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Diagnostic significance of paradoxical left ventricular hypertrophy in detecting cardiac amyloidosis

Shingo Ota [a,*], Yasuhiro Izumiya [b], Ryoko Kitada [b], Takahiro Nishi [a], Akira Taruya [a], Teruaki Wada [a], Masahiro Takahata [a], Yuichi Ozaki [a], Manabu Kashiwagi [a], Yasutsugu Shiono [a], Akio Kuroi [a], Kazushi Takemoto [a], Takashi Tanimoto [a], Hironori Kitabata [a], Daiju Fukuda [b], Atsushi Tanaka [a]

[a] Department of Cardiovascular Medicine, Wakayama Medical University, Wakayama, Japan
[b] Department of Cardiovascular Medicine, Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan

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ABSTRACT

Background: Cardiac amyloidosis (CA) progresses rapidly with a poor prognosis. Therefore, methods for early diagnosis that are easily accessible in any hospital, are required. We hypothesized that based on the pathology of CA, morphological left ventricular hypertrophy (LVH) without electrical augmentation, namely paradoxical LVH, could be used to diagnose CA. This study aimed to investigate whether paradoxical LVH has diagnostic significance in identifying CA in patients with LVH.

Methods: Patients who presented with left ventricular (LV) wall thickness $\geq$ 12 mm on cardiac magnetic resonance (CMR) were enrolled from a multicentre CMR registry. Paradoxical LVH was defined as a LV wall thickness $\geq$ 12 mm on CMR, SV1 + RV5 $<$ 3.5 mV, and a lack of secondary ST-T abnormalities. The diagnostic significance of paradoxical LVH in identifying CA was assessed.

Results: Of the 110 patients enrolled, 30 (27 %) were diagnosed with CA and 80 (73 %) with a non-CA aetiology. The CA group demonstrated paradoxical LVH more frequently than the non-CA group (80 % vs. 16 %, $P <$ 0.001). It was an independent predictor for detecting CA in patients with LVH (odds ratio: 33.44, 95 % confidence interval: 8.325–134.3, $P <$ 0.001). The sensitivity, specificity, positive predict value, negative predict value and accuracy of paradoxical LVH for CA detection were 80 %, 84 %, 65 %, 92 % and 83 %, respectively.

Conclusions: Paradoxical LVH can be used for identifying CA in patients with LVH. Our findings could contribute to the early diagnosis of CA, even in non-specialized hospitals.

1. Introduction

Cardiac amyloidosis (CA) is caused by amyloid depositions within cardiac tissue, it progresses rapidly and is associated with a poor prognosis [1]. Recently, various disease-specific therapies for CA have been introduced to clinical practice; however, the impact of these treatments is often limited in patients with advanced-stage CA [2–4]. Hence, early diagnosis is necessary for optimal management and a more promising prognosis [1]. However, CA is often misdiagnosed, or its recognition is delayed owing to both physician- and disease-related factors, such as a shortage of centres and specialists dedicated to disease management, disease rarity and intrinsic phenotypic heterogeneity [5]. Moreover, cardiac magnetic resonance imaging (CMR) and cardiac scintigraphy with technetium-99 m (^{99m}Tc) labelled bone-seeking tracers, reliable imaging tools for detecting CA, are not readily available, particularly in non-specialized hospitals [1,5]. Therefore, the methods leading to early diagnosis that can be easily accessed in any hospitals are required.

Left ventricular hypertrophy (LVH), caused by hypertrophic cardiomyocytes, is accompanied by characteristic electrocardiographic (ECG) findings such as the Sokolow-Lyon criterion or the presence of secondary ST-T abnormalities, typically in the leads facing the left ventricle (LV) [6–8]. Therefore, these ECG criteria are widely used to screen for the presence of LVH in clinical practice [9]. CA also presents with LVH due amyloid fibrils in the interstitial space of the myocardium. Hence, LV mass increases without true myocyte hypertrophy [1].

Based on these unique pathological features of CA, we hypothesised

* Corresponding author at: Department of Cardiovascular Medicine, Wakayama Medical University, 811-1, Kimiidera, Wakayama, 641-8510, Japan.
E-mail address: shingota@wakayama-med.ac.jp (S. Ota).

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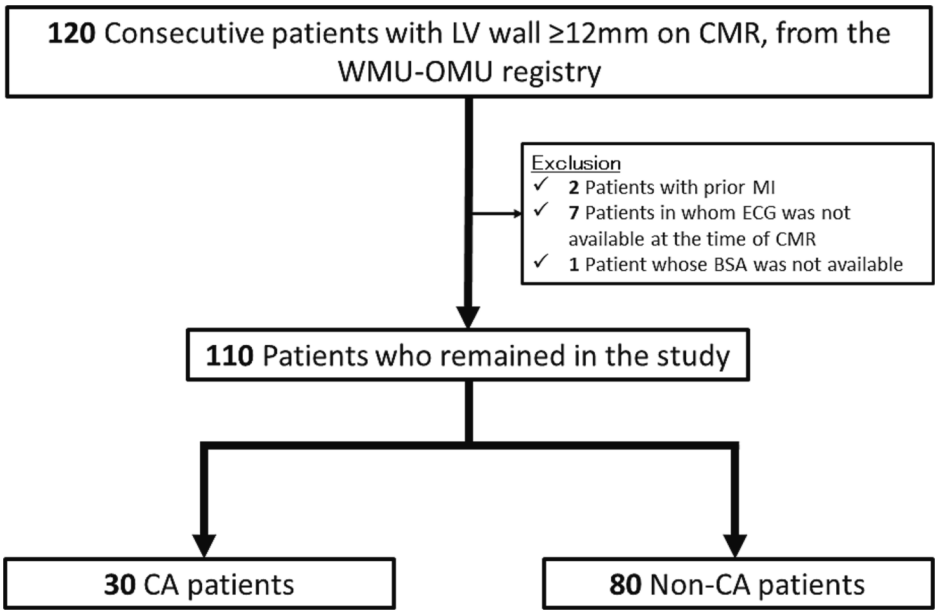

Fig. 1. Patient selection flow chart From the WMU-OMU registry co-managed by Wakayama Medical University Hospital and Osaka Metropolitan University Hospital, including patients who have undergone CMR to assess the aetiology of cardiac hypertrophy. Overall, 120 patients who presented with LV wall thickness ≥ 12 mm on CMR were selected for possible enrolment. Patients with prior MI (n = 2), those without ECG data at the time of CMR (n = 7), or without BSA data (n = 1) were excluded. Of the remaining 110 patients, 30 were definitively diagnosed with CA (CA group) and 80 with cardiac hypertrophy of non-CA aetiology (non-CA group). BSA: body surface area, CA: cardiac amyloidosis, CMR: cardiovascular magnetic resonance imaging, ECG: electrocardiography, LV: left ventricular, MI: myocardial infarction.

that CA would present as morphological LVH without ECG evidence of LVH. This study aimed to investigate whether a lack of LVH findings on ECG has diagnostic significance in identifying CA in patients with morphological LVH.

2. Methods

2.1. Study population

The Wakayama Medical University Hospital and Osaka Metropolitan University Hospital have created and co-managed the cardiac hypertrophy with the CMR registry (WMU-OMU registry), since 2021. It includes patients who have undergone CMR to assess the aetiology of cardiac hypertrophy. Patients with severe aortic stenosis (AS) and those with complete left bundle-branch block (LBBB) were not included. From this registry, we selected 120 patients who presented with LV wall thickness ≥ 12 mm on CMR for possible enrolment. Of the 120 patients, we excluded patients with prior myocardial infarction (n = 2), those without ECG data at the time of CMR (n = 7), and those whose body surface area was not available (n = 1). Of the remaining 110 patients, 30 were definitively diagnosed with CA (CA group) and 80 with cardiac hypertrophy of non-CA aetiology (non-CA group) (Fig. 1).

2.2. Diagnosis criteria of CA

Diagnosis of amyloid deposition was based on Congo red staining and apple-green birefringence visualized using cross-polarized light microscopy. Immunohistochemical staining was performed to confirm the presence of transthyretin or monoclonal light chains in the amyloid deposits. Amyloid light chain CA (AL-CA) was definitively diagnosed via histological evidence of monoclonal light chain deposition in the myocardium. Transthyretin amyloid cardiomyopathy (ATTR-CM) was definitively diagnosed by 1) histological evidence of transthyretin deposition in the myocardium; 2) histological evidence of transthyretin deposition in extracardiac tissue with grade 2 or 3 cardiac uptake at ^{99m}Tc- labelled pyrophosphate (^{99m}Tc-PYP) scintigraphy; or 3) grade 2 or 3 cardiac uptake at ^{99m}Tc-PYP scintigraphy without histological evidence of transthyretin deposition when no monoclonal protein was identified by serum/urine immunofixation and the serum free light chain ratio was in the normal range [10]. The definitive diagnostic method for ATTR-CM was decided by individual physicians.

2.3. ECG measurements

Standard 12-lead ECGs were performed 1 month before the CMR. Measurements were acquired from a digital ECG scan. We defined low voltage in limb leads as the maximum index of the entire QRS complex voltage in all the limb leads ≤ 0.5 mV. We calculated the S-wave amplitude in V1 and the R-wave amplitude in V5 as SV1 + RV5. Secondary ST-T abnormality was defined as the presence of a down-sloping convex ST segment with an inverted asymmetrical T wave in both V5 and V6 leads. Patients with atrial fibrillation were excluded from the analysis of the PR duration.

2.4. Echocardiographic measurements

Standard transthoracic echocardiographic examinations (iE33 and EPIQ, Philips Medical Systems, Amsterdam, Netherlands) were performed in all patients within 1 month of CMR. All echocardiographic analyses were performed using commercially available software (QLAB 10, Philips Medical Systems, Amsterdam, Netherlands). Although LV volumes and ejection fraction (EF) were routinely measured by echocardiography, we used the CMR data as these parameters in this study. The left atrial volume index (LAVI) was measured from the apical four- and two-chamber views, using the biplane Simpson's rule. The E and A waves were measured based on the mitral inflow profile and assessed in the apical four-chamber view using pulsed-wave Doppler echocardiography, with the sample volume placed at the tips of the mitral leaflets during diastole. Patients with atrial fibrillation were also excluded from the analysis of the A wave. The e' velocity from the septal mitral valve annuli was measured in the apical four-chamber view using Doppler tissue imaging of the mitral annulus. We also assessed routinely valvular

lesions in a prescribed way [11].

2.5. CMR protocol and analysis

All CMR examinations were performed using a 1.5-T or 3-T clinical scanner (Intera Achieva, Ingenia Elition; Philips Healthcare, Amsterdam, Netherlands, MAGNETOM Skyra; SIEMENS, Munich, Germany) equipped with a 32-element cardiac phased-array coil for signals, as previously described [12]. During the examination, the patients were continuously monitored using a single-lead ECG, while in the supine position. Contiguous short-axis cine images covering the left ventricle from the base to the apex were acquired using a standard steady-state free precession sequence. Late gadolinium enhancement (LGE)-CMR covering the whole ventricle was performed 10–15 min after intravenous injection of 0.1 mmol/kg gadolinium diethylenetriamine pentaacetic acid (Magnevist, Bayer Schering Pharma AG, Berlin, Germany) if the estimated glomerular filtration rate was > 30 mL/min/1.73 m^2. A three-dimensional inversion-recovery turbo gradient echo sequence was used, and images were obtained during an end-expiratory breath-hold. The inversion time was adjusted to null the signal from the viable myocardium [13].

All CMR analyses were performed using commercially available software (Ziostation 2, Ziosoft Inc., Tokyo, Japan). On cine CMR, endocardial and epicardial borders were delineated on the end-diastolic and end-systolic short-axis slices for quantification of LV volumes, LV EF, and LV mass. We also measured LV wall thickness on short axis view. On LGE-CMR images, the presence of diffuse subendocardial or transmural LGE was visually assessed.

2.6. Definition of paradoxical LVH

The most common ECG diagnostic criteria for LVH are based on measurements of QRS voltages [9]. Criterion based on SV1 + RV5 and ECG findings reflecting repolarization abnormalities due to LVH, secondary ST-T abnormalities, have been widely reported [9]. Therefore, Paradoxical LVH was defined when the following conditions were fulfilled: 1) LV wall thickness ≥ 12 mm on short axis view on CMR, 2) SV1 + RV5 < 3.5 mV, and 3) no secondary ST-T abnormalities.

2.7. Statistical analysis

All statistical analyses were performed using the JMP 14 software (SAS Institute Inc., Cary, NC, USA). Categorical variables are presented as frequency counts and percentages. Comparisons were performed using Fisher's exact test. Continuous variables are presented as median (interquartile range) and compared using the Kruskal-Wallis test. The ECG findings demonstrating $P < 0.05$ in the univariate analysis was selected and a multivariable logistic regression analysis was performed to identify ECG predictors for detecting CA. OR indicates the unit odds ratio. *P*-values were calculated using the Wald test. The sensitivity, specificity, positive predict value (PPV), negative predict value (NPV) and accuracy of paradoxical LVH for detecting CA were calculated. The relationship between SV1 + RV5 voltage and LV mass index was analysed using correlational analyses in patients with and without CA. All tests were two-sided, and statistical significance was set at $P < 0.05$.

3. Results

3.1. Clinical characteristics

Of the 30 patients with CA, 2 (7 %) had AL-CA and 28 (93 %) had ATTR-CM. Amongst the 28 patients with ATTR-CM, 26 (93 %) were diagnosed by histological evidence of transthyretin deposition in the myocardium, and 2 (7 %) were diagnosed by histological evidence of transthyretin deposition in extracardiac tissue with grade 2 or 3 cardiac uptake at ^{99m}Tc-PYP scintigraphy. No patients were diagnosed solely by grade 2 or 3 cardiac uptake at ^{99m}Tc-PYP scintigraphy and an absence of serum and urine monoclonal light chains without the histological evidence of transthyretin deposition. Based on the EF calculated by CMR, 8 (27 %) patients with CA had heart failure (HF) with preserved EF, 6 (20 %) had HF with mildly reduced EF, and 11 (37 %) had HF with reduced EF. Among the 80 patients with a non-CA aetiology, 12 (15 %) underwent right ventricular endocardial biopsy. They were diagnosed with hypertensive cardiomyopathy (n = 2), hypertrophic cardiomyopathy (n = 77) and mitochondrial cardiomyopathy (n = 1).

Table 1
Patients' characteristics.

	CA Group n = 30	**Non-CA Group** n = 80	*P*-value
Age, years	78.5 [74.0–85.0]	67.0 [53.0–74.0]	<0.001
Male, n (%)	23 (77)	55 (69)	0.486
Body surface area, m^2	1.62 [1.51–1.74]	1.64 [1.54–1.79]	0.537
Hypertension, n (%)	13 (43)	37 (46)	0.832
Echocardiographic findings			
E/A	1.20 [0.71–1.85]	0.90 [0.70–1.50]	0.163
Deceleration time, msec	201.0 [177.5–233.8]	218.0 [170.3–260.3]	0.363
E/e'	19.1 [15.0–23.7]	12.4 [9.1–17.1]	<0.001
Left atrial volume index, mL/m^2	39.5 [35.0–52.5]	42.0 [34.0–52.0]	0.694
CMR findings			
LV end-diastolic volume, mL	120.5 [97.0–136.3]	114.9 [94.2–147.2]	0.846
LV end-systolic volume, mL	64.0 [47.0–84.8]	48.9 [37.9–68.7)	0.051
LV ejection fraction, %	43.5 [34.1–55.6]	55.7 [48.0–62.8]	0.002
LV mass, g	140.4 [120.1–181.4]	119.7 [91.6–168.3]	0.035
Diffuse subendocardial or transmural LGE, n (%)	22/23 (96)	0/73 (0)	<0.001
ECG findings			
PR duration, msec	188.0 [175.0–224.0]	170.0 [153.0–189.0]	0.002
QRS duration, msec	102.0 [90.0–128.5]	100.0 [89.3–112.0]	0.281
Atrial fibrillation, n (%)	5 (17)	8 (10)	0.336
Low voltage in limb lead, n (%)	2 (7)	2 (3)	0.299
Paradoxical LVH, n (%)	24 (80)	13 (16)	<0.001

Values are given as median [interquartile range] or n (%).
CA: cardiac amyloidosis, CMR: cardiovascular magnetic resonance imaging, ECG: electrocardiogram, LGE: late gadolinium enhancement, LV: left ventricular, LVH: left ventricular hypertrophy.

There was a significant difference in age between the two groups. There was no significant difference in the frequency of hypertension between two groups. There were significant differences in E/e ($P < 0.001$), LV EF ($P = 0.002$) and LV mass ($P = 0.035$) between the two groups. The frequency of diffuse subendocardial or transmural LGE was also significantly different between two groups ($P < 0.001$) (Table 1).

3.2. ECG findings for detecting CA

The ECG findings are also presented in Table 1. PR duration was longer in patients with CA as compared with those without CA ($P = 0.002$). Paradoxical LVH was also more frequently observed in the CA group than in the non-CA group ($P < 0.001$). There were no differences in the QRS duration, frequency of atrial fibrillation, and low voltage in limb leads between the two groups. There was a positive correlation between SV1 + RV5 voltage and LV mass index in patients without CA ($r = 0.615$, $P < 0.001$), but not in patients with CA ($r = 0.052$, $P = 0.787$).

The multivariate logistic regression analysis demonstrated that paradoxical LVH and PR duration were independent predictors for

Table 2
A multivariable logistic regression analysis for ECG findings for detecting CA.

	Univariate analysis		Multivariate analysis	
	OR (95 % CI)	*P*-value	OR (95 % CI)	*P*-value
PR duration	1.015 (1.003–1.027)	0.015	1.019 (1.005–1.034)	0.010
QRS duration	1.020 (0.999–1.041)	0.054	–	–
Atrial fibrillation	1.800 (0.539–6.015)	0.340	–	–
Low voltage in limb lead	2.786 (0.374–20.73)	0.317	–	–
Paradoxical LVH	20.62 (7.044–60.33)	<0.001	33.44 (8.325–134.3)	<0.001

CA: cardiac amyloidosis, CI: confidence interval, ECG: electrocardiogram, LVH: left ventricular hypertrophy, OR: odds ratio.

detecting CA in patients with cardiac hypertrophy [OR: 33.44, 95 % confidence interval (CI): 8.325–134.3, $P < 0.001$, and OR: 1.019, 95 % CI:1.005–1.033, $P = 0.010$, respectively] (Table 2). The sensitivity, specificity, PPV, NPV, and accuracy of paradoxical LVH for CA detection were 80 %, 84 %, 65 %, 92 % and 83 %, respectively (Fig. 2).

4. Discussion

The major findings of this study demonstrated that 1) paradoxical LVH is an independent predictor for detecting CA in patients with LVH, 2) paradoxical LVH has diagnostic significance for CA with a sensitivity, specificity, PPV, NPV, and accuracy of 80 %, 84 %, 65 %, 92 %, and 83 %, respectively, in patients with LVH.

As cardiomyocyte hypertrophy progresses, electrical activation passes through a larger mass of myocardium, resulting in increased amplitude of the QRS complex, representing ventricular depolarization. In this study, we observed a positive correlation between SV1 + RV5 voltage and the myocardial mass index in the non-CA group. Similarly, when cardiomyocytes are abnormally thickened and electrical activity takes longer to traverse throughout the heart, repolarization is affected, resulting in abnormal ST segments or T waves, referred to as a secondary ST-T abnormality [9]. It has been noted that most patients with hypertrophic cardiomyopathy have some evidence of LVH findings on ECG [7]. This is consistent with these electrophysiological theories. In contrast, CA presents with morphological LVH due to the deposition of amyloid fibrils in the interstitial space of the myocardium without true cardiomyocyte hypertrophy [1]. In this disease, the magnitude of electrical activation to pass through is low due to its prevention by amyloid surrounding cardiomyocytes. Paradoxical LVH reflects the unique electrical-pathological features of CA. Previous studies have shown that 10 %-25 % of patients with ATTR-CM have typical LVH patterns on ECG [14,15]; therefore, there would be a false negative based on paradoxical LVH. However, this study revealed that paradoxical LVH has a high NPV of 92 % for detecting CA in patients with LVH; therefore, paradoxical LVH could be useful in screening patients with CA in those with LVH.

The treatment of CA has advanced considerably in recent years. Novel therapies, such as daratumumab plus bortezomib, and autologous stem cell transplantation have been established for AL amyloidosis [2]. Tafamidis, a transthyretin stabilizer that binds the thyroxine-binding site of transthyretin, has been reported to improve the prognosis of patients diagnosed with ATTR-CM [3]. Additionally, patisiran, an RNAi therapeutic composed of a small interfering RNA formulated as a lipid nanoparticle that enables delivery to hepatocytes, has been reported to decrease LV wall thickness; thus reduces adverse cardiac outcomes in patients with hereditary ATTR-CM [4]. However, the impact of these treatments is limited in patients with advanced-stage CA. Therefore, early detection of CA in patients with cardiac hypertrophy is essential.

Previous studies have reported on the ECG findings of patients with CA, such as low voltage in limb leads, pseudo-infarct pattern, or low voltage/mass ratio [16–24]. However, the diagnostic value is not high, and the calculation of the voltage/mass ratio is complicated. The relative sparing of longitudinal strain in the LV apex, assessed via two-dimensional (2D) speckle tracking echocardiography, has been reported to be highly sensitive and specific for CA diagnosis (sensitivity: 93 %, specificity: 82 %) [25]; however, the accuracy of speckle-tracking echocardiography measurements depends on 2D image quality and it is not possible to track speckles moving out of the scan plane of the 2D image. Moreover, LGE on CMR has a high diagnostic value for identifying CA (sensitivity: 85 % and specificity: 92 %) [26]; however, CMR alone cannot make a definitive diagnosis of CA. Moreover, both speckle-tracking echocardiography and CMR are not readily performed, particularly in non-specialized hospitals. Hence, their use to identify CA is limited in clinical practice compared with paradoxical LVH, which can be conveniently used even in non-specialized hospitals.

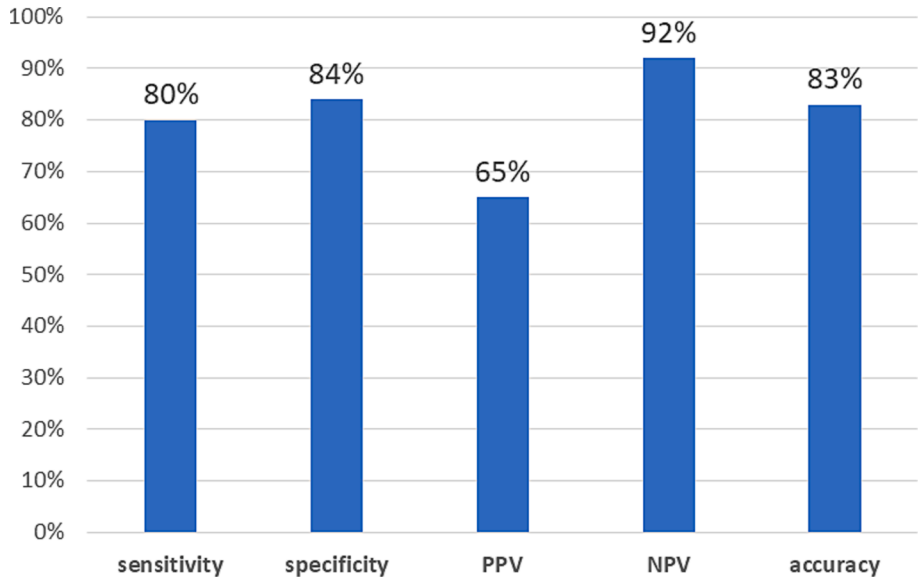

Fig. 2. Diagnostic significance of paradoxical LVH for detecting CA. The sensitivity, specificity, PPV, NPV and accuracy of paradoxical LVH for CA detection were 80%, 84%, 65%, 92% and 83%, respectively. CA: cardiac amyloidosis, LVH: left ventricular hypertrophy, NPV: negative predict value, PPV: positive predict value.

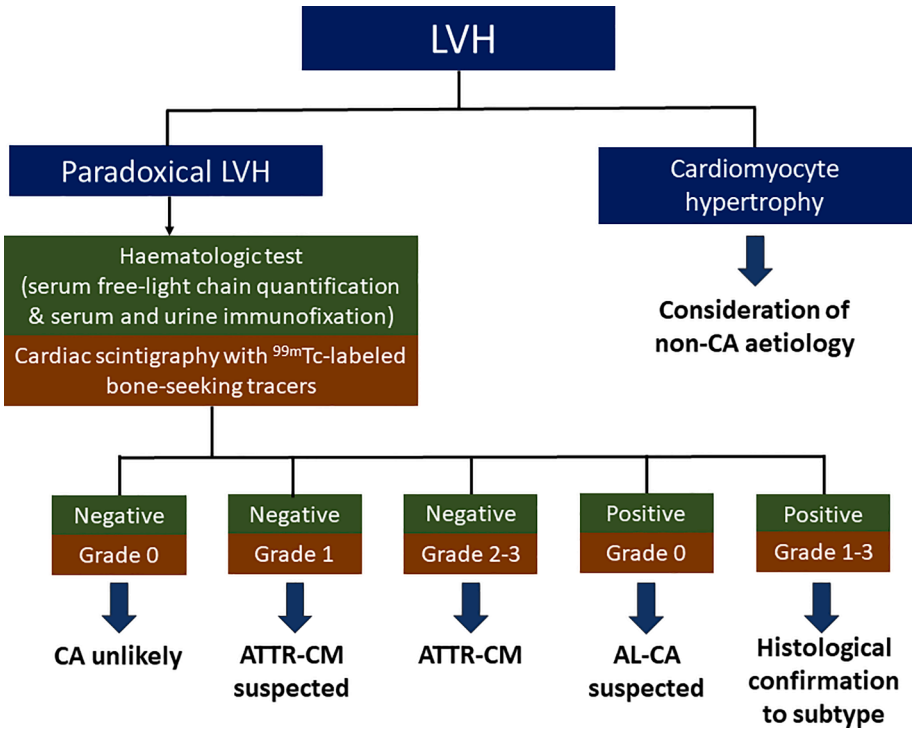

Fig. 3. Diagnostic algorithm of CA based on paradoxical LVH Paradoxical LVH has a high diagnostic value for the identification of CA in patients with cardiac hypertrophy (sensitivity: 80 %, specificity: 84 %, PPV: 65 %, NPV: 92 %, accuracy: 83 %, respectively). For the early diagnosis of CA and typing of the CA phenotype, identification of paradoxical LVH should be followed by cardiac scintigraphy with ^{99m}Tc-labeled bone-seeking tracers and measurement of monoclonal light chains. AL-CA: amyloid light chain cardiac amyloidosis, ATTR-CM: transthyretin amyloid cardiomyopathy, CA: cardiac amyloidosis, LVH: left ventricular hypertrophy, NPV: negative predict value, PPV: positive predict value, ^{99m}Tc: technetium-99 *m*.

Cardiac scintigraphy with ^{99m}Tc labelled bone-seeking tracers is considered a non-invasive imaging modality that can definitively diagnose ATTR-CM [27]. The measurement of monoclonal light chain in serum and urine shows high impact on diagnosing AL-CA [28]. Therefore, for the early diagnosis of CA and typing of the CA phenotype, physicians should screen CA in patients with LVH and utilise cardiac scintigraphy with ^{99m}Tc labelled bone-seeking tracers and monoclonal light chain measurements. Based on a high diagnostic significance of paradoxical LVH for detection of CA, we propose the novel diagnostic algorism of CA in patients with LVH, which is convenient and accessible across hospitals (Fig. 3).

This study had several limitations. First, selection bias should be considered when performing CMR in patients with cardiac hypertrophy. Second, patients with severe AS which might coexist with ATTR-CM and cardiac hypertrophy were not included in this study [29]. Third, patients with a complete LBBB, which makes the ECG diagnosis of LVH impossible, were not included in this study [9]. Forth, a small number of patients with CA may have been included in the non-CA group since not all patients in the non-CA group underwent right ventricular endocardial biopsy, cardiac scintigraphy with ^{99m}Tc labelled bone-seeking tracers or monoclonal light chain measurements. Fifth, in the CA patients, only 2 (7 %) had AL-CA compared to 28 (93 %) patients with ATTR-CM. Given the small number of patients with AL-CA, the study results may be less generalizable for AL-CA. Finally, diffuse subendocardial or transmural LGE was positive in 22 out of 23 patients with CA in this study. The association between the presence and extent of LGE and low electrographic QRS voltage was reported in several cardiomyopathies and myocarditis [30–32]. This may have introduced a bias in favor for paradoxical LVH definition for CA.

5. Conclusions

Paradoxical LVH has a high diagnostic value for the identification of CA in patients with cardiac hypertrophy, and could contribute to the early diagnosis of CA even in non-specialized hospitals.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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