Utility of Combined Indexes of Electrocardiography and Echocardiography in the Diagnosis of Biopsy Proven Primary Cardiac Amyloidosis

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Objective: Primary cardiac amyloidosis (CA) is associated with poor prognosis. However, the noninvasive diagnostic tools are limited. The aim of the study is to assess the utility of combined indexes of electrocardiography (ECG) and echocardiography (ECHO) in the diagnosis of primary CA.

Methods: A total of 20 consecutive patients (7 men, mean age 50 ± 12 years) referred for endomyocardial biopsy (EMB) were included. Eleven of these patients (55%) confirmed primary CA, the rest of 9 patients were EMB negative and used for the control.

Results: The voltage of $S_{V1} + R_{V6} < 1.2$ mV has a sensitivity of 91% and specificity of 89% for the identification of primary CA, yields the positive and negative predictive values of 91% and 89%, respectively. Among ECHO parameters, there were no significant differences between the 2 groups, except for left ventricular ejection fraction ($47 \pm 12\%$ in primary CA vs $67 \pm 11\%$ in the control, $P < 0.001$). However, the combined indexes of ECG and ECHO parameters, including the ratio of $R_1/LVPW$ as well as $R_{V5}/LVPW$ and $R_{V6}/LVPW$, were significantly lower in the patients with primary CA than the control. The ratio of $R_1/LVPW < 0.4$ has the sensitivity of 91% and specificity of 100%, yields the positive and negative predictive values of 100% and 91%, respectively. The ratios of $R_{V5(6)}/LVPW < 0.7$ have the sensitivity of 91% and specificity of 89%, yield the positive and negative predictive values of 91% and 89%, respectively.

Conclusion: Patients with clinically suspected primary CA, combined indexes of ECGs and ECHOs could be used as the noninvasive diagnostic tools.

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Cardiac amyloidosis (CA) is generally associated with a poor prognosis and significantly increased mortality,^{1,2} especially for primary CA, once symptoms of congestive heart failure occurred, the median survival is about 6 months. Early recognition and therapy may improve the outcome. However, the diagnosis of CA can be difficult because the clinical presentation is nonspecific from other type of heart failure or cardiomyopathies. Primary CA is suggested by characteristic echocardiographic (ECHO) findings—namely, thickened ventricular walls and diastolic dysfunction progressing to systolic dysfunction.³ The ECG frequently demonstrates low-voltage and pseudoin-

farction patterns, conduction abnormalities, and arrhythmias. However, each finding alone is nonspecific. In this study, we aimed to determine which combination of ECGs and (or) ECHO parameters correlate with endomyocardial biopsy (EMB) proven primary CA and thus can be used as early noninvasive diagnostic tools.

METHODS

This is a retrospective study of 20 consecutive patients who were referred to the Peking Union Medical College Hospital between September 2006 and October 2009 for EMB because of a clinical

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suspicion of primary CA or other types of myocardial infiltrative disease. Patients were referred for evaluation of heart failure symptoms and concentric myocardial hypertrophy with moderate-to-severe left ventricular diastolic dysfunction on ECHO. There were no other specific criteria for inclusion or exclusion.

We performed a detailed examination of the medical records of these patients. The following information was reviewed and recorded: demographic data, New York Heart Association (NYHA) heart failure class at the time of biopsy, ECGs and ECHOs findings, as well as serum and urine-free light-chain level. A review of the medical records was performed by a team of physicians blinded to the EMB results. Biopsy results were separated from other patient information and introduced into the database after collection of clinical data was completed.

The ECGs were analyzed for the following characteristics: rhythm, conduction abnormalities (i.e., right or left bundle branch block), a low-voltage pattern (defined by sum of the QRS voltage in the limb leads ≤ 0.5 mV⁴), a pseudoinfarction pattern (pathologic Q waves on the ECG, but no coronary artery disease by coronary angiography or computed tomography angiography). In addition, we calculated the sum of QRS voltages in all 12 leads.

The ECHOs were 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. Trans-thoracic ECHO was performed using commercially available GE Vivid 7 Ultrasound machines. IVS and LVPW thicknesses were measured in standard fashion according to American Society of Echocardiography guidelines.⁵ 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 2-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.

The unit of ECG leads voltage is mV, the unit of IVS and LVPW thickness is mm, the ratio between the voltage of ECG lead and IVS or LVPW thickness is mm/mm (1 mV = 10 mm). The ECGs and ECHOs were independently reviewed.

Right ventricular biopsy was performed after obtaining subjects' informed consent. Access was by the right internal jugular venous system and fluoroscopic guidance was used to obtain 4 to 6 samples of myocardium. Biopsies were immediately fixed in buffered formaldehyde solution (10%) and embedded in paraffin within 1 day after fixation. These sections were analyzed with standard hematoxylin-eosin and Congo Red staining for visualization of amyloid deposition in standard fashion. Demonstration of apple-green birefringence when stained with Congo red and viewed under a polarizing microscope confirmed the diagnosis of amyloidosis. All biopsies were examined by a single, experienced pathologist who was blinded to all other study data.

An univariate analyses were performed on all demographic and ECGs as well as ECHOs to determine which set of variables was statistically associated with primary CA. Continuous variables were assessed using the parametric *t*-test for independent samples (e.g., LVEF, the voltage of ECG leads), and all categorical variables were assessed using the chi square test. Those combined variables that were found to be associated with primary CA, an appropriate cutoff value were used to calculate the sensitivity, specificity, positive and negative predictive values.

RESULTS

A total of 20 consecutive patients (7 men, mean age 50 ± 12 years) were evaluated. Eleven of these patients (55%) had an EMB proven CA, all the 11 patients with significant elevated-free light-chain (λ) level in serum ($n = 2$) or urine ($n = 1$), or both ($n = 8$). Of the remaining 9 patients (45%), the diagnosis was hypertrophy with ($n = 7$) or without ($n = 2$) evidence of interstitial fibrosis. The blood pressure was well controlled in both groups with antihypertensive medications. All the patients in primary CA group with at least one negative result of other biopsy tissue before undergoing EMB, other biopsy tissue included abdominal fat, gingiva, and mucous membrane of rectum.

The demographic and clinical characteristics of the patients, according to their biopsy results, are shown in Table 1. Patients in primary CA group were more often male than the control group (55% vs 11%, $P = 0.05$). The primary CA group had a larger percentage of patients with advanced heart

Table 1. Demographic and Clinical Characteristics of Patients

	Primary CA (n = 11)	Control (n = 9)	P Value
Male	6 (55%)	1 (11%)	0.05
Age (years)	50 ± 6	51 ± 20	0.84
Hypertension	3 (27%)	6 (67%)	0.08
Diabetes Mellitus	0 (0%)	2 (22%)	0.19
Coronary artery disease	0 (0%)	3 (33%)	0.07
Atrial arrhythmias	0 (0%)	1 (11%)	0.45
Height (cm)	170 ± 7	168 ± 10	0.99
Weight (kg)	64 ± 8	69 ± 23	0.58
BMI (kg/m ²)	23 ± 3.7	28 ± 3.7	0.10
NYHA class I/II	2 (18%)	7 (78%)	0.01
NYHA class III/IV	9 (82%)	2 (22%)	0.01

failure (NYHA class III/IV) than the control group (82% vs 22%, $P = 0.01$).

Table 2 summarizes the common ECG findings. Table 3 summarizes the voltage sum of single or combined ECG leads. Low-voltage pattern was statistically more prevalent in primary CA group than the control group (45% vs 0%, $P = 0.03$). Pseudoinfarction patterns was more often in the primary CA group than the control group (45% vs 11%), but this did not achieve statistical significance ($P = 0.11$). All the voltage sum of single or combined ECG leads, except lead V_3 , were statistically lower in the primary CA group than the control group.

Table 4 summarizes the ECHO findings. LVEF was lower ($47 \pm 12\%$ vs $67 \pm 11\%$, $P < 0.001$) and pericardial effusion (82% vs 33%, $P = 0.04$) was more common in the primary CA group than the control group.

Table 5 summarizes the combined indexes of ECG and ECHO. All the ratios between the voltage of R wave in lead I, aVL, V_5 or V_6 and LVPW or

Table 2. ECG Findings

	Primary CA (n = 11)	Control (n = 9)	P Value
Atrial fibrillation or flutter	0 (0%)	1 (11%)	0.45
First-degree AVB	2 (22%)	0 (0%)	0.29
RBBB	0 (0%)	1 (11%)	0.45
Low-voltage pattern	5 (45%)	0 (0%)	0.03
Pseudoinfarction pattern	5 (45%)	1 (11%)	0.11

Table 3. Total Voltage of 1 Lead or Voltage Sum of 2 Leads

	Primary CA (n = 11)	Control (n = 9)	P Value
Lead I (mV)	0.48 ± 0.27	1.4 ± 0.59	<0.001
Lead II (mV)	0.48 ± 0.31	1.5 ± 1.2	<0.01
Lead III (mV)	0.51 ± 0.48	1.1 ± 0.58	0.02
Lead aVR (mV)	0.33 ± 0.19	1.3 ± 0.63	<0.001
Lead aVL (mV)	0.45 ± 0.36	1.2 ± 0.72	<0.01
Lead aVF (mV)	0.44 ± 0.38	1.2 ± 1.2	0.07
Lead V_1 (mV)	0.73 ± 0.59	1.9 ± 1.2	0.01
Lead V_2 (mV)	1.8 ± 0.98	2.6 ± 1.0	0.09
Lead V_3 (mV)	2.1 ± 1.0	2.5 ± 0.73	0.26
Lead V_4 (mV)	1.5 ± 0.53	2.7 ± 0.74	<0.001
Lead V_5 (mV)	1.2 ± 0.29	2.1 ± 0.81	<0.01
Lead V_6 (mV)	0.81 ± 0.36	1.8 ± 0.85	<0.01
RI+SII (mV)	0.47 ± 0.74	1.5 ± 0.90	0.01
$S_{V1}+R_{V5}$ (mV)	1.2 ± 0.78	3.2 ± 1.7	<0.01
$S_{V1}+R_{V6}$ (mV)	0.76 ± 0.49	3.0 ± 1.5	<0.001

IVS thicknesses were statistically lower in the primary CA group than the control group, especially the ratios of $R_I/LVPW$ and $R_{V5(6)}/LVPW$.

We define the cutoff value of 1.2 mV for the voltage sum of S_{V1} and R_{V6} , $S_{V1} + R_{V6} < 1.2$ mV optimizes the sensitivity and specificity to predict the presence of CA (Fig. 1), this method yields the positive and negative predictive values of 91% and 89%, respectively. Also, we define the cutoff value of 0.4 for the ratio between voltage of R_I and LVPW thickness, the $R_I/LVPW < 0.4$ has the optimal sensitivity and specificity for the identification of CA (Fig. 2), yields the positive and negative predictive values of 100% and 90%, respectively. Similarly, the $R_{V5(6)}/LVPW < 0.7$ has the optimal sensitivity

Table 4. ECHO Findings

	Primary CA (n = 11)	Control (n = 9)	P Value
IVS (mm)	14 ± 3	17 ± 7	0.24
LVPW (mm)	14 ± 3	12 ± 5	0.29
LVEDD (mm)	42 ± 5	45 ± 7	0.34
LVEDS (mm)	32 ± 6	28 ± 6	0.13
LA (mm)	45 ± 6	44 ± 7	0.69
LVEF (%)	47 ± 12	67 ± 11	<0.001
E/A ratio (<i>t</i> -test)	2.3 ± 0.6	2.4 ± 0.4	0.75
Pericardial effusion	9 (82%)	3 (33%)	0.04

IVS = interventricular septal thickness; LVPW = left ventricular posterior wall thickness, LVEDD = left ventricular end of diastolic diameter, LVEDS = left ventricular end of systolic diameter, LVEF = left ventricular ejection fraction.

Table 5. Combined Indexes of ECGs and ECHO

	Primary CA (n = 11)	Control (n = 9)	P Value
R _I /LVPW (mm/mm)	0.18 ± 0.21	0.90 ± 0.45	<0.001
R _{aVL} /LVPW (mm/mm)	0.17 ± 0.25	0.57 ± 0.42	0.02
R _{V5} /LVPW (mm/mm)	0.45 ± 0.23	1.4 ± 0.56	<0.001
R _{V6} /LVPW (mm/mm)	0.38 ± 0.22	1.1 ± 0.39	<0.001
R _I /IVS (mm/mm)	0.18 ± 0.19	0.73 ± 0.56	<0.01
R _{aVL} /IVS (mm/mm)	0.16 ± 0.20	0.49 ± 0.47	0.05
R _{aVL} /IVS (mm/mm)	0.48 ± 0.28	1.17 ± 0.77	0.01

1 mV = 10 mm. Other abbreviations see Table 4.

and specificity (Figs. 3 and 4), both yield the positive predictive and negative predictive values of 91% and 89%, respectively. Table 6 summarizes the sensitivity, specificity, positive and negative predictive values of the combined indexes.

DISCUSSION

Deposition of amyloid fibrils in myocardial tissue results in concentric myocardial hypertrophy and reduced ventricular compliance with diastolic dysfunction and eventually systolic dysfunction. The clinical presentation of CA varies and may misdiagnose other type of cardiomyopathy. Because of poor prognosis of CA, the early diagnosis and therapy are crucial to improve outcome. However, the noninvasive diagnostic tool is limited, previous investigations have shown that multiple ECG and ECHO findings suggest amyloid but are non-specific in isolation. Murtagh et al.⁶ reported low-voltage (46%) and pseudoinfarction (47%) were the most common ECG findings in 127 biopsy-proven primary CA. Rapezzi et al.⁷ reported 60% patients

Figure 1. The voltage sum of Sv₁ + Rv₆ in the 2 groups.

Figure 2. The ratio between voltage of R_I and LVPW thickness in the 2 groups.

Figure 3. The ratio between voltage of Rv₅ and LVPW thickness in the 2 groups.

with primary CA were low-voltage pattern on ECG, the incidence were higher than other types of CA. In our study, the incidence of low-voltage pattern and pseudoinfarction pattern on ECG are 45% and 45%, respectively, similar with previous studies. Typically, there is ECHO evidence of thickened ventricular and septal walls, a normal or small ventricular size, atrial enlargement, and refractile myocardium,⁸ as well as diastolic dysfunction. The use of a combination of ECG and ECHO parameters increases specificity. Joseph et al.⁹ reported a patient with an ECG that showed a low voltage and an ECHO with an IVS thickness of >1.98 cm will

Figure 4. The ratio between voltage of Rv₆ and LVPW thickness in the 2 groups.

Table 6. Predictive Ability of Combined Indexes

	Sensitivity	Specificity	PPV	NPV
$S_{V1} + R_{V6} < 1.2 \text{ mV}$	91%	89%	91%	89%
$R_I / \text{LVPW} < 0.4 \text{ (mm/mm)}$	91%	100%	100%	91%
$R_{V5} / \text{LVPW} < 0.7 \text{ (mm/mm)}$	91%	89%	91%	89%
$R_{V6} / \text{LVPW} < 0.7 \text{ (mm/mm)}$	91%	89%	91%	89%

1 mV = 10 mm; PPV = positive predictive value; NPV = negative predictive value.

be classified as having amyloidosis, a patient with a low voltage but IVS thickness $< 1.98 \text{ cm}$ would be classified as not having amyloidosis, a positive and negative predictive value were 79% and 88%, respectively. A distinctive characteristic of primary CA is the inverse relationship between ECG voltage and LV mass.¹⁰

To the best of our knowledge, the diagnostic parameters of the aforementioned ECHO and ECG features have not been combined together in a cohort of patients with EMB proven primary CA. In our study, we aimed to establish the sensitivity and specificity of the ratios between ECGs and ECHOs, that are predictive of primary CA. The voltage of $S_{V1} + R_{V6} < 1.2 \text{ mV}$, and the ratio between the voltage of R_I and LVPW thickness < 0.4 , as well as the ratios between the voltage of $R_{V5(6)}$ and LVPW thickness < 0.7 , have the optimal sensitivity and specificity, yield a satisfactory positive and negative predictive values for the identification of primary CA, can be used as an excellent noninvasive diagnostic tools. We propose that in patients with clinical suspicion of primary CA, these parameters can be used for diagnosis.

There are several limitations in our study. First, the number of patients is small, only 11 patients with primary CA were studied. However, the difference of the ratios between ECGs and ECHOs is significant between patients with primary CA and control, so we still think these ratios are very helpful in the diagnosis. Second, all of the patients are primary CA, and the patients in control group are cardiac nonamyloid disease, therefore, we may not use these indexes for the differentiation of primary CA from other types of cardiac disease or from healthy subjects. Third, CA is associated with a variable prognosis. In primary CA, the median sur-

vival is 6 months once heart failure developed.^{11–13} For senile CA, the median survival is 5 years once heart failure developed.¹⁴ Because of therapeutic and prognostic implications, it is important that a tissue diagnosis is made. These noninvasive diagnostic tools could not substitute the EMB.

In conclusion, the voltage of $S_{V1} + R_{V6} < 1.2 \text{ mV}$, and the ratio between the voltage of R_I and LVPW thickness < 0.4 , as well as the ratios between the voltage of $R_{V5(6)}$ and LVPW thickness < 0.7 can accurately predict the presence of primary CA. Patients with clinically suspected primary CA, combined indexes of ECGs and ECHOs could be used as the noninvasive diagnostic tools.

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