Myocardial ischaemia in children with isolated ventricular non-compaction

G. Junga*, S. Kneifel†, A. Von Smekal‡, H. Steinert† and U. Bauersfeld*

*Division of Cardiology, Children's University Hospital Zurich, Zurich, Switzerland; †Clinic of Nuclear Medicine and ‡Department of Radiology, University Hospital Zurich, Zurich, Switzerland

Aims Isolated ventricular non-compaction is a rare congenital cardiomyopathy with a high morbidity and mortality due to malignant arrhythmias and pump failure. Areas affected by non-compaction are characterized by increased trabecularization and deep inter-trabecular spaces. We hypothesized perfusion defects in these areas and performed positron emission tomography to evaluate the myocardial perfusion in non-compacted areas.

Methods and Results Five children (age 10–14 years) with isolated ventricular non-compaction underwent positron emission tomography using N-13-ammonia as flow marker and intravenous dipyridamole for stress testing. Myocardial blood flow was quantified using the positron emission tomography time–activity curves in non-compacted areas and normal myocardium, which were diagnosed by echocardiography, magnetic resonance imaging, and angiography. Coronary angiography, performed in two children with extensive forms of left ventricular non-

compaction, demonstrated normal coronary arteries. Myocardial blood flow measurements at rest and after dipyridamole application demonstrated 16–33% and 32–57% perfusion impairment, respectively, in non-compacted areas compared to normal myocardium. Areas of restricted myocardial perfusion corresponded well to the non-compacted areas, defined echographically and by magnetic resonance imaging.

Conclusion Positron emission tomography demonstrates restricted myocardial perfusion and decreased flow reserve in areas of ventricular non-compaction in children. The myocardial perfusion defects in non-compacted areas may be the cause of myocardial damage and possibly form the basis of arrhythmias and pump failure.
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Key Words: Non-compaction, ischaemia, cardiomyopathy, ventricles, imaging, electrophysiology.

Introduction

Ventricular non-compaction is an extremely rare congenital disorder of the left, right or both ventricles and may be associated with other congenital malformations or occur in isolation; the latter being designated isolated ventricular non-compaction[1–6]. In early embryogenesis, the heart consists of a loose mesh of muscle fibres that normally condense gradually. Physiologically this process is more complete in the left than in the right ventricle, thus flattening the endocardial surface[7]. Due to an unexplained arrest in myocardial morphogenesis, the anatomical pattern of isolated ventricular non-compaction is characterized by prominent trabeculations with deep intertrabecular recesses. This pattern

of isolated ventricular non-compaction has to be distinguished from arrhythmogenic right ventricular dysplasia, which may occasionally present. Typical pattern is right ventricular dilation with local wall bulging, and hypertrophic trabeculae separated by deep fissures in the right ventricular apical region. Arrhythmogenic right ventricular dysplasia is characterized pathologically by right and left ventricular myocardial atrophy and fibrofatty replacement caused by degeneration of right ventricular muscle[8,9]. Spontaneous as well as familial occurrence of isolated ventricular non-compaction have been observed[1]. Occasionally, non-cardiac malformations in association with isolated ventricular non-compaction have been seen[1,10–12]. Prognosis of isolated ventricular non-compaction is apparently grim with a high morbidity and mortality due to heart failure, ventricular arrhythmias, and systemic embolization[13]. The reason for depressed left ventricular function in isolated ventricular non-compaction is unknown. Some authors describe echocardiographic patterns of isolated ventricular non-compaction

resembling those of dilated cardiomyopathy[13]. Others delineate impaired intramural perfusion with subendocardial ischaemia[1]. The purpose of this study was to evaluate the possibility of myocardial ischaemia or impaired coronary reserve in isolated ventricular non-compaction.

Methods

Patients

The study group consisted of five patients (three girls; age 10 to 14 years) with isolated ventricular non-compaction. All the children except one were clinically asymptomatic at diagnosis (age 6·2 to 12·6 years) and during follow-up (25 to 72 months). Referrals were due to cardiac murmurs in four and dyspnoea (NYHA II) in one patient. The study protocol was approved by the ethical committee of the Children's University Hospital, Zurich. Written informed consent was obtained from the parents of the patients.

Electrophysiological testing

Non-invasive electrophysiological tests included a 12-lead electrocardiogram, calculation of QT dispersion, a signal-averaged electrocardiogram, Holter recording and symptom-limited treadmill exercise testing with the standard Bruce protocol. A 12-lead surface electrocardiogram (ECG) at 50 mm . s^{-1} served for the calculation of QT dispersion. Two blinded observers measured the QT intervals manually from the onset of the QRS to the end of the T wave, defined as the return to TP baseline. Three consecutive cycles were measured in each of the standard 12 leads and from the three values a mean QT was calculated. A minimum of seven leads was required for QT dispersion to be calculated. A QT dispersion above 60 ms was considered to be abnormal[14]. Signal average ECGs were recorded on a single electrocardiograph (Marquette Inc., Milwaukee Wisconsin, U.S.A. Case 15) in the recumbent position after sites of lead placement were cleaned with alcohol. Frank X, Y, and Z leads were used. The following signal average ECG variables at the 40–250 Hz filter setting, as calculated by the built-in software, were obtained: (1) standard unfiltered QRS duration in ms (2) total filtered QRS duration in ms (3) duration of high frequency low amplitude signals in ms less than 40 μV (4) root mean square voltage in the terminal 40 ms in μV. Late potentials were judged to be positive if two of the criteria 2–4 were fulfilled. Signal averaged ECG data were interpreted in accordance with data published elsewhere[15]. The Holter ECG was recorded with a Marquette Holter recorder 8500 and analysed utilizing a Marquette 8100 Laser S analysis system. Criteria for supraventricular or ventricular ectopy were more than one premature supraventricular or ventricular beat per hour or repeti-tive forms of ectopic beats[16]. An ischaemic episode was defined as a transient ST depression $\geq 0·1$ mV that persisted for at least 1 min with a consecutive normalization of the ST segment of at least 1 min. Holter recordings were judged to be normal if there was no ectopy, ischaemia, or episodes of bradycardia or tachycardia. The exercise tests and dipyridamole stress test ECG were considered positive if there was more than 1mm horizontal ST-depression at 80 ms after the J-point.

Echocardiography

Two dimensional echocardiograms were recorded with a Hewlett-Packard Sonos 1000 or 2000. Criteria for the diagnosis of isolated ventricular non-compaction were the following: (1) numerous prominent trabeculations in combination with perfused deep inter-trabecular spaces and (2) the absence of any coexisting cardiac anomaly[1,3,13]. Quantitative evaluation of left ventricular dimensions and function was done in accordance with data published elsewhere[17,18]. Isolated ventricular non-compaction zone segments of the left ventricle were identified in the two-dimensional echocardiographic image, using the parasternal long-axis four-chamber view, two-chamber view, and short-axis view. Wall thickness at the site of the most prominent trabeculations (Wmax) was measured in the two-dimensional echocardiographic image using four-chamber views and related to the thickness of the interventricular septum obtained by standard M-mode technique. The ratio Wi (Wi=Wmax/interventricular septum) served as a measure of the severity of isolated ventricular non-compaction on a semiquantitative basis.

Magnetic resonance imaging

The study was performed on a 1·5 T Signa EchoSpeed System (GE Medical Systems, Milwaukee, WI, U.S.A.) equipped with a torso phased-array coil. The patients were placed in the supine position. The ECG was registered for monitoring and gating. After a localizing axial T1 weighted SE sequence of the heart, breath-hold segmented multi-phase (fastcard) GRE sequences with and without phase contrast were acquired in long-axis, two-chamber, four-chamber and short-axis angulation of the heart to depict cardiac anatomy.

Positron emission tomography

Positron emission tomography studies were performed on a GE Advance positron emission tomography scanner (General Electrics, Waukesha, Wisconsin, U.S.A.; axial field of view 35 × 4·25 mm). Perfusion studies were achieved in two-dimensional mode using a dynamic N-13 ammonia protocol (12 × 10 s, 6 × 30 s and

Table 1   Imaging and electrophysiology

	Case 1	Case 2	Case 3	Case 4	Case 5
Sex	Female	Female	Male	Female	Male
Age (years)	14	14	10	13	10
Weight (kg . height^{-1} . cm^{-1})	43/160	39/163	34/143	30/146	25/136
Echocardiography					
IVNC LV segments	1,5,6,7	2,4,5	only RV, apical	1,2,3–7	1,2,3–7+RV apical
LV: ESD/EDD (mm)	30/46	22/39	24/41	35/48	27/35
LV: EF (%)	63	65	58	49	46
Wmax (mm)	17	14	24	38	24
Wi	2·0	2·3	4·3	6·3	3·7
PET (IVNC areas)					
Perfusion:					
rest (ml . min^{-1} . g^{-1})	0·69	0·83	na	na	1·01
stress (ml . min^{-1} . g^{-1})	3·26	2·38	na	na	2·19
CVR	4·72	2·85	na	na	2·18
PET (not IVNC areas)					
Perfusion:					
rest (ml . min^{-1} . g^{-1})	0·82	1·04	1·22	0·87	1·5
stress (ml . min^{-1} . g^{-1})	5·58	3·5	4·53	5·5	5·06
CVR	6·79	3·36	3·71	6·32	3·37
Electrophysiology					
ECG	Sinus bradycardia AV escape beats	Normal	Incomplete right bundle branch block	Bi-atrial dilatation Pre-terminal negative T-waves V_4–V_6	Biventricular hypertrophy
Late potentials	No	No	Yes	Yes	Yes
QT dispersion	Normal	Normal	Normal	Normal	>60 ms
Holter	AV junctional escape beats Rare PVC	Normal	Normal	Normal	Normal
Exercise tests	Normal	Normal	Normal	Positive	Normal
Dipyridamole stress	Normal	Positive	Positive	Positive	Normal

IVNC=Isolated ventricular non-compaction; PET=positron emission tomography; LV segments=left ventricular segments; 1=apical lateral; 2=apical anterior; 3=apical inferior; 4=mid anterior; 5=mid lateral; 6=mid posterior; 7=mid inferior; RV=right ventricle; ESD/EDD=end=systolic/diastolic diameter; EF=ejection fraction; Wmax=wall thickness at the site of the most prominent trabeculation; Wi=wall thickness at the site of the most prominent trabeculation divided by the thickness of the interventricular septum; CVR=coronary vasodilator reserve: ratio of stress and rest perfusion; Dipyridamole-stress=ST-depression under vasodilator stress with dipyridamole; na=not available.

2×300 s frames). For each study, 400 MBq of tracer were administered. Flow values were assessed at rest and under stress conditions 8 min after intravenous infusion of 0·56 mg . kg^{-1} body weight of dipyridamole over 4 min. The images were reconstructed with attenuation correction data obtained from a 20 min transmission scan. Flow values were obtained from affected and non-affected areas in each patient using two-compartment kinetic modelling (K1/k2 with spillover correction)[19]. Coronary flow reserve was calculated as the ratio of stress and rest values.

Heart catheterization

Heart catheterization was conducted in two patients with extensive forms of isolated ventricular non-compaction to exclude associated congenital malformations and for haemodynamic assessment. From a clinical point of view and, seeing that normal epicardial coronary arteries have been reported in other studies, there

was no indication for heart catheterization in the three other children at any time[1,10].

Statistical analysis

Descriptive statistics are reported as mean values ± standard deviation where appropriate. Further statistical analysis was not done due to the small number of patients.

Results

Imaging data and results of electrophysiological tests are shown in Table 1. Only one child presented with symptoms, presumably related to depressed left ventricular function, and was treated with an ACE inhibitor, diuretics and digoxin. Familial recurrence of isolated ventricular non-compaction was not observed. None of

the children had any non cardiac malformation. During a follow-up of up to 6 years no clinical deterioration was noted in any child.

Twelve-lead ECGs were abnormal in three children, although the abnormalities varied from child to child (Table 1). Holter recordings yielded no significant supraventricular or ventricular arrhythmia or ischaemia. Exercise tests demonstrated ST depression in one patient, whereas vasodilator stress with dipyridamole revealed ST depression in three children. Late potentials were detected in three patients with more extensive isolated ventricular non-compaction. One of the three also had an abnormal QT dispersion.

Echocardiography demonstrated decreased systolic function of the left ventricle in two children with marked left ventricular non-compaction (cases 4 and 5). In addition to thickened myocardium of both ventricles, one of these patients also disclosed moderate mitral regurgitation. In the patient with right ventricular non-compaction (case 3) and the two children with less extensive left ventricular non-compaction (cases 1 and 2) global systolic left ventricular function was normal. All patients revealed a markedly thickened myocardium in the isolated ventricular non-compaction areas with subsequent Wi ratios of 2·0 to 6·3.

Cardiac catheterization of the two most severely affected children with left ventricular isolated ventricular non-compaction (cases 4 and 5) confirmed normal epimyocardial coronary arteries. Isolated ventricular non-compaction areas were angiographically concordant with echocardiography. In both patients, ventricular end diastolic and pulmonary arterial pressures were elevated.

Magnetic resonance imaging scans clearly defined the isolated ventricular non-compaction areas (Fig. 1) and were also concordant with angiography and echocardiography. A thrombus as a complication of isolated ventricular non-compaction was detected in the left ventricle of the most severely affected patient, although there were no signs of systemic emboli. The patient was anticoagulated. The thrombus was not detected on a preceding echocardiogram.

Positron emission tomography studies demonstrated the extent of the isolated ventricular non-compaction area in three out of five patients. Reduced coronary flow reserve was clearly revealed in the isolated ventricular non-compaction areas (Fig. 2). However, coronary flow reserve of non-isolated ventricular non-compaction areas was normal in all children. Perfusion assessments of right ventricular myocardium were not conducted in a patient with right ventricular isolated ventricular non-compaction. Due to technical problems the evaluation of isolated ventricular non-compaction areas failed in another child.

Discussion

Heart failure and ventricular arrhythmias are common in isolated ventricular non-compaction. It is suggested
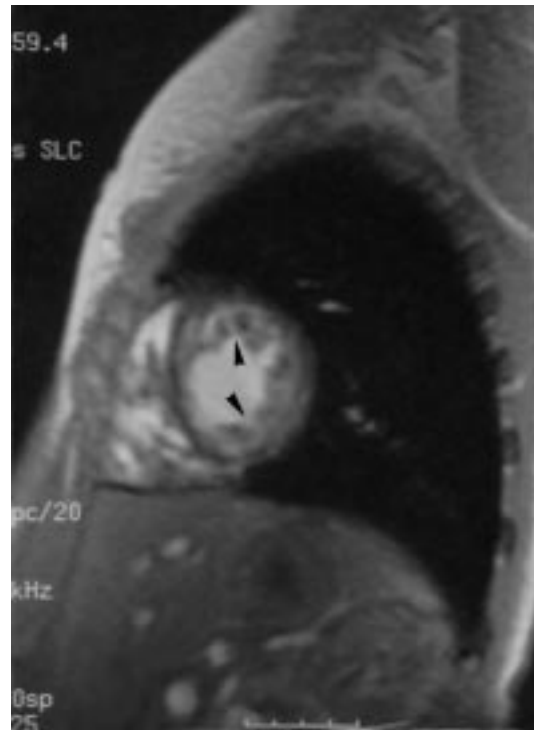

Figure 1 **Short-axis fastcard gradient-echo magnetic resonance images through the left and right ventricle in a 10-year-old boy (case 5) demonstrating deep recesses and prominent trabeculations within the left ventricle typical of isolated ventricular non-compaction (arrows).**

that myocardial ischaemia may play a crucial role in the development of impaired systolic and diastolic ventricular function and ventricular arrhythmias in patients with isolated ventricular non-compaction, similar to ischaemic heart disease[20]. The purpose of this study was to demonstrate potential ischaemia at rest and after pharmacological stress in non-compacted myocardium. Our results demonstrate decreased myocardial perfusion at rest and after vasodilator stress in non-compacted myocardium, compared to non-affected areas in children with isolated ventricular non-compaction. Ventricular dysfunction seems to depend on the extent of isolated ventricular non-compaction. Likewise, prolonged QT dispersion and the occurrence of late potentials are believed to identify an area of slow conduction potentially capable of sustaining re-entry that forms the basis for monomorphic ventricular tachycardia.

Myocardial ischaemia

To date there is little information on the mechanism of ventricular dysfunction in isolated ventricular non-compaction. In a series of eight children published by Chin and associates[1], histological examination of three isolated ventricular non-compaction affected hearts demonstrated a continuous layer of endothelium from the ventricular cavity into the recesses without coronary
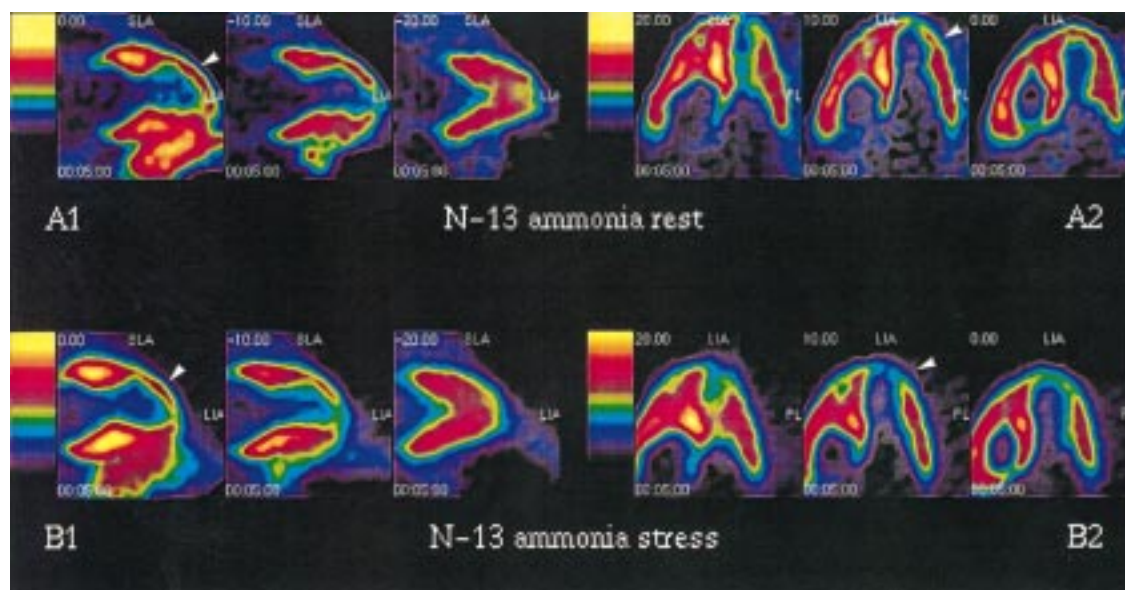
Figure 2 Positron emission tomography in a 10-year-old boy with isolated ventricular non-compaction (case 5) showing corresponding long axis and four-chamber views of the left ventricle on the left (A1, B1) and right (A2, B2) half respectively: reduced perfusion of the anterolateral segments (arrows) of the left ventricle at rest (A1, A2) with aggravation of blood flow reduction under dipyridamole stress (B1, B2).

communications to the ventricular cavity. However, there was evidence of increased subendocardial fibrosis within the areas of non-compacted myocardium. These findings in isolated ventricular non-compaction were confirmed by others[5,6]. Epimyocardial blood flow is normal in isolated ventricular non-compaction, as demonstrated by Chin *et al.*[1], Bleyl *et al.*[10] and in two of our patients by coronary angiography. Thus, neither impaired epicardial coronary blood flow nor coronary communications to the ventricular cavity seem responsible for the fibrosis of the affected myocardium, which might be due to subendocardial ischaemia[5,6,21,22]. Subendocardial ischaemia could be attributed to isometric contraction of the endothelium and myocardium within the deep intra-trabecular recesses.

Positron emission tomography has proved an accurate tool for the assessment of regional myocardial perfusion and metabolism in coronary artery disease in adults[19]. There are only a few reports addressing positron emission tomography in children[23,24]. The results of the present study suggest, for the first time, that myocardial perfusion and coronary flow reserve in areas of isolated ventricular non-compaction are impaired. In three of our cases we could demonstrate depressed regional myocardial perfusion at rest and decreased coronary vasodilator reserve with ST-segment depression in three out of five patients. The underlying mechanism might be failure of the coronary microcirculation to grow with the increase in ventricular mass, or compression of the intramural coronary vascular bed by the hypertrophied myocardium, or a combination of both mechanisms. However, there is still no clear evidence in the literature of a significant reduction of capillaries in the trabeculae of isolated ventricular non-compaction

areas. In contrast to coronary artery disease, with obstruction of epicardial vessels in the entities of hypertrophic and dilated cardiomyopathy, myocardial flow and coronary vasodilator reserve, as an index of coronary microvascular function, are decreased secondary to functional or extravascular abnormalities[25–27]. With the exception of one child (case 5) in our study, the above situation does not appear to be analogous for isolated ventricular non-compaction, although there is no hint of morphologically altered epicardial coronary arteries in the literature to explain our finding of impaired myocardial perfusion in isolated ventricular non-compaction[1,10].

Electrophysiology

No significant arrhythmias were detected in any of our patients by Holter or exercise tests, in contrast to the patients of Ritter *et al.*[13], Chin *et al.*[1] and others[3,10]. Furthermore, we found no electrophysiological abnormalities in the two minor forms of isolated ventricular non-compaction included in our series (cases 1 and 2). Interestingly, electrophysiological tests revealed abnormalities only in the more extensive cases of left ventricular non-compaction (cases 4 and 5) and in a child with isolated right ventricular non-compaction (case 3). Those three showed either late potentials or prolonged QT dispersion, pointing to the occurrence of late depolarization or repolarization in more extensive left or right ventricular forms of non-compaction. These findings were confirmed by Ritter and co-workers[13]. However, intracardiac electrophysiological testing, with programmed ventricular stimulation to determine

whether or not monomorphic ventricular tachycardia is inducible, was not performed in our study, and the cause of the increased arrhythmogenesis in isolated ventricular non-compaction remains unknown. On the other hand, it has been shown in coronary artery disease in adults that the presence of late potentials or a prolonged QT dispersion heralds an increased risk for a subsequent occurrence of sudden cardiac death or sustained monomorphic ventricular tachycardia[28]. Whether fragmented activation or inactivation of non-compacted myocardium in the presence of ischaemia, as shown in our patients, will serve as a prognostic factor in risk stratification of isolated ventricular non-compaction needs further investigation. At the moment, treatment strategies for symptomatic ventricular arrhythmias in isolated ventricular non-compaction are comparable to those currently recommended in cardiomyopathies, with special attention to proarrhythmic drug effects.

Imaging modalities in isolated ventricular non-compaction

Two dimensional echocardiography with colour and Doppler studies is the standard diagnostic procedure for isolated ventricular non-compaction[1,3,13]. This technique allows the determination of localization and extent of isolated ventricular non-compaction, atrial and ventricular sizes, and both systolic and diastolic ventricular function. Magnetic resonance imaging can provide multiple tomographic sections of the ventricles in patients with ventricular and cardiac deformities and has been applied in children with congenital heart disease[29,30]. In this study, echocardiography and magnetic resonance imaging findings demonstrated a good correlation as far as localization and extent of isolated ventricular non-compaction were concerned. Magnetic resonance imaging offered no additional information compared to echocardiography, except for the detection of a thrombus which was hidden in the spongelike myocardium of isolated ventricular non-compaction. Thrombus formation is a potential complication of isolated ventricular non-compaction and necessitates anticoagulant therapy to prevent pulmonary or systemic embolism. Compared to echocardiography, magnetic resonance imaging guarantees more operator independency and might be superior to echocardiography in cases of an impaired echocardiographic imaging quality. These findings confirm observations made with magnetic resonance imaging in isolated ventricular non-compaction of an adult[31].

Study limitations

Because of ethical constraints concerning the administration of radioactive agents to healthy children, comparison of myocardial blood flow in isolated ventricular non-compaction areas were based on flow values measured in the apparently normal myocardium of the patient's heart. The latter values did not differ compared to those obtained in hearts of healthy adults. Normal values of myocardial blood flow by positron emission tomography in children are not available at the moment. Two studies report positron emission tomography data of myocardial perfusion and metabolism exclusively in children with Kawasaki disease[23,24].

Assessment of the extent of isolated ventricular non-compaction in general is not yet standardized. However, our method of creating a ratio of the wall thickness at the site with the most prominent trabecular meshwork and the thickness of the interventricular septum takes age-dependent changes of myocardial dimensions into account. As a reflection of the rare occurrence of isolated ventricular non-compaction our limited series of five patients does not allow statistical analysis.

Conclusion

For the first time, myocardial ischaemia in areas of isolated ventricular non-compaction can be demonstrated. While positron emission tomography, magnetic resonance imaging, echocardiography and angiography are reliable imaging modalities to diagnose isolated ventricular non-compaction, only positron emission tomography provides data to quantify the extent of the myocardial ischaemia. Further investigations are needed to evaluate the prognostic value of myocardial ischaemia in isolated ventricular non-compaction.

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