THE CLINICAL AND ECHOCARDIOGRAPHIC ANALYSIS OF NONCOMPACTION CARDIOMYOPATHY IN MISDIAGNOSIS AND MISSED DIAGNOSIS

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Aim. Echocardiography has become the main mean in detection of noncompaction cardiomyopathy (NCC). However, misdiagnosis and missed diagnosis were common. The aim of this paper was to analyze the misdiagnosis and missed diagnosis of NCC, improve the diagnostic accuracy of this disease.

Material and methods. We retrospectively analyzed the data of 56 subjects who had been clinically diagnosed with NCC in our institution, which included patients' total echocardiographic data since the disease onset. Echocardiographic data and cardiac magnetic resonance (CMR) data were compared with each other.

Results. 17 of the total subjects had been diagnosed with NCC after the first echocardiography at our institution. 39 subjects had not been diagnosed correctly until several times checking of echocardiography. 28 of them had been misdiagnosed as dilated cardiomyopathy (DCM) in local hospitals. All but 2 subjects were inconsistent between echocardiography measurement and CMR. The ratio of N/C was 2,63±0,49 by CMR, and 2,55±0,43 by echocardiography.

Conclusion. Echocardiography can be the first choice of NCC assessment for its advantages of being non-radiative, real-time, economic and characteristic. When the echocardiographic image is not typical in the early stage of NCC, a combination with CMR is necessary.

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Key words: noncompaction cardiomyopathy, echocardiography, cardiac magnetic resonance.

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КЛИНИЧЕСКИЙ И ЭХОКАРДИОГРАФИЧЕСКИЙ АНАЛИЗ СПОНГИОФОРМНОЙ КАРДИОМИОПАТИИ ПРИ ОШИБОЧНОМ ДИАГНОЗЕ И ПРИ ОТСУТСТВИИ ДИАГНОЗА

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Цель. Эхокардиография стала основным средством в обнаружении спонгиоформной кардиомиопатии (NCC). Однако, ошибочный диагноз и отсутствие диагноза, были повсеместными. Целью данной работы является анализ случаев ошибочного диагноза и отсутствия диагноза NCC, чтобы улучшить точность диагностики этого заболевания.

Материал и методы. Мы ретроспективно проанализировали данные 56 пациентов, которые были клинически диагностированы с NCC в нашем учреждении, в исследование были включены полные данные эхокардиографические пациентов с момента начала заболевания. Эхокардиографические данные и данные сердечной магнитно-резонансного исследования (CMR) сравнивались друг с другом.

Результаты. 17-ти пациентам была диагностирована NCC после первого эхокардиографического исследования в нашем учреждении. 39 пациентов не были диагностированы правильно до тех пор, пока несколько раз небыли проверены эхокардиографически. 28-ми из них была ошибочно диагностирована дилатационная кардиомиопатия (DCM) в местных больницах. Все данные, кроме 2-х пациентов, были совмещены между результатами эхокардиографии и CMR. Соотношение N/C 2,63±0,49 было при CMR, и 2,55±0,43 при эхокардиографии.

Заключение. Эхокардиография может быть первым выбором при NCC для оценки, вследствие следующих преимуществ: нерадиационный режим реального времени, экономические затраты и характеристика. Когда эхокардиографическое изображение не является типичным в ранней стадии NCC, то сочетание с CMR необходимо.

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Ключевые слова: спонгиоформная кардиомиопатия, эхокардиография, сердечное магнитно-резонансное исследование.

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Introduction

Noncompaction cardiomyopathy (NCC) is a special and rare kind of inborn cardiomyopathy, which is also known as the spongy myocardium or myocardial sinusoidal persistent state [1–4]. It is characterized by excessive and prominent trabeculations associated with deep recesses that communicate with the ventricular cavity but not the coronary circulation [1–4]. The sponge-like meshwork of fibers and intertrabecular spaces used to be normal structures in the early embryonic development, and become compressed between the 5th and 8th weeks of fetal development [5]. NCC is thought to result from the arrest of myocardial compaction process during that period. It is also associated with other cardiac and systemic anomalies [6]. Heart failure, thromboembolism and malignant ventricular arrhythmias are the most challenging clinical aspects of NCC [7–8], which contribute to the poor survival in these patients [9]. During the last decade, more attention had been paid to this condition, which resulted in an increased detection of NCC cases. However, studies in misdiagnosis and missed diagnosis about NCC were very limited. We retrospectively documented all clinical data and echocardiographic diagnosis of patients who were identified with NCC in our institution.

Material and methods

We retrospectively analyzed the subjects who had been clinically diagnosed with NCC from June 2010 to May

2013. 56 Han Chinese patients were referred to the Second Affiliated Hospital of Nanchang University, China. Informed consents were signed by each patient. We collected patients' total echocardiographic data in the hospital and the local hospitals since the disease onset. All patients were evaluated by medical history, physical examination, 12-lead electrocardiography (ECG), 2-D and doppler echocardiographic examination. Where clinically indicated, 24 h holter monitoring was performed, and all of the subjects accepted cardiac magnetic resonance (CMR) at the same time. Retrospective analysis of echocardiographic and CMR studies were performed by two fully blinded observers (Professor Yanna Liu with 35 years and associate professor Chunquan Zhang with 20 years of experience in imaging diagnosis). An analysis about the patient's total echocardiographic data in the hospital and local hospitals was performed. Echocardiographic data and CMR data were compared with each other. All volumetric measurements were individually performed twice by each observer.

Echocardiography

Comprehensive transthoracic echocardiography was performed by using a commercially available system (iU22, Philips Healthcare, Bothell, WA, USA) equipped with an S5–1 transducer (frequency transmitted 1.7 MHz, received 3.4 MHz), according to a standardized protocol. All images were analyzed offline using the Xcelera workstation (Philips Healthcare, KE, USA). Measurements relating to left heart size and function were performed in accordance with the American Society of Echocardiography (ASE) chamber quantification guidelines of 2006 [10]. Left ventricular (LV) long axis, short axis plane, apical 2-chamber plane and apical 4-chamber plane were used. The location of noncompaction was described by using a 16-segment model proposed by Manuel et al. [11] in Standardized Myocardial Segmentation and Nomenclature for Tomographic Imaging of the Heart. The apex was defined as caudal to the papillary muscles, while the base was defined as the area of the left ventricle cranial to the tips of the mitral valve, with the mid-segment being the area between these 2 segments. The apex was divided into 4 segments, while the base and mid-segment were divided into 6 segments each.

Diagnostic Criteria of LV Noncompaction

There are several definitions that attempt to describe the morphology of LV noncompaction. Although these definitions are available, the criteria proposed by Frischknecht et al. [12] and Stollberger et al. [13] are commonly used. It was reported that 68% of normal person could also have prominent trabeculations [14], however, more than 3 trabeculations were present in only 4% of individuals. Study showed that the combination of the two kinds of standard had a reasonable agreement with the features of NCC [15]. Therefore, in this study, we used the two criteria together. Only when fulfilling them simultaneously, the diagnosis of NCC was confirmed.

• Segmental thickening of myocardial wall of left ventricle with two layers: a thin epicardial layer and a thick endocardial layer with prominent trabeculations and deep recesses. The ratio of noncompacted myocardium to compact myocardium at the end of systole is > 2:1 as shown in Figure 1.

• The trabeculations are usually located on the apical/lateral, middle/bottom walls of the left ventricle. Most noncompacted segments are hypokinetic. The flow between the intertrabecular recesses can be identified by using the color doppler method.

• Presence of more than three trabeculations in the LV wall, with the papillary muscles located at the apex, visible in one image plane.

Diagnostic Criteria of RV Noncompaction

The study of right ventricular (RV) noncompaction is still limited to isolated case reports until now [16, 17]. RV noncompaction was diagnosed in present study only in cases where a bilayered structure with flow within the trabeculaes could be noted in the basal and middle wall of right ventricle, and the ratio of the bilayered structure must > 2:1.

CMR

All CMR exams were performed on a 3.0-T scanner (Signa EXCITE HDx, GE, WI, USA), using a dedicated 8-channel phased array surface cardiac coil. The scanning included black-blood sequences: double inversion recovery fast spin echo (DIRFSE), fat-suppression double inversion recovery fast spin echo (FSDIRFSE), white blood sequences (fast imaging employ steady state acquisition): echo time was 1,4 ms, repetition time 3,2 ms, field of view 35×28cm, matrix 192×224, flip angle 45°, slice thickness 6–8 mm, and bandwidth 125 kHz, perfusion CMR and late gadolinium enhancement (LGE) images. Scanning planes included LV short axis view, LV outflow tract view and long axis view, four-chamber view, two-chamber view, planned on short-axis pilots at 60° angles to each other to visualize all 16 segments according to the American Heart Association recommendation. LGE images in short-axis orientation were acquired for quantification of fibrosis 10 min after application of 0,2 mmol/kg/body weight gadopentetate dimeglumine using a three-dimensional T1-weighted inversion recovery turbo gradient echo sequence. Post-processing software Cardiac function parameters were analyzed offline, using MASS Analysis Plus V4.0.1 (Leiden University Medical Center and MEDIS medical imaging systems, Leiden, NL).

Here we used the ratio of N/C > 2,3 which was proposed by Petersen et al. [18] as diagnostic criterion. It produced a high sensitivity (86%) and specificity (99%) in the diagnosis of NCC: **A** the visual appearance of two distinct myocardial layers: a compacted epicardial layer

Table 1

Demographic and clinical characteristics of the study population

Characteristics	Number of the Patients
Male gender	39 (70%)
Age at diagnosis	49,2±13,4 years
Familial occurrence of sudden death	12
Facial dysmorphism	none
Smoking	8
Alcohol drinking	1
Diabetes	1
Shortness of breath	32 (57,1%)
Recurrent syncope	6 (10,7%)
Edema of the lower limbs	10 (17,9%)
No symptom	8 (14,3%)
Drug therapy	38 (67,9%)
Pacemaker/defibrillator	7 (12,5%)
Radiofrequency ablation	6 (10,7%)
Surgical repair of CHD	5 (8,9%)
NYHA I	10 (17,9%)
NYHA II	14 (25%)
NYHA III	27 (48,2%)
NYHA IV	5 (8,9%)

All values shown as number (%) or mean ± standard deviation.

Abbreviations: NYHA — New York Heart Association functional class, CHD — congenital heart disease.

and a non-compacted endocardial layer as shown in Figure 1; **B** the presence of marked trabeculation and deep intertrabecular recesses within the non-compacted layer; and **C** a non-compacted to compacted myocardial ratio of >2.3 as measured in end diastole in the long axis views.

Statistical Methods

Statistical analysis was performed by using SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA). All continuous data were expressed as mean ± SD according to normal distribution of data in the Kolmogorov–Smirnov test. Categorical variables were expressed as frequencies and percentages. Continuous variables were compared by using the Student t-test. All statistical tests were two-sided. Only P-values < 0,05 were considered to be statistically significant.

Results

General Characteristics

A total of 56 Han Chinese patients were recruited. Their baseline characteristics are summarized in Table 1. Mean age of this cohort was 49,2 years, and 70% of them are male. 12 patients had family history of sudden death. 8 subjects had a history of smoking. Chest distress, shortness of breath, recurrent syncope, and edema of the lower limbs were the main symptoms of these patients. 8 patients had no obvious clinical manifestation. When the diagnosis was established, most patients were with standard anti-heart

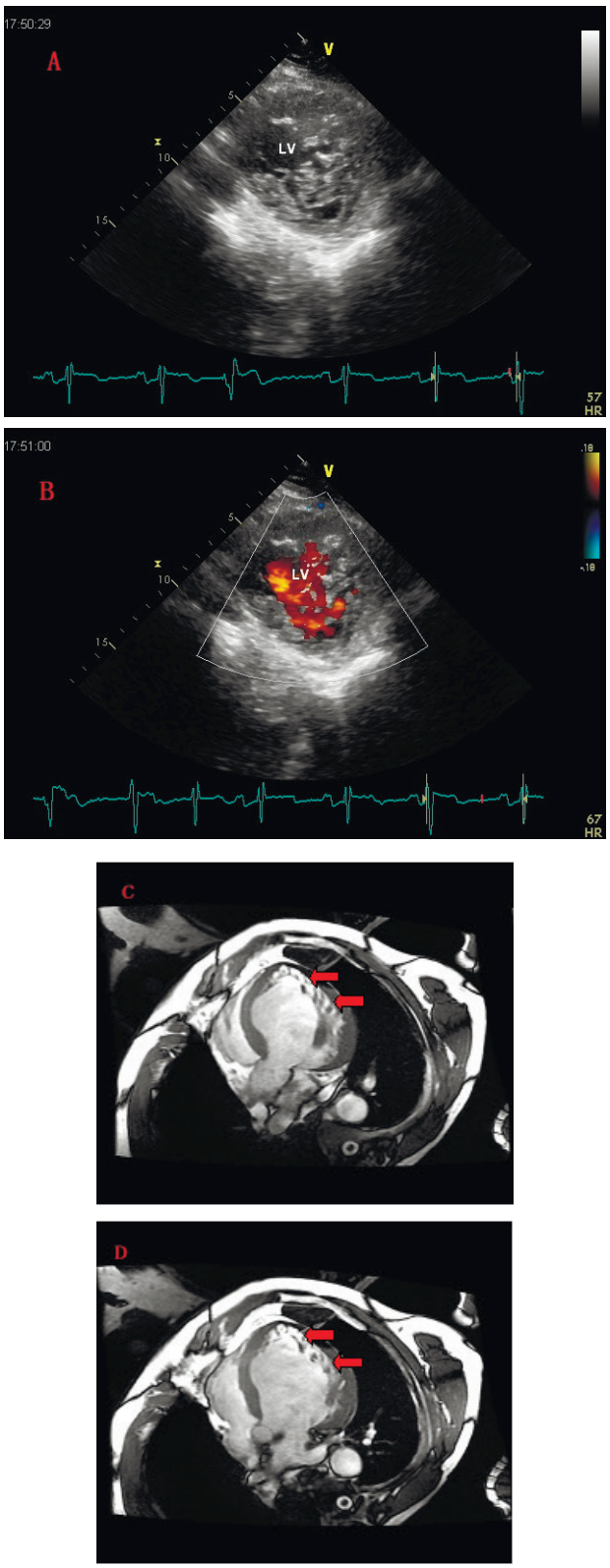

Figure 1. Left parasternal short-axis view at the level of left ventricular apex demonstrates extensive noncompaction (**A**), Short-axis view in which color doppler ultrasound is used to demonstrate flow within the trabeculae that originates from the ventricle cavity (**B**). White blood magnetic resonance images acquired in the LV outflow tract view (**C**) and the four chamber view (**D**). The LV apical, middle anterior and middle posterior trabeculation/non-compaction are clearly visualised (red arrowed).

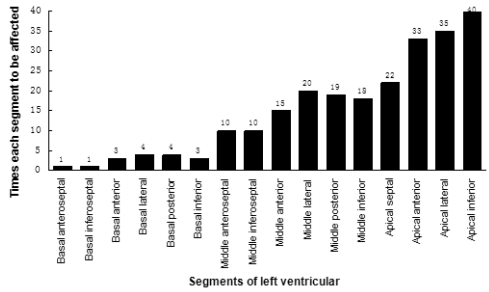

Figure 2. Distribution of left ventricular segments affected by noncompaction.

failure therapy (67,9%), and nearly half (48,2%) of the patients were New York Heart Association Class III at their first assessment. No patient had symptom or sign of facial dysmorphism. The average follow-up was 10 months and 1 case died of respiratory failure during this period.

Echocardiography

Referring to the total echocardiographic times the patients had received since the disease onset, we found that 17 of the 56 patients had been diagnosed with NCC after the first survey in our institution, accounting for 30% of the total subjects. The rest of 39 subjects hadn't been diagnosed correctly until they received several times checking of echocardiography, which were done mostly in local hospitals. Of the 39 subjects, 23 had received the examinations twice, 8 patients triple, 6 patients four times, 1 subject six times, and another one had underwent seven times before they had been finally diagnosed with NCC. The 39 subjects were treated with other diseases prior to our institution, where the diagnosis of NCC was made for the first time. 28 of the 39 subjects had been misdiagnosed as dilated cardiomyopathy (DCM) in the local hospitals, 3 subjects hypertensive heart disease, 2 subjects chronic myocardial infarction, 2 subjects sequela of myocarditis, 1 subject pulmonary heart disease, and 1 for hypertrophic cardiomyopathy. The rest of 2 patients with shortness of breath didn't found any obvious abnormality in the local hospitals.

54 of the total subjects were diagnosed with NCC by echocardiography at our institution, in which 50 subjects were LV noncompaction (LVNC), 3 subjects were RV noncompaction, and 1 was double ventricular noncompaction. The rest of 2 patients who had been diagnosed as DCM were finally proved to be NCC by CMR lately. Mean LV end-diastolic diameter of the cohort was 61,9 mm, and the mean LV ejection fraction was 41,1%, with severe global LV dysfunction (ejection fraction <30%) occurring in 9 patients. 10 patients had a normal ejection fraction. One complicated with left atrium thrombosis had been missed by two dimensional echocardiography checking, and finally was diagnosed by transesophageal echocardiography, as indicated in Table 2. 2 cases merged with atrial septal defect, 1 with atrial septal defect and persistent left superior vena cava, 1 with ventricular septal defect and right coronary sinus tumor, and 1 with patent foramen ovale.

All 16 segments were evaluated successfully in all patients diagnosed with NCC. The most frequently involved segments were apical followed by the posterior, lateral and inferior mid-segments. The pathological myocardium in 16 regions was depicted in Figure 2. The base segment was very infrequently involved. All involved segments were equally hypokinetic compared with surrounding myocardium.

Table 2

Left heart echocardiographic features of the studied population

Feature	Value
LVEDD, mm	61,9±13,1
LVSDD, mm	49,7±13,9
IVSd, mm	9,2±1,8
LVPWd, mm	10±3,3
LVEF, %	41,1±15,0
LA volume, ml	39,7±8,8
LA thrombus, no	1
A-wave velocity (cm/s)	70,8±31,1
E-wave velocity (cm/s)	93,8±41,4
E/A ratio	1,6±0,9
N/C ratio	2,8±0,5

All values shown as number or mean ± standard deviation.

Abbreviations: LVEDD — LV end-diastolic diameter, LVESD — LV end-systolic diameter, IVSd — interventricular septal thickness at diastole, LVPWd — LV posterior wall thickness at diastole, LVEF — LV ejection fraction, LA — left atrium.

Table 3

The affected segmental comparison between echocardiography and CMR

Location of trabeculations	Echocardiography	CMR
Basal anteroseptal	2	0
Basal inferoseptal	2	2
Basal anterior	6	8
Basal lateral	4	6
Basal posterior	4	6
Basal inferior	6	6
Middle anteroseptal	10	6
Middle inferoseptal	10	4
Middle anterior	16	22
Middle lateral	20	24
Middle posterior	22	20
Middle inferior	18	20
Apical septal	20	20
Apical anterior	32	40
Apical lateral	24	30
Apical inferior	42	42

P = 0,80, there is no statistics significance in the affected segments between echocardiography and CMR.

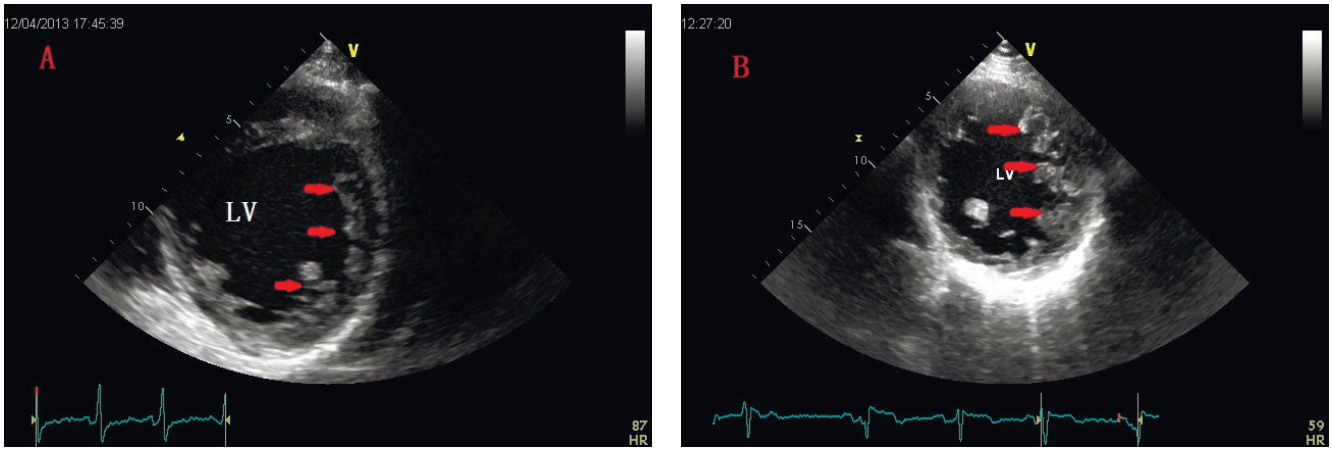

Figure 3. The pattern of inheritance in a family with pathological LV non-compaction. Systolic horizontal short-axis views of father (**B**) and son (**A**) show various degrees of non-compaction (red arrows). Ratio of N/C in **A** is 2.5, and 4.5 in **B**.

Comparison of Echocardiography with CMR in Imaging Data

All of the 56 subjects accepted echocardiography and CMR simultaneously. Of them, 2 patients had been diagnosed as DCM by echocardiography was proved to be NCC by CMR lately. Among the subjects who had consistent diagnosis, CMR showed 256 segments and echocardiography showed 238 segments which were affected by NCC, as indicated in Table 3. There was no significant difference between the capability of CMR and echocardiography to detect the segments which were affected by NCC (P = 0,80). The affected myocardium consisted of two layers: subendocardial noncompacted myocardium and epicardial compacted myocardium. The ratio measurement of N/C was 2,63±0,49 by CMR, and 2,55±0,43 by echocardiography.

Discussion

NCC is a rare disorder, which is considered to be an unclassified cardiomyopathy according to the World Health Organization [5, 19]. Most patients suffer a sudden death or underwent cardiac transplant within six years of diagnosis [5]. NCC is proved to be an autosomal dominant inherited cardiomyopathy [20]. It may be associated with G4.5 or ZASP1 mutation [21]. Mutations of the genes coding the epsilon 14–3–3 can also be the cause of embryogenesis myocardial compacted failure [22]. Endomyocardial biopsy examination is considered as the gold standard for the diagnosis of NCC [2, 5], whereas it is defective in its invasiveness, blindness and technical complexity in operation. Therefore, the diagnosis of NCC is usually made by using echocardiography, and increasingly MRI [1, 15]. This retrospective study in the Han Chinese patients firstly documented the specific misdiagnosis and missed diagnosis for NCC.

Due to it's mature technology, convenience, economy, and no radiation, echocardiography has been used as the main method to diagnose NCC [4, 5]. In this study, the diagnostic rate of NCC was 96,4%, and the detection rate to other cardiac deformities is 100% by echocardiography. Numerous studies have confirmed that it can display the characteristic changes of NCC [1–5]. However, since the low incidence, and the diversity of clinical manifestations, most radiologists especially community doctors lack of a clear understanding to this disease, which leads the missed diagnosis and misdiagnosis rates of NCC to be very high. In present study, 70% of the patients had several times of echocardiography in local hospitals. Extension of the diagnostic period not only makes the treatment be delayed, also aggravates the economic burden of patients.

As NCC is a hereditary disease, the ultrasound doctors should ask in details about the patients' family or personal medical history before checking. Special emphasis must be placed on the patients who have a family history of NCC. An echocardiographic screening is required to their first-degree relatives when necessary. In present study, 12 patients had family history of sudden death, and 2 of them were parent-child relationship. Sudden cardiac death happened in 3 elder sisters of the father who was hospitalized because of chest tightness and shortness of breath for four years. When screening was carried out on the son who was clinically asymptomatic, we found that the LV myocardium in the apex was divided into two layers in which the ratio of N/C was 2.5 as indicated in Figure 3, and his heart function was normal. There is a general agreement that NCC can exist in isolation, but it may also coexist with other congenital heart [23] and neuromuscular [24] diseases. When NCC is found in a patient, we cannot satisfied with current diagnosis, and should scan carefully in multiple planes to exclude other malformations. 5 cases coexisted with other cardiac malformations in present study, and all of them were diagnosed by echocardiography. The blood flow between noncompacted myocardium is very slow and clogged, which allows mural thrombus to form. The lowest flow velocity between the noncompacted myocardium reached to 18 cm/s in present study. This

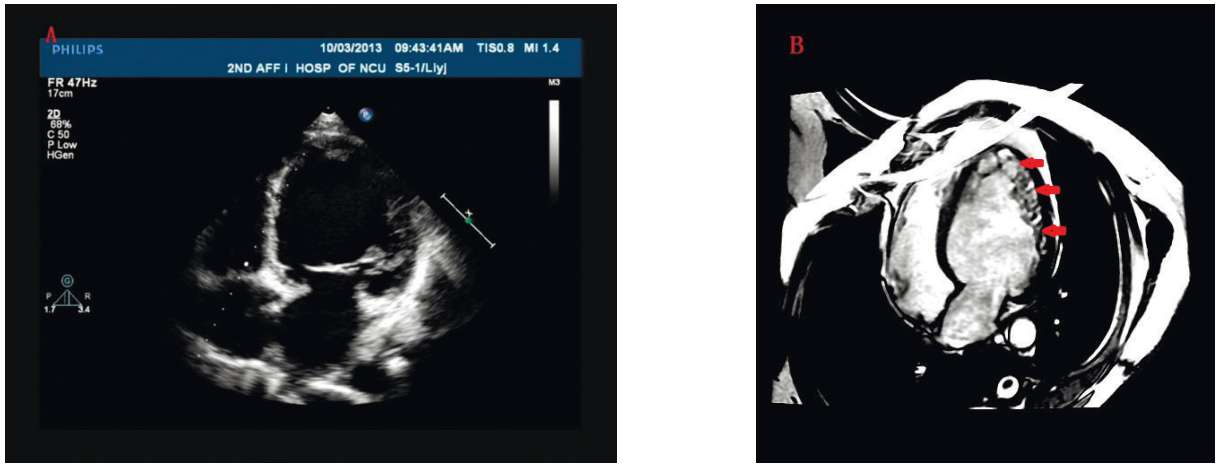

Figure 4. The apical 4-chamber plane, which was detected by echocardiography showed the enlargement of left ventricle, and the thickening of lateral wall was considered to be caused by DCM (**A**). But CMR showed trabeculation and deep intertrabecular recesses (**B**), LGE didn't find any abnormal enhancement within the myocardium, and made the diagnosis of NCC.

kind of thrombus adds a wall falls off easily form embolus, produces viscera embolism with dangerous. In present study, 1 case coexisted with left atrial thrombus. We did not find it in conventional echocardiography, and it was finally diagnosed by transesophageal echocardiography.

Studies indicated that hypertrophic trabecular could also be found in the heart of normal people [14], but the ratio of N/C was <2. Therefore, the diagnosis of NCC should be cautious. We must rule out other congenital or acquired heart diseases such as DCM before the diagnosis was set up. Measurements and ratios must be integrated with clinical, pathophysiologic and evolving genetic variables to make an accurate diagnosis, and avoid overdiagnosis. A pathoanatomic study also found more than 3 trabeculations were present in only 4% of individuals [1]. Thus in present study, we used two echocardiographic definitions to identify NCC, which assessed the number and size of trabeculations, as well as the relative thickness of the non-compacted layer. Thus, we believe that we have avoided overdiagnosis to the most extent. Cardiac enlargement and cardiac function decline are the common performance in NCC and many other kinds of heart diseases. The key to differentiate them is to follow the diagnostic criteria of NCC strictly, that is particularly important as the morphologic appearance of increased trabeculations may be produced if oblique views of the ventricle are used for detecting [15]. Present study found that NCC was most probable to be misdiagnosed as DCM, accounting for 50% of the total cases. Essentially there are several important differences among them. DCM is mainly characterized by ventricular chamber enlargement, ventricular wall becomes thin evenly, and endocardium is smooth [25]. It was reported that the expansion tended to be more spherical, and the hypertrophic trabecular located in the lateral wall of LV more often in DCM [26]. However, NCC usually have several segments that are noncompacted, apex is the segment which is the most easy to be affected. [1] The pathological change of NCC is endomyocardial fibrosis [5], while the typical myocardial fibrosis in DCM mostly happen in the mid-myocardium of the basal septum [27]. NCC must also be differentiated from diseases that may lead to obstruction of the outflow of the left ventricle, such as hypertensive heart disease, aortic valve lesion etc. All NCC imitators should be considered when making a diagnosis.

NCC is predominantly a genetic cardiomyopathy with variable clinical presentations ranging from asymptomatic to severe [28]. Parts of the patients are asymptomatic or only have mild symptoms for many years. Heart function can also be within normal range, and clinical diagnosis is therefore difficult. More attention should be paid to this situation when checking, observing myocardial situation from the bottom to the apex of the heart carefully, zooming in the suspicious segment partially.

RV noncompaction is especially rare [15]. In this study we reported 3 cases of RV noncompaction and a biventricular noncompaction. As trabeculation is the normal anatomic structure of RV apex, which runs from the septum to the apex, it is difficult to define RV noncompaction. Thus, we used a bilayered myocardial segment in the basal and middle wall, whose ratio must be > 2:1 as standards defined.

Due to the multiple positions and sequences, high soft-tissue resolution and spatial resolution, CMR is being used in diagnosis of NCC gradually [29, 30]. Studies show that CMR can display the pathological cardiac muscle more clearly, and is easier to detect the apex and lateral wall of left ventricle [29–31]. Because of highly variable LV trabeculation, qualitative or even semi-quantitative parameters to differentiate normal compaction of the myocardium in healthy subjects from NCC or from other cardiomyopathies like DCM or hypertrophic cardiomyopathy (HCM) might be difficult by using echocardiography. AS LGE affords high quality myocardial

definition. It has been used as a gold-standard in the identification and characterization of cardiac masses and cardiomyopathies. It can also identify the internal structure of myocardium, distinguish fibrotic myocardium from the normal one [31–32].

Grothoff et al. [20] found that none of the NCC patients demonstrated intramyocardial LGE, however, LGE was found in all DCM and HCM patients. The findings were same as other studies that also stated a lack of LGE in NCC [33, 34].

What's more, the phase-sensitive inversion recovery sequence has shown advantages in visualization of fibrosis in regard to image quality and reproducibility compared with standard magnitude detection [35]. It can clearly show the location and scope of myocardial fibrosis and may have prognostic implications [2]. In present study, all subjects were found fibrosis, which located under the endocardium. 2 of them were diagnosed as DCM by echocardiography firstly, but CMR showed that the myocardial fibrosis located under the endocardium, and proved that they were not DCM but NCC, as displayed in Figure 4. However, CMR is expensive, and has many contraindications. The patients who have cardiac pacemaker, metal dentures or those who suffer from claustrophobia and cardiac surgery can't accept CMR examination [36]. What's more, most of the NCC patients have cardiac insufficiency. The patients cannot lay down and control their breath for a long time, which will make the quality of CMR image very poor. Therefore, the application of CMR is limited.

There are some limitations in this study. Firstly, larger samples are necessary to evaluate trabecular patterns and further refine the ability to diagnose NCC. Secondly, as the main clinical manifestation of these patients is heart failure, a long-term follow-up to them is needed to assess the patient's prognosis. Finally, we have not addressed the issue of myocardial biopsy and genetic testing, which is an important future research and highly relevant clinical consideration.

Conclusion

Echocardiography can be the first choice of NCC assessment for its advantages of being non-radiative, real-time, economic and characteristic. When the echocardiographic image is not typical in the early stage of NCC, a combination with CMR is necessary.

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