cohort of CA patients, low voltage on limb leads and pseudo-infarct pattern were the most common ECG findings. Atrial arrhythmia and atrioventricular block were the most common arrhythmias in CA patients. The combination of low voltage on limb leads and pseudo-infarct pattern had high specificity and positive predictive value for the diagnosis of CA.

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