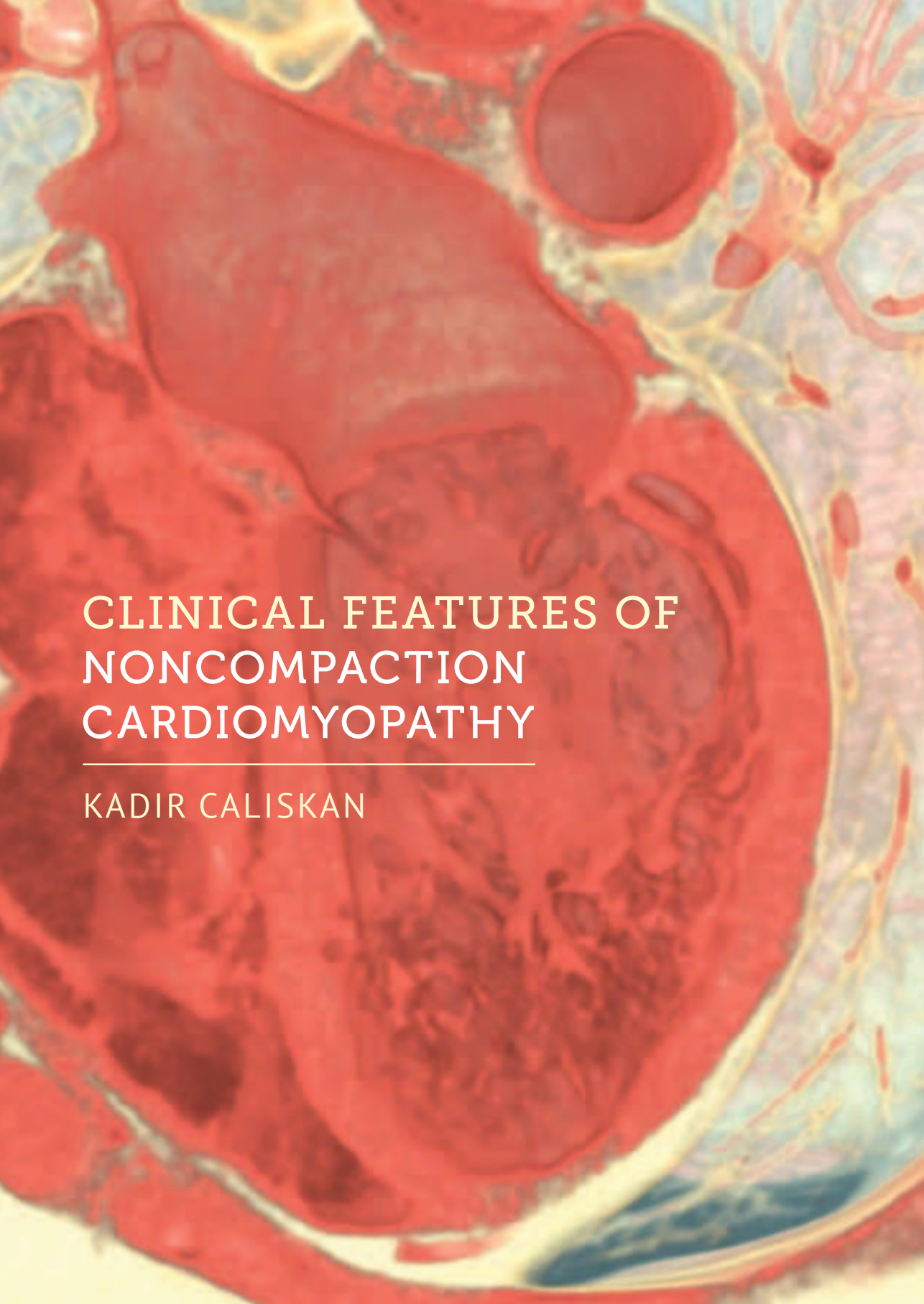

CLINICAL FEATURES OF NONCOMPACTION CARDIOMYOPATHY

KADIR CALISKAN

Clinical Features of Noncompaction Cardiomyopathy

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CONTENTS

INTRODUCTION

Cardiomyopathies are diseases of the heart muscle, classically classified according to distinct structural and functional features.[1] The earlier classification of hypertrophic, dilated and restrictive cardiomyopathies, was extended with arrrhythmogenic right ventricular cardiomyopathy / dysplasia and unclassified cardiomyopathies.[2-3] Conditio sine qua non was that the specific morphological and functional abnormalities could not be explained by significant coronary artery disease, hypertension, valvular heart disease or congenital heart disease.

More recently *noncompaction* cardiomyopathy (NCCM) is recognized as a separate disease entity after the first report by Engberding and Bender in 1984 of a rare case with persistent myocardial sinusoids and later Chin et al. in 1990 described a series of 8 pediatric and adolescent patients with increased trabeculation of the left ventricular endocardium.[4-5] Noncompaction cardiomyopathy has been the subject of an increasing amount of reports in the medical literature (March 2012: 1064 publications; source: http://www.ncbi.nlm.nih.gov/pubmed) and is now recognized as a primary, predominantly genetic disorder of the myocardium.[6-7]

The classic clinical presentation included severe heart failure, malignant ventricular arrhythmias, thrombo-embolic events and sudden cardiac death.[8-11] Noncompaction was characterized by an excessively prominent trabecular meshwork and deep intertrabecular recesses, as seen early in human embryogenesis.[12-13] Therefore, the primary patho-physiological hypothesis was that incomplete compaction of the loose myocardial meshwork during gestation resulted in a noncompacted, heart, prone to heart failure, arrhythmias and intracardiac thrombus formation.[14-15] The diagnosis was established by imaging of the ventricular walls and cavities, classically by two-dimensional transthoracic echocardiography with color Doppler flow. Diagnostic criteria proposed by Jenni et al. include abnormally thickened ventricular walls with a two-layered structure, consisting of thickened, noncompacted (NC) endocardial myocardium and a thin compacted (C) epicardial myocardium (maximal end-systolic ratio NC/C > 2 at parasternal short axis view).[16] The abnormal structures of NCCM could be identified as deep intertrabecular recesses with color Doppler flow as well as regional hypokinesia. Other imaging modalities like left ventricular (LV) angiography, computed tomography, contrast echocardiography and magnetic resonance imaging (MRI) have also been used to visualize these recesses.[17-20]

Increased awareness of this disease entity made us recognize more and more cases of noncompaction cardiomyopathy, especially with help of modern imaging modalities like contrast echocardiography and MRI allowing better visualization the left ventricular cavity.[21] But a lot of questions remained open on many clinical aspects of this new entity, as the available literature was based on several case reports and small case series.

Therefore, we started in 2005 to gather these extra-ordinary cases in a specialized NCCM outpatient clinic and included their clinical data in a prospective registry to combine the

experience and initiate clinical research. In this context, it is worth mentioning that the Thoraxcenter, Erasmus MC already was a national referral center for cardiomyopathies, advanced heart failure and heart transplantation since several decades.

The questions to be answered in this yet rare, "orphan" diseases were: how is the prevalence of familial disease and genetics of this disease? Is the prognosis indeed as grave as the first case series and reports did suggest? Excessive trabeculations are the hallmark of this disease, but is there any correlation between the extent and severity of the trabeculations and the clinical features? Has the abnormal two-layered pattern of myocardium, functional consequences? What are the diagnostic challenges in the era of modern imaging technologies? What is the prevalence of malignant ventricular arrhythmias and sudden cardiac death? How to predict and how to treat? Is there an alternative explanation for the prominent trabeculations?

Therefore, the aim of this thesis was to seek answers to the above-mentioned questions. An overview of the current literature with emphasis on the clinical, familial and genetic features of NCCM is presented in **Chapter 1**.

At this moment the diagnosis of NCCM relies fully on abnormal morphology as demonstrated by an imaging modality. In **Chapter 2**, we describe the use of left ventricular angiogram in the diagnosis of NCCM.

The first case series described a high morbidity and mortality with ventricular tachycardia and death or transplantation (47%!) at follow-up. Recent case series describe a better prognosis, albeit with limited follow-up time. In **Chapter 3**, we describe the clinical course and long-term (>5 years) outcome of NCCM patients in the current intensive treatment era.

NCCM is characterized by a prominent trabecular meshwork and deep intertrabecular recesses. Although systolic dysfunction is common, limited information is available on differences in wall motion of the normal compacted and noncompacted segments. In **Chapters 4 and 5** we study the relation of left ventricular systolic function and the extent and severity of noncompaction with three-dimensional echocardiographic analysis and tissue Doppler images.

The diagnosis of noncompaction cardiomyopathy (NCCM) remains subject to controversy. Because NCCM is probably caused by an intrauterine arrest of the myocardial fiber compaction during embryogenesis, it may be anticipated that the myocardial fiber helices, normally causing left ventricular (LV) twist, will also not develop properly. The resultant LV rigid body rotation may strengthen the diagnosis of NCCM. In **Chapters 6 and 7** we present the results of studies on LV twist characteristics and its use for the diagnosis of NCCM. In **Chapter 8**, we give an overview of the current controversies and possibilities of diagnostic imaging modalities.

The prevention of malignant ventricular arrhythmias and sudden cardiac death (SCD) is one of the major challenges in cardiomyopathies despite several decades of research and appropriate risk stratification to reduce SCD remains very difficult. The prevalence of malignant

ventricular arrhythmias, appropriate risk stratification and prevention of SCD is NCCM is even more obscure. In **Chapter 9**, we comment on the usefulness of invasive electrophysiological studies in this risk stratification process.

Implantable cardioverter-defibrillators (ICDs) are frequently used for primary and secondary prevention in different cardiomyopathy patients, but data about ICD's in NCCM are scarce. In **Chapter 10**, we described our clinical experience with ICD's for primary and secondary prevention and long-term outcome in NCCM patients.

Last years, there is increasing evidence that early repolarization (ER) is associated with malignant ventricular arrhythmias, including ventricular fibrillation and SCD. A possible mechanism is increased trabeculation with deep intramyocardial invagination (a hallmark of NCCM!); carrying the Purkinje system deeper into myocardium resulting in delayed depolarization and inhomogenous repolarization. In **Chapter 11,** we studied the prevalence of ER in NCCM pts, especially in those primarily presenting with malignant ventricular arrhythmias or sudden cardiac death.

Soon after the first case reports of NCCM, familial and genetic etiology has been suspected and different mutations in different genes had been described. Nevertheless, a major genetic cause for familial NCCM remained to be identified. Therefore, we performed a systematic family study, with extensive cardiological and DNA diagnostic work-up, which we described in **Chapters 12, 13 and 14**.

More than two decades after the first proposed diagnostic criteria, the diagnosis of NCCM still relies on abnormal morphological features with excessive trabeculations. The distinction however of subjects with a high incidence of prominent trabeculations, especially those with chronic pressure or volume overload, from patients with NCCM remains a major challenge. In **Chapters 15 and 16**, we describe two cases with excessive trabeculations challenging the diagnosis of NCCM.

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Noncompaction Cardiomyopathy

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INTRODUCTION

Noncompaction of the left ventricle or *noncompaction cardiomyopathy* (*NCCM*) is a relatively new clinicopathologic entity, first described by Feldt et al. in 1969.[1] NCCM is characterized by a prominent trabecular meshwork and deep intertrabecular recesses communicating with the left ventricular (LV) cavity, morphologically reminiscent of early cardiac development, and is therefore thought to be caused by an arrest of normal embryogenesis of the myocardium.[2, 3] Initial presentation includes congestive heart failure, thrombo-embolic events, and (potentially lethal) arrhythmias, including sudden cardiac death. NCCM may be a part of a more generalized cardiomyopathy, involving both the morphologically normal and the predominantly apical, abnormal LV segments. The cardiologic features of NCCM range from asymptomatic in adults to severe congenital forms.[4–7]

Recently, NCCM was classified by the American Heart Association (AHA) as a separate primary, genetic cardiomyopathy, based on the predominant myocardial involvement and genetic etiology.[8] The European Society of Cardiology (ESC) considers NCCM as unclassified, due to the lack of consensus whether NCCM is a separate individual cardiomyopathy or a nonspecific morphological trait that can be found solitary or in combination with other forms of cardiomyopathy like hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), or with congenital heart disease.[9] The majority of NCCM diagnosed in adults is isolated. Nonisolated forms of NCCM are more frequent in childhood and may cooccur with congenital heart malformations, or may be part of a malformation or chromosomal syndrome.7 The combination of NCCM and neuromuscular disor-ders is observed in adults as well as in children.The majority of NCCM, isolated and nonisolated, is hereditary and NCCM appears to be genetically het-erogenous.[10, 11] An important proportion of isolated NCCM in children and adults has been associated withmutations in the same *sarcomere* genes that areinvolved in HCM, DCM, and restrictive cardiomyopa-thy (RCM).[10] Absence of a genetic defect does not pre-clude a genetic cause of NCCM. In approximately half of the familial NCCM, the genetic defect remains unkown.[11] Shared sarcomere defects and the occurrence of HCM and DCM in families with NCCM patients indicate that at least some forms of NCCM are part of a broader cardiomyopathy spectrum. The literature differentially refers to this form of cardiomyopathy as left ventricular noncompaction (LVNC), noncompaction cardiomyopathy (NCCM), noncompaction of the left ventricular myocardium (NCLVM), left ventricular hypertrabeculation (LVHT), spongiform cardiomyopathy, embryonic myocardium, honeycombed myocardium, persisting myocardial sinu-soids, myocardial dysgenesis, ventricular dysplasia, or spongy myocardium. In analogy with the nomenclature of hypertrophic (HCM) and dilated cardiomyopathy (DCM), the term noncompaction cardiomyopathy is preferable. Therefore, noncompaction cardiomyopathy, abbreviated as NCCM, will be used in this chapter to denote this entity.

1.1 DEFINITION

NCCM is defined by prominent *trabeculations* on the luminal surface of the left ventricular apex, the lateral wall, and rarely the septum in association with deep recesses that extend into the ventricular wall, which do not communicate with the coronary circulation. It is associated with a clinical triad of heart failure, arrhythmias, and/or thrombo-embolic events.[12, 13] Diagnosis of NCCM relies on two-dimensional transthoracic echocardiography and/or cardiac magnetic resonance imaging (MRI) (Table 6.1). Improvements in cardiac imaging techniques have led to increased recognition and diagnosis of NCCM. Figure 6.1 displays echocardiographic and cardiac MRI images of two NCCM patients, showing the abnormal segmental trabeculations as the hallmark of this new entity.

Features of noncompaction observed in cardiologic patients and normal controls illustrate the necessity of defining criteria in order to differentiate accurately normal physiological trabecularization from NCCM.[14]

Table 6.1 Echocardiographic diagnostic criteria for NCCM

I. Chin et al.2
Focusing on trabeculae localized at the LV apex on the parasternal short axis and apical views and on LV free-wall thickness at end-diastole NCCM is defined by a ratio of X/Y ≤ 0.5 with
X = distance from the epicardial surface to the trough of the trabecular recess
Y = distance from the epicardial surface to the peak of the trabeculation

II. Jenni et al.[12]
1. An excessively thickened left ventricular myocardial wall with a two-layered structure consisting of a compact epicardial layer (C) and a noncompacted endocardial layer (NC) of prominent trabeculations and deep intertrabecular recesses
2. A maximal end-systolic NC/C ratio > 2, measured at the parasternal short axis
3. Color Doppler evidence of deep perfused intertrabecular recesses
4. Absence of coexisting cardiac anomalies

III. Stollberger et al.[15]
1. More than three trabeculations protruding from the left ventricular wall, apical to the papillary muscles and visible in a single image
2. Perfusion of the intertrabecular spaces from the ventricular cavity visualized on color Doppler imaging.

In 1990, the first diagnostic criteria for NCCM by Chin et al. were derived from the observations made in eight NCCM patients.[2] These diagnostic criteria defined NCCM by the ratio of the distance from the epicardial surface to the trough of the trabecular recess (X) to the distance from the epicardial surface to the peak of the trabeculations (Y), with ratio X/Y ≤ 0.5.

More than a decade later, Jenni et al. proposed new diagnostic criteria for isolated NCCM, consisting of four echocardiographic features: (1) an excessively thickened left ventricular myocardial wall with a two-layered structure consisting of a compact epicardial layer (C) and a noncompacted endocardial layer (NC) of prominent trabeculations and deep intertrabecular recesses; (2) a maximal end-systolic *NC/C ratio* > 2, measured at the parasternal short axis; (3) color-Doppler evidence of deeply perfused intertrabecular recesses; (4) absence of coexisting cardiac anomalies.[12]

In 2002, Stollberger et al. proposed other diagnostic criteria for NCCM, wherein the diagnosis was a function of the number of trabeculations (>3) protruding from the left ventricular wall, apically to the papillary muscles and visible in a single image plane with obligatory perfusion of the intertrabecular spaces from the ventricular cavity visualized on color-Doppler imaging.[15]

More recently, MRI criteria for NCCM introduced by Petersen et al. indicated that a noncompacted/compacted ratio (NC/C) of >2.3, measured in end-diastole, can differentiate with sufficient sensitivity between the normal variation of noncompaction of the LV in the population, noncompaction in other cardiovascular disorders, and NCCM.[16]

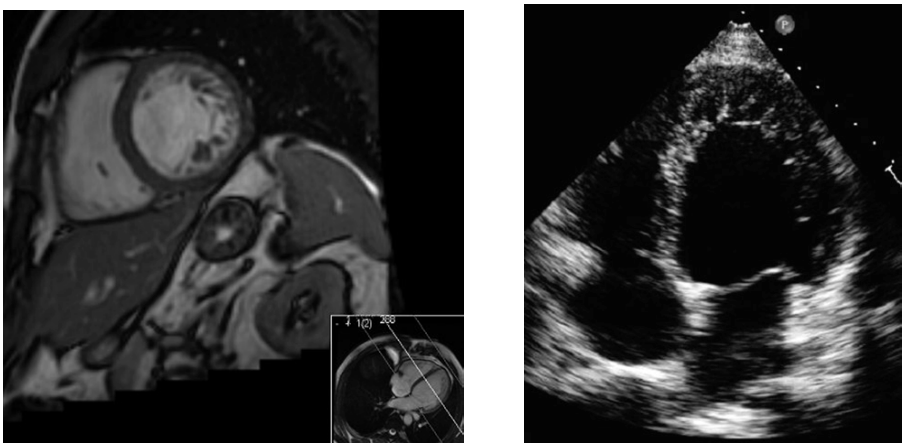
The most recent classification system of NCCM as proposed by Belanger et al. (2008) included dividing noncompaction into four categories (none, mild, moderate, and severe) according to noncompaction to compaction ratio and the size of the noncompaction area.[13]

This new classification scheme used the following criteria: (1) absence of congenital heart disease, hypertrophic or infiltrative cardiomyopathy, and coronary artery disease; (2) evidence of prominent trabeculations in the apex in any view (noncompacted to compacted ratio does not require to be >2); (3) concentration of the noncompacted area in the apex; (4) blood flow through the area of noncompaction.

The Jenni echo criteria have been the most convenient to work with in daily clinical practice and have been most widely applied in studies. However, further efforts to reach universal consensus with respect to the diagnosis of NCCM are clearly needed. A disparity in diagnosis has been observed when comparing the application of three different sets of NCCM criteria (Chin, Jenni, and Stollberger) in a cohort of 199 heart failure patients; 79% fulfilled the Chin criteria, 64% fulfilled the Jenni criteria, and 53% the criteria proposed by Stollberger. In only 30% of patients, there was consensus among the three criteria on the diagnosis. Moreover, 8.3% of normal controls fulfilled one or more criteria with a higher prevalence in black controls.[14]

For now, it is disputable whether any of these diagnostic criteria are sufficiently sensitive to diagnose patients with mild noncompaction, and identify patients who may benefit from careful surveillance. For instance, in NCCM family studies, a substantial proportion of (mostly asymptomatic) relatives showed mild to moderate features of NCCM.[11] Longitudinal studies of mild forms of NCCM will be needed to determine whether the current diagnostic criteria

are suitable for diagnosis of family members in familial NCCM, or should be adapted in analogy to the criteria proposed for diagnosis of attenuated forms of familial HCM in relatives.



A B

Fig. 6.1 (a, b) Cardiac MRI and echocardiography of a 43-year-old patient illustrating a two-layered myocardium with prominent intertrabecular recesses

1.2 PATHOLOGY

1.2.1 Macroscopy

The noncompacted endocardial layer of the myocardium comprises excessively numerous and prominent trabeculations with deep intertrabecular recesses that extend into the compacted myocardial layer. The apical and mid ventricular segments of the left ventricular inferior and lateral wall are predominantly affected.[17, 18]

In a pathoanatomical study of NCCM, Burke et al. described the morphology and microscopy of 14 pediatric NCCM cases.[18] The macroscopic appearance varied from anastomosing trabeculae to a relatively smooth endocardial surface, with narrow openings of the recesses to the ventricular cavity. Three types of recess patterns were distinguished: (1) anastomosing broad trabeculae; (2) coarse trabeculae resembling multiple papillary muscles; (3) interlacing smaller muscle bundles or relatively smooth endocardial surface with compressed invaginations, identified primarily microscopically (Fig. 6.2). In this study, no morphological differences were found between isolated and non isolated NCCM.[18]

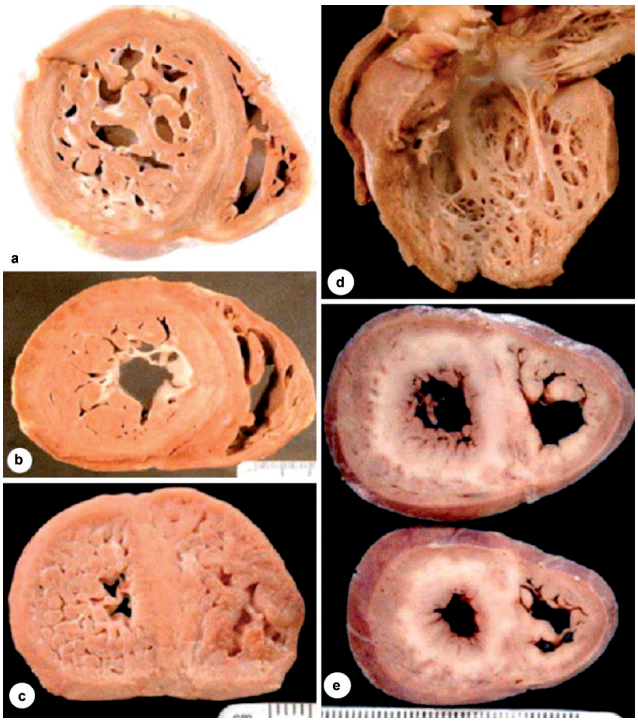


Fig. 6.2 NCCM gross pathology with a variety of NCCM patterns: (**a**) Anastomosing broad trabeculae. (**b**) Coarse trabeculae resembling multiple papillary muscles. (**c**) Interlacing smaller muscle bundles resembling a sponge. (**d**) Trabeculae viewed en face. (e) Subtle NCCM on gross section, requires histological confirmation (Reproduced from Burk et al.[18] With permission)

Jenni et al. described pathology of seven adult NCCM cases.[12] The pathoanatomical localization of the noncompacted myocardium corresponded to the echocardiographic findings. Two patients also showed involvement of the right ventricular apex.[12]

In a review of published pathology of NCCM, Stollberger et al. distinguished three particular morphologic features of NCCM in adults and children: (1) Extensive spongiform transformation of the LV. (2) Prominent coarse trabeculations and deep recesses, covered with endocardial tissue and not communicating with coronary arteries. (3) Dysplastic thinned myocardium with excessive trabeculations.19 The first morphology was frequently associated with other cardiac malformations, compared to the second and third.

In 1987, in an autopsy study of 474 normal hearts of all ages, it was found that prominent trabeculations may be observed in as many as 68% of the hearts, although more than three trabeculations were only identified in 3.4%.[20]

1.2.2 Microscopy

Two patterns of myocardial structure in the superficial noncompacted layer in NCCM have been described by Burke et al.: (1) anastomosing muscle bundles forming irregularly branching endocardial recesses with a staghorn-like appearance; (2) multiple small papillary muscles, resulting in an irregular surface appearance (Fig. 6.3).[18] In most patients, these patterns overlapped. Endocardial fibrosis with prominent elastin deposition was found in all 14 cases and subendocardial replacement fibrosis, consistent with microscopic ischemic infarcts, was present in 10.[18] Right ventricular involvement was identified in six cases.[18]

Histological examination in another study showed that ventricular endocardium covered the recesses in continuity with the LV cavity and identified ischemic lesions in the thickened endocardium and the prominent trabeculae.[12] Interstitial fibrosis ranged from absence to severe. No fiber disarray was identified in any of these cases. Signs of chronic inflammation and abnormalities of intramyocardial blood vessels were present in some patients.[12]

In one adult case report, abundant extracellular matrix and myocardial fiber disarray were reported.[21]

Freedom et al. proposed two criteria for the pathological diagnosis of NCCM: (1) absence of well-formed LV papillary muscles and (2) histological verification of more than 50% penetration of invaginated endocardial recesses toward the epicardial surface. The endothelium that covers the recesses extends close to the surface of the compact layer. The recesses neither communicate nor connect with the coronary circulation.[22]

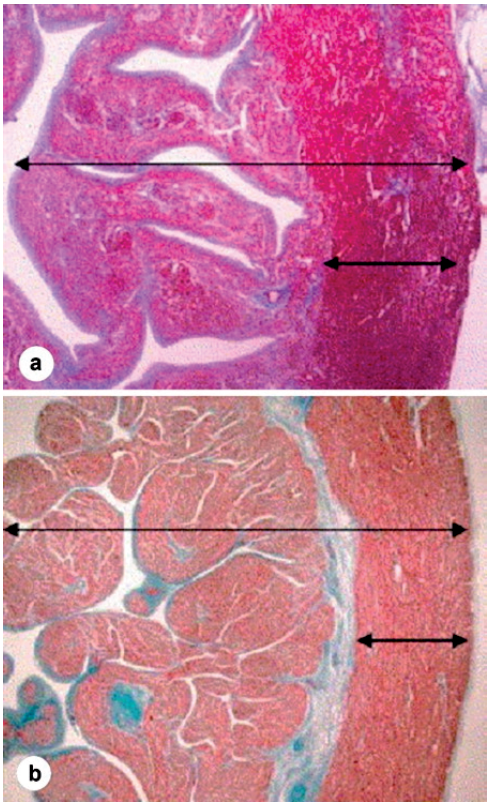


Fig. 6.3 Histological features in NCCMThe ratio of noncompact versus compact myocardium is larger than 2. (**a**) Relatively smooth endocardial surface (*left*) with anastomosing broad trabeculae. (**b**) Polypoid pattern of trabeculae; prominent fibrous band separating the noncompact from the compact myocardium (Reproduced from Burke et al.18 With permission)

2 EPIDEMIOLOGY

Estimates of prevalence of NCCM were derived from large retrospective studies of patients referred for echocardiography. Population studies for NCCM have not been performed. In 1997 Ritter et al. identified NCCM in 17 of 37,555 (0.045%) patients who had an echocardiographic exam.[23] Similarly, in 2006 Aras et al. reported a prevalence of 0.14% in over 42,000 patients and in 2008 Sandhu identified definite or possible NCCM in 13/4,929 (0.26%) patients referred for echocardiography.[24,25] Prevalence was much higher (3.7%) in patients selected for a LV ejection fraction ≤ 45%.[25] Depending on the diagnostic criteria applied, even higher prevalence of NCCM (15.8% by Belanger; 23.6% by Kohli) were reported recently, indicating that NCCM may be more prevalent than previously indicated.[13, 14] A substantial proportion of individuals is asymptomatic, suggesting that true prevalence of NCCM may be higher, because asymptomatic individuals may go unnoticed in the studies

of cardiologic patients.[11, 13] In a large study on childhood cardiomyopathies, NCCM was the most frequent cardiomyopathy after DCM and HCM, with an estimated prevalence of 9% in pediatric cardiomyopathies.[26]

3 ETIOLOGY AND MOLECULAR GENETICS

The etiology of NCCM is rapidly being unravelled as more and more genetic defects in different genes are found, indicating that NCCM is genetically heterogeneous. Causes for acquired NCCM are scarce. One report suggested that candida sepsis was associated with cardiologic features mimicking NCCM.27 Currently, genetic defects are identified in 42% of NCCM patients (35% of adults and 78% of children).[10] Most genetic defects are inherited as autosomal dominant trait (Table 6.2), with exception of rare genetic causes of syndromal NCCM, predominantly diagnosed in children. A small proportion of patients have a de novo mutation.

However, absence of a genetic defect does not exclude a genetic etiology. By performing systematic cardiologic family studies, it was shown that no genetic defect could be found in approximately half of the familial forms of NCCM, indicating that further studies are needed to find additional genetic causes for NCCM.[11]
There is evidence that some forms of NCCM are part of a spectrum of cardiomyopathies, including hypertrophic, dilated, and restrictive cardiomyopathy. A shared etiology consisting of genetic defects in the same sarcomere genes, sometimes even with identical mutations, has been found in these types of cardiomyopathy. Co-occurrence of NCCM, HCM, and DCM within families endorses a shared genetic susceptibility to these different forms of cardiomyopathy.[10,11] The phenotypic variability of cardiomyopathies within families, including variability in age at onset and severity of clinical features, might be explained by additional modifying factors, additional genetic variants or defects, or may depend on yet unidentified exogenous or systemic factors

3.1 Molecular Defects in NCCM

Isolated NCCM has been associated with mutations in 14 different genes (Table 6.2). Defects in sarcomere genes have been identified to be the most prevalent genetic cause occurring in 33% of all patients with isolated NCCM.11 In two DNA studies in cohorts of approximately 60 isolated NCCM patients, mutations were identified in 17–41% of the patients depending on the number and choice of analyzed genes.[10,28] In the study by Dooijes et al. of 56 patients, the yield was slightly higher 41% in all and 50% in case of confirmed familial disease.[11] In children with isolated NCCM, the yield of testing for sarcomere genes was as high as 75%.[10,11]

Over 40 different mutations in sarcomere genes encoding thick (*MYH7*), intermediate (*MYBPC3*), and thin filaments (*TNNT2*, *TNNI3*, *TPM1*, *ACTC*) have been described. In particular in *MYH7,* the most frequent NCCM-associated gene, accounting for up to 21% of isolated NCCM (19% in adults and 25% in children).[10,28] Fifty percent of the *MYH7* mutations currently associated with NCCM cluster in the ATPase active site of the head-region in the N-terminal part of MYH7.10 This is an evolutionary well-conserved region of MYH7. As the ATP-ase, active site is required for normal force production, impaired force generation might play a role in the etiology of NCCM. Mutations in this region have been associated with NCCM with or without Ebstein anomaly.[28, 29] Other *MYH7* mutations (30%) were found in the C-terminal rod-region of the MYH7 protein that plays an important role in the formation of the core of the thick filament. Mutations in this region of the gene are more commonly associated with skeletal myopathies. Relatively few cardiomyopathy mutations are situated in this region.

Sarcomere mutations were common causes for NCCM in adults as well as in children.[10, 11] Multiple or compound/double heterozygous mutations were identified in 25% of the children and in 10% of the adult NCCM patients.[10] HCM complex genotypes have been described in 7%.[30] In HCM, double heterozygosity for truncating sarcomere mutations have been previously associated with severe congenital forms mostly inherited in an autosomal recessive mode.[31–33] In NCCM, double mutations were associated with severe disease in two children and were also observed in adults.[10]

Nonsarcomere genetic causes for isolated NCCM include mutations in the calcium-handling genes calsequestrin (*CASQ2*) and phospholamban (*PLN*), in taffazin (*TAZ*), a-dystrobrevin (*DTNA*), lamin A/C (*LMNA*) and LIM domain binding 3 (*LDB3*), potassium voltage-gated channel (*KCNH2*), and sodium channel type 5 (*SCN5A*) genes.[34–36] However, mutations in these genes were only rare causes of NCCM in single families.[37]

Table 6.2 Genes associates with noncompaction cardiomyopathy (NCCM)

Gene	Locus	Protein	Other associated disorders	Reference
ACTC1	15q14	a-Cardiac actin	Hypertrophic and dilated cardiomyopathy	10,11, 28, 50
			Congenital myopathy with fiber-type disproportion	
CASQ2	1p13.3-p11	Calsequestrin	Catecholaminergic polymorphic ventricular tachycardia	10, 11
			Hypertrophic cardiomyopathy	
DTNA	18q12.1-q12.2	a-Dystrobrevin		35, 134
KCNH2	7q35-q36	Potassium voltage-gated channel, subfamily H,	Long QT syndrome 2 Short QT syndrome	135
LDB3a	10q22.2-q23.3	LIM-Domain binding protein	Dilated cardiomyopathy Late onset distal myopathy	10, 11, 36, 134, 136
			Myofibrillar myopathy	

LMNA	1q21.2	Lamin A/C	Dilated cardiomyopathy	10, 11, 61, 62
			Emery--Dreifuss muscular dystrophy	
			Lipodystrophy	
			Restrictive dermopathy	
			Werner syndrome	
			Hutchinson--Gilford Progeria	
			Limb girdle muscular dystrophy 1B	
			Charcot--Marie--Tooth 2B1	
MYBPC3	11p11.2	Cardiac myosin-binding protein C	Hypertrophic and dilated cardiomyopathy	10, 11
MYH7	14q12	ß-Myosin heavy chain	Hypertrophic, dilated, and restrictive cardiomyopathy	10, 11, 28, 29
			Myosin storage myopathy	
			Distal myopathy	
			Scapuloperoneal myopathy	
PLN	6q22.1	Phospholamban	Hypertrophic and dilated cardiomyopathy	10, 11
SCN5A	3p21	Sodium channel type 5 a-subunit	Long QT syndrome 3 Brugada syndrome	137
			Sick sinus syndrome	
			Familial heart block	
			Paroxysmal ventricular fibrillation	
			Cardiac conduction defect	
			Dilated cardiomyopathy	
TAZb	Xq28	Taffazin	Barth syndrome Dilated cardiomyopathy	10, 11, 35, 134, 136, 138–145
TNNI3	19p13.4	Cardiac troponin I	Hypertrophic, dilated, and restrictive cardiomyopathy	10, 11
TNNT2	1q32	Cardiac troponin T	Hypertrophic, dilated, and restrictive cardiomyopathy	10, 11, 28
TPM1	15q22.1	A-tropomyosin	Hypertrophic and dilated cardiomyopathy	10, 11

Except *TAZ* related disorders, all are autosomal dominantly inherited
aCypher/ZASP
bG4.5

The absence of a mutation in approximately half of familial NCCM could be explained by phenotype assignment errors, the involvement of other yet unidentified genes, the presence of mutations in non-analyzed gene sequences, and incomplete sensitivity of the methods used.[10]

4 PATHOGENESIS

Mutations in different genes associated with NCCM affect different mechanisms in the cardiomyocyte leading to changes that may individually cause NCCM or lead to a common cellular disturbance resulting in NCCM.

Mutations in sarcomere genes may have their effect through defective force generation (either by a dominant negative mechanism where the mutant protein acts as a "poison polypeptide" or by haploinsufficiency resulting in less protein); mutated cytoskeletal proteins may lead to a defective force transmission; myocardial energy deficits may be the result of mutations in ATPregulatory genes and a fourth possible mechanism is abnormal calcium homeostasis either due to changes in calcium availability or myofibrillar sensitivity for calcium.[38] The development of NCCM features might be a compensatory response to dysfunction in one of these mechanisms.

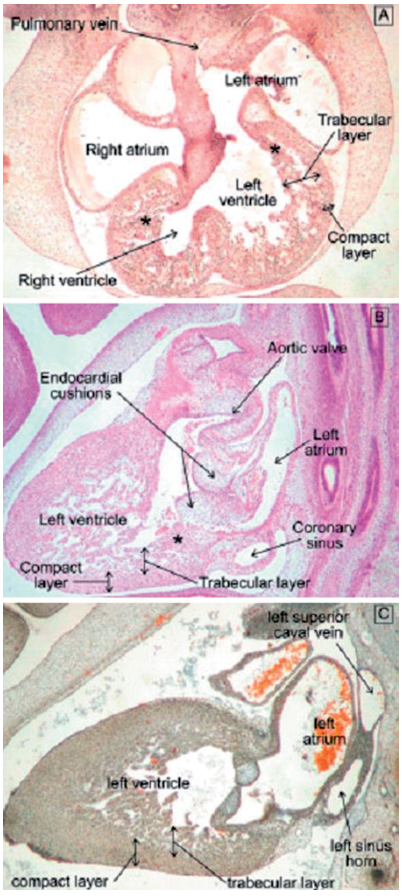


Fig. 6.4 Human embryos at Carnegie stage 16 (**a**), stage 18 (**b**) and after closing of the embryonic interventricular foramen. During development, there is an extensive trabecular layer forming the greater part of the ventricular wall thickness compared to the extent of the compact layer. The

trabecular layer becomes compacted and forms the papillary muscles of the atrioventricular valves (*asterisks*) (Reproduced from Freedom et al.22, with permission)

The variable phenotypic expression of (sarcomere) gene mutations leading to different types of cardiomyopathy has not been explained. The localization of the mutations may partly explain phenotypic diversity. Another theory is "dose-effect"; the extent of the defective mechanism may determine which phenotype develops. Third, there might be independent pathways leading to the different cardiomyopathies. Finding identical mutations in different phenotypes suggests a role for additional factors, either environmental or molecular.

4.1 Isolated NCCM

The first hypothesis on the pathogenesis of NCCM stemmed from observations that the morphology of NCCM was reminiscent of the embryonic stages of cardiac development. Consequently, it was postulated that NCCM could be the result from an arrest of compaction of myocardial fibers.[39] Figure 6.4 illustrates the striking resemblance between NCCM and the physiological embryonic noncompaction in the 8th– 10th embryonic week. However, the possible mechanisms causing the arrest remain unclear. Epicardium The first hypothesis on the pathogenesis of NCCM stemmed from observations that the morphology of NCCM was reminiscent of the embryonic stages of cardiac development. Consequently, it was postulated that NCCM could be the result from an arrest of compaction of myocardial fibers.39 Figure 6.4 illustrates the striking resemblance between NCCM and the physiological embryonic noncompaction in the 8th– 10th embryonic week. However, the possible mechanisms causing the arrest remain unclear. Epicardium derived cells are thought to play an important role in myocardial architecture and in the development of noncompaction.[40, 41] Mutations in genes involved in myocardial genesis like peroxisome proliferator activator receptor binding protein (*PBP*), jumonji (*JMJ*), FK506 binding protein (*FKBP12*), transcription factor specificity protein (*Sp3*), homeobox factor *NKX2.5*, bone morphogenetic protein [10] (*BMP10*) lead to congenital NCCM in knock out mice.[42–46] However, in human NCCM, no mutations in these genes have been described.With the co-occurrence of congenital heart disease and permission) noncompaction is predominantly observed in children.
Until now, there is very little insight into factors that influence the variability in age at onset and severity of symptoms of NCCM, or any other familial form of cardiomyopathy.

4.2 NONISOLATED NCCM

NCCM has been observed in a number of neuromuscular disorders, metabolic and mitochondrial disease, congenital malformations, and chromosomal syndromes.
Some of these disorders may share pathogenetic mechanisms with NCCM. Alternatively, NCCM might be secondary to other cardiac malformations or other malformations or even

vice versa. Another possibility is that the co-occurrence is coincidental. Congenital heart malformations for instance are relatively frequent (birth prevalence 0.008) and may therefore occasionally coincide with NCCM without a mutual etiology.

4.3 Congenital heart Disease

In the majority of patients, NCCM is diagnosed in adulthood, similar to HCM and DCM, which are rarely congenital.[47, 48] Of course, it could be that in NCCM the lesions detected in adult patients were present from birth on, but remained unnoticed until symptoms developed and high-resolution cardiac imaging techniques were applied. However, the detection of sarcomere defects in NCCM patients may suggest otherwise, since mutations in sarcomere genes are known to cause late-onset HCM and DCM. Similarly, sarcomere mutations might lead to late onset NCCM. Longitudinal cardiologic studies of unaffected carriers of pathogenic mutations are necessary to provide insight whether noncompaction may develop later in life. The pathogenetic mechanism(s) of sarcomere defects in cardiomyopathies are not fully understood. It is possible that the pathological myocardial changes in the adult onset sarcomere related cardiomyopathies are caused by a compensatory response to impaired myocyte function resulting from mutations in the sarcomere genes.[38, 49]
Tsai et al. showed that 78% of 46 children with NCCM had a congenital heart defect.[7] The large number of structural heart malformations reported in association with noncompaction are presented in Table 6.3, indicating that septal defects, patent ductus arteriosus, and Ebstein's anomaly are the most prevalent congenital heart defects in NCCM.

Increasingly, *congenital cardiac malformations* (septal defects, Ebstein anomaly, patent ductus arteriosus, Fallot's tetralogy, aortic coarctation, and aortic aneurysms) are being reported in familial cardiomyopathies (HCM, DCM, and NCCM) linked to sarcomere mutations, suggesting that these specific sarcomere defects may have been involved in cardiac morphogenesis[11, 29, 50–54] But since there is rarely more than one patient with a congenimyopathy (*LDB3* or *Cypher/ZASP*), limb girdle muscutal heart defect, even in families with multiple cardiolar dystrophy (LGMD) (*LMNA*), scapuloperoneal myomyopathy patients, the association of sarcomere defects pathy (*MYH7*), myosin storage distal myopathy (*MYH7*), and heart defects still demands further exploration.

Table 6.3 Congenital heart disease associated with noncompaction cardiomyopathy (NCCM)

Congenital heart disease in NCCM	Proportion of CHD In NCCM studies[a]	Case reports	References
Aberrant origin of right/left subclavian artery	1/12 (8%)	1	146, 147
Absent aortic valve		1	148
Anomalous pulmonary venous return	2/26 (8%)		18, 146
Aortic coarctation	6/204 (3%)		7, 11, 113, 146, 149
Aortico-left ventricular tunnel		1	150
Aortic stenosis	2/46 (4%)	2	7, 22, 151
Aortopulmonary window	1/21 (5%)		113
Atrial septal defect	22/135 (16%)	3	7, 11, 29, 113, 152, 153
Atrio-ventricular diverticulum		1	154
Bicuspid aortic valves	3/64 (5%)	3	7, 113, 119, 155
Bicuspid pulmonary valve	1/14 (7%)		18
Cardiac aneurysms		4	81, 156–158
Coronary ostial stenosis	1/14 (7%)		18
Cor triatriatum	1/46 (2%)		7
Dextrocardia	2/58 (3%)	1	1, 7, 146
Dextro malposed great arteries	1/12 (8%)		146
Dextroversion		1	159
Double inlet left ventricle	1/46 (2%)		7
Double orifice mitral valve		4	160–162
Double outlet right ventricle	1/54 (2%)		149
Ebstein's anomaly	6/117 (5%)	10	7, 11, 153, 163–168
Fallot's tetralogy	1/71 (1%)	1	11, 147
Hypoplastic left heart syndrome	3/54 (6%)		149
Hypoplastic right ventricle	3/58 (5%)		7, 146
Isomerism of the left atrial appendage	4/66 (6%)	8	22, 146, 149, 169
Left-sided superior vena cava	1/46 (2%)		7
Mitral valve atresia		1	148
Mitral valve cleft	2/54 (4%)	1	149, 158

Aberrant origin of right/left subclavian artery 1/12 (8%) 1 146, 147

Table 6.3 (continued)

Congenital heart disease in NCCM	Proportion of CHD In NCCM studies[a]	Case reports	References
Mitral valve dysplasia	2/14 (14%)		18
Mitral valve prolaps	1/46 (2%)		7
Patent ductus arteriosus	16/182 (9%)	1	7, 11, 149, 153
Persistent left superior vena cava	1/14 (7%)	1	18, 157
Pulmonary atresia	6/125 (5%)	1	11, 149, 153
Pulmonary valve dysplasia	2/14 (14%)		18
Pulmonary stenosis	4/97 (4%)	1	11, 18, 146, 153
Single ventricle	1/12 (8%)	1	146, 170
Subaortic membrane	2/55 (4%)		149
Transposition of the great arteries	1/46 (2%)	1	7, 171
Tricuspid atresia	2/54 (4%)		149
Tricuspid valve dysplasia	1/14 (7%)		18
Ventricular septal defect	23/218 (11 %)	3	1, 7, 11, 18, 113, 146, 149, 151, 157

[a]Cumulative number of NCCM patients with congenital heart defect (CHD) described in one or more NCCM studies

4.4 Neuromuscular Disease

Similar to HCM and DCM, NCCM has been associated with neuromuscular disorders. Stollberger and Finsterer identified NCCM-like morphological features in Duchenne and Becker muscular dystrophy and in myotonic dystrophy (see chapter *neuromuscular disorders*).[55–58] The gene mutated in Duchenne and Becker muscular dystrophy is a part of the dystrophine complex, a complex of muscle membrane associated proteins, connecting the cytoskeleton to the surrounding extracellular matrix and may also play a role in cell signaling. The dystrophine gene is expressed in skeletal and cardiac myocytes. A large proportion of patients and also female carriers have cardiac symptoms, including DCM.[59,60] Other genes previously associated with neuromuscular disorders, like adult onset myofibrillarall expressed in cardiac and skeletal muscle tissue.

and Barth syndrome (*TAZ*) have recently been associated with isolated NCCM (Tables 6.1 and 6.4). ZASP, lamin A and C, ß-myosin heavy chain, and taffazin are ZASP has a function in cytoskeletal assembly. Mutations in ZASP can lead to DCM and to skeletal myopathy. Lamin A and C, proteins situated in the nuclear membrane, play an important role in maintaining nuclear architecture. *LMNA* mutations have been described in three NCCM patients.[11,61,62] In one of them, there was familial limb girdle muscular dystrophy (LGMD) as well as DCM.[11] Over 200 mutations have been described in *LMNA*, causing over 20 different phenotypes, including isolated DCM, LGMD, Emery–Dreifuss muscular dystrophy, Hutchinson–Gilford progeria, partial lipodystrophy, and peripheral neuropathy. For many of the phenotypes, there is no clear genotype--phenotype correlation, phenotypes may overlap, and different phenotypes are associated with single mutations.[62] Up to 25% of patients with an LMNA

mutation may remain cardiologically asymptomatic.[63] The ß-myosin heavy chain is part of type II myosin that generates the mechanical force needed for muscle contraction.
Tafazzins have no known similarities to other proteins. Two regions of the protein may be functionally significant, one serving as a membrane anchor and soluble cytoplasmic protein and the other may serve as an exposed loop, interacting with other proteins.

Table 6.4 Neuromuscular disorders associated with noncompaction cardiomyopathy (NCCM)/ hypertrabeculation

Neuromuscular disorders	Gene	Inheritance	Features	Reference
Adenosine Monophosphate Deaminase 1 (MADA deficiency)	*AMPD1*	AD	Exercise-induced myopathy, muscle weakness, cramps; prolonged fatigue after exertion; benign congenital hypotonia	172
Becker and Duchenne muscular dystrophy	*DMD*	XR	Muscle weakness and wasting; hypotonia; waddling gait; pseudohypertrophy; cognitive impairment; cardiomyopathy; respiratory failure	55–57, 132,173, 174
Charcot--Marie--Tooth 1A (HMSN IA)	*PMP22*	AD	Distal limb muscle weakness and atrophy; distal sensory impairment	175
Myotonic dystrophy I	*DMPK*	AD	Myotonia; weakness; muscle wasting; adult cognitive deterioration; cataract; arrhythmia	58, 176, 177
Myotonic dystrophy II	*ZNF9*	AD	Muscle pain; myotonia; weakness (proximal/deep finger/neck flexor); cataract; cardiac conduction abnormalities; palpitations; tachycardia; hypogonadism; frontal balding	178
Infantile epilepsy-encephalopathy syndrome (Ohtahara syndrome)	*ARX*	XR	Age-dependent epileptic encephalopathy with "burst-suppression" on EEG; physical and mental retardation	179
Limb girdle muscular dystrophy 1B	*LMNA*	AD	Muscle weakness and wasting restricted to the limb musculature, proximal greater than distal	11, 132
Succinate dehydrogenase deficiency		AR	Encephalomyopathy; cardiomyopathy; generalized muscle weakness; cerebellar ataxia; optic atrophy; tumor formation in adulthood	180

AD **autosomal** dominant, *XR* X-linked recessive, *AR* autosomal recessive

4.5 Mitochondrial

Mitochondrial disorders often lead to multi-organ disease, including central and peripheral nervous system,eyes, heart, kidney, and endocrine organs. One of the cardiac features observed in mitochondrial disease is noncompaction cardiomyopathy. Cardiac features may be the first or only feature in patients suffering from a mitochondrial disorder. In a study of 113 pediatric patients with mitochondrial disease, NCCM was identified in 13%.65 Pignatelli et al. showed that 5 of the 36 pediatric NCCM patients who underwent a skeletal muscular biopsy, had morphologic and biochemical evidence for a mitochondrial defect, including a partial deficiency of complex I-III of the mitochondrial respiratory chain.66 Mutations in mitochondrial DNA (mtDNA) and in nuclear DNA have been identified in the mitochondrial

disorders associated with NCCM.[67–69] Table 6.4 presents a list of neuromuscular disorders in which NCCM has been identified. In addition, one case of noncompaction in a patient with Friedreich ataxia has been reported.64 Friedreich ataxia is associated with symmetric, concentric, hypertrophic cardiomyopathy.

4.6 Syndromes

NCCM can occur as part of a *syndrome* in combination with dysmorphic features and other congenital malformations. When there are other congenital defects or when there are dysmorphic features in a patient, one of the listed syndromes in Table 6.5 or one of the *chromosomal defects* in Table 6.6 could be considered in the differential diagnosis.

Table 6.5 Syndromes associated with noncompaction cardiomyopathy (NCCM)/hypertrabeculation 13

Syndrome	Gene	Inheritance	Features	Reference
Barth syndrome/3-methylglutaconic aciduria	*TAZ*	XR	Growth retardation, dilated cardiomyopathy, skeletal myopathy, intermittent lactic acidemia, granulocytopenia, recurrent infections	35, 37, 134, 136, 138–145
Branchio-oto-renal syndrome I/Melnick Fraser syndrome	*EYA1*	AD	Long narrow face; hearing loss (sensory/conductive/mixed); preauricular pits; microtia; cup-shaped ears; lacrimal duct stenosis; cleft palate; bifid uvula; branchial cleft fistulas/cysts; renal dysplasia/aplasia; polycystic kidneys; vesico-ureteric reflux	181
Congenital adrenal hypoplasia	*NR0B1*	XR	Failure to thrive; hypogonadotropic hypogonadism; cryptorchidism; hyperpigmentation; primary adrenocortical failure; adrenal insufficiency; gluco-mineralocorticoid insufficiency; salt-wasting; delayed puberty	66
Contractural arachnod-actyly/Beals syndrome	*FBN2*	AD	Marfanoid habitus; micrognathia; frontal bossing; crumpled ear helices; ectopia lentis; high-arched palate; septal defects; bicuspid aortic valve; mitral valve prolapse; patent ductus arteriosus; aortic root dilatation; pectus carinatum; kypkoscoliosis; hip/knee/elbow contractures; arachnodactyly; ulnar deviation of fingers; talipes equinovarus; hypoplastic calf muscles; motor development delay	182
Cornelia de Lange Syndrome I	*NIPBL*	AD	Short stature; microcephaly; long philtrum; micrognathia; low-set ears; sensorineural hearing loss; synophrys; myopia; long curly eyelashes; ptosis; anteverted nostrils; depressed nasal bridge; cleft lip/palate; thin upper lip; widely spaced teeth; congenital heart defect; pyloric stenosis; hypoplastic male genitalia; structural renal anomalies; phocomelia; oligodactyly; syndactyly of 2nd and 3d toes; single transverse palmar crease; cutis marmorata; hirsutism; low posterior hair line; mental retardation; language delay; automutilation	113
Leopard syndrome	*PTPN11* *RAF1*	AD	Short stature; triangular face; low-set ears; sensorineural hearing loss; hypertelorism; ptosis; epicanthal folds; broad flat nose; cleft palate; short neck; pulmonic stenosis; HCM; subaortic stenosis; complete heart block; bundle branch block; winged scapulae; hypospadia; absent/hypoplastic ovary; unilateral renal agenesis; spina bifida occulta; dark lentigines (mostly neck and trunk); café-au-lait spots	183
Melnick Needles osteodysplasty	*FLNA*	XD	Short stature; micrognathia; large ears; hypertelorism; exophthalmos; cleft palate; misaligned teeth; long neck; mitral/tricuspid valve prolapse; NCCM; pulmonary hypertension; pectus excavatum; omphalocele; hydronephrosis; tall vertebrae; bowing of humerus/radius/ulna/tibia; short distal phalanges of the fingers; pes planus; coarse hair; delayed motor development; hoarse voice	184

Nail Patella Syndrome	*LMX1B*	AD	Short stature; sensorineural hearing loss; ptosis; cataract; cleft lip/palate; malformed sternum; hypoplasia of first ribs; glomerulanephritis; renal failure; scoliosis; elbow deformities; hypoplastic or absent patella; clinodactyly; talipes equinovarus; longitudinal ridging nails; slow nail growth; koilonychias; anonychia; aplasia pectaralis minor/biceps/triceps/quadriceps	185, 186
Noonan syndrome	*PTPN11* *KRAS* *SOS1* *RAF1*	AD	Short stature; triangular face; low-set ears; hypertelorism; downslanting palpebral fissures; epicanthal folds; myopia; micrognathia; high arched palate; low posterior hairline; webbed neck; septal defects; pulmonic stenosis; patent ductus arteriosus; pectus carinatum superiorly/pectus excavatum inferiorly; cryptorchidism; clinodactyly; woolly hair; mental retardation (mild); bleeding tendency; malignant schwannoma	187
Roifman syndrome		XR	Short-trunk dwarfism; long philtrum; strabismus; narrow and downslanting palpebral fissures; long eyelashes; retinal dystrophy; narrow upturned nose; NCCM; hepato-splenomegaly; spondylo-epiphyseal dysplasia; eczema; hyperconvex nails; hypotonia; (mild) mental retardation; hypogonadotropic hypogonadism; recurrent infections; antibody deficiency	188
Syndromic microphtalmia/MIDAS syndrome (MIcrophtalmia, Dermal Aplasia, Sclerocornea)	*HCCS*	XD	Short stature; microcephaly; hearing loss; microphtalmia; sclerocornea; cataract; iris coloboma; retinopathy; septal defects; cardiac conduction defects; cardiomyopathy; overriding aorta; anteriorly placed anus; hypospadia; linear skin defects; corpus callosum agenesis; hydrocephalus; mental retardation; seizures	189, 190

AD autosomal dominant, *XD* X-linked dominant, *XR* X-linked recessive

Table 6.6 Chromosomal defects associated with noncompaction cardiomyopathy (NCCM)

Chromosomal defects	Features	Reference
Deletion		
1p36	Microcephaly; sensorineural hearing loss; deep-set eyes; flat nose; cleft lip/palate; cardiomyopathy; septal defects; patent ductus arteriosus; dilated aortic root; feeding problems; gastro-oesophageal reflux; short fifth finger and clinodactyly; mental retardation (severe); seizures; hypotonia	
1q43-q43	Microcephaly; upslanting palpebral fissures; epicanthus, broad nasal bridge, micrognathia; low set ears; bow-shaped upper lip; widely spaced teeth; short webbed neck; congenital heart defects; mental retardation (severe); speech impairment; seizures; corpus callosum agenesis	
5q35.1q35.3	Facial hirsutism; synophrys; downslanting palpebral fissures; atrial septal defect and patent ductus arteriosus; NCCM with sick sinus syndrome and second degree heart block; feeding problems; gastro-oesophageal reflux; joint hypermobility	
22q11.2	Velo-cardio-facial syndrome: short stature; microcephaly; retrognathia; narrow palpebral fissures; square nasal root; prominent tubular nose; cleft palate; velopharyngeal insufficiency; congenital heart defect (85%): ventricular septal defect; Fallot's tetralogy; inguinal/umbilical hernia; slender hands and digits; learning disability; mental retardation; schizophrenia; bipolar disorder	
4q trisomy/1q monosomy	Senile-like appearance; narrow palpebral fissures; telecanthus; epicanthus; broad nasal bridge; low-set ears; long philtrum; dimple below lower lip; anteriorly displaced anus; rocker-bottom feet; mental retardation; hypotonia, hypoplastic corpus callosum	

Trisomy	Microcephaly; hypotelorism; cleft lip/palate; coloboma; low-set ears; septal defects; patent ductus arteriosus Polydactyly; overlapping fingers; mental retardation (severe); hypotonia; seizures	13
Trisomy	Short stature; bachycephaly; flat facial profile; conductive hearing loss; epicanthal folds; upslant; iris brushfield spots; protruding tongue; congenital heart malformation; duodenal atresia; Hirschsprung disease; joint laxicity; single transverse palmar crease; excess nuchal skin; mental retardation; hypothyroidism; leukemia	21
Mosaic trisomy	Microcephaly; hypertelorism; preauricular pits/tags; low-set ears; micrognathia, long philtrum; septal defects; double aortic arch; clinodactyly; hypoplastic nails; hemiatrophy; mental retardation	22
45,X0	Turner syndrome: short stature; short webbed neck; low hair line; broad nasal bridge; low-set ears; congenital heart defects: aortic coarctation; bicuspid aortic valves; aortic dilatation; lymph-edema of hands and feet; renal abnormalities: single horseshoe kidney; renal vascular abnormalities; delayed puberty; amenorrhea; infertility; hypothyroidism	
6p24.3-21.1	NCCM; bradycardia; pulmonary valve stenosis; atrial septal defect; left bronchial isomerism; azygous continuation of the inferior vena cava; polysplenia; intestinal malrotation	
11p15	NCCM; mild pulmonary stenosis; mild mitral valve prolapse; atrial septal defect	202

4.7 Miscellaneous

NCCM has been described in patients with heterotaxy with polysplenia, polycystic kidney disease, congenital adrenal hyperplasia, nephropathic cystinosis, and myelofibrosis.[11, 66, 70–74] Whether these co-occurrences are coincidental or represent shared etiologies with NCCM is unknown.

Among the possibly acquired forms of NCCM, there are reports about an infectious cause.27 Recently, an etiologic role for macroand microvascular abnormalities was suggested.[75–84] NCCM has also been described in patients with coronary heart disease.[85–87]

Since coronary artery disease is a frequent disorder, this association may well be coincidental. Aortic elasticity was significantly altered in a group of 20 NCCM patients (aortic stiffness index of 8.3 ± 5.2).[78]

Microvascular abnormalities in NCCM including decreased coronary flow reserve with wall motion abnormalities in more extended regions of the myocardium than the noncompacted area have been observed.[77]

In addition, several case studies reported hypoperfusion of the noncompacted region in NCCM patients using myocardial perfusion SPECT, positron emission tomography,Thalliumm yocardialimaging,orMRI.[75, 76, 79, 80, 82, 83]

It is thought that fibrosis, thrombus formation, hypokinesis, and necrosis may be the underlying mechanisms of hypoperfusion.[76, 79, 80]

Other pathogenic hypotheses for NCCM include adaptation to changes in the cardiovascular and/or hemodynamic climate; myocardial dissection or tearing of the inner layer of the cardiac muscle due to dilatation.[19,22]

5 CLINICAL ASPECTS

Heart failure is among the most frequent presentations of NCCM, followed by supraventricular and ventricular arrhythmias, including sudden cardiac death, and thrombo-embolic events. However, as in other cardiomyopathies, there is a great variability in presentation, even within families, ranging from a fully asymptomatic course to severe heart failure necessitating cardiac transplantation. The age of presentation is also highly variable varying from prenatal and neonatal diagnosis to diagnosis at the age of 94 years.[6, 11, 88–93] Prenatal diagnostic imaging detects more often bilateral ventricular hypertrophy/*hypertrabeculation*s than the typical left ventricular morphologic changes observed postnatally and in adults (unpublished observation). The fourth to fifth decade is the median age for diagnosis in adult isolated NCCM, constituting a relatively young population in adult cardiologic practice. Many patients remain asymptomatic and may be detected due to an asymptomatic heart murmur, or by chance by preoperative cardiac evaluation or medical assessment for insurance or jobs or because they participated in cardiologic family screening, after a relative had been diagnosed with NCCM.[11, 13] Symptomatic patients may present clinical symptoms of dyspnea, fatigue (atypical) chest pain, and/or (pre) syncope. NCCM may also present as a peripartum cardiomyopathy.[11, 94–96] Review of the literature revealed a male to female ratio of almost 2:1.[19] This gender difference cannot be fully explained by the occurrence of X-linked forms of NCCM. Different *arrhythmias* and *conduction disorders* may occur in NCCM patients (Table 6.7). None of physiological trabeculations.[13] Secondary forms of (acquired) NCCM may be the result of hypertension, chronic volume or pressure overload,[97] ischemic heart disease or extreme physical activity (i.e., athletes), leading to NCCM-like abnormalities. These are referred to as pseudo-noncompaction cardio myopathy or an NCCM look-alike. Hypertensive patients are diagnostically challenging, because of the occurrence of LV hypertrophy due to hypertension. Further studies are needed to confirm whether excessive trabeculation is more prevalent in specific ethnic groups, as suggested by one study.[14] Furthermore, dilated, hypertrophic, and ischemic cardiomyopathy may be mistaken for NCCM or vice versa, due to prominent trabeculations or abnormal myocardial thickening. Candida sepsis with intramyo cardial abscesses and intramyocardial hematoma may mimic NCCM.[27, 98, 99] The neuromuscular disorders, syndromes, and chromosomal abnormalities mentioned earlier (Tables 6.3–6.5) should be considered in the differential diagnosis of nonisolated NCCM, especially when NCCM occurs in patients with dysmorphism, growth retardation, or skeletal muscle weakness.

Table 6.7 Arrhythmia and conduction disorders associated with noncompaction cardiomyopathy (NCCM)

	Reference
Atrial fibrillation	15, 113, 203
Atrioventricular nodal re-entrant tachycardia	
Bigemini ventricular extra systole	
Complete atrioventricular block	1, 158, 205, 206
Complete left bundle branch block	109, 146
Giant P-waves and focal atrial tachycardia	
Long QT syndrome 2	135
Narrow QRS complex	106, 107, 110
Persistent atrial standstill	208
Sick sinus syndrome	209
Sinus bradycardia	153, 210
Supraventricular tachyarrhythmia	7, 113, 130, 146, 211
Ventricular fibrillation	106, 205, 212
Ventricular tachycardia	7, 79, 106, 109, 210
Wolff–Parkinson–White syndrome	2, 7, 146, 210, 213

these arrhythmias is characteristic or pathognomonic for NCCM. Thrombo-embolic events may include stroke (cerebrovascular event or transient ischemic attack), peripheral embolism, and mesenterial thrombosis.

6 DIFFERENTIAL DIAGNOSIS

The definitive diagnosis of NCCM relies on the morphological features of the LV myocardium, as defined by an imaging modality, like echocardiography, MRI, CT, or LV angiography. The variability in the extent of physiological trabecularization may complicate distinction of NCCM from normal physiological left ventricular trabeculations. Especially in the area around the base of the papillary muscles of the mitral valve, more trabeculations may be present. However, in the normal heart, there is no excessive segmental thickening (due to hypertrabeculation) like in NCCM and the thickness of these physiological trabeculations does not exceed the thickness of the compact layer. Also, the area of noncompaction is larger in NCCM than in Arrhythmia/conduction disorders associated with NCCM

7 THERAPY, FOLLOW-UP, AND PROGNOSIS

7.1 Therapy and follow-up

Current guidelines for heart failure, arrhythmias, cardiac resynchronization therapy, and ICD implantation for primary and secondary prevention are applied for NCCM.[100–102] b-*Blockers* and *Angiotensin-convertingenzyme (ACE) – inhibitors* are the cornerstones of the treatment in the presence of LV dysfunction and/or arrhythmias. Establishing an expert consensus rapport, similar to HCM, based on case reports, small cohorts and clinical registries would be recommended since no have been conducted, and clear-cut evidence-based clinical guidelines for this disorder are therefore missing.[103] An important issue is the use of prophylactic anticoagulants, in view of frequent thrombo-embolic events. The early case reports and case series emphasized the high risk of thrombo-embolism and advised routine anticoagulation therapy. However, a review of 22 publications addressing the issue concluded that thromboembolic events are rare in NCCM.[104] Fazio et al. came to the same conclusion.[105] Currently, in our hospital, anticoagulation therapy is advised only in patients with an ejection fraction less than 40% (cut off arbitrary), paroxysmal or persistent atrial fibrillation and/or previous thrombo-embolic events. Successful cardiac resynchronization therapy has been described in several NCCM patients, leading to left ventricular reverse remodeling and an increase in left ventricular function.[106–110] Heart transplantation has been performed in some NCCM patients with severe heart failure.[3, 11, 23, 111–117] Left ventricular restoration surgery has been reported successful in a single patient.[118] Treatment with an implantable cardioverter defibrillator (ICD) will be discussed further on. The indication for cardiologic follow-up depends on individual symptoms and cardiac abnormalities. In asymptomatic patients with preserved LV function, annual or biannual cardiologic follow-up is recommended, including ECG and echocardiography. If necessary, these could be extended with 24-h-Holter monitoring and exercise-testing. When EF is below 50%, b-blocker therapy and ACE-inhibitors should be prescribed, especially when NCCM is accompanied by hypertension or arrhythmias.

8 RISK STRATIFICATIONAND INDICATION FOR ICD

Patients at the highest risk for sudden death are patients who previously experienced (aborted) cardiac arrest, ventricular fibrillation, and sustained VF. Family history of sudden death, unexplained syncope (especially during exercise), abnormal blood pressure response during exercise tests, frequent premature ventricular beats on the resting ECG, and /or nonsustained ventricular tachycardia on Holter monitoring and significantly impaired left ventricular function may be considered risk factors. The results from longitudinal studies and the understanding of underlying disease mechanisms will hopefully help to gain more insight into the risk factors and allow more appropriate risk stratification.[128]

Consensus and guidelines for prophylactic ICD treatment in NCCM patients are also needed. Regular ICD indications include primary and secondary prevention. For secondary prevention, i.e., after a previous episode of aborted cardiac death or collapse due to sustained VT or VF, current ICD guidelines advise ICD implantation. In the Rotterdam NCCM cohort of 67 patients, an ICD was indicated in 42% according to the current ICD guidelines (*n* = 28:21 primary and 7 for secondary prevention). After long-term follow-up, appropriate ICD therapy occurred only in patients with secondary prevention (*n* = 3). Inappropriate ICD therapy occurred in 33% of the patients with primary prevention and in 29% of the patients with secondary prevention.[129] In another study, follow-up of 12 patients who received an ICD showed overall appropriate therapy in 42% in primary and secondary prevention combined.130 In primary prevention, 25% of ICD therapy was appropriate opposed to 50% in secondary prevention.[130] This accentuates the need for further research of appropriate risk stratification of sudden cardiac death in patients with NCCM.

9 CARDIOGENETIC ASPECTS

9.1 Molecular and Cardiologic Family Screening

Familial NCCM has been estimated to occur in 18–71% of adults with isolated NCCM, mostly consistent with an autosomal dominant mode of inheritance, indicating the importance of informing and examining relatives of patients with isolated NCCM.[2, 11, 24, 66, 120, 131–133]

Since extensive family studies showed that the majority of affected relatives are asymptomatic, cardiologic evaluation should include all adult relatives irrespective of medical history. Obviously, taking a family history is by itself insufficient to identify familial disease, given the high frequency of asymptomatic disease in families.[11] In families where a pathogenic mutation has been identified, relatives can be offered predictive DNA analysis. In families without a pathogenic mutation, cardiac family screening remains the method of choice to identify relatives at risk of developing symptomatic cardiomyopathy, who may benefit from early treatment.

Apart from NCCM, other cardiomyopathies may co-occur within families, like hypertrophic and dilated cardiomyopathy, so cardiac screening should aim at identifying all cardiomyopathies. Cardiac screening of relatives may show minor abnormalities not fulfilling NCCM criteria, which may be difficult to differentiate from normal physiologic trabecularization. Hypothetically, these minor abnormalities might develop into NCCM eventually. Longitudinal studies of patients with mild NCCM features are needed to investigate the natural history of these forms of noncompaction."

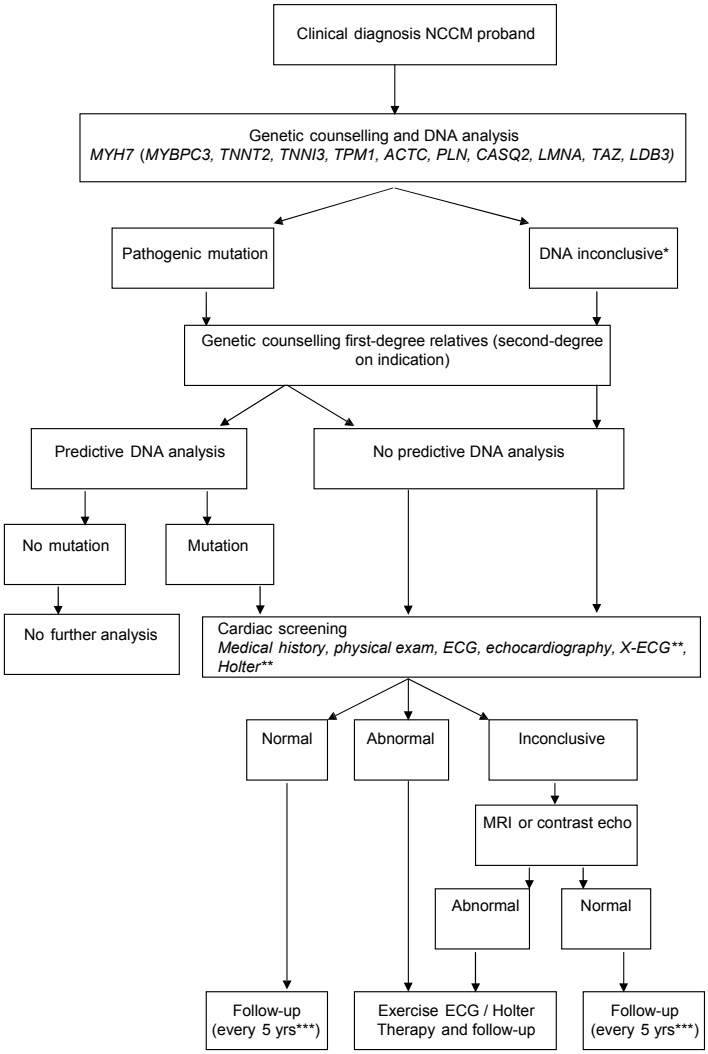
9.2 Genotype–Phenotype Correlations

Molecular studies of NCCM have thus far shown that there are few recurrent mutations.10 Therefore, it is difficult to establish genotype--phenotype correlations. Additionally, intrafamilial phenotypic variability complicates predictions based on an identified mutation. Multiple (truncating) sarcomere mutations appear to result in a more severe phenotype with childhood onset.10, 11 Multiple mutations identified in adults mostly also comprise involvement of a nonsarcomere gene. Adult patients with multiple mutations seem to have more symptoms than adults with a single mutation.10, 11 These observations may indicate that the combination of a sarcomere mutation and a nonsarcomere mutation causes a less severe phenotype than when a patient has two sarcomere mutations. Mutations in *DTNA* and *TAZ* seem to transfer the strongest predisposition to childhood onset NCCM.

9.3 Molecular Strategies

The proposed strategies for the molecular and cardiologic evaluation of NCCM are depicted in the flowchart in Fig. 6.5. Extensive genetic screening may lead to the identification of a molecular defect in over 40% of isolated NCCM patients and in half of these patients an *MYH7* mutation is found.10 *MYH7* gene sequencing should be considered as an initial approach, being the most prevalent cause for NCCM in adults and children. Further molecular analyses of the other genes within the NCCM spectrum, which quantitatively have a relatively modest contribution to NCCM morbidity, may be considered when no mutation in *MYH7* can be identified. Sarcomere gene analysis is also warranted in pediatric patients, given the high percentage of sarcomere mutations in this group.10 When an adult or pediatric patient is severely affected, screening for a second molecular defect is advised, given the high frequency of multiple mutations in NCCM.

Fig. 6.5 Flowchart for family screening in NCCM * Including unclassified variants; ** if clinically indicated; *** earlier when symptomatic



10 SUMMARY

NCCM is a relatively new, genetically heterogeneous, cardiomyopathy. Clinical presentation and prognosis range from asymptomatic disease with no or slow progression, to severe disabling, rapidly progressive cardiac failure. Initial presentation includes the triad of heart failure (potentially lethal) arrhythmias and/or thrombo-embolism. In adults, the majority of NCCM is isolated.

The first clinical presentation of NCCM may occur at all ages, even prenatally. In childhood, clinical features are often more severe and NCCM is frequently associated with congenital heart defects. The echocardiographic diagnostic criteria as proposed by Jenni et al. are convenient in daily practice and currently the most widely applied. The general cardiac guidelines for chronic heart failure and ICDs are suitable and applicable to the NCCM population.

In as much as 41% of isolated NCCM, molecular testing may yield a genetic defect, mostly in sarcomere genes. The *MYH7* gene is the most prevalent disease gene. The nonisolated forms of NCCM are caused by a range of different (rare) genetic defects. Until now, in half of familial isolated NCCM, the genetic defect remains unknown. Genetic defects in a large number of sarcomere and other cardiomyopathy genes and in genes primarily associated with skeletal myopathies indicate that NCCM may result from a wide range of pathophysiologic mechanisms.

Shared genetic defects and familial aggregation of NCCM, HCM, and DCM indicates that NCCM may be part of a broad spectrum of cardiomyopathies.

The genetic etiology of NCCM requires that patients and their relatives are offered genetic testing and counseling. This may include (predictive) molecular analysis of relatives, when applicable, and/or cardiac evaluation of at-risk relatives, even when they are as yet asymptomatic.

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Left ventricular angiogram in a patient with noncompaction cardiomyopathy

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A 50-year-old female was referred for cardiac screening because of sudden cardiac death of her 48 year-old brother. She had no cardio-pulmonary complaints and her physical examination was unremarkable.

Electrocardiography demonstrated sinus rhythm and normal QRS duration without any repolarization abnormality.

A 24-hours Holter monitoring revealed sinus rhythm and no ventricular arrhythmias. Echocardiography disclosed a moderately diminished, diffuse left ventricular dysfunction with suspected hypertrophy of apical, mid-posterior end mid-inferior ventricular walls.

Patient subsequently underwent left heart catheterisation to exclude ischemic cardiomyopathy. Coronary angiography showed normal coronary arteries. Left ventricular angiogram (LV) in right anterior oblique projection (figure 1 and movie 1) showed an excessively prominent trabecular zone with a spongy appearance of the myocardium in apical, inferior and anterior and to a lesser extent the posterolateral segment. These findings were highly suspicious for left ventricular noncompaction or noncompaction cardiomyopathy (NCCM), which was confirmed by subsequent contrast echocardiography (figure 2), multislice CT-scan (figure 3) and magnetic resonance imaging (MRI) of the heart (figure 4 and movie 2).

NCCM is yet rare, unclassified form of cardiomyopathy.[1] Incidence of this unique cardiomyopathy is estimated to be 0.05% in adults. It is characterized by excessively thickened, irregular endocardial surfaces with prominent trabeculations and intertrabecular recesses. Patients with NCCM can be either asymptomatic or develop diastolic and/or systolic dysfunction with heart failure, ventricular arrhythmias or systemic emboli.[2]

As this disease is not widely known, its diagnosis is frequently missed or misclassified.

The standard diagnostic procedure for NCCM is two-dimensional echocardiography with colour-Doppler studies. In case of planned diagnostic heart catheterisation or impaired echocardiographic imaging quality, LV angiogram can be helpful in further diagnostic process.

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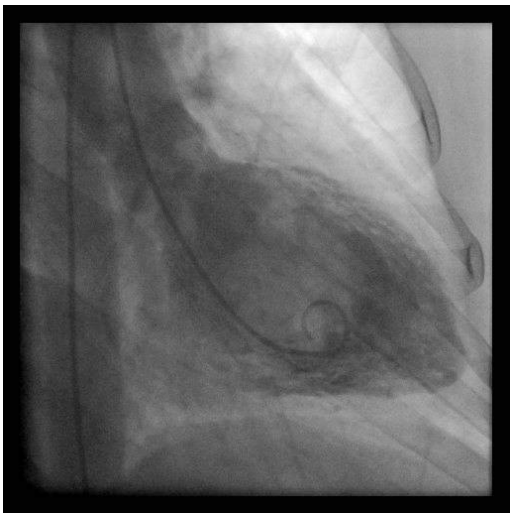

Figure 1. Left ventricular angiogram of this patient showing extensive hypertrabeculation, mostly of the apical segments.

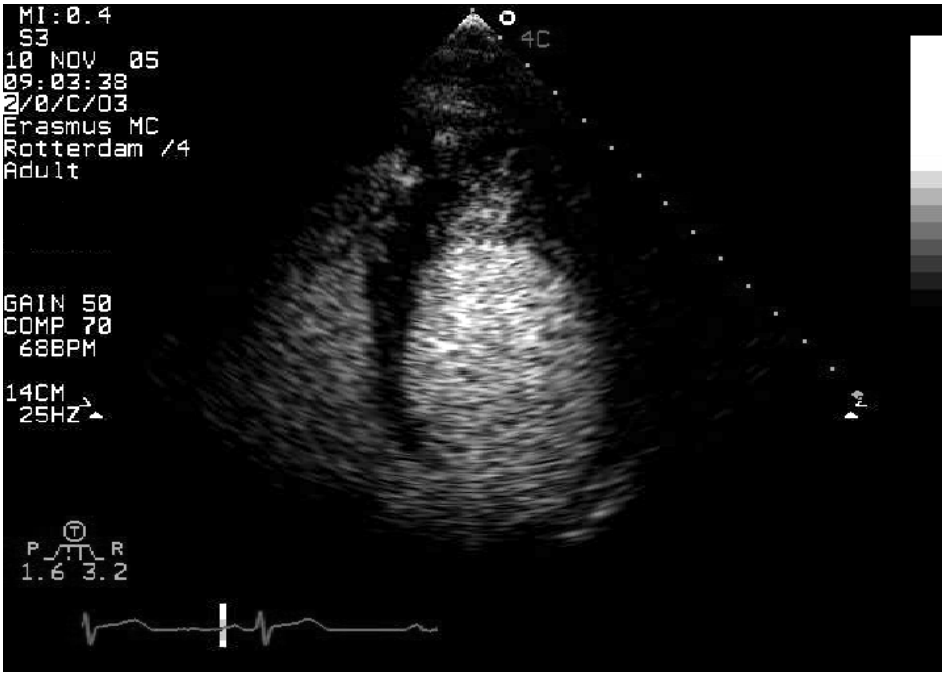

Figure 2. Two-dimensional contrast echocardiography apical four-chamber view: excessive and prominent trabeculation of the left ventricle apical segments is visible. Communication between the recesses and ventricular cavity is clearly demonstrated with a contrast agent.

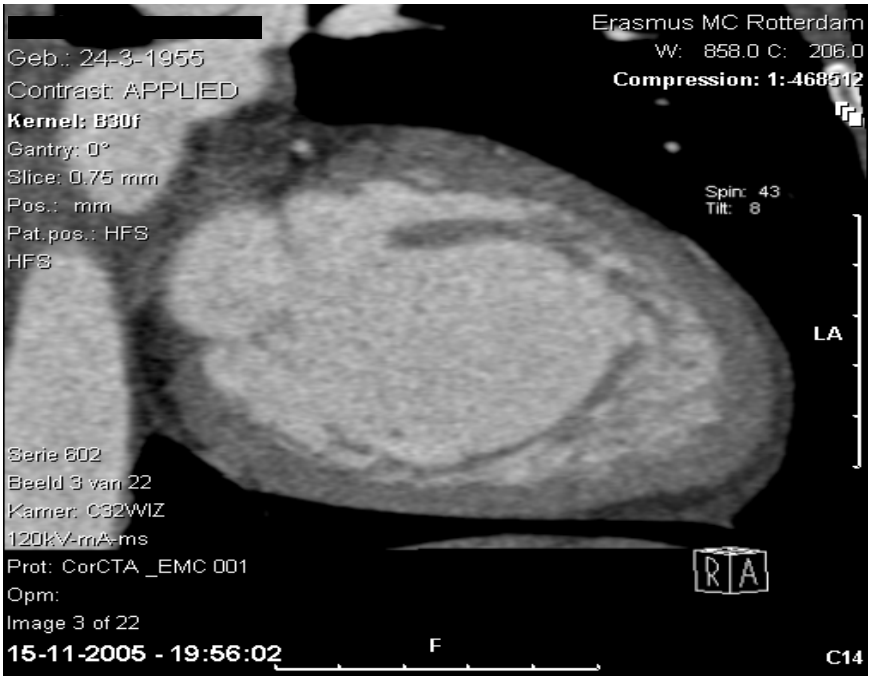

Figure 3. Multislice CT-scan of the LV ventricle showing an excessive and prominent trabeculations; the small line consists the compacted area, and the large line the noncompacted area.

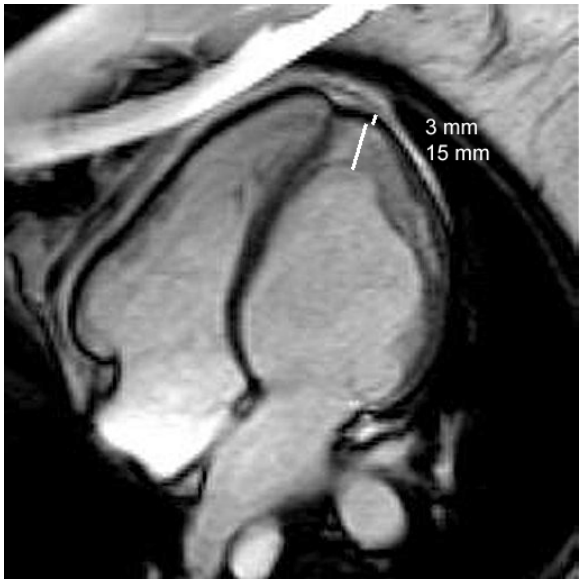

Figure 4. Four chamber MRI view of the heart, demonstrating the hypertrabeculation of apical and lateral walls of the left ventricle; the ratio of noncompacted to compacted myocardium is here maximal five.

Long-term follow-up of patients with noncompaction cardiomyopathy

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ABSTRACT

Background. Noncompaction cardiomyopathy (NCCM) is a primary cardiomyopathy, characterized by increased trabeculations of the left ventricular wall and frequent familial occurrence. Patients may be asymptomatic at the time of diagnosis or can present with arrhythmias, sudden cardiac death, heart failure (HF), and thrombo-embolic events The aim of this study was to describe the long-term clinical course of NCCM patients.

Findings. Ninety consecutive NCCM patients (median age 39 [IQR 31-51] years; 47% male) were treated according to current guidelines and followed-up for a median of 4.9 years {IQR 2.1-9.3]. Eighty-eight percent of patienst were treated with angiontensine-converting enzyme inhibitors, 83% with beta-blockers and 59% with implantable cardioverter-defibrillators. Survival without heart transplantation was excellent with an The 8-years Kaplan-Meyer estimated survival without transplantation was 98% in the 52 patients presenting without HF and 80% in the 38 patients presenting with HF (P =0.02). In patients presenting with HF 13 (34%) developed worsening HF whereas in the non-HF group 9 (17%) patients developed HF. In univariate analysis, only severity of HF predicted survival without heart transplantation (HR 6.5, 95% CI [1.15-36.78], p=0.03). Severe LV dysfunction was associated with a strong trend to predict these events (HR 7.12, 95% CI [0.88-58.45], p=0.07).

Implications. With modern state-of-the-art therapy, prognosis of NCCM is determined mainly by the presence of HF at presentation. Patients without HF at presentation have an excellent long-term survival.

Keywords: noncompaction cardiomyopathy, clinical presentation, treatment, long-term follow-up and prognosis.

INTRODUCTION

In 1984, Engberding and Bender described a 33 years old patient with persistent myocardial sinusoids as a rare congenital anomaly.[1] Six years later, Chin et al. published a series of 8 pediatric and adolescent patients (of whom three prematurely deaths) with increased trabeculations of the left ventricular (LV) endocardium and described isolated noncompaction of LV myocardium as a separate disease entity.[2] Currently, NCCM is viewed as a primary cardiomyopathy, with a mostly autosomal dominant inheritance pattern.[3] Patients may be asymptomatic at the time of diagnosis or can present with arrhythmias, sudden cardiac death, heart failure (HF), and thrombo-embolic events.[4-5]

In initial case series a high morbidity and mortality was described with ventricular tachycardia's (VT) in 41% and death or transplantation in 47% at follow-up. [4] However, in recent case series a better prognosis is described, albeit with limited follow-up time.[5-8] The aim of the present study was to describe long-term outcome in NCCM patients treated according to current guidelines.[9-10]

METHODS

Study population

The study cohort consisted of 90 consecutive adult NCCM patients (age ≥ 18 years, see Figure 1) who were diagnosed and prospectively followed since 2005 at the outpatient clinic in the Thoraxcenter, Erasmus MC, a tertiary referral center. The diagnosis of NCCM was established according to echocardiographic criteria, as described by Jenni et al.:[11]

- An excessively thickened LV myocardial wall with a two-layered structure comprising a compacted epicardial layer and a noncompacted layer of prominent trabeculations on the endocardial side.
- A non-compacted/compacted myocardial thickness ratio ≥ 2 measured at the moment of maximal thickness in end-systole at the parasternal short axis.
- Color-Doppler evidence of deep inter-trabecular recesses in communication with the LV cavity.
- Absence of significant coexisting cardiac anomalies such as hypertension, coronary artery disease or valvular heart disease.

Data collection and analysis

Detailed data were registered at the time of clinical presentation in our center, including age, gender, height, weight, blood pressure, cardiac diagnosis, New York Heart Association (NYHA) functional class, and use of medication. The date of first presentation was used as

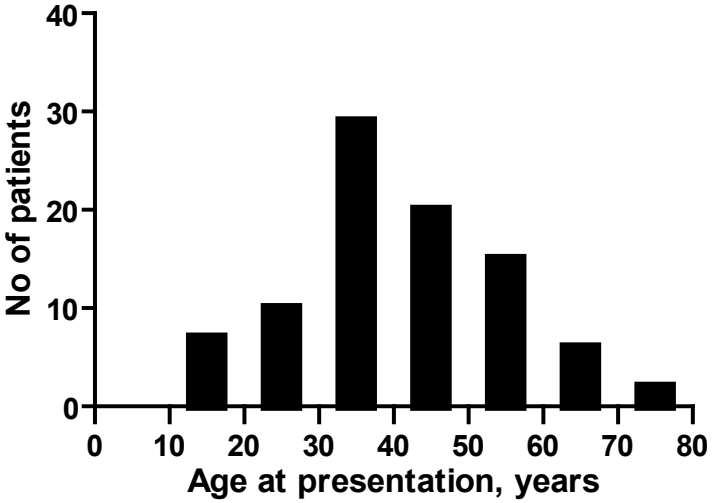


Figure 1. Numbers of patients with noncompaction cardiomyopathy, according the age of presentation (n=90).

the starting point of survival analyses. Survival status was assessed at follow-up visits and through Municipal Civil Registries in December 2011 and was available for all patients.

LV end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD) were obtained by two-dimensional transthoracic echocardiography. The absence of significant valvular abnormalities or other abnormalities was recorded. Measurements of LV volumes and ejection fraction were not made because of the inherent problem to identify the endocardial border in the presence of extensive trabeculations. Fractional shortening (= (LVEDD-LVESD)/LVEDD x 100%) was calculated as a measure of systolic LV function. Quantification of LV dimensions and severity of LV dysfunction as measured by FS, was defined according to published guidelines. [12]

Heart rate, PQ, QRS and QTc intervals were measured from the ECG at presentation. The QTc interval was calculated after correction for heart rate with Bazett's formula. The presence of ventricular ectopy and (non-) sustained VT was identified on 24 hour Holter monitoring.

All patients were followed at the outpatient clinic including ECG and echocardiography every 6 to 12 months or more frequently, according to clinical status. The development of new HF, the progression of HF, hospitalization and death were recorded. Dosing of the HF drugs, and choice of anti-arrhythmic drugs, was left to the treating cardiologist. An internal cardiac defibrillator was implanted in 53 (59%) patients as described elsewhere,[13] 15 (17%) for secondary prevention and 38 (42%) for primary prevention. This device was interrogated every 3 months and in the event of new symptoms or device discharges.

Statistical Analysis

Continuous variables are summarized by mean ± SD or median and interquartile range (25th, 75th percentile) as appropriate. Categorical variables are presented as frequencies and percentages. Comparison of continuous variables, between groups, was made by unpaired Student's t-test or the Mann–Whitney U test. When comparing frequencies, where applicable, the Chi-square or Fisher's exact test was used. Kaplan-Meyer survival curves were constructed, censoring at latest date of follow-up, heart transplantation or death. These were compared with the Kaplan-Meyer survival of an age and sex matched control group (N=8550) from the national statistics authority Statistics Netherlands. Differences between pairs of survival curves were tested by the log-rank test.

Univariable Cox regression analysis was used to predict the occurrence of death or heart transplantation by the following variables: age at presentation, male gender, NYHA class III-IV, QRS duration, left bundle branch block, LV hypertrophy on ECG, LA diameter, LVEDD, LVESD, the extent of LV nomcompaction, severe LV dysfunction and fractional shortening. Hazard ratios were calculated with corresponding 95% confidence intervals. Multivariate analysis was not attempted because of the low number of events. All tests were two-tailed and P-values less than 0.05 were considered statistically significant.

RESULTS

Baseline characteristics

Baseline demographic and clinical characteristics of the 90 NCCM patients are summarized in Table 1. HF was the primary presentation in 38 (42%) of patients (including 7 patients with concomitant atrial fibrillation), 8 (9%) patients presented with atrial arrhythmias, 6 (7%) with sustained ventricular tachycardia and 8 (9%) with ventricular fibrillation. Nine patients (10%) presented with thrombo-embolic events, including 7 (8%) with cerebrovascular accidents. Seven (8%) patients presented with palpitations without significant arrhythmias except frequent premature ventricular extra-systoles. Fourteen (16%) patients were detected by chance, like pre-operative screening or other reasons.

Echocardiographic evaluation showed mild LV dilatation (mean 58 ± 9 mm) in non-HF patients and moderate LV dilatation (66 ± 11 mm) in HF patients Fractional shortening was moderate to severely (FS<20%) depressed in the 81% HF patients and 35 % in non-HF patients. However, there was no difference in extend of noncompaction between HF and non-HF patients.

During a median follow-up time of 4.9 years [range [0.4-39.5 years], 42% of HF and 81% of non-HF patients remained in good functional class (Table 2). Survival was excellent in patients presenting without HF: 8-years estimated Kaplan-Meyer survival without transplantation was 98 %. This was comparable with the age and sex-matched controls (N=8550) in the general population, but significantly lower (80 %; p=0.02) in those patients presenting with HF

Table 1. Baseline characteristics of noncompaction cardiomyopathy patients with or without HF at primary presentation**.**

	Total N=90	HF N=38 (42%)	No HF N=52 (58%)	P-value
Demographic / clinical parameters				
Age at presentation, median [IQR], y	39 [31-51]	39 [32-53]	39 [30-50]	0.82
Male sex	42 (47)	21 (55)	21 (40)	0.52
Familial noncompaction cardiomyopathy	45 (50)	14 (37)	31(62)	0.05
Familial history of sudden cardiac death	14 (16)	4 (11)	10 (19)	0.38
Electrocardiography				
1st degree atrio-ventricular block	10 (11)	8 (21)	2 (4)	0.02
QRS duration, msec	112 ± 33	118 ± 46	97 ± 46	0.02
Corrected QT interval, msec	420 ± 36	428 ± 40	415 ± 33	0.09
Left ventricular hypertrophy	25 (28)	16 (42)	9 (17)	0.02
Left bundle branch block	26 (29)	14 (37)	11 (21)	0.15
Right bundle branch block	2 (2)	1 (3)	1 (2)	1.0
Echocardiography				
Left atrial dimension, mm	42 ± 10	47 ± 9	39 ± 9	0.0001
Left ventricular end-diastolic diameter, mm	61 ± 11	66 ± 11	58 ± 9	0.0004
Left ventricular end-systolic diameter, mm	49 ± 12	55 ± 11	44 ± 10	<0.0001
Fractional shortening, %	20 ± 8	15 ± 6	24 ± 7	<0.0001
Left ventricular noncompacted segments, %	56 ± 13	57 ± 12	54 ± 16	0.41
Maximal noncompacted + compacted thickness, mm	23 ± 5	24 ± 3	23 ± 6	0.48
Maximal noncompacted /compacted ratio	2.5 ± 0.3	2.5 ± 0.3	2.5 ± 0.3	0.66
24 h-Holter				
Number of premature ventricular complexes / 24h, median {IQR]	44 [8-1173]	114 [4-1154]	23 [6-1231]	0.39
Non-sustained ventricular tachycardia's	8 (9)	1 (3)	7 (13%)	0.13

Variables are presented as mean ± SD or number (%) unless indicated otherwise. IQR denotes interquartile range.

(see Figure 1). In the latter group, five patients died (three due progressive HF) and three patients underwent cardiac transplantation because of end-stage HF. In the non-HF group only one patient died from a non-cardiac cause. Nevertheless 9 non-HF patients developed HF (17 %).In 32 (62%) an ICD were implanted: in 18 (35%) primary prevention and in 14 (27%) patients for secondary prevention because of sustained VT or VF Survival without transplantation or appropriate ICD therapy was comparable among non-HF and HF patients (85% vs. 76%; p=ns; Figure 3).

Only a few thrombo-embolic events were observed: none in the HF group in which 32 (84%) of patients used oral anticoagulants and two (4%) in the non-HF group in which 26 (50%) of patients used oral anticoagulation. The two thrombo-embolic events in the non-HF group

Table 2. Long-term outcome of noncompaction cardiomyopathy patients.

	Total n=90	HF n=38 (42%)	No HF N=52 (58%)	P-value
Median follow up [IQR], months	4.9 [2.1-9.3]	6.0 [2.3-11.3]	4.5 [2.1-7.5]	0.88
Death	6 (7)	5 (11)	1 (2)	0.08
• Progressive HF	3 (3)	3 (8)	0	0.07
• Non-cardiac	3 (3)	2 (5)	1 (2)	0.57
Heart transplantation	3 (3)	3 (8)	0	0.07
Progressive HF	13 (14)	13 (34)		
New onset HF	9 (10)		9 (17%)	
NYHA class (HTX free survivors)				0.15
• I	58 (64)	16 (42)	42 (81)	
• II	14 (16)	9 (24)	5 (10)	
• III	9 (9)	5 (13)	4 (8)	
Arrhythmias				
• Supra-ventricular	15 (17)	7 (18)	8 (15)	0.78
• Sustained VT / appropriate ICD therapy	13 (14)	5 (13)	8 (15)	1.0
• Aborted sudden cardiac death	2 (2)	1 (3)	1 (2)	1.0
Syncop	1 (1)	0	1 (2)	1.0
Thrombo-embolic events	2 (2)	0	2 (4)	0.51
Implantable cardioverter-defibrillator	53 (59)	22 (58)	32 (62)	0.82
Cardiovascular drugs at last FU				
• Coumadins	58 (64)	32 (84)	26 (50)	0.0009
• ACE-I / ARB	79 (88)	38 (100)	41 (79)	0.002
• Beta-blockers	75 (83)	35 (92)	40 (77)	0.08
• Loop diuretics	51 (57)	38 (100)	14 (27)	0.01
• Aldosteron antagonist	25 (28)	21 (55)	4 (8)	<0.0001
• Digoxine	20 (22)	13 (34)	7 (13)	0.02
• Amiodaron	14 (16)	6 (16)	8 (15)	1.0

Variables are presented as numbers(percentages) unless indicated otherwise. HTX denotes heart transplantionIQR, interquartile range; VT, ventricular tachycardia; FU, follow-up; ACE-I, angiotensine converting enzyme; ARB, Angiotensine II –receptor antagonists.

included one patient with moderate LV dysfunction (FS 20%), but without anticoagulation and another in a patient with paroxysmal atrial fibrillation, severe LV dysfunction and thrombo-embolic event in the history on chronic anticoagulation, but temporarily interrupted peri-operatively. With univariate analysis, only severity of HF (NYHA III-IV) appeared to predict survival without heart transplantation (HR 6.5, 95% CI [1.15-36.78], p=0.03). Severe LV dysfunction was associated with a strong trend to predict these events (HR 7.12, 95% CI [0.88-58.45], p=0.07).

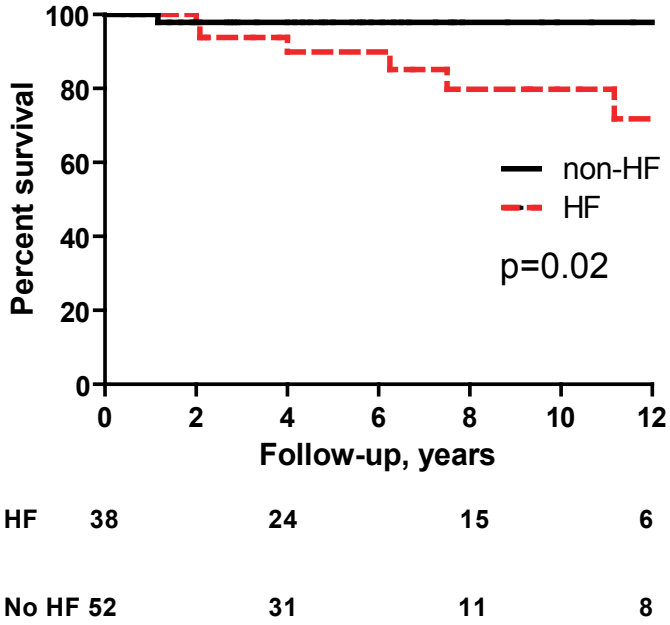


Figure 2. Event free Kaplan-Meijer survival free curve for death or heart transplantation according the primary presentation (HF versus non-HF).

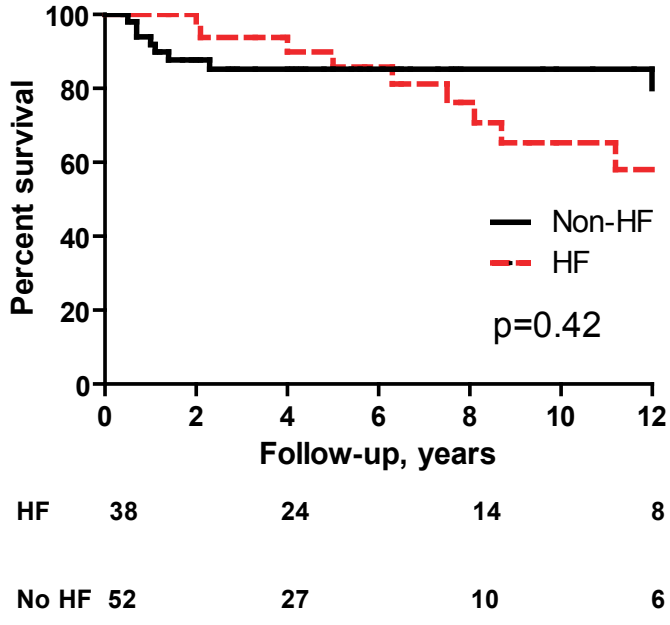


Figure 3. Event free Kaplan-Meijer survival free curve for appropriate ICD therapy, death or heart transplantation according the primary presentation (HF versus non-HF).

DISCUSSION

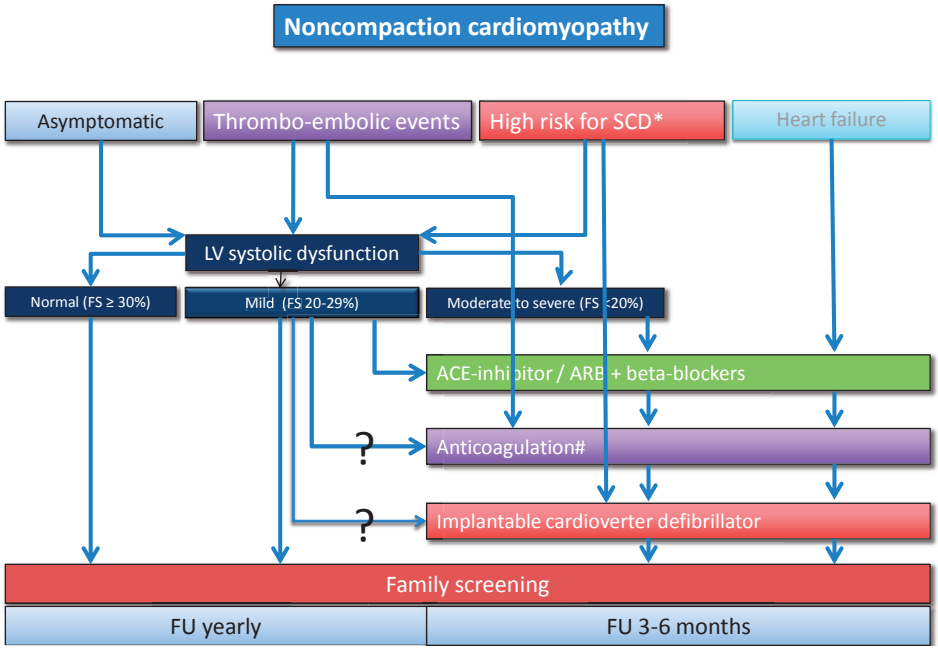
The main findings of this study is that NCCM patients presenting without HF, have an excellent long-term survival, provided that these patients are optimally treated with appropriated drug therapy and, in selected patients, prophylactic ICD implantation for primary or secondary prevention of sudden cardiac death.[14-15] These findings have important implications for the counseling of the NCCM patients and their relatives, and provide a basis to propose a guideline for management of NCCM.

Noncompaction cardiomyopathy is a relatively rare, primary cardiomyopathy which may lead to HF, thrombo-embolic events and sudden cardiac death.[16] In the first case series high rates of mortality and morbidity were reported with 47% death or transplanted, 41% VTs and 24% thrombo-embolic events.[4] In more recent reports, a more favourable outcome is shown.[5-8] In one series the mortality rate was 11%, cardiac transplantation 9% and VT's 7% at an average follow-up of 2.3 years.[7] Importantly, most of these patients with events suffered also from HF (31%). Also, in another series none of the asymptomatic patients died or needed cardiac transplantation at a median follow-up of 2.7 years, while the other events occurred in 31% of symptomatic patients.[8] In our study with longer follow-up these findings are confirmed. At a median follow-up of 4.9 years, cardiac death or heart transplantation occurred only in patients presenting with HF, while survival without transplantation was excellent in those without HF. Eight years transplant free survival was 98% and 80% in those without and with HF at presentation. These findings may underscore the need of regular follow-up of all NCCM patients, whether symptomatic or not, given the fact that the majority of the patients needed active drug treatment or ICD implantation.[8] Indeed, liberal use of currently available drug and device treatment in selected patients appears appropriate when LV dysfunction or significant ventricular arrhythmias are noted.[8,15]

A pattern of successive reports of poor and better prognosis is not unique to NCCM. Similarly, the first studies in hypertrophic cardiomyopathy reported a very poor prognosis with latter studies reporting a better outcome.[17] This is probably due to selection of the sickest patients for early referral to tertiary centers with subsequent referral of patients with milder symptoms and their asymptomatic relatives.[18] In NCCM, increasing knowledge among physicians and better imaging modalities also may explain this phenomenon.

Apart from sudden cardiac death, which may be prevented in part by timely implantation of an ICD, and LV dysfunction, which may be managed by appropriate drug therapy, patients with NCCM may develop intra-ventricular thrombosis and subsequent emboli. At long-term follow-up we observed only two such cases, both in patients with moderate to severe impaired LV function, but the majority of the patients (84 % in HF versus 50 % in non-HF patients) were already empirically treated with preventive anticoagulation. Thus a more

Table 3. Strategy proposal for clinical management of patients with noncompaction cardiomyopathy.



LV denotes left ventricle; FS, fractional shortening; SCD, sudden cardiac death; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensine II-receptor antagonist.
* See the discussion section.
# In particular in patients with atrial fibrillation or previous thrombo-embolic event.

liberal prescription of anticoagulants appears appropriate. Based on our observations and those from other patient series, we developed a treatment guideline for NCCM as shown in Table 3. The primary presentation, i.e. symptoms and signs at diagnosis, combined with the severity of LV dysfunction, guides the appropriate drugand device treatment strategy. In patients with HF and /or significant LV dysfunction, treatment with beta-blockers, ACE-inhibitors and anticoagulants is appropriate. ICD implantation is appropriate in all patients presenting with sustained VT or VF and in selected patients with potentially high risk features, including (unexplained) syncope, non-sustained VTs at Holter monitoring, early repolarization at surface electrocardiogram and / or a family history of premature sudden cardiac death.[13] Further evidence, to improve outcome in patients with this rare disease, could come from multicenter registry-based studies, similar to those in other cardiomyopathies.[19-20] Furthermore, large case series like the present study remain an important source of information to develop an appropriate diagnostic strategy and to improve treatment of NCCM.

CONCLUSIONS

With current cardiovascular therapeutic modalities, the prognosis of noncompaction cardiomyopathy is mainly determined by absence or presence of HF symptoms. Patients without HF have an excellent long-term (8-years) survival, comparable with the general population, probably with the help of routine intensive follow-up and treatment.

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Reduced regional systolic function is not confined to the noncompacted segments in noncompaction cardiomyopathy

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ABSTRACT

Background: Isolated ventricular noncompaction (IVNC) is a relatively rare genetic primary cardiomyopathy. The aim of the present study was to investigate with regional real-time three-dimensional echocardiographic analysis whether there is a difference between the contribution of noncompacted and compacted left ventricular (LV) segments to global LV dysfunction in patients with IVNC.
Methods: The study comprised 289 segments of 17 patients with stringent diagnostic criteria for IVNC. Their results were compared to 153 segments of 9 control subjects. The systolic performance of compacted and noncompacted LV segments was assessed using the wall motion score during 2D echocardiography. The 3D images were acquired with a RT3DE system with X4 matrix-array transducer and were used for the regional volume measurements.
Results: Wall motion score index was markedly abnormal in the compacted LV segments of IVNC patients but significantly less abnormal compared to the noncompacted segments (2.21 ± 0.63 vs. 2.01 ± 0.74, p b 0.05). No relationship was found between the number of noncompacted segments per patient and LV ejection fraction or end-diastolic volume. In the IVNC patients, noncompacted and compacted LV segments had comparable increased 3D regional volumes and reduced systolic function.
Conclusions: These results suggest that systolic LV dysfunction observed in IVNC is not confined to noncompacted LV segments.

Keywords: Three-dimensional echocardiography; Noncompaction cardiomyopathy; Regional function

1. INTRODUCTION

Noncompaction of the ventricular myocardium is a relatively new clinicopathologic entity. It was first described in 1984 by Engberding and Bender [1] and is characterized by a pattern of prominent trabecular meshwork and deep intertrabecular recesses communicating with the left ventricular (LV) cavity. Isolated ventricular noncompaction (IVNC) is thought to be caused by arrest of normal embryogenesis of the endocardium and myocardium. Results of recent studies confirmed the hypothesis that IVNC is part of a more widespread cardiomyopathy, involving both the morphologically normal and dysmorphic segments [2–6].

Accurate characterization of regional LV function requires a thorough evaluation of the entire LV. Real-time threedimensional echocardiography (RT3DE) allows fast acquisition from a single acoustic window of dynamic pyramidal data that encompasses the entire LV. Recent studies have demonstrated the value of RT3DE in the evaluation of global and regional LV function [7–13]. Bodiwala et al. [14] confirmed the usefulness of RT3DE in the evaluation of NCCM.

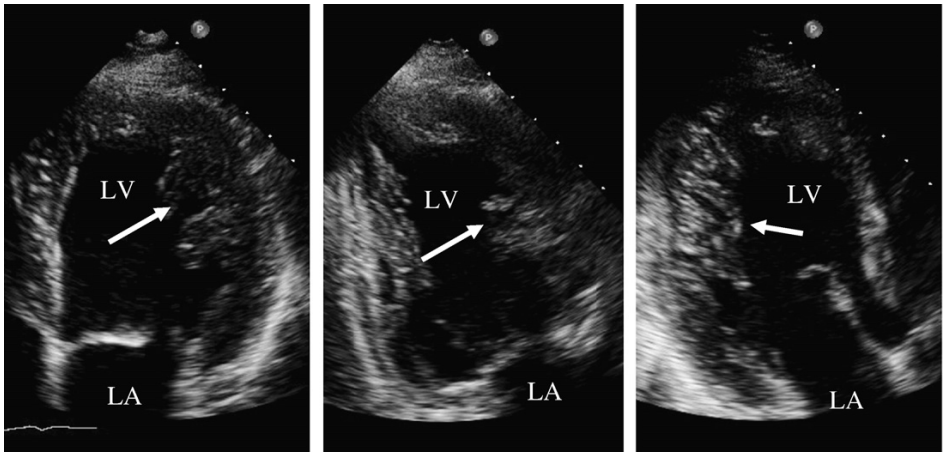

Fig. 1. Two-dimensional echocardiogram (apical 4-chamber, left; 2-chamber, middle; 3-chamber, right) showing prominent trabeculations and recesses in a patient with a noncompacted left ventricle (arrows). Abbreviations: LA = left atrium, LV = left ventricle.

The aim of the present study was to investigate with regional RT3DE analysis whether there is a difference between the contribution of noncompacted and compacted LV segments to global LV dysfunction in patients with IVNC.

2. MATERIALS AND METHODS

2.1. Study population

The study comprised 289 segments of 17 patients with stringent diagnostic criteria for IVNC (absence of significant valvular heart disease and normal coronary arteries). Their results were compared to 153 segments of 9 control subjects without LV wall motion abnormalities. Specific echocardiographic diagnostic criteria for IVNC were (Fig. 1):

(1) An excessively thickened LV myocardial wall with a
2-layered structure comprising a compacted layer on the epicardial side and a noncompacted layer of prominent trabeculations and deep intertrabecular recesses on the endocardial side.
(2) A noncompacted/compacted myocardium thickness
ratio N 2 measured at the moment of maximal thickness in end-systole.
(3) Color-Doppler evidence of deep intertrabecular recesses in communication with the LV cavity.
(4) Absence of coexisting cardiac anomalies.

score (WMS; 1 = normal motion, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic) and was expressed in terms of the WMS index (the WMS divided by the number of analysed segments). According to the recommendations of the American Heart Association on standardized myocardial segmentation and nomenclature for tomographic imaging of the heart, a 17-segment model was used [15]. Echocardiograms were analysed by blinded observers (AN and OIIS).

2.2. 2D imaging

The systolic performance of compacted and noncompacted LV segments was assessed using the wall motion

2.3. RT3DE imaging

Harmonic RT3DE imaging was performed using a fully sampled X4 matrix-array transducer (2–4 MHz), which utilizes 3000 active elements to obtain from a single apical window a pyramidal dataset that contains the entire LV. 3D images were optimized by modifying the gain, brightness, compression, and time-gain compensation controls. RT3DE datasets were then acquired using the wide-angle acquisition mode (93° × 80°) in which four wedge-shaped subvolumes (93° × 20°) were obtained over 8 consecutive cardiac cycles during a breath-hold. Acquisition of each subvolume was triggered to the ECG R-wave of every second heartbeat to allow sufficient time for the probe to be recalculated and each subvolume stored.

2.4. RT3DE volume measurements

QLAB software (Philips, Best, The Netherlands) was used for analysis of 3D data. Non-foreshortened apical 2and 4chamber views were extracted from the pyramidal dataset from the first frame in the loop, which corresponded to LV end-diastole. In each patient, five anatomic landmarks were manually identified, including two points to identify the mitral valve annulus in each of the two apical views and one point to identify the apex in either view. Following manual identification of these points, the program automatically identified the 3D endocardial surface using a deformable shell model. Adjustments to the automatic surface detection could be performed at this time, if necessary. LV end-diastolic volume was automatically computed directly from voxel counts. Then, LV end-systole was selected by identifying the frame with the smallest LV cavity cross-sectional area in both apical views. Regional ejection fractions were calculated from all regional end-diastolic and end-systolic volumes. To study the effect of noncompacted neighbour segments to the contractile function of compacted segments, the number of noncompacted neighbour segment (0 to 4) was assessed for each compacted segment.

2.5. Statistical analysis

Descriptive data for continuous variables are presented as mean ± SD. Continuous data were compared with Student t test. A p value b 0.05 was considered statistically significant. The intraobserver and interobserver variabilities were calculated as the absolute difference in a variable measured at two times divided by the mean value of the two measurements times 100%.

3. RESULTS

3.1. Clinical data

Clinical characteristics of the 17 patients with typical features of IVNC and the 9 control subject are presented in Table 1.

3.2. 2D echocardiographic data

One hundred thirty-one of the 289 LV segments (45%) were noncompacted. In Fig. 2 the localisation and distribution of the noncompacted LV segments according to the 17segment model are shown. The WMS index was markedly abnormal in the compacted LV segments of IVNC patients but significantly less abnormal compared to the noncompacted segments (2.21 ± 0.63 vs. 2.01 ± 0.74, p b 0.05). In Table 2 the characteristics of LV wall motion contractility of noncompacted and compacted segments are reported. No relationship was found between the number of noncompacted segments per patient and LV ejection fraction (EF) (r2 = 0.12, p = 0.17) or end-diastolic volume (EDV) (r2 = 0.005, p = 0.78).

Table 1 Clinical and echocardiographic characteristics of IVNC patients.

Characteristic	IVNC patients (n = 17)	Controls(n =9)
Age (years)	45 ± 20	42 ± 15
Gender (M/F)	9/8	6/3
Diabetes mellitus (%)	9 (53)	4 (44)
Hypercholesterolaemia (%)	10 (59)	5 (55)
B-blockers (%)	16 (94)*	2 (22)
ACE-inhibitors (%)	15 (88)*	2 (22)
Diuretics (%)	7 (41)*	1 (11)
End-diastolic LV volumes (ml)	151 ± 61*	114 ± 26
End-systolic LV volumes (ml)	94 ± 44*	44 ± 14
LV ejection fraction (%)	38 ± 12*	62 ± 7
Noncompacted segments per patient	7.6 ± 4.5	0

Abbreviations: LV: left ventricular, M: male, F: female.
*p b 0.05 vs. controls.

A segment was defined as noncompacted if 75% of the segment showed noncompaction. The study was approved by the institutional review board and all patients gave informed consent.

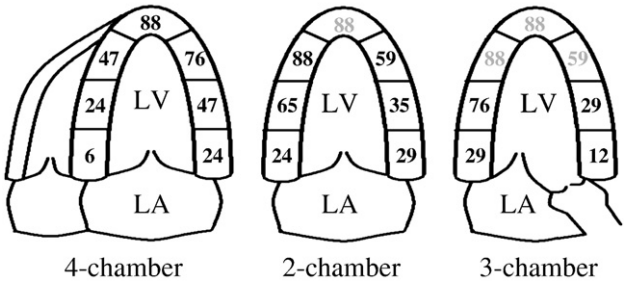

Fig. 2. Prevalence (in percentages) of noncompacted segments in patients with typical features of IVNC for all individual left ventricular segments.

Table 2 Comparison of wall motion characteristics in noncompacted and compacted segments in IVNC patients.

Noncompacted segments (n = 131)	Compacted segments (n = 158)	p value	
Normal	14 (11%)	40 (25%)	b 0.001
Hypokinesis 77 (59%)	78 (49%)	0.13	
Akinesis	39 (30%)	38 (24%)	0.33
Dyskinesis	1 (1%)	2 (1%)	0.68

3.3. 3D echocardiographic data

As seen in Table 3, both regional end-diastolic and endsystolic LV volumes were increased and regional ejection fraction was decreased in noncompacted and compacted LV segments.

Regional LV ejection fraction values at various levels (basal, midventricular and apical level) are shown in Fig. 3. As seen in Fig. 4, the number of noncompacted neighbour segments did not influence regional ejection fraction of compacted LV segments. The number of non-compacted segments did not show any correlation with any echocardiographic parameters.

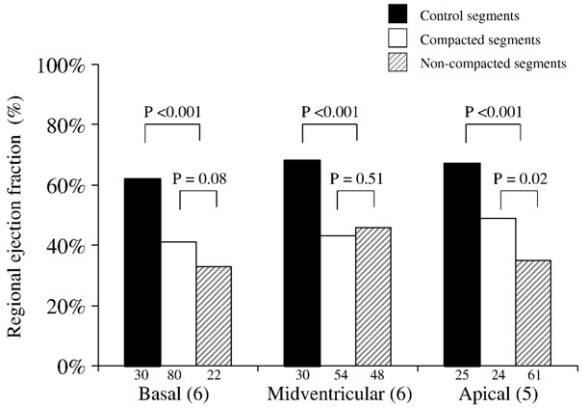

Fig. 3. Regional ejection fraction at various levels of the left ventricle in noncompacted and compacted segments and in controls.

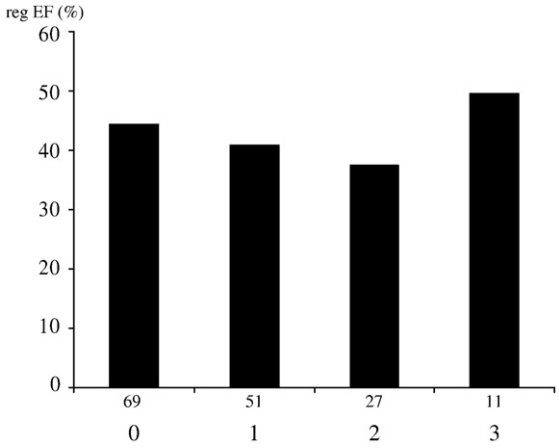

Fig. 4. Regional ejection fraction of compacted segments depending on the number of noncompacted neighbour segments.

Table 3 Regional volumes and ejection fractions of noncompacted and compacted segments in IVNC patients.

	Noncompacted segments (n = 131)	Compacted segments (n = 158)	Controls (n = 153)
Regional EDV (ml) 8.0 ± 4.5*	8.5 ± 3.6*	5.0 ± 2.9	
Regional ESV (ml)	4.6 ± 3.3*	4.9 ± 2.7*	1.9 ± 1.2
Regional EF (%)	40 ± 23*	44 ± 18*	62 ± 13

Abbreviations: EDV: end-diastolic volume, ESV: end-systolic volume, EF: ejection fraction.
*p b 0.001 vs. controls.

3.4. Intraobserver and interobserver variabilities

In our department the percent intraobserver variability was, respectively, 8.1 ± 8.3% for regional EDV, 10.1 ± 8.0% for endsystolic volume (ESV) and 8.0 ± 8.9% for EF. The percent interobserver variability was, respectively, 12.0 ± 11.1% for EDV, 14.0 ± 12.5% for ESV and 10.0 ± 9.1% for EF.

4. DISCUSSION

The aim of the present study was to systematically analyse with RT3DE the contributions of noncompacted and compacted segments to global LV systolic dysfunction in patients with typical features of IVNC. The results indicate that noncompacted and compacted LV segments have comparable increased regional volumes and reduced systolic function. These results suggest that systolic LV dysfunction observed in IVNC is not confined to noncompacted LV segments.

IVNC is a relatively rare genetic primary cardiomyopathy, in which both sexes are affected [16,17]. This cardiomyopathy can be familial or sporadic [16]. The sporadic type, however, in some patients may be due to chromosomal abnormalities.

IVNC in the majority of adults is an autosomal dominant disease, but X-linked disorder has also been described [18]. Some of the most mutated genes that are responsible for the disease are (G4.5 (tafazzin gene): α-dystrobrevin gene (DTNA); FKBP12 gene; lamin A/C gene; Cypher/ZASP (LIM, LDB3) gene); and some genotype-phenotype correlations (i.e., Becker muscular dystrophy, Emery–Dreifuss muscular dystrophy or Barth syndrome) [18]. IVNC believed to be the result of arrest of normal endomyocardial morphogenesis in the developing fetus leaving numerous, excessively prominent trabeculations and deep intertrabecular recesses in a segmental distribution usually from the apex [16,17,19]. These produce a typical honeycomb-like appearance when sectioned transversely. The LV is always affected; on occasion the right ventricle can also be affected. Recent studies have shown that IVNC may become clinically apparent late in adulthood as a result of arrhythmias or progressive LV dysfunction with or without LV dilation [4,20]. Fazio et al. [21] found a strong correlation between systolic and

diastolic dysfunction in IVNC by tissue Doppler imaging: in fact all patients with diastolic dysfunction also presented a severe reduction of the systolic function. Moreover, IVNC has been found to be associated with mitral annulus enlargement and functional impairment [22]. Increased left atrial ejection force as a characteristic of atrial systole (which is a part of ventricular diastole) has been demonstrated in IVNC suggesting compensating left atrial work against the dysfunctional LV in a RT3DE study [23].

It has been suggested that noncompacted and compacted LV segments provide different contributions to overall systolic LV dysfunction [24]. In our study, three quarters of compacted LV segments showed wall motion abnormalities. This number is consistent with results published by others who described the presence of wall motion abnormalities in the majority (58% to 82%) of compacted LV segments in IVNC patients [4–6]. Although there was a significant greater impairment in the WMS index for noncompacted LV segments, the actual difference in WMS index (0.20) with compacted LV segments in our IVNC patients was rather small. Lofiego et al. [24] described relatively less impairment in the WMS index for noncompacted segments compared to compacted LV segments. The authors explained their findings by the lower parietal stress (an unmeasured variable) rather than less intrinsic depressed contractility of the more hypertrophied noncompacted LV segments. However, our data are not readily comparable with study of Lofiego et al. [24]. In our study the 17-segment LV model was used, which makes comparison difficult with this report, in which the 16-segment LV model was used. Theoretically, some of our NCCM patients could be expected to undergo significant remodeling that resulted in dysfunction of segments that are not directly affected by the primary disease. Over time, this could lead to secondary dilation, hypertrophy or deterioration of distant myocardium leading to progressive heart failure. Regional wall motion abnormalities were more severe in our patients, moreover a smaller number of NCCM patients were assessed, which should be considered as an important limitation of our study.

To better elucidate regional LV function we measured regional volume changes with RT3DE. Regional ejection fraction was severely impaired in both noncompacted and compacted LV segments. It should be noticed that tethering by neighbouring noncompacted LV segments might cause regional systolic dysfunction of compacted LV segments. However, regional ejection fraction of the compacted LV segments was independent on the number of neighbouring noncompacted LV segments. So, it seems unlikely that tethering plays a major contribution in regional dysfunction of compacted LV segments. More definite answers on dysfunction of compacted LV segments should come from strain rate studies, [25] although due to the nature of the noncompacted myocardium (with a very difficult fibre orientation) the calculation of regional deformation will be very difficult. In addition, it is impossible to trace the true endocardial border in the noncompacted segments with the deep endocardial recesses. However, since the volume in the recesses is most likely completely squeezed out during systole (ejection fraction in the order of 100%) the actual regional ejection fraction

in noncompacted segments will be in reality somewhat higher. This only underscores the findings of abnormal regional ejection fraction in the compacted segments.

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No Relationship Between Left Ventricular Radial Wall Motion and Longitudinal Velocity and The Extent and Severity of Noncompaction Cardiomyopathy

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ABSTRACT

Background. Noncompaction cardiomyopathy (NCCM) is characterized by a prominent trabecular meshwork and deep intertrabecular recesses. Although systolic dysfunction is common, limited information is available on differences in wall motion of the normal compacted and noncompacted segments. The purpose of this study was to assess radial wall motion and longitudinal wall velocity in patients with NCCM, according to the extent and severity of noncompaction.

Methods. The study comprised 29 patients in sinus rhythm (age 41 ± 15 years, 15 men), who fulfilled stringent diagnostic criteria for NCCM and compared to 29 age and gender matched healthy controls. Segmental radial wall motion of all compacted and noncompacted segments was assessed with the standard visual wall motion score index and longitudinal systolic (Sm) wall velocity with tissue Doppler imaging of the mitral annulus. For each LV wall a normalized Sm value was calculated. The extent and severity of NC in each LV segment was assessed both in a qualitative and quantitative manner.

Results. Heart failure was the primary clinical presentation in half of the patients. NCCM patients had a wall motion score index of 1.68 ± 0.43 and a normalized Sm of 82 ± 20%. The total and maximal noncompaction scores were not related to the wall motion score index and the normalized Sm. NCCM patients with and without heart failure had similar total and maximal noncompaction scores.

Conclusions. In NCCM patient's radial wall motion and longitudinal LV wall velocity is impaired but not related to the extent or severity of noncompaction.

Key Words

Noncompaction cardiomyopathy, LV function, heart failure, tissue Doppler imaging

INTRODUCTION

Noncompaction of the left ventricle (LV) or noncompaction cardiomyopathy (NCCM), is a relatively new clinico-pathologic entity, first described by Engberding and Bender in 1984.[1] It is characterized by a prominent trabecular meshwork and deep intertrabecular recesses communicating with the LV cavity and is thought to be caused by an arrest of normal embryogenesis of the myocardium.[2-3] The noncompacted (NC) LV segments often show abnormal wall motion. However, NCCM may be a part of a more generalized cardiomyopathy, involving both the morphologically normal and abnormal LV segments. Unfortunately, still limited information is available on differences in wall motion of the normal compacted (C) and abnormal NC segments.[4-6] Therefore, the purpose of this study was to assess radial wall motion and longitudinal wall velocity in patients with NCCM, according to the extent and severity of NC.

METHODS

Study population

The study comprised 29 consecutive patients in sinus rhythm (age 41 ± 15 years, 15 men), who fulfilled the following stringent diagnostic criteria for NCCM, as described by Jenni et al.[7]

1. An excessively thickened LV myocardial wall with a two-layered structure comprising a C layer on the epicardial side and a NC layer of prominent trabeculations and deep intertrabecular recesses on the endocardial side (Figure 1).
2. A NC/C myocardial thickness ratio > 2 measured at the moment of maximal thickness in end-systole at the parasternal short axis (Figure 1).
3. Color-Doppler evidence of deep intertrabecular recesses in communication with the LV cavity.
4. Absence of coexisting cardiac anomalies (eg hypertension, coronary artery disease, valvular or congenital heart disease).

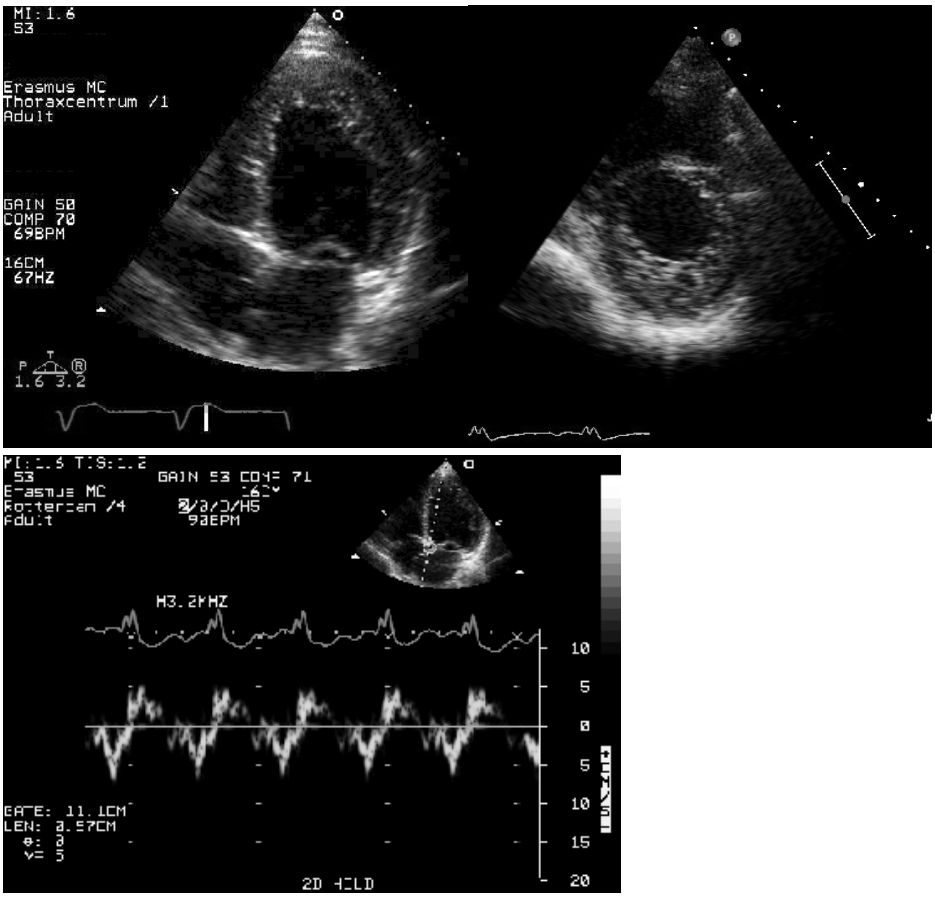

Figure 1. Echocardiographic features of a 58-years-old male with chronic heart failure due to familial noncompaction cardiomyopathy; (a) the apical 4-chamber view shows extensive trabeculations, especially in the apical and lateral LV walls. (b) The parasternal short axis view in end-systole, the NC/C ratio is >2 (respectively dashed line and small bar). (c) Low septal Sm (normal value 8.3 ± 1.5 cm/s).

Radial LV wall motion

According to the recommendations of the American Heart Association on standardized myocardial segmentation and nomenclature for tomographic imaging of the heart, a 17-segment model was used[8] Radial wall motion of all C and NC LV segments was assessed using the standard wall motion score (1 = normal motion, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic). Global LV function was subsequently expressed in terms of a wall motion score index. No measurements of LV volumes and ejection fraction were made because of the inherent problem to identify the endocardial border in the presence hypertrabeculation.

Longitudinal LV wall motion

Tissue Doppler imaging was applied by placing the sample volume at the side of the mitral annulus in apical 4, 2, and 3-chamber views. Gain and filter settings were adjusted as needed to eliminate background noises and to allow for a clear tissue signal. To acquire the highest tissue velocities the angle between the Doppler beam and the longitudinal motion of the investigated structure was adjusted to a minimal level. The systolic velocities of the mitral annulus (Sm) were recorded end-expiratory at a sweep speed of 75 or 100 mm/s and measured using electronic calipers with EnConcert software (Philips, Best, and The Netherlands). For each patient, the average of three measurements was calculated. Normal Sm values for the posteroseptal (8.3 ± 1.5 cm/s), anterolateral (9.4 ± 0.6 cm/s), anterior (8.8 ± 1.6 cm/s), inferior (9.1 ± 1.8 cm/s), inferolateral (9.6 ± 0.6 cm/s), and anteroseptal (7.3 ± 1.3 cm/s) LV walls were derived from 29 for age and gender matched healthy controls (mean age 43 ± 7 year, 15 men) without hypertension or diabetes, and with normal left atrial and LV function and morphology. Subsequently, for each LV wall a normalized Sm value was calculated as: wall specific Sm in NCCM patient / wall specific Sm in control subjects x 100%.

Extent and severity of noncompaction

The extent and severity of NC in each LV segment was assessed quantitatively by measuring the NC and C myocardial wall thickness with electronic calipers. A severity score was calculated for each LV segment by one experienced observer (KC): 2 points were given if noncompaction was clear with prominent trabeculations present (NC/C ratio ≥2), 1 point was given if prominent trabeculations were present but not fulfilling the Jenni criteria (NC/C ratio >1.0 but <2.0). In addition, from these quantitative measurements the most prominent noncompacted segment with the highest (i.e. maximal) NC/C ratio was identified in each of the 6 individual LV walls (excluding the apical cap).

The data are collected and analyzed in accordance with hospital institutional review board policies.

Statistical analysis

Descriptive data for continuous variables are presented as mean ± SD. Continuous data were compared with the Student *t* test. Linear regression analysis with Pearson's correlation was performed to examine the relationship between the radial and longitudinal LV wall motion and the extent and the severity of noncompaction. A 2-sided P value <0.05 was considered statistically significant. For all analysis, commercially available software package was used (Prism 5, GraphPad Software Inc., www.graphpad.com).

Results

The clinical and echocardiographic data of the 29 patients with typical features of NCCM are summarized in Table 1. Heart failure was the primary clinical presentation in half of the patients. In the majority of the cases (n=18 (62 %), the NCCM was familial.

Table 1. Clinical and echocardiographic characteristics of all patients.

Age, years	41 ± 15
Male, n (%)	15 (52)
Presentation, n (%)	
Heart Failure	16 (55)
Arrhythmias	5 (17)
Screening	5 (17)
Other	3 (10)
NYHA, n (%)	
I	13 (45)
II	11 (38)
III	5 (17)
IV	0
Left atrium, mm	38 ± 7
LV end-diastolic diameter, mm	53 ± 7
LV end-systolic diameter, mm	40 ± 8
Interventricular septum, mm	9 ± 2
Fractional shortening, %	25 ± 9
Wall motion score index	1.68 ± 0.43
PA systolic, mm Hg	25 ± 6
Noncompacted segments, %	50 ± 15
Absolute mean Sm ± SD, cm/s	7.1 ± 1.6
Normalized mean Sm, %	82 ± 20

Values in mean ± standard deviation or numbers (%).

Radial wall motion

Interobserver agreement for segmental analysis of radial wall motion between two observers (KC and MLG) was 76 % in both noncompacted and compacted LV segments with a kappa values of 0.60 and 0.56, respectively. NCCM patients had a wall motion score index of 1.68 ± 0.43. The total and maximal NC/C ratio scores were not related to the wall motion score index (R^2 0.09 and 0.02 respectively) (Figures 2a and c).

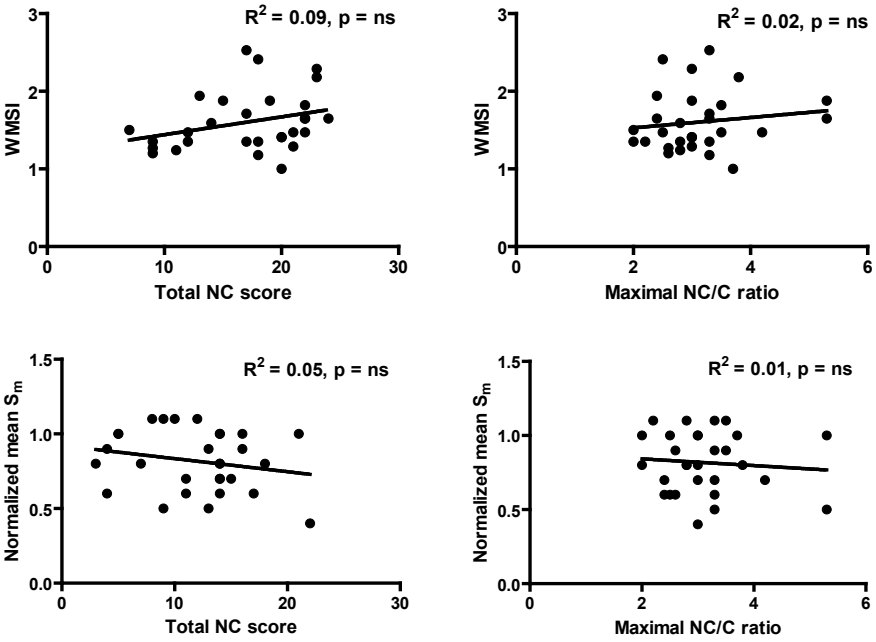

Figure 2. Relation between the wall motion score index and the total noncompaction score (2a), and the maximal noncompaction score (2b).

Longitudinal wall motion

NCCM patients had a normalized Sm of 82 ± 20%. The total and maximal NC scores were not related to the normalized Sm (R^2 0.02, 0.05 and 0.01 respectively) (Figures 3a and b and 4a and b).

NCCM patients with versus patients without heart failure

All parameters of systolic LV function (fractional shortening, wall motion score index, normalized Sm) were significantly lower in NCCM patients with heart failure (Table 2). However, no differences were seen between NCCM patients with and without heart failure in the total and maximal NC scores.

Figure 3. Relation between the mean normalized systolic mitral annular velocities (Sm) and the total noncompaction score (3a), and the maximal noncompaction score (3b).

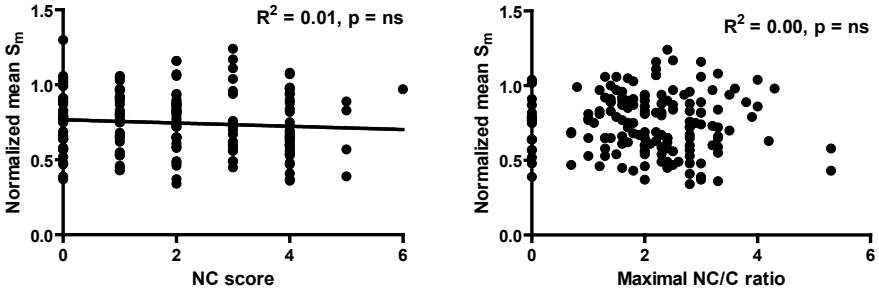

Figure 4. Relation between normalized systolic mitral annular velocities (Sm) and the total noncompaction score (4a), and the maximal noncompaction score (4b) in individual LV walls.

Table 2. Clinical and echocardiographic data of patients with and without heart failure.

	Heart failure N = 16	No heart failure N = 13	P-value
Age, years	44 ± 14	37 ± 15	ns
Male, n (%)	9 (56)	6 (46)	ns
LBBB, n (%)	3	0	ns
LVH, n (%)	2	3	ns
Left atrium, mm	38 ± 6	38 ± 7	ns
LV end-diastolic diameter, mm	55 ± 7	51 ± 8	ns
LV end-systolic diameter, mm	43 ± 8	36 ± 7	0.02
Interventricular septum, mm	10 ± 2	8 ± 2	ns
Fractional shortening, %	22 ± 8	30 ± 7	0.01
Wall motion score index,	1.75 ± 0.40	1.39 ± 0.21	0.01
PA systolic, mm Hg	28 ± 7	22 ± 4	0.02
Noncompacted segments, %	49 ± 15	52 ± 15	ns
Normalized mean Sm, %	75 ± 20	93 ± 16	0.02

Values in mean ± standard deviation or numbers (%).
LBBB: left bundle branch block, LVH: left ventricular hypertrophy on ECG.

DISCUSSION

The main finding of this study is that in patients with NCCM both radial and longitudinal LV wall motion is impaired but not related to the extent and severity of noncompaction. The extent and severity of noncompaction was also not related to systolic dysfunction or HF symptom presentation, in line with the previous publications and confirming that the cardiomyopathy in NCCM is not regional but global problem.[4, 6]

According to the last AHA scientific statement NCCM is classified as a primary, genetic cardiomyopathy.[9] The distinct phenotype of cardiomyopathy fits probably within the spectrum

of abnormalities triggered by sarcomere gene defects.[10-12] The most common presentation in NCCM patients is systolic heart failure, less frequent presentations include ventricular arrhythmias and thrombo-embolic complications, including cerebro-vascular accidents en peripheral emboli.[3, 13-15]

The NC segments in NCCM patients often show abnormal wall motion.[4] However, NCCM may be a part of a more generalized cardiomyopathy, involving both the morphologically normal and abnormal segments. As described before in other studies[4] the wall motion score index was abnormal in NCCM patients, and both the NC and C segments showed abnormal wall motion. However, our study is the first to demonstrate that there is no relation between the extent and severity of NC and wall motion. It should be noted that visually studying wall motion is problematic because of its subjective nature. However, interobserver segmental agreement was near-identical in noncompacted and compacted LV segments (76% versus 76% with kappa values of 0.60 and 0.56, respectively). [16] In our opinion, measurement of LV volumes and ejection fraction is not an alternative because of the inherent problems of the technique and the impossibility of tracing the true endocardium because of the trabecular structures. To better elucidate global and regional LV function we measured longitudinal LV function with tissue Doppler imaging.The advantage of assessment of mitral annular velocities is that the region of interest from which the measurements are taken (the mitral annulus) is not involved in the process of NC but the measurements reflect function of walls involved in the process of NC. Regional longitudinal LV function was impaired, confirming previous findings by us on regional volume changes assessed by three-dimensional echocardiography, although in the patients without heart failure it was quite normal. Importantly, regional longitudinal LV function was impaired irrespective of the extent and severity of NC. Interestingly, our study confirms recent findings by Tufekcioglu *et al.* that NCCM patients with heart failure show more abnormal parameters of systolic LV function but not a greater involvement of NC.[5] These data further support our findings. This implies also that for example the extent and severity of NCCM could not been used for prediction LV dysfunction and / or heart failure in individual patients and that the patho-physiology of the LV dysfunction / heart failure in NCCM yet to be defined.

More definite answers on dysfunction of C versus NC LV segments should come from speckle tracking echocardiographic strain and strain rate studies,[17] although due to the nature of the NC myocardium (with a very difficult fibre orientation) calculation of regional deformation may be difficult.[18-19]

Previously, the role of tissue Doppler imaging has been shown in establishing the diagnosis of HCM in patients with LVH and permitting the early identification of subclinical myocardial abnormalities of contraction and relaxation velocities, before hypertrophy is manifest.[20] This may be also relevant to the asymptomatic NCCM patients and relatives and yet to be studied.

The main limitations of this study is the small numbers of the study populations, the methods used to assess the left regional left ventricular function and absence of long –term follow up data correlating the tissue Doppler imaging and clinical outcomes.

CONCLUSIONS

In NCCM patient's radial wall motion and longitudinal LV wall velocity is impaired but not related to the extent or severity of noncompaction cardiomyopoathy. Both affected (noncompacted) and seemingly non-affected (compacted) segments contribute to reduced LV function in this cardiomyopathy. This suggests that the LV dysfunction in NCCM is not regional but global problem.

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Left Ventricular Solid Body Rotation in Noncompaction Cardiomyopathy: a Potential New Objective and Quantitative Functional Diagnostic Criterion?

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ABSTRACT

Background: Left ventricular (LV) twist originates from the interaction between myocardial fibre helices that are formed during the formation of compact myocardium in the final stages of the development of myocardial architecture. Since noncompaction cardiomyopathy (NCCM) is probably caused by intrauterine arrest of this final stage, it may be anticipated that LV twist characteristics are altered in NCCM patients, beyond that seen in patients with impaired LV function and normal compaction.

Aims: The purpose of this study was to assess LV twist characteristics in NCCM patients compared to patients with non-ischemic dilated cardiomyopathy (DCM) and normal subjects.

Methods and Results: The study population consisted of 10 patients with NCCM, 10 patients with DCM, and 10 healthy controls. LV twist was determined by speckle tracking echocardiography. In all controls and DCM patients, rotation was clockwise at the basal level and counterclockwise at the apical level. In contrast, in all NCCM patients the LV base and apex rotated in the same direction.

Conclusions: These findings suggest that 'LV solid body rotation', with near absent LV twist, may be a new sensitive and specific, objective and quantitative, functional diagnostic criterion for NCCM.

Abbreviations

LV = Left ventricle (or ventricular)
NCCM = Noncompaction cardiomyopathy
STE = speckle tracking echocardiography
DCM = Dilated cardiomyopathy

Key words

Speckle tracking echocardiography
Noncompaction cardiomyopathy
Left ventricular rotation

Left ventricular (LV) twist, defined as the wringing motion of the heart as the apex rotates with respect to the base around the LV long-axis, has an important role in LV ejection and filling [1,2]. The final stage of the development of myocardial architecture is characterized by the formation of compact myocardium and development of oppositely wound epicardial and endocardial myocardial fibre helices [3,4]. LV twist originates from the dynamic interaction between these helices. Noncompaction cardiomyopathy (NCCM) is a heterogeneous disorder probably caused by intrauterine arrest of the final stage of cardiac embryogenesis (5). It may be anticipated that LV twist characteristics are altered in NCCM patients, beyond that seen in patients with impaired LV function and normal compaction.

Recently, speckle-tracking echocardiography (STE) has been introduced as a new method for angle-independent quantification of LV twist [6]. Speckles are natural acoustic markers that occur as small and bright elements in conventional grayscale ultrasound images. The speckles are the result of constructive and destructive interference of ultrasound, back-scattered from structures smaller than a wavelength of ultrasound [7]. This gives each small area a rather unique speckle pattern that remains relatively constant from one frame to the next. Therefore, a suitable pattern-matching algorithm can identify the frame-to-frame displacement of a speckle pattern, allowing myocardial motion to be followed in two dimensions.

This study sought to assess LV twist characteristics by STE in NCCM patients compared to patients with non-ischemic dilated cardiomyopathy (DCM) and normal subjects.

METHODS

Study participants

The study population consisted of 10 patients with NCCM (mean age 41 ± 16 year, 6 men), 10 patients with DCM (mean age 47 ± 13 year, 5 men), and 10 healthy controls (mean age 43 ± 8 year, 5 men) without hypertension or diabetes, and with normal left atrial dimensions, LV dimensions, and LV function. Only subjects in sinus rhythm with good two-dimensional image quality were enrolled. An informed consent was obtained from all subjects and the institutional review board approved the study.

Diagnostic criteria for NCCM and non-ischemic DCM

NCCM patients strictly fulfilled all 4 echocardiographic diagnostic criteria for NCCM according to Jenni et al. [8]: [1] absence of co-existing cardiac abnormalities (including coronary stenoses); [2] a 2-layered structure of the LV wall, with the end-systolic ratio of noncompacted to compacted layer >2; [3] finding this structure predominantly in the apical and mid-ventricular areas; and [4] blood flow directly from the ventricular cavity into the deep intertrabecular recesses as assessed by Doppler and contrast echocardiography [9]. Hypertensive heart disease was excluded by clinical and echocardiographic examinations (septal thickness < 13 mm).

DCM was characterized by ventricular chamber enlargement and systolic dysfunction, based on current guidelines [10]. All NCCM and DCM patients had undergone coronary angiography to exclude coronary artery disease.

Echocardiography

Two-dimensional grayscale harmonic images at a frame rate of 60 to 80 frames/s were obtained in the left lateral decubitus position using a commercially available ultrasound system (iE33, Philips, Best, The Netherlands), equipped with a broadband (1-5MHz) S5-1 transducer (frequency transmitted 1.7MHz, received 3.4MHz). Measurements of LV dimensions, volumes, fractional shortening, and ejection fraction were obtained in accordance with the recommendations of the American Society of Echocardiography [11]. According to the recommendations of the American Heart Association on standardized myocardial segmentation and nomenclature for tomographic imaging of the heart, a 17-segment model was used for the assessment of regional LV wall motion [12]. Parasternal short-axis images at the basal level (showing the tips of the mitral valve leaflets), with the cross section as circular as possible, were obtained from the standard parasternal window, in which the LV and aorta were most in-line with the mitral valve tips in the middle of the sector. To obtain a short-axis image at the apical level (just proximal to the level with LV luminal obliteration at the end-systolic period) the transducer was positioned 1 or 2 intercostal spaces more caudal as previously described by us [13]. From each short-axis image, three consecutive end-expiratory cardiac cycles were acquired and transferred to a QLAB workstation (Philips, Best, The Netherlands) for off-line analysis.

Data analysis

Analysis of the datasets was performed using QLAB Advanced Quantification Software (version 6.0, Philips, Best, The Netherlands) that was recently validated against MRI for assessment of LV twist by speckle tracking [14]. To assess LV rotation, six tracking points were placed manually (after gain correction) on an end-diastolic frame in each parasternal short-axis image on the midmyocardium. In NCCM patients the tracking points were placed in the inner to midsection of the compacted part of the muscle. Tracking points were separated about 60° from each other and placed on 1 (anteroseptal insertion into the LV of the right ventricle), 3, 5, 7, 9 (inferoseptal insertion into the LV of the right ventricle) and 11 o'clock to fit the total LV circumference. LV rotation was estimated as the average angular displacement of all six tracking points relative to the center of a best-fit circle through the same tracking points. Rotation data were exported to a spreadsheet program (Excel, Microsoft Corporation, Redmond, WA) to determine LV peak rotation and time-to-peak LV rotation at the different short-axis planes, instantaneous peak LV twist (apical LV peak rotation – basal LV peak rotation), and time-to-peak LV twist. Counterclockwise rotation and twist as viewed from the apex was expressed as a positive value, clockwise rotation and twist was expressed

as a negative value. To adjust for intersubject differences in heart rate, the time sequence was normalized to a percentage of systolic duration. The end of systole was defined as the point of aortic valve closure.

Statistical Analysis

Continuous variables were presented as mean ± SD, and tested for normality. Categorical data were expressed as percentages. Variables were compared using the Student's *t* test, the Chi-square test or ANOVA when appropriate. A *P* value <0.05 was considered statistically significant. To test the intraobserver variability, measurements were repeated 4 weeks apart by the same observer (BVD) on the same echocardiographic loop for 10 randomly selected subjects. To test interobserver variability, a second observer (MLG) who was unaware of the results of the first measurements, performed repeated measurements on the same randomly selected subjects. Variability was calculated as the mean percent error, derived as the absolute difference between the two sets of measurements, divided by the mean of the measurements. Intraand inter-observer variability for all parameters varied from 2.1% to 6.3% and 4.2% to 8.7% respectively.

RESULTS

Subject characteristics

All clinical and traditional echocardiographic characteristics in controls, DCM and NCCM patients are shown in Table 1. Controls had a significantly shorter QRS duration, smaller LV dimensions and volumes, and higher LV fractional shortening and ejection fraction compared to NCCM and DCM patients. Regional wall motion was normal in all segments in controls (P < 0.001 vs. DCM and NCCM), none of the segments in DCM patients (P <0.001 vs. NCCM), and in 27% of the compacted, and 11% of the non-compacted segments in patients with NCCM.

LV rotation in NCCM

In all controls and DCM patients, LV rotation was clockwise at the basal level and counterclockwise at the apical level. In contrast, in all NCCM patients the LV base and apex rotated in the same direction. The LV rotated as a solid body in a clockwise direction in 7 NCCM patients, and in a counterclockwise direction in 3 NCCM patients (Figure 1). LV basal rotation (-2.7° ± 1.1° vs. -3.6° ± 2.0° vs. -3.5° ± 1.0°, P = NS) was comparable in controls, DCM patients, and the 7 NCCM patients with clockwise solid body rotation. In the 3 NCCM patients with counterclockwise solid body rotation, LV basal rotation (3.4° ± 1.8°) was significantly different from LV basal rotation in controls and DCM patients (both P <0.001). LV apical rotation was significantly lower in both NCCM patients with clockwise (-2.5° ± 1.1°, P <0.001)

Table 1. Characteristics of NCCM, DCM, and Controls

		NCCM (n = 10)	DCM (n = 10)	Controls (n = 10)
Clinical data				
Age, years		41 ± 16	47 ± 13	43 ± 8
Men, n (%)		6 (60)	5 (50)	5 (50)
QRS duration, ms		116 ± 38	117 ± 34	89 ± 8*
Bundle branch block (left/right/ aspecific), n		2 / 0 / 1	3 / 0 / 0	0 / 0 / 0
Echocardiographic data				
LV-EDD, mm		56 ± 8	67 ± 12	50 ± 6*
LV-ESD, mm		44 ± 9	55 ± 14	34 ± 6*
LV fractional shortening, %		23 ± 6	18 ± 9	32 ± 7*
LV-EDV, ml		152 ± 52	167 ± 55	115 ± 23*
LV-ESV, ml		92 ± 43	117 ± 44	44 ± 15 †
LV ejection fraction, %		38 ± 13	30 ± 9	62 ± 7 †
Regional wall motion	Compacted	Non-compacted		
Segments, n (%)	94 (55)	76 (45)	170 (100)	170 (100)
Normal, n (%)	25 (27) ††	8 (11) ††	0 (0)	170 (100) ‡
Hypokinesis, n (%)	49 (52)	46 (61)	100 (59)	0 (0) ‡
Akinesis, n (%)	20 (21)**	18 (24)**	64 (38)	0 (0) ‡
Dyskinesis, n (%)	0 (0)	4 (5)	6 (3)	0 (0)

Data are presented as mean ± SD. NCCM = noncompaction cardiomyopathy, DCM = dilated cardiomyopathy, LV = left ventricular, EDD = end-diastolic dimension, ESD = end-systolic dimension, EDV = end-diastolic volume, ESV = end-systolic volume. *P <0.05, †P <0.01, ‡P <0.001 vs. NCCM and DCM, **P <0.05, ††P <0.001 vs. DCM

and counterclockwise (4.2° ± 1.0°, P <0.05) solid body rotation, and DCM patients (2.6° ± 1.4°, P <0.001) as compared to controls (7.2° ± 2.0°). There were no differences in basal and apical time-to-peak rotation between controls, DCM, and NCCM (Table 2). Typical examples of rotation-time curves in controls, DCM and NCCM are shown in Figure 2.

LV twist in NCCM

Even though rotation at the basal and apical level was in the same direction in NCCM, there was still a small instantaneous LV twist because of differences in the degree and timing of peak rotation at the LV basal and apical level. Nevertheless, LV twist in both the NCCM patients with clockwise (-2.0° ± 0.9°) and counterclockwise solid body rotation (2.5° ± 1.0°) was significantly lower compared to DCM patients (5.4° ± 2.5°, both P <0.01) and controls (9.4° ± 3.7°, P <0.001 and <0.01, respectively).

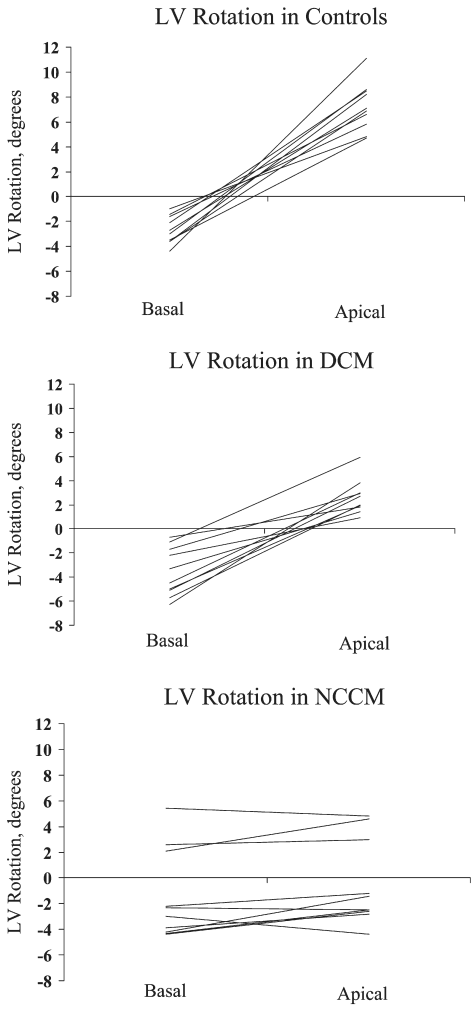

Figure 1. Basal and apical left ventricular rotation in controls (left), dilated cardiomyopathy (middle), and non-compaction cardiomyopathy (right).

Counterclockwise vs. clockwise rotation in NCCM

No significant differences in clinical or traditional echocardiographic data between NCCM patients with LV rotation in a clockwise or counterclockwise direction could be identified, although patients with counterclockwise LV rotation tended to have a shorter QRS duration (90 ± 12ms vs. 127 ± 41ms). In both NCCM patients with a left bundle branch block and the NCCM patient with aspecific intraventricular conduction delay, solid body rotation was in a clockwise direction.

Table 2. Left Ventricular Rotation and Twist in NCCM, DCM, and Controls

	NCCM (n = 10)				DCM (n = 10)	Controls (n = 10)
	Clockwise		Counterclockwise			
LV Rotation		n		n		
Basal, degrees	-3.5 ± 1.0	7	3.4 ± 1.8†‡	3	-3.6 ± 2.0	-2.7 ± 1.1
Apical, degrees	-2.5 ± 1.1†‡	7	4.2 ± 1.0**	3	2.6 ± 1.4‡	7.2 ± 2.0
LV Twist, degrees	-2.0 ± 0.9*†	2	2.5 ± 1.0*‡	8	5.4 ± 2.5**	9.4 ± 3.7
Time-to-peak LV Rotation						
Basal, %	82 ± 28		83 ± 30		91 ± 18	89 ± 19
Apical, %	93 ± 29		93 ± 30		89 ± 23	94 ± 8
Time-to-peak LV Twist, %	94 ± 12		97 ± 15		93 ± 17	93 ± 5

Data presented as mean ± SD. Time-to-peak LV rotation and time-to-peak LV twist as a percentage of duration of systole. Abbreviations are as in Table 1. *P <0.01, ††P <0.001 vs. DCM, **P <0.05, †P <0.01, ‡P <0.001 vs. Controls

DISCUSSION

The main findings of our study are 1) in patients with DCM LV basal rotation is clockwise and LV apical rotation is counterclockwise as in normal controls but LV apical rotation is of a lesser magnitude (LV twist is less), and 2) in NCCM patients LV apical rotation is also of a lesser magnitude but in contrast to normal controls and DCM, LV basal and LV apical rotation are in the same direction ('LV solid body rotation').

The development of the myocardial architecture of the heart wall passes through several distinct steps [15]. In the early tubular heart, the myocardium has an epithelial nature with just a few layers of cells. The next step is the cavity-specific formation of sheet-like myocardial protrusions into the lumen, so-called trabeculations. These early trabeculations effectively increase the myocardial surface area, enabling the myocardial mass to increase in the absence of a coronary circulation. Currently, there is no consensus on what happens to this trabecular layer. Although some state that the trabeculations become compacted to form the compact wall of the ventricular mass [15], others claim that this is most unlikely [16], supported by a lack of proof for the former theory. Anyway, the final stage of the development of myocardial architecture is characterized by the development of a multilayered spiral system in the compact myocardium, coinciding with invasion of the coronary vascular system from the epicardium [3,4]. The different layers of the spiral system can be revealed by the technique of peeling. It can be seen that there is an ordered structure for the ventricular mass, albeit that the aggregated myocytes do not form clearly separable fibres, nor are the layers isolated by supporting scaffolds of connective tissue [17]. In the matured heart, the ventricular mass is arranged in the form of a modified blood vessel, with each myocyte anchored to its neighbor within a three-dimensional myocardial mesh [18]. Streeter et al. [19] introduced the myocyte helix angle, representing the angle between the myocytes, as projected onto

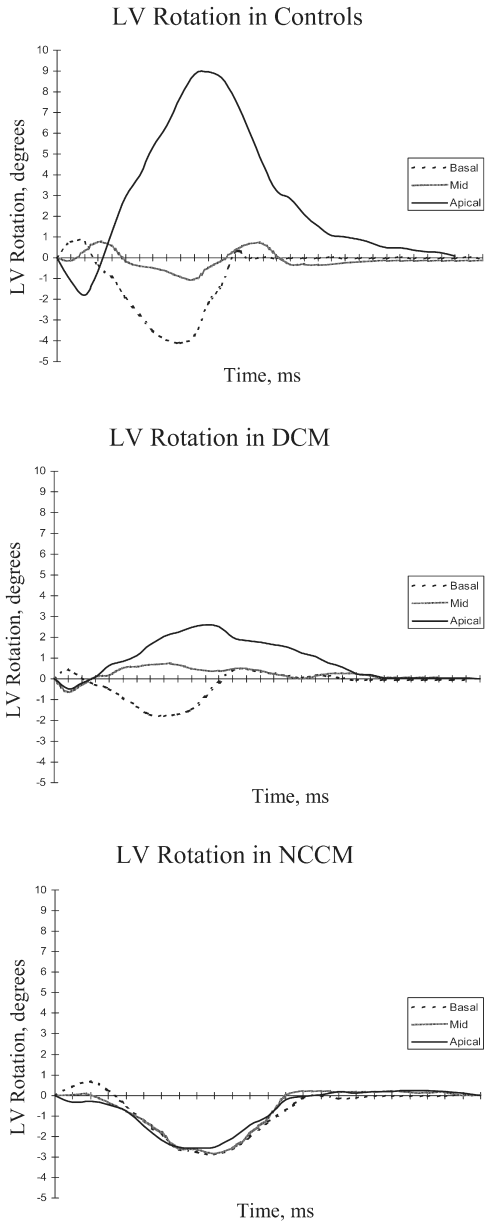

Figure 2. Typical examples of rotation-time curves during one complete cardiac cycle in controls (left), dilated cardiomyopathy (middle), and noncompaction cardiomyopathy (right).

the circumferential-longitudinal plane, and the circumferential axis. The myocyte helix angle changes continuously from the subendocardium to the subepicardium, typically ranging from +60° at the subendocardium to -60° at the subepicardium [20]. LV twist originates from the dynamic interaction between the oppositely wound subepicardial and subendocardial

myocyte helices [21]. Furthermore, transmural oriented myocytes may be necessary to ensure stability of the shape of the ventricular walls throughout this twisting deformation (17). The direction of LV twist is governed by the epicardial myocytes, mainly owing to their longer arm of movement [22]. Mathematical models have shown that this counterdirectional helical arrangement of muscle fibres in the heart is energetically efficient and is important for equal redistribution of stresses and strain in the heart [23].

NCCM is a heterogeneous disorder probably caused by intra-uterine arrest of compaction of the myocardial fibres during embryogenesis [5]. Due to this arrest of myocardial compaction it may be anticipated that the characteristic spiral helix will also not develop. Absence of the endocardial helix would lead to increased clockwise basal and counterclockwise apical LV rotation, due to loss of the counteracting activity. On the other hand, absence of the epicardial helix would lead to counterclockwise basal and clockwise apical LV rotation. Therefore, based on our results, the assumption has to be made that both helices must be involved to a similar extent in NCCM. LV solid body rotation with near absent LV twist may be one of the main mechanisms of impaired LV function in NCCM patients. In healthy neonates with an immature heart LV solid body rotation has also been described with basal and apical rotation being in a counterclockwise direction [24]. Why some of our patients show clockwise and others counterclockwise LV solid body rotation remains unclear at this moment. Nevertheless, it is striking that all patients who showed the neonatal form of LV solid body (counterclockwise) rotation had no evidence for abnormal LV conduction, evidenced by a normal QRS duration.

At present, there is no consensus on how to precisely define NCCM. Recently, Kohli et al. [25] studied 199 patients referred to a dedicated heart failure clinic. There was an unexpectedly high percentage of patients that could be identified as having NCCM: 23.6% of the patients fulfilled one or more of the echocardiographic criteria currently used for the identification of NCCM [8,26,27]. This high percentage suggests that current diagnostic criteria may be too sensitive. Furthermore, there was a poor correlation between the echocardiographic definitions, with only 29.8% of the identified NCCM patients fulfilling all three criteria. We propose 'LV solid body rotation' as a new sensitive and specific, objective and quantitative, *functional* criterion, supplementing the classic subjective *morphologic* NCCM criteria (8,26,27).

It should be noticed that others, in contrast to our findings, have occasionally described LV solid body rotation in DCM patients [28]. Although it cannot be excluded that in these patients the diagnosis NCCM was overlooked, the true specificity of LV solid body rotation for the diagnosis of NCCM may be lower than that in our study. Other studies should confirm our data before this new criterion should be used clinically.

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Diagnostic Value of Rigid Body Rotation in Noncompaction Cardiomyopathy

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ABSTRACT

Background: The diagnosis of noncompaction cardiomyopathy (NCCM) remains subject to controversy. Since NCCM is probably caused by an intra-uterine arrest of the myocardial fibre compaction during embryogenesis, it may be anticipated that the myocardial fibre helices, normally causing left ventricular (LV) twist, will also not develop properly. The resultant LV rigid body rotation (RBR) may strengthen the diagnosis of NCCM. The purpose of the current study was to explore the diagnostic value of RBR in a large group of patients with prominent trabeculations.

Methods: The study comprised 15 dilated cardiomyopathy (DCM) patients, 52 healthy subjects, 52 patients with prominent trabeculations, of whom a clinical expert in NCCM defined 34 as having NCCM. LV rotation patterns as determined by speckle tracking echocardiography and defined as 1A) completely normal rotation: initial counterclockwise basal, and clockwise apical rotation, followed by end-systolic clockwise basal, and counterclockwise apical rotation, 1B) partly normal rotation: normal end-systolic rotation, but absence of initial rotation in the other direction, and 2) RBR: rotation at the basal and apical level predominantly in the same direction.

Results: The majority of normal subjects had LV rotation pattern 1A (98%), whereas the 18 subjects with hypertrabeculation not fulfilling diagnostic criteria for NCCM predominantly had pattern 1B (71%), and the 34 NCCM patients pattern 2 (88%). None of the DCM patients showed RBR. Sensitivity and specificity of RBR for differentiating NCCM from "hypertrabeculation" were 88% and 78%, respectively.

Conclusions: RBR is an objective, quantitative, and reproducible functional criterion with good predictive value for the diagnosis of NCCM as determined by expert opinion.

Key words

Speckle Tracking Echocardiography
Noncompaction cardiomyopathy
Diagnosis
Cardiac mechanics

Abbreviations

NCCM =	noncompaction cardiomyopathy
LV =	left ventricle (or ventricular)
RBR =	rigid body rotation
STE =	speckle tracking echocardiography
Rot_{max} =	left ventricular peak systolic rotation during ejection
$Twist_{max}$ =	instantaneous left ventricular peak systolic twist

Noncompaction cardiomyopathy (NCCM) is a myocardial disorder characterized by excessive and prominent trabeculations associated with deep recesses that communicate with the left ventricular (LV) cavity but not the coronary circulation.[1] Although NCCM was included in the 2006 World Health Organization classification of primary cardiomyopathies,[2] it remains subject to controversy owing to lack of consensus on its aetiology, pathophysiology, diagnosis, and management.[3] The normal LV consists of obliquely oriented muscle fibres that vary from a smaller-radius, right-handed helix at the subendocardium to a larger-radius, left-handed helix at the subepicardium.[4] The functional consequence of this three-dimensional helical structure is a cyclic systolic twisting deformation, resulting from opposite clockwise basal rotation and counterclockwise apical rotation.[5] LV twist plays a pivotal role in the mechanical efficiency of the heart, making it possible that only 15% fibre shortening results in a 60% reduction in LV volume.[6] Changes in LV twist have been reported in a variety of cardiac diseases.[7-8] Our group recently reported nearly absent LV twist in a small group of NCCM patients due to rotation of the basal and apical ends of the LV in the same direction, leading to rigid body rotation (RBR) with decreased circumferential-longitudinal shear deformation. We hypothesized that RBR may be a new objective functional diagnostic criterion for NCCM.[9] The purpose of the current study was to further explore the diagnostic value of RBR in a larger group of patients with prominent trabeculations.

METHODS

Study participants

The study population consisted of 30 patients diagnosed before 2008 with NCCM by expert opinion (of whom 10 were included in a previous study on LV twist in NCCM),[9] and 22 consecutive patients with prominent trabeculations (visual estimated end-systolic ratio of noncompacted to compacted layer >1.5) who underwent echocardiography in 2008, identified by one physician highly experienced with echocardiography (MLG). All patients were in sinus rhythm and had good echocardiographic image quality that allowed for complete segmental assessment of LV rotation at both the basal and apical LV level. During the enrolment of the 52 patients, 18 other patients (26%) were excluded because of suboptimal echocardiographic image quality not fulfilling this criterion. None of the patients had known coronary artery disease (excluded by coronary angiography), hypertension or significant valvular heart disease. Patients were compared to 52 healthy – for age and gender matched – control subjects without hypertension or diabetes, and with normal left atrial dimensions, LV dimensions, and LV function. Furthermore, 15 dilated cardiomyopathy (DCM) patients with LV volumes and ejection fraction comparable to the NCCM patients were included as well. All subjects gave informed consent and the institutional review board approved the study.

Diagnostic criteria for NCCM

Two methods were used in order to diagnose NCCM in the 52 patients. The first method was based on the echocardiographic diagnostic criteria for NCCM according to Jenni et al.[10]: [1] a 2-layered structure of the LV wall, with the end-systolic ratio of non-compacted to compacted layer >2 (Figure 1); [2] finding this structure predominantly in the apical and mid-ventricular areas; and [3] blood flow directly from the ventricular cavity into the deep intertrabecular recesses as assessed by Doppler echocardiography. The noncompacted to compacted ratio was quantitatively assessed, with help from electronic calipers, by one observer (MLG) blinded to the results of LV twist and the expert opinion. In the other method the diagnosis of NCCM was based on expert opinion. One clinical expert in NCCM diagnosis (KC) used in addition to the Jenni criteria also the Stöllberger criteria,[11] information on the history of the patient (including the family history) and magnetic resonance imaging data, but was also blinded to the LV twist results. The 30 patients with a previously established diagnosis of NCCM were revised according to these methods as well.

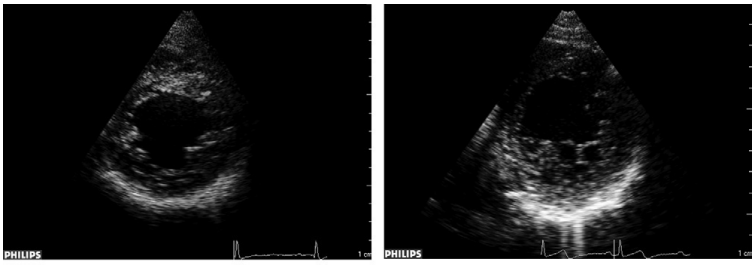

Figure 1. Example of echocardiographic short-axis images of both subjects with hypertrabeculation and noncompaction cardiomyopathy (NCCM) patients.

Echocardiography

Two-dimensional grayscale harmonic images were obtained in the left lateral decubitus position using a commercially available ultrasound system (iE33, Philips, Best, The Netherlands), equipped with a broadband (1-5MHz) S5-1 transducer (frequency transmitted 1.7MHz, received 3.4MHz). All echocardiographic measurements were averaged from three heartbeats. Measurements of LV dimensions, volumes, fractional shortening, and ejection fraction were obtained in accordance with the recommendations of the American Society of Echocardiography.[12] The LV was divided into 9 segments to describe the location of noncompacted segments: one apical, four mid-ventricular and four basal segments (with an anterior, inferoseptal, anterolateral and inferior segment each).[10]

To optimize STE, images were obtained at a frame rate of 60 to 80 frames/s. Parasternal short-axis images at the LV basal level (showing the tips of the mitral valve leaflets) with the cross section as circular as possible were obtained from the standard parasternal position,

defined as the long-axis position in which the LV and aorta were most in-line with the mitral valve tips in the middle of the sector. To obtain a short-axis image at the LV apical level (just proximal to the level with end-systolic LV luminal obliteration) the transducer was positioned 1 or 2 intercostal spaces more caudal as previously described by us.[13] From each short-axis image, three consecutive end-expiratory cardiac cycles were acquired and transferred to a QLAB workstation (Philips, Best, The Netherlands) for off-line analysis.

Speckle tracking analysis

Analysis of the datasets was performed using QLAB Advanced Quantification Software version 6.0 (Philips, Best, The Netherlands), which was recently validated against magnetic resonance imaging for assessment of LV twist.[14] To assess LV rotation, six tracking points were placed manually (after gain correction) on the mid-myocardium on an end-diastolic frame in each parasternal short-axis image. In areas of hypertrabeculation the tracking points were placed in the inner to midsection of the compacted part of the muscle. Tracking points were separated about 60° from each other and placed on 1 (30°, anteroseptal insertion into the LV of the right ventricle), 3 (90°), 5 (150°), 7 (210°), 9 (270°, inferoseptal insertion into the LV of the right ventricle), and 11 (330°) o'clock to fit the total LV circumference. After positioning the tracking points, the program tracked these points on a frame-by-frame basis by use of a least squares global affine transformation. The rotational component of this affine transformation was then used to generate rotational profiles.

Data were exported to a spreadsheet program (Excel, Microsoft Corporation, Redmond, WA) to determine LV peak systolic rotation during the isovolumic contraction phase (Rot_{early}), LV peak systolic rotation during ejection (Rot_{max}), and instantaneous LV peak systolic twist ($Twist_{max}$, defined as the maximal value of instantaneous apical systolic rotation – basal systolic rotation). Counterclockwise rotation and twist as viewed from the apex was expressed as a positive value, clockwise rotation and twist was expressed as a negative value. End-systole was defined as the point of aortic valve closure. In the current study, different LV rotation patterns were recognized (Figure 2):

1) Normal rotation

A. Completely normal rotation, characterized by initial counterclockwise and end-systolic clockwise basal rotation, and initial clockwise and end-systolic counterclockwise apical rotation

B. Partly normal rotation, characterized by end-systolic clockwise basal rotation, and end-systolic counterclockwise apical rotation, but absence of either or both initial counterclockwise basal rotation or initial clockwise apical rotation

2) RBR

A. Clockwise RBR, characterized by clockwise basal and apical rotation throughout systole

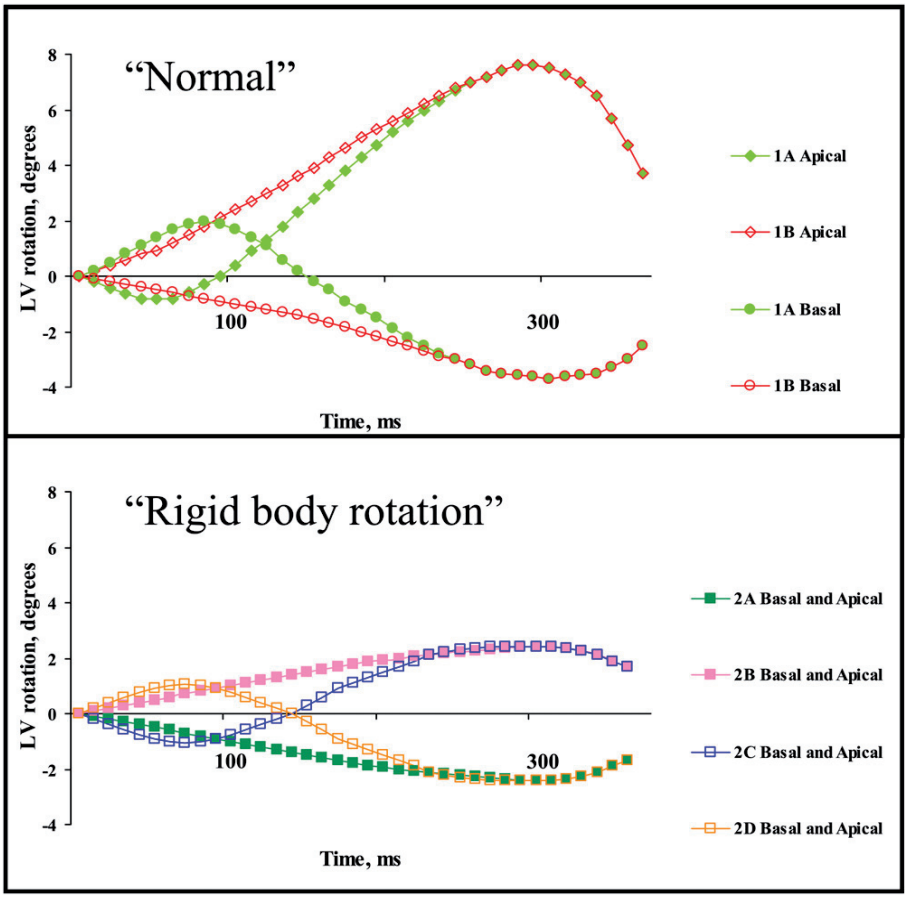

Figure 2. Schematic graphs of left ventricular rotation patterns in healthy controls, subjects with hypertrabeculation, and noncompaction cardiomyopathy patients. LV = left ventricular

B. Counterclockwise RBR, characterized by counterclockwise basal and apical rotation throughout systole
C. Initial clockwise, followed by counterclockwise RBR.
D. Initial counterclockwise, followed by clockwise RBR.

Statistical Analysis

Measurements are presented as mean ± SD. Variables were compared using Student's *t* test, or Chi-square test when appropriate. A P value < .05 was considered statistically significant. Intraobserver and interobserver variability for LV twist were 5% ± 4% and 9% ± 4%, respectively, in-line with our previous report on the feasibility of LV twist measurement using speckle tracking echocardiography.[15] To test the reproducibility of LV rotation patterns in the current study, speckle tracking analysis was repeated by a different physician (FK) in all patients. There was 100% agreement on the observed LV rotation patterns.

RESULTS

Characteristics of the study population

Revision of the 30 patients with a previously established diagnosis of NCCM, led to confirmation of the diagnosis in 29 by the Jenni criteria and in all 30 by expert opinion. Of the 22 patients with various degrees of hypertrabeculation, 7 were classified as having NCCM by the Jenni criteria, and 4 by expert opinion. The remaining patients were classified as "subjects with hypertrabeculation". So, in total 36 patients were diagnosed as NCCM by the Jenni criteria, and 34 by expert opinion. In four patients the expert diagnosis was discrepant from the Jenni criteria, based on information about race, family history, LV function, and results of magnetic resonance imaging. Clinical and conventional echocardiographic characteristics of the study population are shown in Table 1.

Table 1. Characteristics of the study population

	NCCM		Hypertrabeculation		DCM	Controls
	Jenni criteria (n = 36)	Expert opinion (n = 34)	Jenni criteria (n = 16)	Expert opinion (n = 18)	(n = 15)	(n = 52)
Clinical data						
Age, years	43 ± 15	44 ± 14	48 ± 18	46 ± 19	41 ± 14	44 ± 15
Men, n (%)	19 (53)	18 (55)	8 (50)	9 (47)	7 (47)	27 (52)
QRS duration, ms	105 ± 23	106 ± 27	111 ± 26	108 ± 25	115 ± 30	88 ± 8‡
Bundle branch block (left/ right/aspecific), n	5 / 0 / 2	5 / 0 / 2	3 / 0 / 2	3 / 0 / 2	4 / 0 / 1	0 / 0 / 0
Echocardiographic data						
LV-EDD, mm	57 ± 8	57 ± 7	53 ± 6	54 ± 7	63 ± 4	50 ± 6*
LV-ESD, mm	45 ± 8	45 ± 9	40 ± 10	41 ± 10	50 ± 8	34 ± 6†
LV fractional shortening, %	22 ± 7	22 ± 8	24 ± 8	24 ± 9	21 ± 6	32 ± 7‡
LV-EDV, ml	149 ± 50	150 ± 53	146 ± 53	145 ± 48	160 ± 55	115 ± 23‡
LV-ESV, ml	90 ± 42	89 ± 41	81 ± 45	82 ± 46	110 ± 45	44 ± 15‡
LV ejection fraction, %	42 ± 14	40 ± 12	44 ± 17	45 ± 18	38 ± 9	62 ± 7‡
Ratio of non-compacted to compacted layer	2.6 ± 0.5	2.6 ± 0.5	1.7 ± 0.3	1.7 ± 0.3	NA	NA
Non-compacted segments, n	3.9 ± 2.5	3.8 ± 2.4	2.9 ± 1.6	3.0 ± 1.8	0 ± 0	0 ± 0
Absolute $Twist_{max}$, degree	3.9 ± 2.2§	4.1 ± 2.2§	7.1 ± 4.9	6.9 ± 5.4	6.1 ± 2.3	10.1 ± 2.3‡

Data are presented as mean ± SD. NCCM = noncompaction cardiomyopathy, DCM = dilated cardiomyopathy, LV = left ventricular, EDD = end-diastolic dimension, ESD = end-systolic dimension, EDV = end-diastolic volume, ESV = end-systolic volume, NA = not available, $Twist_{max}$ = left ventricular peak systolic twist. *P <0.05, †P <0.01, ‡P <0.001 vs. NCCM and hypertrabeculation, §P <0.05 vs. hypertrabeculation

LV rotation and twist in normal subjects and DCM patients

In all but one normal subject initial counterclockwise rotation at the LV basal level and initial clockwise rotation at the LV apical level could be identified (basal Rot_{early} 2.0 ± 1.2 degree, and apical Rot_{early} -0.8 ± 0.6 degree, respectively). Furthermore, peak end-systolic rotation was always in a clockwise direction at the LV basal, and in a counterclockwise direction at the LV apical level (basal Rot_{max} -3.6 ± 1.8 degree, apical Rot_{max} 7.2 ± 2.9 degree, respectively), leading to a $Twist_{max}$ of 10.1 ± 2.3 degree. Although initial counterclockwise rotation at the LV basal level and initial clockwise rotation at the LV apical level was absent in 9 (60%) DCM patients (LV rotation pattern 1B), none of the DCM patients showed RBR (Table 2).

Table 2. Left ventricular rotation patterns in noncompaction cardiomyopathy, hypertrabeculation, dilated cardiomyopathy and controls

Rotation pattern		Jenni criteria[7]		Expert opinion		DCM	Controls
		NCCM (n = 36)	Hypertrabeculation (n = 16)	NCCM (n = 34)	Hypertrabeculation (n = 18)	(n = 15)	(n = 52)
Normal	1A	0	4	0	4	6	51
	1B	6	8	4	10	9	1
	Total	6	12	4	14	15	52
Rigid body rotation	2A	13	1	13	1	0	0
	2B	2	0	2	0	0	0
	2C	1	1	1	1	0	0
	2D	14	2	14	2	0	0
	Total	30	4	30	4	0	0

Rotation patterns as described in methods. NCCM = noncompaction cardiomyopathy, DCM = dilated cardiomyopathy

LV rotation and twist in NCCM patients and subjects with hypertrabeculation

The distribution of LV rotation patterns in NCCM patients and subjects with hypertrabeculation identified by the Jenni criteria and expert opinion, is shown in Table 2. Sensitivity of RBR for differentiating NCCM from "hypertrabeculation" was 83% vs. 88%, specificity 75% vs. 78%, positive predictive value 88% vs. 88%, negative predictive value 67% vs. 78%, and accuracy 81% vs. 85%, when the diagnosis was based on the Jenni criteria vs. expert opinion, respectively (all P = NS) (Table 3). None of the NCCM patients showed completely normal LV rotation (LV rotation pattern 1A) (Figure 3). Absence of completely normal LV rotation (in other words, presence of either LV rotation pattern 1B or RBR) had a sensitivity for differentiating NCCM from "hypertrabeculation" according to the Jenni criteria vs. the expert opinion of 100% vs. 100%, specificity of 25% vs. 22%, positive predictive value of 75% vs. 71%, negative predictive value of 100% vs. 100%, and accuracy of 77% vs. 73%, respectively (all P = NS). Even though rotation at the basal and apical level was in the same direction in the majority of NCCM patients, there was still some instantaneous LV twist

Table 3. Diagnostic value of left ventricular rigid body rotation for diagnosis of noncompaction cardiomyopathy in 52 patients with prominent trabeculations

	Jenni criteria[7]	Expert opinion
Sensitivity, %	83	88
Specificity, %	75	78
Positive predictive value, %	88	88
Negative predictive value, %	67	78
Accuracy, %	81	85

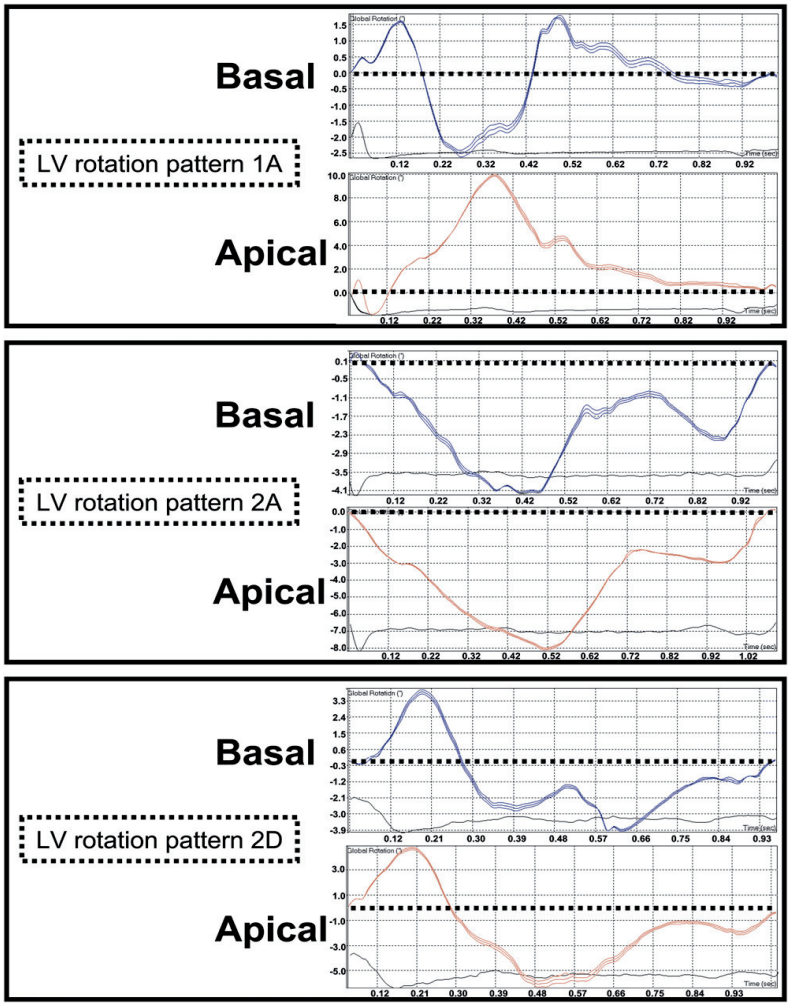

Figure 3. Examples of a normal subject with left ventricular rotation pattern 1A (upper panel), and noncompaction cardiomyopathy patients with left ventricular rotation pattern 2A (middle panel) and 2D (lower panel). The electrocardiogram is displayed at the bottom of each graph. The dotted line represents zero degrees rotation. X-axis: time in seconds, Y-axis: global rotation in degrees. LV = left ventricular

because of differences in the degree of rotation at the LV basal and apical level. Nevertheless, absolute (neglecting the clockwise or counterclockwise direction) $Twist_{max}$ was decreased in NCCM patients as compared to subjects with hypertrabeculation, both when subjects were classified according to the Jenni criteria and expert opinion (3.9 ± 2.2 vs. 7.1 ± 4.9 degree, and 4.1 ± 2.2 vs. 6.9 ± 5.4 degree, respectively, both P <0.05).

Relation of clinical and echocardiographic characteristics to LV rotation pattern

LV rotation patterns 2A and 2D (Figure 3) were relatively abundant in NCCM patients (according to Jenni criteria in 36% and 39%; according to expert opinion in 38% and 41%, respectively). LV ejection fraction was lower in NCCM patients with LV rotation pattern 2A as compared to pattern 2D (both as diagnosed by Jenni criteria and expert opinion, 34 ± 15 % vs. 44 ± 9 %, P <0.05), whereas only a trend in decreased LV twist could be identified in these patients (3.5 ± 2.5 degree vs. 4.6 ± 1.8, P <0.10). The remaining NCCM patients with RBR (2 with LV rotation pattern 2B, 1 with pattern 2C) had relatively preserved LV ejection fractions (48%, 53%, and 51%, respectively).

A diversity in LV rotation patterns was seen in NCCM patients with left bundle branch block (1B, 2A, and 2C in one, 2D in two) and subjects with hypertrabeculation and left bundle branch block (1B in two and 2D in one).

Seventeen patients had familial NCCM. There were 4 families with more than 1 member included in the study (3 families with 2 first-degree relatives, and 1 family with 3 first degree-relatives). All these latter 9 patients had LV rotation pattern 2D. The remaining 8 patients with familial NCCM who did not have any first-degree relatives included in the study showed diverse LV rotation patterns (6 with 2A, 1 with 2B, and 1 with 2C).

DISCUSSION

Echocardiography is currently the reference standard for the diagnosis of NCCM,[16] although this recently has been doubted.[17] The most important conclusion of the present study is that RBR is an objective, quantitative, and reproducible functional criterion with good predictive value for the diagnosis of NCCM as established by expert opinion.

Normal LV rotation and twist

LV rotation and twist in the normal heart is characterized by an early systolic counterclockwise basal rotation and clockwise apical rotation, and an end-systolic peak rotation in a clockwise direction at the LV basal level and a counterclockwise direction at the LV apical level. This twisting deformation is supposed to be a result of the dynamic interaction of oppositely wound subepicardial and subendocardial myocyte helices.[18] The direction of peak systolic

LV twist is governed by the subepicardial fibres, mainly owing to their longer arm of movement.[19] The early systolic LV twist in the opposite direction is explained by the predominant mechanical activity that develops along the subendocardial helix of myocardial fibres during isovolumic contraction. The shortening of this subendocardial helix is accompanied with stretching of the outer subepicardial fibres.[20-21] This biphasic deformation satisfies isovolumic mechanics: shortening in one direction is accompanied with stretching in the other direction.[22] Furthermore, stretching of myofibres during isovolumic contraction is important in initiating a "stretch activation response," an intrinsic length-sensing mechanism that allows muscle to adjust the force and
duration of subsequent shortening.[23] Peak systolic LV twist plays a pivotal role in the mechanical efficiency of the heart, making it possible that only 15% fibre shortening results in a 60% reduction in LV volume.[6] Furthermore, mathematical models have shown that the counterdirectional arrangement of muscle fibres in the heart is energetically efficient and is important for equal redistribution of stresses and strain in the heart.[24] Finally, rapid diastolic LV untwisting appears to be a manifestation of elastic recoil, critically linking systolic contraction to diastolic filling.[25] In the current study, all but one of the healthy controls showed this normal LV rotation pattern. Most subjects with hypertrabeculation, not classified as NCCM by either the Jenni criteria or expert opinion, showed LV rotation pattern 1B, characterized by normal end-systolic clockwise basal rotation and end-systolic counterclockwise apical rotation, but absence of either or both initial counterclockwise basal rotation or initial clockwise apical rotation. Hypertrabeculation in these patients may prevent proper functioning of the subendocardial helix of myofibres that, as mentioned before, normally causes the early systolic oppositely directed LV twist. Patients diagnosed with NCCM never showed entirely normal LV rotation, and the vast majority had RBR (predominantly instantaneous rotation at the basal and apical level in the same direction).

Pathophysiology of RBR in NCCM

The development of the myocardial architecture of the heart wall passes through several distinct steps.[26] In the early tubular heart, the myocardium has an epithelial nature with just a few layers of cells. The next step is the cavity-specific formation of sheet-like myocardial protrusions into the lumen, so-called trabeculations. These early trabeculations effectively increase the myocardial surface area, enabling the myocardial mass to increase in the absence of a coronary circulation. Currently, there is no consensus on what happens to this trabecular layer. Although some state that the trabeculations become compacted to form the compact wall of the ventricular mass,[26] others claim that this is most unlikely,[27] supported by a lack of proof for the former theory. Anyway, the final stage of the development of myocardial architecture is characterized by the development of a multilayered helical system in the compact myocardium, coinciding with invasion of the coronary vascular system from the epicardium. Since NCCM is probably caused by an intra-uterine arrest of the compaction

of the myocardial fibres during embryogenesis,[16] it may be anticipated that the myocardial fibre helices, and thus LV twist, will also not develop properly. Currently, there is no formal evidence from pathoanatomical studies in favour of or against this hypothesis. Notomi et al. showed that infants have RBR due to basal rotation in an abnormal counterclockwise direction.[28] Furthermore, in a pilot study we found RBR, with nearly absent LV twist, in all 10 investigated NCCM patients, whereas none of 10 dilated cardiomyopathy patients included in the same study showed RBR. This RBR represents systolic basal and apical LV rotation in the same direction and may be related to the absence or abnormal functioning of the myocardial fibre helices.[9] In the present study, more NCCM patients were included, and after analyses of the LV rotation patterns in these patients, two distinct patterns of RBR could be identified. One pattern was characterized by RBR in one direction (either clockor counterclockwise) throughout the cardiac cycle, whereas in the other pattern there was RBR in one direction (either clockor counterclockwise) in early systole, followed by RBR in the opposite direction until end-systole. No clinical or echocardiographic characteristics related to either clockwise or counterclockwise RBR could be identified. LV ejection fraction was comparable between NCCM patients and subjects with hypertrabeculation, suggesting that RBR may be related specifically to the pathophysiology of NCCM and is not just a non-specific marker of myocardial dysfunction. Also, since NCCM patients have decreased LV twist but a comparable LV ejection fraction, it seems that there must be increased deformation in another direction in NCCM patients. Further studies are needed to test this hypothesis.

Interestingly, all familial NCCM patients showed RBR. Since the diagnosis of NCCM seems most certain in patients with familial NCCM, this finding underscores the excellent sensitivity of RBR for NCCM. Of additional interest is our finding that first-degree NCCM relatives from the same family had identical LV rotation patterns, suggesting a genetic-functional relationship in NCCM.

Diagnostic echocardiographic criteria

In the earliest proposed echocardiographic criteria for diagnosis of NCCM, Chin et al.[29] suggested assessment of the *end-diastolic* X to Y ratio, where X is the distance from the epicardial surface to the trough of the trabecular recess, and Y is the distance from the epicardial surface to the peak of the trabeculation. The subsequent criteria proposed by Jenni et al.[10] rely on measurement of the maximal *end-systolic* thickness of the noncompacted layer and compacted layer of the myocardium. Stöllberger et al.[11, 30] highlighted the difficulties in differentiating between papillary muscles, aberrant bands, false tendons, and trabeculations. According to Stöllberger et al. the presence of more than three coarse, prominent trabeculations located apically to the papillary muscles, characterizes NCCM. By definition these trabeculations should move synchronously with the myocardium, surrounded by intertrabecular spaces perfused from the ventricular cavity, and should not be connected to the papillary muscles.[11] In the current study primarily the "Jenni criteria" were used, since these

criteria are most often used in daily clinical practice in our department. From the current study it may be concluded that RBR has a good predictive value for the diagnosis of NCCM as established by either the "Jenni criteria" or expert opinion based on multiple criteria. Of note, patients with ischemic cardiomyopathy were not included in this study. Patients with apical infarction may show RBR as well (unpublished data). However, these patients usually show other clinical abnormalities, such as angina or wall motion abnormalities, that allow differentiation from NCCM. Conversely, absence of RBR may raise questions about the correct diagnosis of NCCM. The advantage of RBR over currently used diagnostic criteria for NCCM[10-11, 29] is that it is objective, quantitative, and extremely reproducible. In addition to the more subjective criteria by Jenni et al.[10] and Stöllberger et al.[11, 30] we suggest that RBR, as a *functional* diagnostic criterion, should be present for a definite diagnosis of NCCM, although the *morphologic* criteria should be fulfilled as well.

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Diagnostic uncertainties and future perspectives in noncompaction cardiomyopathy

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ABSTRACT

***Background*—**Noncompaction cardiomyopathy (NCCM) is a new pathoanatomic entity, disputably believed to result from abnormal arrest in embryonic endomyocardial morphogenesis. During almost three decades of research of NCCM, more knowledge has developed alongside diagnostic uncertainties and precise definition. In this article, we present these uncertainties and provide perspectives on how to overcome these challenges.

***Areas covered*—**the uncertainties, about NCCM regarding nomenclature, classification, pathophysiology, and limitations of the current diagnostic criteria will be reviewed. The application of newer imaging modalities will be contrasted in relation to conventional assessments. Finally, future aspirations will be outlined out providing a more thoughtful appraisal towards NCCM diagnosis.

***Expert opinion*—**our current understanding of NCCM is limited by heterogeneity of disease spectrum and phenotype-genotype overlap with other cardiac anomalies. Selection bias, small sampling, and retrospective nature limit most of published studies on NCCM. There are three main research fields related to NCCM: pathoanatomic studies, imaging studies, and genetic screening. Besides conventional echocardiography, imaging should include both structural (cardiac MRI, contrast and 3D echocardiography) and functional diagnosis using deformation imaging. These research aspects should be integrated in a collaborative international registries of nonselective populations in order to achieve better understanding and optimal diagnosis of NCCM. Moreover, it holds the promise of the detection of earlier stages of disease. A clear pathoanatomic cut-off definition of NCCM should be the initial step towards uniform imaging diagnosis.

Key Words Noncompaction, cardiomyopathy, left ventricle, function, heart failure, echocardiography, magnetic resonance imaging

INTRODUCTION

Noncompaction of the left ventricle (LV) or noncompaction cardiomyopathy (NCCM), is a relatively new clinico-pathologic entity, first described by Engberding and Bender in 1984[1]. It is characterized by a prominent trabecular meshwork and deep intertrabecular recesses communicating with the LV cavity. Our understanding of the NCCM entity has developed over the past three decades due to increased awareness, the emergence of new technical advances among several imaging modalities as well as genetic studies. To date however, echocardiography remains the predominant diagnostic tool. The aim of this review is to discuss the uncertainties that exist in the diagnosis of NCCM and outline some perspectives into overcoming these uncertainties.

2 METHODOLOGY

We searched MEDLINE and PubMed for original articles focusing on NCCM that were published earliest possible date through January 2012. The search terms we used were "noncompaction," "non-compaction", "hypertrabeculation(s)", "spongy myocardium", and "myocardial sinusoids. Search criteria were exclusive for papers in English-language and full-text papers. Searches were also conducted for key authors in this field and the reference lists of identified articles were examined for further relevant papers. In this review we incorporated, the most relevant and influential articles in the field.

3 UNCERTAINTIES OF DEFINITION

Noncompaction cardiomyopathy is a disease entity of morphologic "abnormal" myocardial trabeculations that acquired several names over the history of disease recognition. Hypertrabeculation of the LV was first recognised in 1932,[2] isolated LV sinusoids or spongy myocardium in 1984,[3] but isolated LV noncompaction was mentioned not earlier than 1990.[4] The term "isolated" was used to differentiate a disease entity in contrast to other disease states possibly associated with trabeculations. In fact, LV noncompaction was first reported in association with congenital heart diseases,[2] and has subsequently been reported in association with ventricular septal defects,[5] double-orifice mitral valve,[6] Ebstein's anomaly of the tricuspid valve,[7] and bicuspid aortic valve[8]. LV noncompaction has also been described as part of syndromes, particularly when associated with neuromuscular diseases[9].

More important, a uniform pathoanatomic definition of NCCM remains controversial. There is no agreement on pathoanatomic cut-off of normal versus abnormal trabeculations. Few pathological series describing gross and microscopic findings of NCCM exist. Boyd et al. found

trabeculations in 70% of normal hearts[10]. Burke et al. found no clear-cut morphological distinction between "isolated" and "secondary" NCCM[11]. Stollberger et al. found extensive trabeculations in an explanted heart without echocardiographic evidence of NCCM[12]. The high intraventricular pressure that led to flattening of non-compacted layer might explain the disagreement between echocardiographic and pathological findings. Recently, Roberts et al. identified only seven out of 18 gross photographs of the heart in adults in peer-reviewed journals as clear examples of NCCM or hypertrabeculation. According to the authors, one explanation is related to the way of cutting the heart specimen, where fresh cuts according to the flow of blood result in flattened cardiac chambers and then comparison of the thickness of the compacted to that of the noncompacted portions of the cardiac ventricles is more difficult to discern. Cuts of the ventricles made parallel to the posterior atrioventricular sulcus after fixation appears to provide the best opportunity of demonstrating LV hypertrabeculation if present[13].

4 CLASSIFICATIONS OF NCCM

There are two proposals for classification of NCCM; the 2006 American Heart Association (AHA)[14] and the 2008 European Society of Cardiology (ESC) classification of cardiomyopathies[15]. NCCM is considered a distinct primary genetic cardiomyopathy by the AHA[14]. In contrast, according to the ESC, it is not clear whether NCCM is a separate cardiomyopathy, or merely a congenital or acquired morphological trait shared by many phenotypically distinct cardiomyopathies[15].

5 PATHOPHYSIOLOGY AND THEORIES OF ORIGIN

The key histological finding in NCCM is spongy myocardium, characterized by prominent and excessive trabeculations with correspondingly deep recesses within the hypertrophied wall[16]. Several theories about the aetiology of NCCM exist. It is widely believed that NCCM is a primary genetic disease that causes abnormal arrest in embryonic endomyocardial morphogenesis. This is known as the *congenital noncompaction theory*. Supporting this pathogenetic hypothesis is the fact that most cases of NCCM appear to be present since birth. Another view of the congenital theory is the *compensation hypothesis*, which suggests that the genetic defect is not directly responsible for disabling the normal embryonic compaction process but rather it impairs ventricular morphology or function through another mechanism. The noncompaction then arises as an adaptive reaction to compensate for the abnormally contracting myocardium. Compaction of the myocardium usually occurs between weeks five and eight of embryonic life and begins in the septum and base of the heart and

from epicardium to endocardium[17]. The latter might explain why the apex and lateral LV free wall are most frequently involved in NCCM. However, the congenital theory is largely based upon similarities in appearance between the embryonic heart and NCCM without definitive proof. Furthermore, it is assumed that without the process of compaction of the endocardium, capillary networks are not formed, leaving noncompacted endocardial islands which are poorly connected to the coronary circulation. This in turn is a substrate for ischemia and infarctions. In this context , it is very interesting to see loose, spongy myocardium in patients with congenital coronary arterial fistula mimicking NCCM[18]. Other pathogenetic processes thought to be involved in NCCM include dissection of the myocardium, unsuccessful attempts towards myocardial hypertrophy, and compensatory hypervascularization[19]. Some authors have opposing views to explain the aetiological nature of NCCM and believe it may be acquired due to ischemic heart disease or myocarditis[20]. According to this *acquired hypothesis*, it is thought that microcirculatory dysfunction or metabolic disorders give rise to myocardial ischemia and micro-infarcts, which then induce a hypertrabeculation reaction[21]. This argument is largely based on the discovery of subendocardial fibrosis on examination of some hearts affected by non-compaction. Supporters of *the acquired theory* suggested that myocarditis might be responsible for some cases and recent reports of regression of non-compaction of the left ventricle[22]. Noteworthy, therapy-induced reverse LV remodelling and changes in intraventricular dynamics or loading conditions could be associated with morphologic changes in the severity of "hypertrabeculation" or noncompacted segments.

6 GENETIC UNCERTAINTIES

6.1 Genetic findings, genetic overlap and heterogeneity

Sporadic and familial incidence of NCCM has been reported[4], with X-linked, autosomal-dominant and autosomal-recessive inheritance[23-26]. Many gene mutations have been identified including G 4.5 encoding taffazin (X-linked Barth syndrome)[24], alpha dystrobrevin (cytoskeletal protein component), ZASP (Z-line protein that is expressed in the cytoplasm), mutations in the genes encoding the thick and thin filaments of the cardiac sarcomere proteins, and lamin A/C[15, 23, 27, 28]. Our group and others have found evidence for an overlapping genetic background with sarcomere gene mutations, encompassing noncompaction, hypertrophic and dilated cardiomyopathies[26, 29]. Likewise, others have identified the E101K mutation of the alpha-cardiac actin in families with NCCM, septal defect and apical hypertrophic cardiomyopathy[30]. Several case reports link NCCM with other diverse genetic defects with no single pathological model to fit in all cases[26]. The distinct phenotype of cardiomyopathy fits probably within the spectrum of abnormalities triggered by sarcomere gene defects[31, 32]. However, genetic disorders are identified in only half of the reported cases of NCCM[20]. Finally, the causality / specificity of the troponin T (TTNT2) mutation (previously reported in

a NCCM family) was investigated in mice. TTNT2 deficient mice developed a dilated heart (cardiomyopathy) but without the NCCM specific trabeculations[33].

7 DIAGNOSIS

7.1 Electrocardiographic criteria

An abnormal electrocardiogram (ECG) is usually seen in nearly 90% of both children and adults with NCCM[34-39]. Electrical axis deviation, conduction defects, repolarisation abnormalities, and arrhythmias, such as atrial fibrillation and ventricular tachycardia have been reported[35-37]. The most frequently seen ECG findings were left bundle branch block and atrial fibrillation in a large series of adults with NCCM and in the French NCCM registry[34, 40]. Wolf–Parkinson–White (WPW) syndrome was commonly seen in paediatric patients with NCCM[38, 39]. Contrary, none of the adult patients in the largest two published series had WPW syndrome[34, 35]. Unfortunately, none of the ECG abnormalities is specific to the disease but may be more related to the severity of cardiomyopathy. Recently, we found a high (75%) incidence of early repolarization in NCCM presenting with malignant ventricular arrhythmias, not uncommonly encountered in patients with NCCM[41].

7.2 Imaging

7.2.1 Conventional echocardiography diagnostic criteria

Transthoracic echocardiography is used as the initial method in the diagnosis and monitoring of NCCM[42, 43]. Several echocardiographic criteria for the diagnosis of NCCM have been proposed **(Table 1)**[4, 19, 43-46] In 1990 Chin *et al.* studied 8 patients and focused mainly on the depth of the trabeculations in the LV apex and the thickness of the LV free wall from papillary muscle to apex. NCCM was defined by the presence of X / Y < 0.5, where: X = distance from the epicardial surface to the trabecular recess; Y = distance from the epicardial surface to the peak of trabeculations. These criteria were applied to LV apical trabeculations in subxiphoid or apical four-chamber views at *end-diastole*[4].

A decade later, Jenni *et al.* in analogy of Chin *et al.*[4] proposed new criteria to define NCCM based on anatomical validation of echocardiographic findings in 7 patients[42, 43]. In absence of coexisting cardiac abnormalities, three findings were required to establish the diagnosis of NCCM: (1) a two-layered structure is seen, with a compacted thin epicardial band and a much thicker noncompacted endocardial layer of trabecular meshwork with deep endomyocardial spaces, (2) a maximal *end-systolic* ratio of noncompacted to compacted layers of >2 in the parasternal short-axis view and (3) Doppler evidence of deep perfused intertrabecular recesses from the LV cavity[43].

Stollberger *et al.* [19] initially focussed on the number of LV trabeculations. More than three trabeculations protruding from the LV wall, apically to the papillary muscles, visible in a single image plane are needed to establish the diagnosis of NCCM, in addition to Doppler evidence of deep perfused intertrabecular recesses from the LV cavity. In a more recent analysis,[45] the criteria of a two-layered myocardial structure, best visible at end-systole, synchronous motion of the trabeculations with the compacted myocardium were added.

Belanger *et al.* focused more on assessment of severity of NCCM by using the thickness and area of noncompacted regions[44]. In the latter study, the presence, the ratio of the maximum linear length of noncompacted to compacted myocardium and the planimetered noncompacted area on apical 4-chamber view were used to classify 380 patients as controls, mild, moderate, and severe NCCM.

Despite being, the most commonly used imaging modality in establishment of NCCM diagnosis echocardiography has some limitations. Pathoanatomic correlation of echocardiographic finding was performed on only three patients by Chin et al.[4], nine patients by Oeschslin et al.[42] and seven patients by Jenni et al.[43]. Robust data about sensitivity and specificity of the different echocardiographic criteria compared with pathoanatomic findings are lacking. Poor endocardial border definition can be a problem, which could be overcome by using intravenous contrast agents or cardiac MRI.

7.2.2 Newer echocardiographic diagnostic tools

Newer echocardiographic modalities such as contrast,[47, 48] tissue Doppler imaging,[49, 50] speckle tracking[51, 52], and three-dimensional echocardiography[53, 54] may help in the diagnosis and understanding pathophysiologic aspects of NCCM. Contrast-enhanced twoand three-dimensional echocardiography has been very helpful in better endocardial border delineation[47, 48, 55, 56] Assessment of radial and longitudinal myocardial velocity and strain measured by tissue Doppler imaging or speckle tracking echocardiography could help in quantifying effects of noncompacted versus compacted myocardium on both regional and global cardiac function[49, 57]. Both systolic and diastolic tissue Doppler mitral annular velocities are significantly reduced in patients with NCCM compared with normal controls, and a reduced early diastolic lateral mitral annular velocity <7.8 cm/s helps to poor clinical outcome in children with NCCM[58]. Speckle tracking echocardiography also allows the study of LV twist that seems reduced in NCCM, and may even reveal a functional pattern of rigid body rotation[52, 59]. This latter finding supports *the congenital theory* according to which the myocardial layers are abnormally developed with absence of the normal helical fiber structure of the heart. These data conform to Bellavia *et al.*[51] who showed impaired LV rotation, twisting, and systolic strain in patients with NCCM regardless of LV ejection fraction and tissue Doppler measurements. In addition, apical LV rotation, LV torsion and torsion rate had the highest diagnostic accuracy to discriminate patients with NCCM from healthy controls. However, Pacileo *et al.*[60] showed prolonged but preserved LV systolic twist in 14 asymptomatic patients with NCCM compared

to control subjects. Probably this reflects differences in heterogeneity of the cases and /or the severity of the disease. Altered mitral annular geometry and impaired annular function in patients with NCCM have been found with three-dimensional echocardiography[53].

7.2.3 Magnetic resonance imaging (MRI)

The excellent tissue-blood contrast of MRI allows for better visualization of trabeculations, in particular when echocardiography windows are poor. Therefore, cardiac MRI is considered as the gold standard for assessment of LV function. A specific MRI criterion based on an end-diastolic ratio of compacted to noncompacted myocardium >2.3 in long-axis views was used for the diagnosis of NCCM[61]. Jacquier et al. used end-diastolic frames combining both long and short axis views to calculate LV trabeculations mass. Epicardial and endocardial contours were outlined in a semi-automatic fashion including papillary muscles and trabeculations to calculate global LV mass. To calculate LV compacted mass LV trabeculations were excluded from tracing. A ratio of >20% of LV trabecular mass compared to global LV mass has been proposed as a diagnosticum[62]. However, it should be noticed that the proposed MRI criteria were derived from small, selected populations. Another limitation of the MRI criteria is related to the slice selection and partial volume effects of single view of MRI images, which might lead to over/underestimation of the size and or mass of trabeculations[62]. A recent finding of mid-myocardial fibrosis on MRI images in patients with NCCM, unrelated to noncompacted regions could open new areas of research towards better understanding of the disease[49, 63]. Recently, Dawson et al. used cardiac MRI to separate normal LV trabeculations from pathological noncompaction in 120 volunteers. All healthy ventricles had a visible trabeculated layer in one or more segments and ageand sex-related morphometric differences in the apparent trabeculated and compacted layer thicknesses were identified with systolic thinning of the visible trabeculated layer that contrasted with compacted myocardial wall thickening[64].

7.2.4 Diagnostic uncertainties

The diagnosis of NCCM still represents a major dilemma more than two decades after the first proposed diagnostic criteria. It should be well recognized that the criss-crossing meshwork of thin muscle bundles **(Figure 1)** at the apical third of the left ventricle and thick muscle bundles aligning the myocardial wall are normal structures[10, 65]. Up to 70% of hearts display at least one prominent LV trabeculation, with two or more present in 36%[10]. Furthermore, false tendons extending between the septum and the papillary muscles are present in 0.5%,[66] and multiple bellies of the papillary muscle or additional papillary muscles may be present. Even when NCCM exists as a separate disease entity, there will be patients with a less severe phenotype that will be hard to distinguish from normal anatomy. Also, in pathology studies it has been shown that a hypertrabecularization pattern resembling NCCM was present in 43% and 28% of patients with dilated cardiomyopathy and ischemic heart disease, respectively[67]. In another study by Kohli *et al.* in 24% of patients of patients

with systolic heart failure, and 8% of normal controls one or more of the echocardiographic criteria for NCCM **(see Table1)** were seen[68]. Other subjects known with a high incidence of prominent trabeculations include those with chronic pressure or volume overload such as endurance athletes **(Figure 2),** patients with valvular heart disease **(Figure 3),** and blacks[68, 69]. Finally, as mentioned before, HCM patients not only share genetic overlap with NCCM but also may show mixed phenotypes **(Figure 4).** A typical phenotype of a patient with NCCM on two-dimensional echocardiography without **(Figure 5),** with contrast **(Figure 6)** enhanced endocardial borders, three-dimensional echocardiography, and cardiac MRI **(Figure 7)** is shown**.**

An important limitation of current diagnostic criteria of NCCM is the fact that all echocardiographic definitions are based on small studies with apparently gross morphologic changes[4, 42]; the commonly used Jenni criteria were based on a post-mortem study in seven subjects with prominent trabeculations[43]. In addition, marked differences in diagnostic definitions exist **(Table 1),** not only in morphological analysis (extent and/or severity of trabecularisations) but also in timing of analysis (end-systolic frames versus end-diastolic frames) and cross-section of analysis (short-axis versus long-axis). Echocardiographic views are operator-dependent and off-axis views may affect the morphologic assessment of myocardial trabeculations. As a result, marked differences exist in functional and morphological patient characteristics in studies **(Table 2)**[34, 49, **53**, 70-72]. In another study, improved hemodynamic status and lesser dilatation of the LV, reduced the ratio and the amount of noncompaction, which might be interpreted as a regression of NCCM[22]. In a recent study, the interobserver agreement of counting the number of trabeculations and measuring the ratio of noncompacted to compacted regions was poor[73].

Challenges in the diagnosis of NCCM are not limited to echocardiography but also extend to the proposed MRI criteria. Poor reproducibility of quantification of LV mass and LV non-compacted mass in patients with NCCM has been reported[74]. This could be due to the slice thickness of MRI images and the seemed inferior spatial resolution of MRI compared to echocardiography.

Table 1. Diagnostic criteria of patients with noncompaction cardiomyopathy

Study	Patients	Echo views	NC/C ratio	Relative size of trabeculations	Blood flow in recesses	Location of trabeculations	Number of trabeculations	Timing of analysis	Exclusion of other cardiac diseases
Echo									
Chin *et al.*[4]	8	SAX + LAX	>2	-	no	LV apex and free wall	No	end-diastole	No congenital cardiac malformations
Jenni *et al.*[43]	34[#]	SAX	>2	-	yes	LV apex, mid-lateral, mid-inferior	No	end-systole	No other congenital or acquired heart disease
Bellanger *et al.*[44]	60	SAX + LAX	yes[$]	yes[&]	yes	LV apex	"excessive"	end-systole	No evidence of congenital heart disease, hypertrophic or infiltrative cardiomyopathy, or documented coronary artery disease
Stöllberger *et al.*[45]	104	SAX + LAX	>2	-	yes	LV wall, apically to the papillary muscles	>3 in single view	end-diastole[¶] end-systole[¶]	Not reported
MRI									
Petersen *et al*[61].	7	AP4CH	>2.3	-	-	LV apex, mid-anterior, mid-inferior, basal anterior	no	end-diastole	The study separated NCCM from: athletes heart, hypertrophic and dilated cardiomyopathy, hypertensive heart disease, and aortic stenosis
Jacquier *et al.*[62]	16	SAX	-	Yes[*]	-	-	no	end-diastole	Based on Jenni criteria plus: the study separated NCCM from: hypertrophic and dilated cardiomyopathy, and healthy controls

Abbreviations: C = compacted, NC = non-compacted; LAX = long-axis view, SAX = short-axis view, LV = left ventricular, AP4CH = apical 4-chamber

& = relative size in area: mild <2.5 cm^2, moderate 2.5 – 5.0 cm^2, severe >5 cm^2

* = relative size in mass >20%

$ = relative ratio mild 0-1, moderate 1-2, severe >2

= including 7 patients with anatomical validation

¶ = end-diastole to examine trabeculations, end-systole to confirm presence of a two-layered myocardium

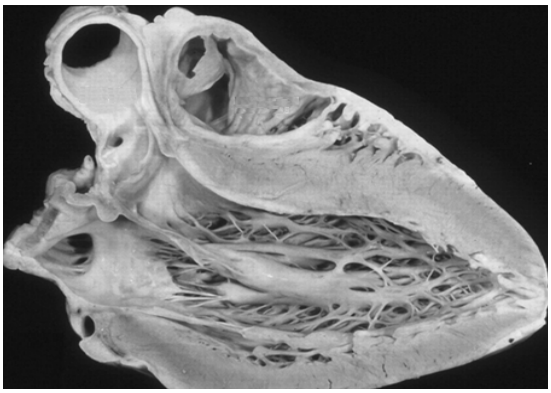

Figure 1. The endocardial aspect of the ventricle is characterized by a criss-crossing meshwork of thin muscle bundles (trabeculations) at the apical third as seen in a longitudinal anatomical section of a normal left ventricle.
(Reprinted with permision from Ho SY. Anatomy and myoarchitecture of the left ventricular wall in normal and in disease. Eur J Echocardiogr 2009 Dec;10(8):iii3-7)

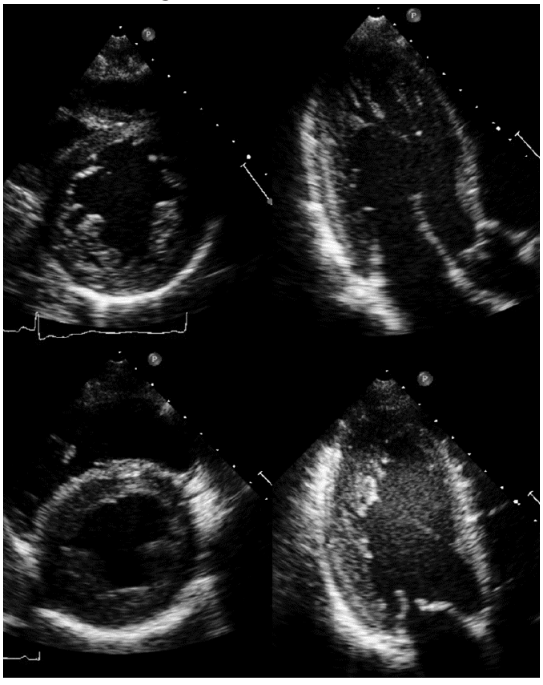

Figure 2. Prominent or excess trabeculations that could be mistaken for noncompaction cardiomyopathy diagnosis in two professional athletes (athlete #1 top, athlete #2 bottom)

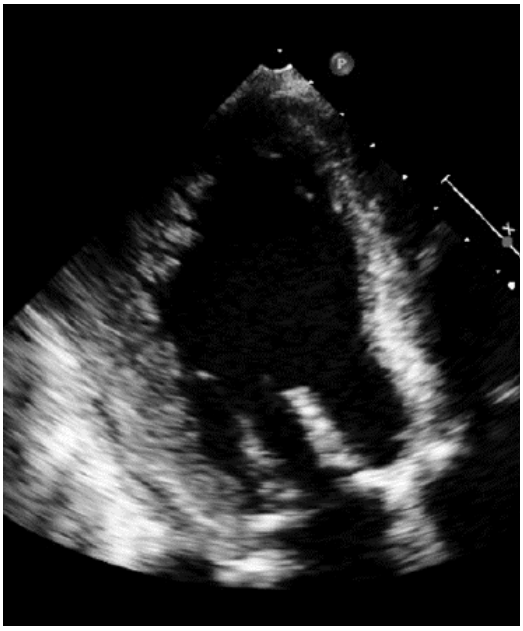

Figure 3. Prominent or excess trabeculations in a patient with aortic stenosis (The patient does not fulfil all Jenni criteria)

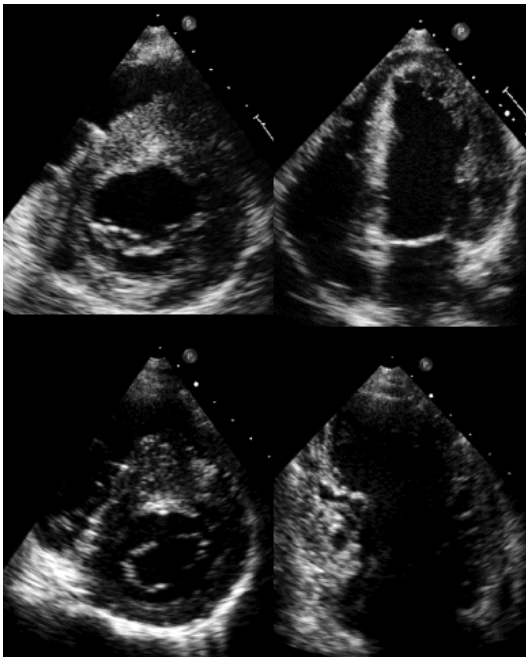

Figure 4. Phenotypic overlap in a HCM patient showing prominent trabecularisations in the anterolateral (patient #1, top) and inferior wall (patient #2, bottom)

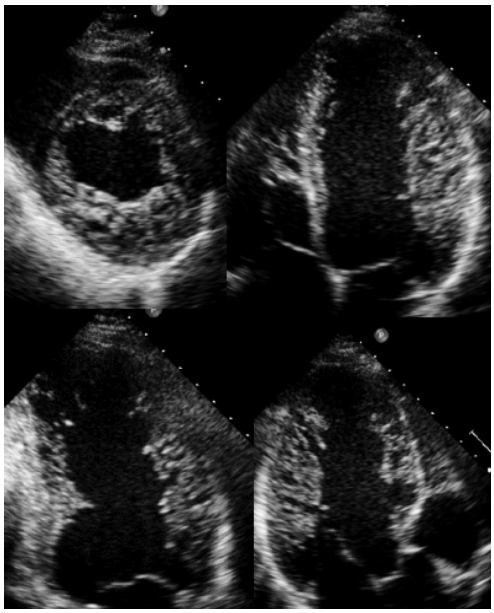

Figure 5. Typical phenotype of noncompaction cardiomyopathy in short-axis view (top left), apical four-chamber view (top right), apical two-chamber view (bottom left) and apical long-axis views (bottom right). Note the presence of trabeculations in posterior wall, anterior septum and lateral wall of the left ventricle.

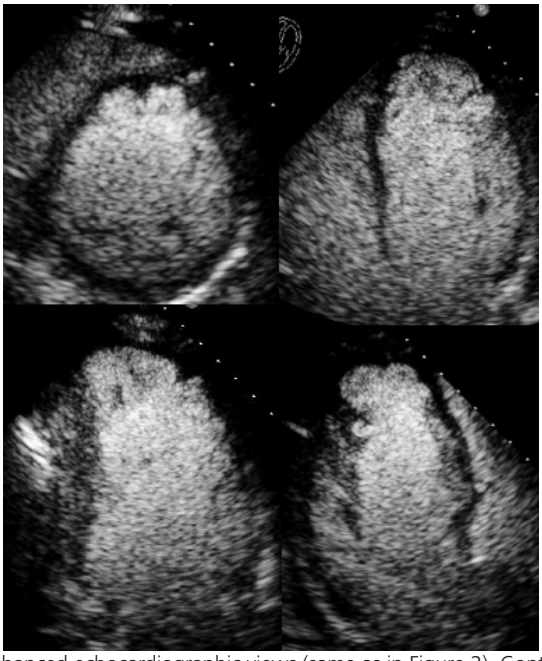

Figure 6. Contrast-enhanced echocardiographic views (same as in Figure 2). Contrast echocardiography is used to prove the continuity of blood from left ventricular cavity into intertrabecular recesses and to enhance the endocardial border delineation.

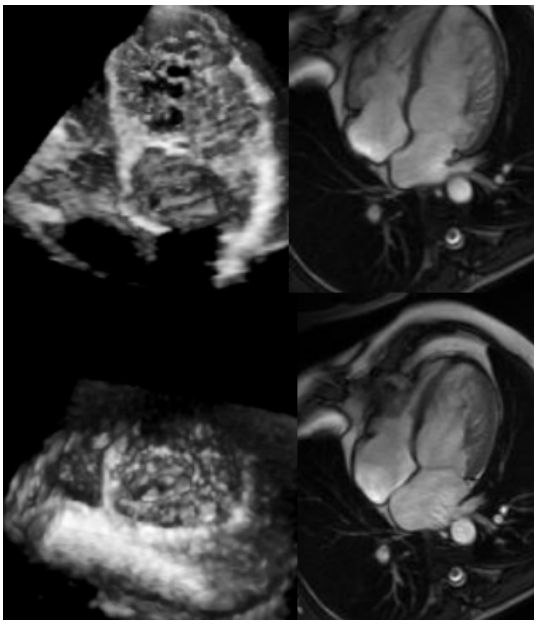

Figure 7. Several images from a patient with noncompaction cardiomyopathy: apical four-chamber (top left) and short-axis (bottom left) views on three-dimensional echocardiography, and apical four-chamber views at end-diastole (top left) and end-systole (bottom right) on cardiac magnetic resonance imaging.

Table 2. Main clinical and echocardiographic characteristics of adult patients diagnosed with NCCM among selected studies containing over 60 patients.

Variable	Aras *et al.*[70]	Loefigo *et al.*[72]	Thoraxcenter [41, 49, 52, 53, 59, 82, 83]	Habib *et al.*[34]	Stolberger *et al*[40].
Year of publication	2006	2007	2011	2011	2011
Demographics					
Number of patients per study	67	65	90	105	162
Age at diagnosis	41	47	41 ±14	45	53
Male sex	66%	37%	47%	66%	72%
Familial clustering	33%	NR	50%	8%	NR
Neuromuscular disorder	0%	9%	2%	NR	74%#
Main echocardiographic characteristics					
Left ventricular ejection fraction (mean ± SD)	44 ± 14	32 ± 10	38±12	46 ± 18	NR
Number of noncompacted segments	6.9 ± 1.9	6.0 ± 3.0	7.6 ± 4.5	5.2 ± 1.8	NR
Localisation of trabeculations					
Apex	100%	92%	~100%	~100%	94%
Inferior wall	~90%	25%	~60%	~40%	NR
Anterior wall	~50%	48%	~45%	~30%	3%
Posterior wall	~90%	80%	~55%	NR	15%

Lateral wall	100%	74%	~80%	~80%	49%

# 99 out of 134 neurologically examined patients
NR = not reported

7.3 Prevalence

The lack of clear definition and still limited awareness of the disease entity among physicians precludes clear knowledge of disease prevalence. The prevalence of NCCM among adults has been reported as 0.014% to 0.26% of adults referred to echocardiographic laboratory[42, 75].

8 NCCM IN PAEDIATRIC VERSUS ADULT POPULATIONS

The main differences reported between paediatric and adult populations of NCCM are the more associated congenital heart disease and WPW syndrome in the paediatric population. The latter carries a poorer prognosis than the disease reported in adult populations[76]. Mortality rates have been reported 6 times higher in patients with non-isolated compared with isolated NCCM in some series[71]. Most poor outcomes occurred during the first year after presentation[77]. The clinical spectrum is therefore different in adults from that in the paediatric population, because many patients with congenital heart disease and significant cardiomyopathy might have died before adulthood. Another difference between paediatric and adult populations of NCCM is the temporarily recovery of LV systolic function in paediatric patients. Pignatelli et al. have described a prominent clinical pattern described as "undulating phenotype" among the paediatric patients with NCCM who have depressed systolic LV contractility followed by a period of recovery and then further deterioration in systolic LV function[38]. This undulating phenotype has not seen in adults with NCCM. In the same study, unlike in adults, the interventricular septum was involved in several paediatric patients.

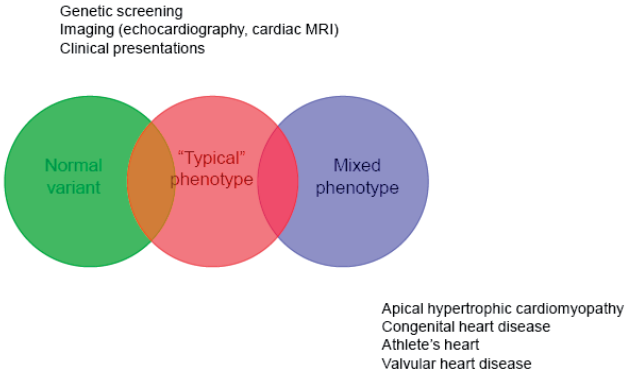

Figure 8. In real world, based on genetic testing, imaging (echocardiography and cardiac magnetic resonance imaging), and clinical characteristics , non-compaction cardiomyopathy "typical phenotype" is overlapped by excess trabeculations, "normal variant" or other cardiac abnormalities "mixed phenotype"

9 EXPERT OPINION

9.1 The current challenges

There are uncertainties in all aspects of NCCM from the very basic definition to prognosis. We support the notion that NCCM is predominantly a genetic cardiomyopathy with variable morphological, functional, and clinical presentation. However, there is lack of clear consensus on what should be described as NCCM and what is the position of NCCM among other cardiomyopathies[78, 79]. This is illustrated by the different opinion in the AHA and ESC guidelines[14, 15], and by the described different morphological and functional patient characteristics. The morphologic picture is a continuum of LV trabeculations that extends from normal subjects to very severe forms of NCCM **(Figure 8).** There is no proof that any of the morpho-anatomic definitions is correct, or could be applied to a general population including different ethnic groups, both genders, and to children and adults. New imaging tools, and in particular the use of contrast-enhancement, may be helpful[47, 48, 53, 80, 81].

Severe trabeculations represent another diagnostic challenge in evaluation of LV volumes and ejection fraction because of the inherent problems of the technique and the impossibility of tracing the true endocardium because of the trabecular structures. In such situations, the use of tissue Doppler and speckle tracking imaging may be an alternative to assess LV function. However, an index or cut-off value of global and regional LV function is yet to be developed. Finally, the altered orientation of myocardial fibres in patients with NCCM could be challenge in assessment of deformation imaging.

9.2 Future perspectives

More definite answers on the nomenclature, classification, pathophysiology, and outcome are needed to define the NCCM disease entity. Large international, multicentre prospective registries and consensus statement like in ARVC are crucial steps to clarify current uncertainties. Alongside, pathoanatomic correlation of the imaging data should be sought in larger series. Due to the genetic heterogeneity and lack of clear view on the genotype-phenotype relationship of NCCM, more genetic counselling, DNA diagnostics, and cardiological family screening should be encouraged. Based on pathologic, clinical, and genetic analysis, a new classification should be proposed clearly defining 1) physiological trabeculations, 2) prominent non-pathological trabecularization, 3) possible NCCM, and 4) definite NCCM. Two forms of the disease should be recognized, an isolated, mainly adult form of the disease and NCCM associated with congenital heart diseases and neuromuscular diseases. Parameters should not only include the presence or absence of other concomitant cardiac diseases (congenital, valvular), the size, location and severity of excessive trabeculations, but also LV functional parameters (impaired LV function, rigid body rotation), and possible genetic mutations.

HIGHLIGHTS

- Noncompaction cardiomyopathy is mostly a primarily genetic disease characterized by excessively prominent trabecular meshwork of the left ventricular walls, possibly resulting from intrauterine arrest of the normal process of myocardial compaction.
- A clear cut-off between normal and disease in ventricular trabeculations is missing.
- Four morphological definitions of noncompaction cardiomyopathy based on conventional echocardiography and morphological definitions based on cardiac magnetic resonance imaging have been proposed.
- Newer imaging modalities such as deformation imaging have potential for adding functional diagnostic criteria to firmly establish diagnosis of noncompaction cardiomyopathy.
- Large international, multicentre prospective registries and consensus statement like in Arrhythmogenic Right ventricular Cardiomyopathy are needed to establish uniform diagnosis of noncompaction cardiomyopathy. In these studies, morphological and functional imaging, pathoanatomic correlation along with genetic screening and clinical follow-up should be included.
- A new classification should be proposed clearly defining 1) physiological trabeculations, 2) prominent non-pathological trabecularization, 3) possible NCCM, and 4) definite NCCM.

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Empty handed: a call for an international registry of risk stratification to reduce the 'sudden-ness' of death in patients with non-compaction cardiomyopathy

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Isolated left ventricular (LV) non-compaction or non-compaction cardiomyopathy (NCCM) is a relatively new and rare clinicopathologic entity, first described by Engberding and Bender in 1984.[1] Since then, many case reports and a few case series are published.[2,3] The clinical presentation includes congestive heart failure, supra-and ventricular arrhythmias, and thrombo-embolic events. It is recently classified as a primary cardiomyopathy.

Morphologically, it is characterized by a prominent trabecular meshwork and deep intertrabecular recesses communicating with the LV cavity and is thought to be caused by an arrest of normal embryogenesis of the myocardium.[2] It is hypothesized that intrauterine arrest of the normal compaction in the embryonal heart results in a 'spongy' heart, characterized abnormal trabeculation, especially confined to the LV apical segments. Therefore, the diagnostic criteria fully rely on the imaging modality, especially transthoracic echocardiography, contrast echocardiography, or MRI. Most of the cases are familial and show genetically heterogenous patterns. However, there is strong evidence that at least a part of the NCCM population are caused by sarcomeric gene mutations. These data suggest that NCCM could be a part of spectrum of cardiomyopathies, consisting of dilated and hypertrophic cardiomyopathy.

The clinical spectrum of NCCM shows a highly variable clinical presentation, ranging from asymptomatic to severely symptomatic with end-stage heart failure, lethal arrhythmias, and/or thrombo-embolic events. The first clinical case series described a high risk of ventricular tachy-arrhythmias and sudden cardiac death (SCD)[2] identifying malignant ventricular arrhythmias as a major clinical issue. However, recent studies show a more benign natural history, including lower risk for (malignant) ventricular arrhythmias.[3] This explains the continuing discussion about the real incidence and prevalence of malignant ventricular arrhythmias in NCCM patients, including sustained ventricular tachycardia (VT) and ventricular fibrillation (VF).[2–5]

Based on the above-mentioned facts, the study published of the journal by Steffel et al.[6] is interesting and it tries to assess the possible role of invasive electrophysiology testing. The authors collected the electrophysiologic study (EPS) results of 24 patients, in a retrospective fashion. Inducible ventricular tachyarrhythmias were found in 38% of the patients and only 17% of them had sustained VT or VF. During a follow-up period, only the minority of patients implanted with an implantable cardioverter–defibrillator (ICD) had appropriate therapy. Interestingly, none of the 12 patients in the non-inducible group had VT or VF occurred. The fact that the seven patients with inducible supraventricular tachycardias also included two with an accessory pathway [Wolf-Parkinson-White (WPW) syndrome] draws attention to the heterogeneity of the study population, in view of the frequent coincidence of congenital heart diseases such as Epstein's anomaly with WPW syndrome. In view of the frequent coincidence of congenital heart diseases such as Ebstein's anomaly with WPW syndrome, at least some patients with NCCM may have sarcomeric gene mutations.[7] The conclusion that EPS testing may be of limited value for risk stratification for SCD, sounds fair despite the limitations of the study. The authors recommend prophylactic ICD implantation only after individual clinical

risk stratification. We can only agree with that and support the need for prospective long-term FU studies. Indeed, the only way for appropriate risk stratification is collecting relevant clinical data in a multi-centre, prospective registry and follow-up studies. The authors of this editorial strongly believe that this could, in this information technology area, easily be done in the form of a web-based national, and international registry.

Additional problem in this yet rare clinical entity is that the underlying arrhythmogenic substrate is not known and therefore changes and progression of the arrhythmogenic substrate in the long term remains speculative. This is consistent with the findings of the authors, since most of their patients had relatively preserved LV function. This suggests that the degree of LV dysfunction, which is generally an indication of the severity of disease, could probably not be used to predict malignant ventricular arrhythmias.[8] This is in line with our clinical experience that among high-risk NCCM patients with severe LV dysfunction and heart failure who receive an ICD for primary prevention, none had appropriate shock, unlike those who received an ICD for secondary prevention.[9]

To put into perspective and to understand the reason for significant limitations of EPS-based risk stratification, we have to look into this issue of risk determination from a broader perspective. EPS in clinical decision-making in patients at risk of SCD has dramatically changed over the past decades. Although the annual incidence of SCD in the general population is 0.1–0.2%, specific subgroups of patients (coronary artery disease and reduced LV function, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy, Brugada syndrome, long QT syndrome, and non-compaction cardiomyopathy) are at higher risk.[10] Programmed ventricular stimulation (PES) with intracardiac electrical stimulation and recording began in 1972, when Wellens et al.[11] had introduced this technique for the evaluation of VT. Programmed ventricular stimulation is used for the induction of VT, as the rhythm generally has re-entry because of the scar tissue. The ease of VT induction is related to the substrate, and to the aggressiveness of the used protocol. Sustained or haemodynamically unstable monomorphic VT, sustained polymorphic VT and VF induced with less than three extrastimuli are considered positive result.[12]

The general concept of EPS was to test the electrical vulnerability of the myocardium, thus the inducibility of VT with anti-arrhythmic medication: patients whose arrhythmia remained inducible with drug therapy had a worse outcome. In the 1980s, it became clear that anti-arrhythmic medication may harm more patients than they benefit, and the development and successful implantation of ICD reduced the number of serial EPS. Two landmark trials, the MADIT and the MUSTT, demonstrated in the late 1990s that patients with coronary artery disease who are at high risk (reduced LV function and inducible ventricular arrhythmias) benefit from ICD implantation as a primary prevention. EPS, as a risk stratification tool, showed modest positive and poor negative predictive values in these studies. Furthermore, recent data from the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation

(DEFINITE) trial has proven that EPS does not provide data that are useful in assigning risk in patients with non-ischaemic-dilated cardiomyopathy. For high-risk groups of patients with coronary artery disease, the annual incidence of SCD can be 10–20%, so the majority of these patients will never develop fatal arrhythmias. On the other hand, in absolute numbers, due to a greater population at risk, most SCD occurs in patients who are apparently at lower risk. Consequently, there is a need to better identify patient who are at the highest risk of SCD, and will benefit from ICD implantation, which is not without complications. Using PES, the specificity of induced arrhythmias among non-ischaemic patients is controversial. The performed studies had small number of patients, and on the top of that the stimulation protocols were different. The most common finding with PES in 38% of these patients is inducible polymorphic VT or VF, but it has limited clinical significance. This suggests that the positive predictive value of induced polymorphic ventricular arrhythmias is low in the population with non-ischaemic-dilated cardiomyopathy.

For routine EPS for risk stratification in patients with NCCM, currently there is no evidence in the daily practice, in spite of the article by Steffel et al. Until we have larger, prospective studies with long-term follow-up, EPS probably should be reserved for research protocols, including long-term FU studies. Certainly, in specific clinical situations such as unexplained syncope or palpitations, the EPS remains mandatory. Until we have reliable prospective data, it remains reasonable to use the current guidelines for management of patients with ventricular arrhythmias and the prevention of SCD in non-ischaemic cardiomyopathy patients. It is, likely that the 'classical ICD trials' also included non-compacted patients, because this diagnosis was frequently overlooked or misclassified because of the unawareness of clinicians and less-advanced imaging modalities.

In conclusion, these findings support that EPS as a risk stratification tool is most accurate in patients with dense scar as a stable arrhythmogenic substrate. Based on the above-mentioned facts and the results of Brilakis et al.,[13] invasive EPS in its present form is insufficient to identify high-risk cardiomyopathy patients.

Conflict of interest: none declared.

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Indications and Outcome of Implantable Cardioverter-Defibrillators for Primary and Secondary Prophylaxis in Patients with Noncompaction Cardiomyopathy

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ABSTRACT

Background. Noncompaction cardiomyopathy (NCCM) is a rare, primary cardiomyopathy, with initial presentation of heart failure, emboli, or arrhythmias, including sudden cardiac death. ICD's are frequently used for primary and secondary prevention in different cardiomyopathy pts, but data about ICD in NCCM is scarce. The aim of this study was, therefore, to investigate ICD indications and outcomes in NCCM patients.

Methods and Results. We collected prospective data from our NCCM cohort (n=77 pts, mean age: 40 ± 14 years). ICD was implanted in 44 (57 %) pts with NCCM according to the current ICD guidelines for non-ischemic cardiomyopathies; in 12 for secondary prevention (7 x ventricular fibrillation, 5 x sustained ventricular tachycardia (VT) and in 32 patients for primary prevention (heart failure / severe LV dysfunction). During a mean follow-up of 33 ± 24 months, 8 patients presented with appropriate ICD shocks due to sustained VT after median 6.1 [1-16] months. This included 4/32 (13 %) patients in the primary prevention group and 4/12 (33%) in the secondary prevention group (p=0.04). Nine patients presented with inappropriate ICD therapy: 6 (19%) in the primaryand 3 (25%) in the secondary prevention group, at a median follow up of 4 [2-23] months.

Conclusions. In our cohort of NCCM patients, an ICD was frequently implanted for primary or secondary prevention of sudden cardiac death. At follow up, frequent appropriate ICD therapy was observed in both groups, supporting the application of current ICD guidelines for primary and secondary prevention of sudden cardiac death in NCCM.

Keywords: implantable cardioverter-defibrillator; noncompaction cardiomyopathy; sudden cardiac death, primary and secondary prevention

INTRODUCTION

Ventricular arrhythmias are common in patients with cardiomyopathy with or without heart failure, ranging from premature ventricular complexes (PVC's) to sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) with cardiac arrest or sudden death[1]. Current guidelines recommend implantation of an ICD in patients with impaired left ventricular function (LVEF ≤ 35%) caused by coronary artery disease or cardiomyopathy.[2-3] Noncompaction cardiomyopathy (NCCM) is a relatively rare clinico-pathologic entity, first described by Engberding and Bender in 1984.[4] It is a primary cardiomyopathy, with strong familial inheritance.[5] The clinical presentation includes congestive heart failure, thrombo-embolic events, supraventricularand ventricular arrhythmias and sudden death.[6] The diagnosis according to the criteria proposed by Jenni et al [7] relies on cardiac imaging: echocardiography, preferably using echo contrast, or MRI. Ventricular tachyarrhythmia's, including cardiac arrest due to ventricular fibrillation, are reported in 38 to 47% and sudden death in 13 to 18% of adult patients with NCCM.[6, 8] Therefore, implantation of an ICD in these patients is a valid option; although in previous trials no known NCCM patients were included. Information on the long-term prognosis after ICD therapy in such patients is limited. Therefore in our study we investigated the indications and outcome of NCCM patients without or with an ICD for primaryor secondary prevention of sudden cardiac death according the current ICD / heart failure guidelines, and sought to identify predictors of appropriate and inappropriate shocks and sudden death in these patients.

METHODS

Study Population

The study cohort consisted of 77 consecutive adult NCCM patients (age ≥ 18 years) who were followed at the outpatient NCCM clinic in the Thoraxcenter, a tertiary referral centre. An ICD was implanted in 44 (57%) patients for primaryor secondary prevention of sudden death according to the current ICD guidelines for non-ischemic cardiomyopathies.[2-3] The diagnosis of NCCM was made according to stringent echocardiographic criteria, as described by Jenni et al[7, 9]:

1. An excessively thickened left ventricular (LV) myocardial wall with a two-layered structure comprising a compacted (C) epicardial layer and a noncompacted (NC) layer of prominent trabeculations on the endocardial side.
2. A NC/C myocardial thickness ratio ≥ 2 measured at the moment of maximal thickness in end-systole at the parasternal short axis.
3. Color-Doppler evidence of deep inter-trabecular recesses in communication with the LV cavity.

4. Absence of coexisting cardiac anomalies such as hypertension, coronary artery disease, valvularor congenital heart disease.

The patients were prospectively followed and the relevant data was collated in the Thoraxcenter NCCM registry and analyzed in accordance with hospital institutional review board policies.

Baseline data

Detailed baseline data prior to ICD implantation were registered including age, gender, height, weight, blood pressure, cardiac diagnosis, New York Heart Association (NYHA) functional class at the time of implantation, and use of cardiac drugs, including anti-arrhythmic drugs. The most recent echocardiogram prior to ICD implantation was used to determine left ventricular end-diastolic (LVED) and end-systolic diameter (LVES), and the presence or absence of significant valvular abnormalities. No measurements of LV volumes and ejection fraction were made because of the inherent problem to identify the endocardial border in the presence hypertrabeculation. Global LV function was estimated using a visual assessment performed by two experienced observers (KC and MLG) and clasified as 1=normal LV function, 2= mild LV dysfunction, 3=moderate LV dysfunction and 4=severe LV dysfunction. Additionally, fractional shortening (= (LVED-LVES)/LVED x 100%) was measured. Heart rate, PQ, QRS and QTc intervals were measured on the ECG prior to ICD implantation. The presence of ventricular ectopy and (non-) sustained VT was identified on 24 hour Holter monitoring.
ICD's were implanted for either primaryor secondary prevention. *Secondary prevention* was defined in patients having sustained ventricular tachycardia (i.e. VT lasting > 30 sec or hemodynamically compromising), documented or after cardiac arrest due to ventricular fibrillation. *Primary prevention* was defined as patients with severe LV dysfunction with (N=25) or without heart failure (N=7). In patients with a severe LV dysfunction and no heart failure, a presumed additional risk factor was required including a family history of SCD (N=4), non-sustained VT's in a 24-h Holter (N=2) and / or unexplained syncope (N=1). ICD was combined with biventricular pacing in patients with symptoms and signs of heart failure, severe LV dysfunction and QRS duration of ≥ 120 ms. The clinical response was evaluated according to the NYHA functional class with regular follow-up every 3-6 months. Detailed information concerning the ICD implantation was collected, including ICD type, lead type, defibrillation threshold, duration of intervention, and duration of postoperative stay.

ICD programming

For all patients, ICD programming was intended to avoid inappropriate device therapy and tailored according to the clinical presentation. The majority of devices were programmed in a dual-zone detection configuration (75%), mean ventricular tachycardia detection interval was 351 ± 28 ms, mean fibrillation detection interval was 275 ± 18 ms. ICD therapy in the lowest detection zone consisted of antitachycardia pacing followed by cardioversion.

Antitachycardia pacing was programmed as 3 to 5 sequences of 8 pulses. In the fibrillation detection zone, only shock therapy was activated.

ICD Complications

Early (intervention-related) and late complications (> 30 days) were documented and included pocket hematoma, pleural effusion, lead failure, thrombo-embolic events, pneumothorax, haemothorax, T-wave oversensing, pocket and other infections. Follow-up data was obtained from our prospective ICD registry and by reviewing medical records and stored intracardiac electrocardiograms.

ICD Interventions (shocks and anti-tachypacing)

An appropriate shock was defined as a shock, delivered in response to a ventricular arrhythmia. An inappropriate shock was a shock, delivered for reasons other than ventricular arrhythmia. The collated data included appropriate and inappropriate interventions (shocks and anti-tachypacing), ICD re-interventions, and cardiac and non-cardiac death. In our institute a strict follow-up (every 3–6 months) is standard after ICD implantation.

STATISTICAL ANALYSIS

Continuous variables are summarized by mean ± SD or median and interquartile range (25th, 75th percentile) depending on normality of distribution. Categorical variables are represented in frequencies and percentages. Descriptive statistics for nominal data were expressed in absolute numbers and percentages. After checking for normality, mean values and standard deviations were calculated for normally distributed continuous variables. Medians and ranges were computed for continuous variables with non-normal distribution. Comparison of continuous variables between groups was made by unpaired Student's t-tests. In the case of a skewed distribution, the Mann–Whitney U test was used. When comparing frequencies, the Chi-square or Fisher's exact test was used, where applicable. Cumulative Kaplan–Meier survival curves were constructed for each outcome variable. Patients without inappropriate or appropriate interventions, respectively, were censored at the date of most recent follow-up. Univariable Cox regression analysis was used to evaluate the prognostic significance of the following variables concerning the occurrence of appropriate or inappropriate shocks: age at ICD implantation, presentation, NYHA, history of atrial arrhythmias, beta-blocker or ACE-inhibitor / AT2-antagonist or amiodaron use, ICD type, bundle branch block, QTc width, impaired systemic ventricular function (FS < 20 %). Hazard ratios (95% CI) are presented. Multivariate analysis was not attempted due to the low number of events. All tests were two-tailed and a P-value less than 0.05 were considered statistically significant. As there was a high amount of testing, we present exact P-values to show the significance of the findings.

All statistics were performed using SPSS version 16.0. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

RESULTS

Patient characteristics

Baseline demographic and clinical characteristics of all 77 NCCM patients are summarized in *Table 1.* Forty-four patients received an ICD, 12 for secondary prophylaxis after cardiac arrest or ventricular tachycardia and 32 as primary prophylaxis. Median follow-up after ICD implantation was 26 months [range: 1–130]. Mean age at ICD implantation was 46 ± 15 years (figure 1A). By definition, heart failure was the main presenting symptom in the primary prevention group (figure 1B). Positive family history of SCD was one of the contributing factors for ICD implantation. There was no difference in the family history of cardiomyopathy or sudden cardiac death (SCD) between the primary and secondary prevention groups.

The ECG in patients receiving an ICD showed more frequent bundle branch block and longer QRS and QTc durations than those without an ICD. However, there were no significant differences in the ECG's between the primaryand secondary prevention groups. Similarly, the 24-hour Holter data showed more non-sustained VT and more PVC in the ICD recipients than in other patients. In the secondary prevention ICD patients PVC and VT were more frequent than in the primary prevention group.

Patients in the secondary prevention group, firstly presenting with VT / VF, were younger and generally healthier than those receiving an ICD for primary prevention. In the former, LV systolic function was relatively preserved and these patients had no signs of heart failure at first presentation or at follow up. Patients receiving an ICD for primary prevention had larger LA and LV dimensions and a lower fractional shortening. Interestingly, there was a trend to more pronounced trabeculation in the primary prevention group, although the total percentage of the noncompacted segments was not significantly different. Overall the morphological extent and the severity of NCCM could not be related to the presenting clinical symptoms or signs.

Table 1. Baseline characteristics of NCCM patients stratified against the primary or secondary ICD indication.

	No ICD (n= 33)	ICD (n= 44)	*P*	Primary prevention (n= 32)	Secondary prevention (n=12)	*P*
Demopgraphics						
Age at presentation, yrs (±SD)	38 ± 15	42 ± 13	ns	44 ± 14	40 ± 13	ns
Age at implantation, yrs (±SD)	-	46 ± 15	-	48 ± 15	41 ± 14	ns
Male, n (%)	15 (46)	22 (50)	ns	17 (73)	5 (42)	ns
Primary presentation, n (%)						
• Heart failure	12 (36)	21 (48)		20 (63)	0	
• Supraventricular arrhythmias	1 (3)	6 (14)		6 (19)	0	
• Ventricular arrhythmias	0	12 (27)		0	12 (100)	
• Palpitations	2 (6)	4 (9)		4 (13)	0	
• Thrombo-embolic events	6 (18)	3 (7)		3 (9)	1	
• Other	12 (36)	3 (7)		3 (9)	1	
NYHA, n (%)			ns			0.10
• I	13 (39)	11 (25)		5 (16)	6 (50)	
• II	14 (42)	16 (36)		12 (38)	4 (33)	
• III	6 (18)	16 (36)		14 (44)	2 (17)	
• IV	0	1		1 (3)	0	
Family history of NCCM	11 (33)	22 (44)	ns	17 (53)	5(42)	ns
Family history of SCD	3 (9)	13 (30)	0.03	9 (28)	4 (33)	ns
Current medication, n (%)						
• Coumadin	17 (53)	33 (75)	0.05	27 (82)	6 (18)	0.02
• Beta-blockers	21 (64)	37 (84)	0.04	28 (84)	9 (75)	ns
• ACE-I / ARB	23 (70)	40 (91)	0.02	32 (100)	8 (67)	0.001
• Loop diuretics	13 (39)	27 (61)	0.06	24 (75)	3(25)	0.02
• Aldosteron antagonists	10 (30)	17 (39)	ns	16 (50)	1 (8)	0.01
• Digoxine	4 (12)	11 (25)	ns	11 (34)	0	0.02
• Amiodaron	1 (3)	8 (18)	ns	7 (22)	1 (8)	ns
• Other anti-arrhythmic agents	0	3 (7)		1	1	
Electrocardiographic data						
• Heart rate, bpm (mean ± SD)	79 ± 20	73 ± 9	0.08	74 ± 10	71 ± 8	ns
• Atrial fibrillation, n (%)	1 (3)	6 (14)	0.11	5 (16)	1 (8)	ns
• QRS duration, ms (mean ± SD)	100 ± 23	122 ± 36	0.003	125 ± 35	114 ± 39	ns
• QTc, ms (mean ± SD)	401 ± 29	430 ± 40	0.001	428 ± 39	437 ± 45	ns
• LBBB / RBBB, n (%)	4 (12)	17 (37)	0.01	14 (44)	3 (25)	ns
Holter data						
• PVC's in 24-h Holter, median [25-75 % quartile]	8 [2-109]	727 [8-2563]	0.008	526 [5-2092]	2061 [25-6000]	ns
• Nonsustained VT, n (%)	2	15	0.003	8	7	0.03
Echocardiograpic data						
• LA dimension, mm	40 ± 7	43 ± 10	ns	46 ± 9	37 ± 11	0.009

• LV end-diastolic diameter, mm	57 ± 9	63 ± 10	0.006	66 ± 10	56 ± 8	0.003
• LV end-systolic diameter, mm	45 ± 11	52 ± 12	0.03	55 ± 12	42 ± 10	0.003
• Fractional shortening, %	21 ± 8	19 ± 8	ns	17 ± 6	25 ± 10	0.003
• Global LV function by visual assessment	2.6 ± 1.2	3.2 ± 1.1	0.04	3.6 ± 0.8	2.3 ± 1.3	0.0005
• LV noncompacted segments, n (mean ± SD)	5.2 ± 1.6	4.6 ± 1.2	ns	4.8 ± 1.3	4.2 ± 0.9	ns
• Maximal myocardial thickness, mm (mean ± SD)	24 ± 4	23 ± 4	ns	24 ± 4	21 ± 3	0.03
• Maximal noncompacted / compacted ratio (mean ± SD)	2.7 ± 0.6	2.8 ± 0.6	ns	2.9 ± 0.7	2.5 ± 0.4	0.07

LV indicates left ventricle; LA , left atrium; PVC, premature ventricular complex; QTc, corrected QT interval; LBBB, left bundle branch block; RBBB, right bundle branch block; ns, not significant (p>0.10).

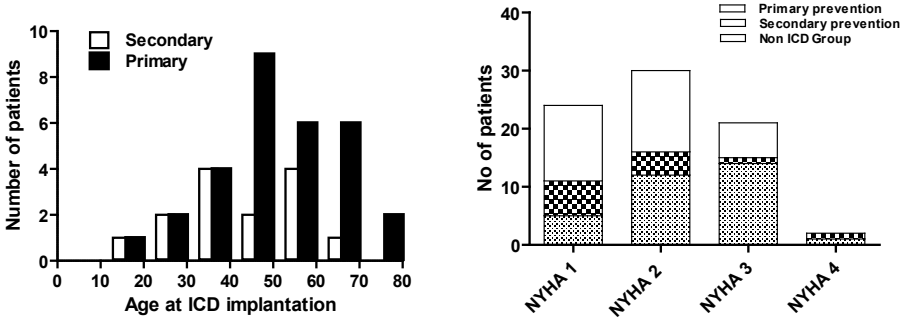

Figure 1. Age at ICD implantation (A) and NYHA class (B) in NCCM patients according to primary or secondary ICD indications.

ICD indications (table 2)

By definition in the primary prevention group the indication for ICD was heart failure or significant LV dysfunction. Two patients had a history of unexplained syncope without documented ventricular arrhythmias, including noninvasive and invasive electrophysiological testing. In the secondary prevention group 7 patients presented with cardiac arrest and 5 with sustained VT.

Table 2. ICD related data in 44 adult NCCM patients

	Primary prevention (n=32)	**Secondary prevention (n=12)**	***P***
Factors contributing to ICD indication*, n (%)			
• Heart failure due to systolic LV dysfunction	27 (84)	1 (8)	<0.001
• Asymptomatic LV dysfunction	5 (16)	3 (25)	ns
• Family history of SCD	9 (28)	4 (33)	ns
• Heart failure and LBBB	8 (25)	1 (8)	ns
• Sudden cardiac arrest / VF	0	7 (58)	<0.001

• Sustained VT	0	5 (42)	<0.001
• Syncope	2 (6)	2 (17)	ns
• Advanced AV block	1 (3)	0	ns
Type of the ICD, n (%)			
• VVI	12 (38)	8 (67)	0.10
• DDD	10 (31)	1(8)	ns
• Biventricular	10 (31)	3(25)	ns
Mean follow up, months	34 ± 26	29 ± 20	ns
Appropriate ICD therapy (ATP/shocks), patients, n (%)	4 (13)	4 (33)	ns
• Median time to any appropriate ICD therapy, days	240	182	ns
• Sustained VT	4	4	ns
• VT cyclus, ms, [range]	310 [280-325]	280 [240-310]	ns
• Sustained VF	0	0	
Inappropriate ICD shocks: patients, n (%)	6 (19)	3 (25)	ns
• Median time to ICD shock, days	130	50	
• AF	3	0	
• Sinus tachycardia	1	1	
• T-wave oversensing	1	1	
• Noise (lead fracture)	1	1	

SCD indicates sudden cardiac death; LBBB, left bundle branch block; VT, ventricular tachycardia; VF, ventricular fibrillation; AV, atrio-ventricular; AF, atrial fibrillation; ns, not significant (p>0.10).
*One or more item possible.

Biventricular pacemaker-ICD

In 10 patients the primary prevention group (31%) and 3 in the secondary prevention group (25%), the ICD was combined with a biventricular pacemaker, because of moderate to severe heart failure (NYHA class 2 or 3) in the presence of left bundle branch block (QRS width: 166 ± 22 ms). The clinical response to cardiac resynchronization therapy was favorable in 12 of these 13 patients (92 %) with improvement of the functional NYHA class from 2.8 ± 0.6 to 1.3 ± 0.6 (p<0.0001).

Complications and re-interventions

In 5 (11%) patients an early complication was reported, i.e. within 30 days of implantation: 2 patients with lead dislodgements, 2 patients with a pneumo-thorax, and one with a pocket infection. Late serious complication, which occurred after a median follow up of 9 months, included 2 patients with pericardial effusion and 2 with lead failures.

Appropriate and inappropriate ICD interventions (figure 2 A and 2B)

During a mean follow-up of 33 ± 24 months, 8 patients (4 primary, 4 secondary prevention) received appropriate ICD therapy (3 ATP; 5 shock), The median time to any appropriate ICD

therapy, ATP or shock, was 182 and 240 days respectively in the secondary and primary prevention group. Inappropriate ICD therapy, all shocks, was equally distributed in the primaryand secondary prevention groups. The majority of inappropriate therapy was triggered by oversensing (T-wave and noise). With univariate analysis, none of the recorded baseline characteristics appeared to predict appropriate or inappropriate therapies in our patient population. Multi-variable analysis was not attempted due to the low number of events.

Death or heart transplantation

During a mean follow up of 34 ± 26 months, two patients died due to end-stage heart failure and two patients were transplanted within the primary prevention group with chronic heart failure and severe LV dysfunction patients. No patients in the secondary prevention group were death or transplanted during a mean FU of 29 ± 20 months. In the non-ICD group two patients died; one patient from end-stage heart failure (earlier ICD refused) and one due to primary liver failure (mean FU of 56 ± 36 months)

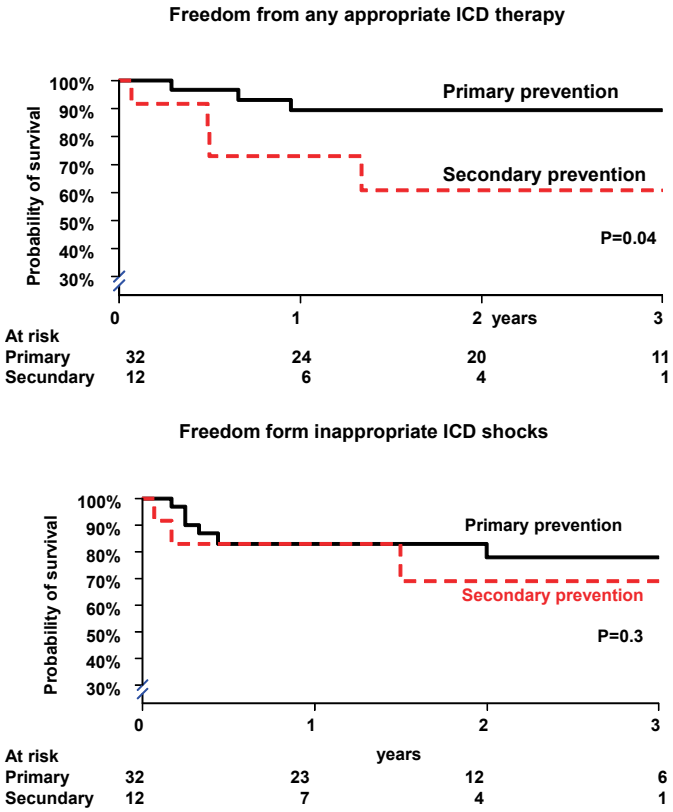

Figure 2. Kaplan-Meyer survival curves for freedom from *appropriate* and *inappropriate* ICD interventions in patients with NCCM according primary or secondary ICD indications.

DISCUSSION

According to current guidelines prophylactic ICD's were implanted for primary or secondary prevention of sudden cardiac death in our cohort of patients with NCCM. In total 44 out of 77 patients (57 %) received an ICD, most frequently (32 patients) for primary prevention. The relatively high percentage of appropriate shocks for sustained VT in our population confirms that these NCCM patients are at high risk for SCD and that implanting an ICD in these patients is appropriate, even though no patients with NCCM were included in previous trials which are the basis of the current guidelines. In fact, our data suggests that broader use of ICD therapy might be appropriate in clinical practice.

VT, degenerating into VF, is the most common pathway for sudden cardiac death (SCD) in patients with chronic heart failure and a non-ischemic cardiomyopathy, although brady-arrhythmic death and electromechanical dissociation in patients with progressive heart failure, has been reported.[9] In this context, it is interesting to see that all the appropriate ICD interventions in our patients were due to (fast) VT's, although, we do not know whether the initial rhythm from our SCD / VF patients were also started with a VT.

The implantable cardioverter-defibrillator (ICD) is the single most effective therapy to prevent sudden death in patient's resuscitated from sudden cardiac arrest or after an episode of ventricular tachycardia (VT). Therefore, ICD implantation is indicated for secondary prevention of SCD in survivor's of cardiac arrest or sustained VT.[2] In our cohort of NCCM patients, who presented with sustained VT or VF, there was a 33 % risk of recurrent sustained VT followed by appropriate ICD shocks after a median FU period of 26 months. Similarly, Kobza R et. al. reported 37% appropriate shocks during a mean follow up of 40 months among 30 NCCM patients with an ICD [10]. In a large ICD registry with predominantly patients with ischemic heart disease, 40 % of patients had appropriate ICD shocks while 16 % suffered inappropriate shocks.[11] In another series of 811 ICD patients, of whom 391 (48 %) had a non-ischemic cause, 22 % had an appropriate ICD shock and 17 % inappropriate shocks after a median follow-up period of 46 months.[12] These observations support our policy of applying the current guidelines to implant an ICD for primary prevention, based upon the presence of heart failure and /or severe LV dysfunction in combination with other (presumed) high risk factors in patients with NCCM.

NCCM is most likely a congenital cardiomyopathy, with a poor prognosis for certain adult patients.[7] The clinical presentation is highly variable, ranging from asymptomatic to end stage heart failure, lethal arrhythmias and /or thrombo-embolic events.[8] Furthermore, the first clinical case series described a high risk of ventricular tachy-arrhythmias and sudden cardiac death.[6] More recent reports show a more benign natural history, with lower risk for (malignant) ventricular arrhythmias.[13] The precise substrate for malignant ventricular ar-

rhythmias in the NCCM patients is not known.[14] The progression of the disease and evolution of the arrhythmic substrate remains speculative. Histological examination shows myocardium around deep intra-trabecular recesses which may serve as slow conducting zones with re-entry. Furthermore impaired flow reserve, causing intermittent ischemia, may play a role.[15] However, inducibility of sustained ventricular tachycardia during electrophysiological study has little value as a tool for risk stratification in patients with NCCM.[16].[14] Given the results of our study, representing the largest reported cohort of NCCM patients, ICD implantation should be considered for the primary prevention of sudden cardiac death due to malignant ventricular arrhythmias in patients with NCCM and impaired left ventricular function.

Specific risk factors for sudden cardiac death in NCCM patients have not been identified. In our cohort, severe LV dysfunction or dilatation were not prominent in the secondary prevention group with a history of sustained VT or VF, which makes it difficult to rely on the severity of the LV dysfunction for risk stratification for SCD. Frequent PVC's in patients with a prior myocardial infarction have been associated with an increased risk of death.[17] In contrast, in patients with non-ischemic cardiomyopathy, PVC's do not appear to be associated with a worse prognosis although data is limited.[18] Interestingly, there were more PVC's in our patients treated with an ICD than in the non-ICD NCCM patients. Furthermore there was a trend with higher numbers of PVC's in the secondary prevention group presenting with VT or VF, compared with those receiving an ICD for primary prevention. Non-sustained VT's at 24 hour Holter recording were also more frequent in the VT/VF group, as compared to the primary prevention patients and to those without ICD. This is in accordance with the association between NSVT and mortality which has been demonstrated in patients with ischemic and hypertrophic cardiomyopathy.[19] Other potential risk factors for sudden cardiac death in NCCM patients, like positive family history, syncope or inducible VT/VF must be taken into account, given the evidence in hypertrophic cardiomyopathy[20]. In this context, it is worth mentioning, that sarcomeric gene mutations were reported in the NCCM population, this implies that NCCM is part of a broader spectrum of cardiomyopathies, including hypertrophicand dilated cardiomyopathy.[5] Indeed, the strong familial character of this potentially devastating disease, warrants further research for appropriate risk stratification, especially in the asymptomatic patients or relatives carrying NCCM genes.

In addition to the psychological, social, legal or financial issues, there are several other complications associated with ICD therapy.. The incidence of major and minor complications have been reported in a prospective study of 778 patients receiving a transvenous ICD.[21] The rate of freedom from any adverse event at 1, 3, and 12 months was 79, 68, and 51 percent, respectively. In the present study, the complication rate was similar, with 11 % early and 9 % late ICD lead or procedural complication.

STUDY LIMITATION

This was a prospective observational study performed in a tertiary referral center to evaluate the indications and outcome of the prophylactic ICD therapy in patients with NCCM. Therefore, no reliable estimate could be made of the real incidence of the malignant ventricular arrhythmias resulting in sudden cardiac death. The study is also limited by the relatively small cohort, the lack of a control group of NCCM patients with similar characteristics without ICD and the small numbers of events. Nevertheless this represents the largest cohort looking into this rare entity.

CONCLUSION

Our data supports the use of current ICD guidelines for primary and secondary prevention of sudden cardiac death in NCCM patients. Further research is needed to develop more specific risk stratification and selection of NCCM patients in high risk of sudden cardiac death, especially in the asymptomatic NCCM patients and their relatives.

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The prevalence of early repolarization in patients with noncompaction cardiomyopathy presenting with malignant ventricular arrhythmias

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ABSTRACT

Background. Early repolarization (ER) is associated with malignant ventricular arrhythmias, including ventricular fibrillation (VF) and sudden cardiac death (SCD). One possible mechanism is increased trabeculation with deep intramyocardial invagination, carrying the Purkinje system deeper into the myocardium resulting in delayed depolarization and inhomogenous repolarization. Noncompaction cardiomyopathy (NCCM) is a recently classified, primary cardiomyopathy with excessive trabeculations. In these patients ventricular arrhythmias, including sustained VT and VF, occur frequently. The aim of this study was to determine the prevalence of ER in NCCM pts, especially in those primarily presenting with malignant ventricular arrhythmias or SCD.

Methods We analyzed prospective data from our NCCM registry including 84 patients, median age: 40 [3-79] years.

Results. Fourteen patients (17%) initially, presented with sustained VT (n=5) or VF (n=9) and 70 (83%) with heart failure or else. After the exclusion of 20 patients with left bundle branch block, 25 (39 %) NCCM patients had ER; three (6%) located in inferior leads, 14 (27%) in lateral leads and 8 (15%) in both. None had ER in leads V1 to V3. In those presenting with VT/VF 9/12 (75%) had ER (two in inferior leads, three in lateral leads and four in both), versus 16/52 (31%) in the other patients (p=0.02). If the NCCM population was dichotomized according to the presence or absence of ER, the long-term outcome for VT/VF appeared worse in the ER positive patients (p=0.05).

Conclusion. There is a high prevalence of ER in NCCM patients, especially in those who present with malignant ventricular arrhythmias.

Keywords: early repolarization, noncompaction cardiomyopathy, risk factors, ventricular tachycardia, ventricular fibrillation, sudden cardiac death

INTRODUCTION

Early repolarization (ER) and J-point elevation are common in the general population, in particular in healthy young individuals, black males and athletes. Until recently these ECG findings were considered benign.[1] In recent years however, a high prevalence of ER has been reported in athletes experiencing cardiac arrest or sudden death, in patients with in idiopathic ventricular fibrillation (VF) and in patients with a short QT syndrome.[2-4] Recent data suggest that in particular subjects with a horizontal or descending ST-segment morphology, are at risk for cardiac arrest, while a rapidly ascending or up sloping ST-segment carry a low risk.[5-6] Increased left ventricular (LV) trabeculation with deep endomyocardial invagination may be a cause of ER.[3, 7]

Noncompaction cardiomyopathy (NCCM) is a recently classified, primary cardiomyopathy with excessive trabeculation and a strong familial occurrence. [8] The clinical presentation includes congestive heart failure, thrombo-embolic events, supra-ventricular and ventricular arrhythmias and sudden cardiac death (SCD).[9] The diagnosis relies on morphological findings with cardiac imaging, in particular echocardiography or magnetic resonance imaging (MRI).[10] Malignant ventricular arrhythmias, including sustained ventricular tachycardia (VT) and, ventricular fibrillation (VF), have been reported in 38 to 47% and sudden cardiac death in 13 to 18% of adult patients with NCCM.[8-9] It should be appreciated that his could be an over-estimation due to selection bias in tertiary referral centers and that the majority of patients with NCCM presenting with VT /VF have no history of cardiac symptoms or signs.[11] There is little data to predict sudden cardiac death or malignant arrhythmias in NCCM patients.[12] Given the emerging association of ER with malignant ventricular arrhythmias in different patient populations[2-4] and possible patho-physiological association of ER with increased LV trabeculation (a hallmark of NCCM!),[7] we determined the prevalence, the type and outcome of early repolarization in NCCM, especially in those patients, primarily presenting with sudden cardiac death or malignant ventricular arrhythmia's.

METHODS

Study Population

The study cohort consisted of 84 consecutive adult NCCM patients (age ≥ 18 years) who were followed prospectively form 2005 to 2011 at the outpatient clinic in the Thoraxcenter, Erasmus MC, a tertiary referral center. The diagnosis of NCCM was established according to stringent echocardiographic criteria, as described by Jenni et al. [10] (see for example figure 1B and D):

- An excessively thickened left ventricular (LV) myocardial wall with a two-layered structure comprising a compacted epicardial layer and a noncompacted layer of prominent trabeculations on the endocardial side.
- A non-compacted/compacted myocardial thickness ratio ≥ 2 measured at the moment of maximal thickness in end-systole at the parasternal short axis.
- Color-Doppler evidence of deep inter-trabecular recesses in communication with the LV cavity.
- Absence of coexisting cardiac anomalies such as hypertension, coronary artery disease or valvular heart disease.

Patients were prospectively followed and the data were collated in the Thoraxcenter NCCM registry and analyzed in accordance with hospital institutional review board policies.

Data collection

Detailed data were registered at the time of clinical presentation and at follow-up, including age, gender, height, weight, blood pressure, cardiac diagnosis, New York Heart Association (NYHA) functional class, and use of cardiac drugs, including anti-arrhythmic drugs.

Left ventricular end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD) were obtained by two-dimensional transthoracic echocardiography. The presence or absence of significant valvular abnormalities or other abnormalities was recorded. Global LV function was estimated by visual assessment by two experienced observers and clasified as 1=normal LV function, 2= mild LV dysfunction, 3=moderate LV dysfunction and 4=severe LV dysfunction. Measurements of LV volumes and ejection fraction were not made because of the inherent problem to identify the endocardial border in the presence of extensive trabeculation. Fractional shortening (= (LVEDD-LVESD)/LVEDD x 100%) was measured.

All available ECG's (N=724; N=724; 11 ± 8 ECG's / patient)) at presentation and at follow up, were analyzed. Early repolarization was defined by consensus by two independent observers blinded to the clinical data. In 2 patients the two observers did not agree and a third observer was asked to decide upon the presence or absence of ER. Early repolarization was defined as elevation of the J point ≥0.1 mV, with QRS slurring or notching in more than two leads in the inferior leads (II, III, and aVF) or lateral leads (I, aVL, and V4 tot V6) as described by Haissaguerre et al (for example see figure 1A and C).[2] ST-segments patterns were defined as rapidly ascending/up sloping if the ST-segment was >0.1mV within 100 msec after the J point and horizontal/descending if this was ≤ 0.1.[5] The anterior precordial leads (V1 to V3) were excluded from analysis to avoid the inclusion of patients with arrhythmogenic right ventricular dysplasia or Brugada syndrome. ECG's with left bundle branch block (but not right bundle block) or nonspecific intra-ventricular conduction delay (i.e. QRS duration ≥ 120 ms) were regarded as not interpretable for ER. Heart rate, PQ, QRS and QTc intervals were

measured using ECG at presentation. The QTc interval was calculated after correction for heart rate with Bazett's formula. The presence of ventricular ectopy and (non-) sustained VT was identified on 24 hour Holter monitoring.

All patients were followed at the clinic for clinical review, ECG and echocardiography every 6 to 12 months or more frequently, according to clinical status. The choice of medication, including heart failure drugs, and anti-arrhythmic drugs, was made by the treating cardiologist. 48 (57%) patients received an implantable defibrillator according the current guidelines as described elsewhere.[11] The device was interrogated every 3 months or when necessary in the event of the onset of symptoms or device discharges.

Statistical Analysis

Continuous variables are summarized by mean ± SD or median and interquartile range (25th, 75th percentile) where appropriate. Categorical variables are presented as frequencies and percentages. Comparison of continuous variables between groups, was made by unpaired Student's t-test or the Mann–Whitney U test. When comparing frequencies, the Chi-square or Fisher's exact test were used, where applicable. Cumulative Kaplan–Meier survival curves were constructed for each outcome variable. All tests were two-tailed and P-values less than 0.05 were considered statistically significant. Fourteen patients presented initially with sustained VT or VF. This "VT/VF group" was compared with the other patients (n=70) with initial presentation of heart failure or for other reasons.

RESULTS

Baseline demographic and clinical characteristics of the 84 NCCM patients are summarized in *Table 1.* The primary presentation was sudden cardiac arrest, VF or sustained VT in 14 (17 %) patients and heart failure, unexplained palpitation, atrial fibrillation, cerebro-vascular accident or another reason in 70 (83 %) patients. There was no significant difference in the family history of cardiomyopathy or sudden cardiac death between these two groups.
After exclusion of 20 (24%) patients with left bundle branch block, 25 of the remaining 64 (39 %) NCCM patients had ER: 3 (6%) located in inferior leads, 14 (27%) in lateral leads and 8 (15%) in both (figure 2). None had ER in leads V1 to V3, like in Brugada syndrome. Nine out of 12 patients presenting with VT/VF (75%) had ER; two in inferior leads, three in lateral leads and four in both. Furthermore, ER was observed in 16 out of the other 52 patients (31 %; p=0.02) (Table 1 and Figure 1). In 4 out of 12 VT/VF patients and 5 patients from the other group, the ER was horizontal or descending, which was almost statistically significant (p=0.06). The location of ER in VT/VF group was more frequently inferior or infero-lateral than in non VT/VF group (p=0.004). Race had no effect on the prevalence of ER.

The presence or absence of ER was not consistent over time. In the majority (71 %) of the patients ER was dynamic. ER became more prominent in 43 % of the patients and less prominent in 29%. At long term FU, however, we observed no relation between concomitant presence of ER and acute clinical presentation at the emergency department, documented cardiac events or severity of the arrhythmias.

In the non VT/VF group, LV dysfunction and LV dilatation were observed more frequently than in those presenting with VT/VF, as might be expected due to the higher prevalence of heart failure. These patients also had more prominent trabeculations (both maximal myocardial thickness and noncompacted / compacted segment ratio). However, the percentage noncompacted (NC) segments were similar in both groups. Also, there was no correlation between the presence or absence of ER and the distribution or severity of the noncompacted segments along the inferior or lateral LV walls. (Figure 2A and B) The height of ER was at least 1 mm in both groups of patients; in 2 non VT/VF patients, the maximum height was above 2 mm. The 24-hour Holter recordings showed both frequent premature ventricular complexes (PVC's) and nonsustained VT's in patients presenting with VT/VF, reflecting the greater ventricular electrical instability in those patients.

Table 1. Baseline characteristics

	VT / VF group	Other group	P-Value
	N=14	N=70	
Demographic / clinical			
Age of presentation, median, range, y	37 [18-61]	40 [17-77]	0.5
Male sex, N (%)	8 (57)	32 (45)	0.6
Black, N (%)	0	11 (15)	0.2
Asian	0	3 (4)	
Presentation, N (%)			
• Heart failure,		27 38)	
• Atrial arrhythmias,		9 (13)	
• Ventricular tachycardia	5 (36)		
• Ventricular fibrillation	9 (64)		
• Thrombo-embolic events		9 (13)	
• Palpitations*		11 (15)	
• Other		12 (17)	
Familial NCCM	4 (29)	29 (41)	0.5
Familial SCD	3 (21)	11 (15)	0.7
Electrocardiographic			
Atrial fibrillation	0	8 (11)	0.3
1st degree AV block, N (%)	1 (7)	8 (11)	
QRS duration, mean SD, ms	104 ± 10	112 ± 32	0.5
QTc. ms	417 ± 35	418 ± 38	0.9

LVH	1 (7)	15 (21)	0.3
LBBB	2 (14)	18 (26)	0.5
RBBB	1 (7)	1 (1)	
Early repolarizations	9 (64)	16 (23)	0.003
• Inferior only	2 (14)	1 (1)	
• Lateral only	3 (21)	11 (16)	
• Both	4 (29)	4 (6)	
• Horizontal/descending	4 (29)	5 (7)	0.006
Echocardiography			
LA dimension, mean SD, mm	33 ± 12	43 ± 9	<0.001
LV end-diastolic diameter, mean SD, mm	55 ± 7	62 ± 11	0.02
LV end-systolic diameter, mm	41 ± 8	50 ± 12	0.01
Fractional shortening, %	25 ± 9	20 ± 8	0.02
LV noncompacted segments, %	51 ± 15	55 ± 15	0.5
Maximal NC+C thickness, mm (mean SD)	21 ± 3	24 ± 4	0.03
Maximal NC / C ratio (mean SD)	2.4 ± 0.3	2.8 ± 0.6	0.07
Holter data			
Number of PVC's / 24h, median[IQR]	25 [0.5-3359]	16 [1-526]	0.09
Nonsustained VT, n (%)	3 (21)	13 (18)	0.8
ICD, n (%)	14 (100)	34 (49)	
• VVI	12	16	
• DDD	0	7	
• BiV	2	11	
Drug treatment, n (%)			
• Beta-blockers	12 (61)	61 (87)	0.2
• Amiodaron	2 (14)	7 (10)	0.6
• Sotalol	1 (7)	1 (1)	0.3
• Class 1 AAD	1 (7)	2 (3)	0.4
• Digoxine	0	8 (11)	0.2
• ACE-I / AT-2	9 (64)	63 (90)	0.006
• Loop diuretics	3 (21)	35 (50)	0.04
• Spironolacton	1 (7)	19 (27)	0.1

LV indicates left ventricle; LA , left atrium; PVC, premature ventricular complex; QTc, corrected QT interval; LBBB, left bundle branch block; RBBB, right bundle branch block; AAD, antiarrhythmic drugs.

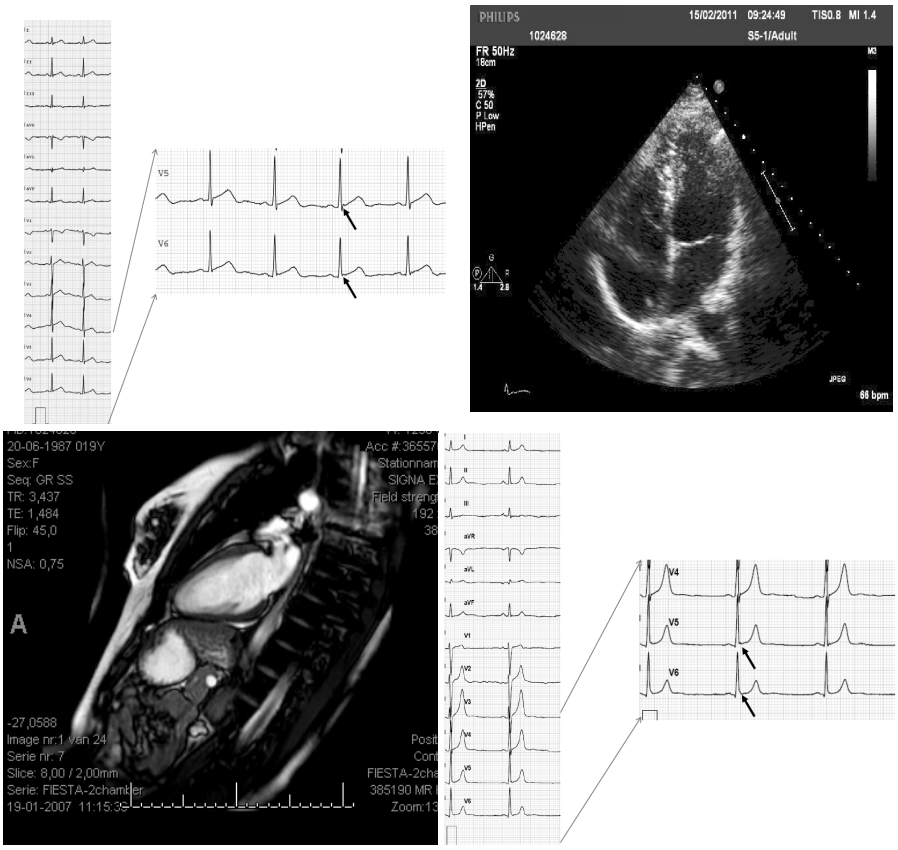

Figure 1A. Leads V5-V6 on the surface electrocardiogram of a 19 year old female with noncompaction cardiomyopathy, who survived a sudden cardiac arrest due to ventricular fibrillation (VF); there were early repolarizations both in inferior and lateral leads (arrows only for leads V5-V6 shown). **B.** Four-chamber echocardiographic view of this patient demonstrating extensive trabeculation in the apical en lateral LV walls (arrows). **C.** Two-chamber MRI view demonstrating extensive trabeculation in apical, anterior and inferior LV walls (arrows). **D.** Leads V5-V6 from a 37 year old male with early repolarization, who was resuscitated due to ventricular fibrillation 10 minutes before the end of a marathon.

Figure 2. Distribution of hypertrabeculaltion according the presence or absence of early repolarization in in apical, mid and basal regions of inferior (A) en lateral (B) left ventricular walls.

Median follow-up was 46 [IQR 18-86] months for VT/VF group and 67 [ICR 36-115] months for the other group (p=0.26). Four patients were lost to follow-up, one in the VT/VF group and three in the other group. Medical treatment was comparable in both groups. At long term follow-up VT/VF free survival (including appropriate ICD therapy) was significantly shorter in the VT/VF group (figure 3). If the NCCM population was dichotomized according to the presence or absence of ER, VT/VF free survival appeared worse in ER positive patients

(p=0.05; figure 3 B). There was no statistical significance seen when the analysis was applied for a subgroup of patients with ICD for primary prevention (p=0.19). None of these patients developed heart failure, while there were two cardiac transplants and four deaths in de the non VT/VF group. Two deaths were due to progressive heart failure and two due to non-cardiac disease.

Table 2. Long-term outcome after initial presentation according to the primary presentation.

	VT / VF group	Other group	P-Value
	N=14	N=70	
Median follow up, IQR, months	46 [18-86]	67 [36-115]	0.3
Ventricular arrhythmia's, n(%)	5 (36)	7 (10)	0.03
• Sustained VT / ICD therapy	5 (36)	6 (9)	
• VF	0	1 (1)	
Heart Failure, n (%)	0	13 (19)	0.11
HTX, n (%)	0	2 (3)	1.0
Death, n (%)	0	4 (6)	1.0

VT/VF indicates ventricular tachycardia/ventricular fibrillation; IQR, interquartile range; HTX, heart transplantation.

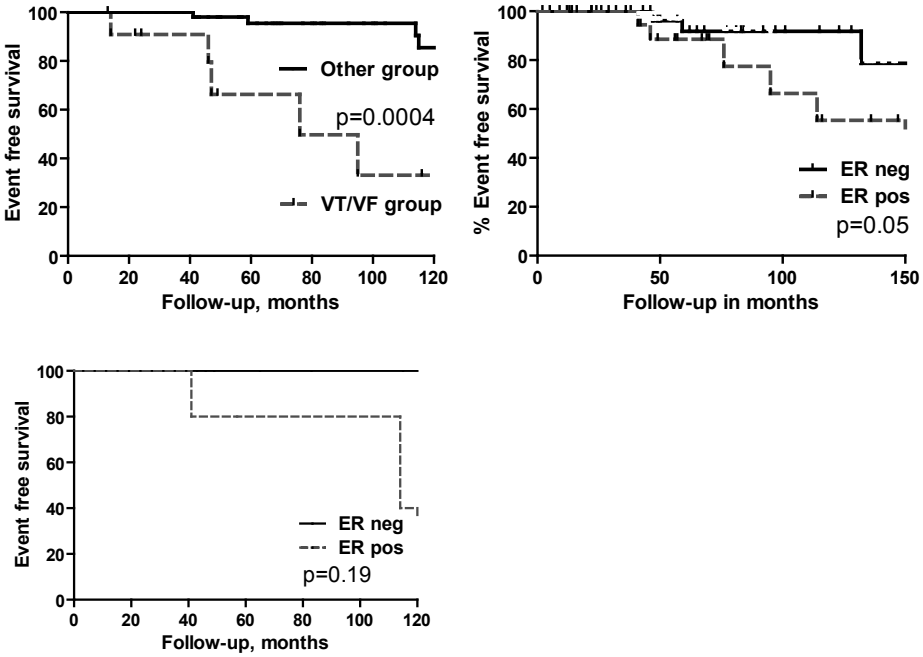

Figure 3. Kaplan-Meyer curves for VT/VF free survival in noncompaction cardiomyopathy patients (A) according the primary presentation (VT / VF group versus non-SCD group), if dichotomized according to the presence or absence of ER (B) and in ICD patients with only primary prevention indication (C).

DISCUSSION

Early repolarization is frequently observed in the young, in black males and in athletes. It also may be present in healthy adult subjects (3-14%) and was therefore considered to be a benign phenomenon.[1] However, in recent years a high prevalence of early repolarization has been reported in patients presenting with cardiac arrest or sudden cardiac death. [13-14] For example, a multicenter study reported early repolarization in one third of patients with idiopathic ventricular fibrillation.[2] In the present study we observed a high prevalence of ER in NCCM patients, especially in those patients presenting with malignant ventricular arrhythmias (75 %). Interestingly, early repolarization was also frequently observed (31%) in NCCM patients not presenting with ventricular arrhythmias.

Pathophysiology

The pathophysiology of ER and associated arrhythmias remains unclear.[15] Increased regional trabeculation, with deep intramyocardial invaginations carrying the Purkinje system deeper into the mid-myocardium, as in NCCM[10], may result in inhomogeneous depolarization and repolarization. This transmural heterogeneity may result in development of (malignant) ven-

tricular arrhythmias. Variable clinical conditions like hypothermia, increased vagal tone after meals and during the night and in athletes have also been associated with ER and J point elevation. In contrast, adrenergic stimuli suppress ER and associated arrhythmic events.[16] This explains the dynamic nature or lability of ER in a given patient.

It is unknown, whether specific genetic factors related to the cardiac ion-channels influence the vulnerability for ventricular arrhythmias with ER, but recent reviews suggest that ER is caused by dominance of I_{to}-mediated current of the ventricular epicardium.[17] This hypothesis is supported by evidence obtained in arterially perfused canine wedge preparations.[18] Interestingly, in the same report, ER was accentuated by excision of the endocardial layers. This is in agreement with our recent findings that normal LV twist is absent in patients with NCCM, which is probably due to an inmature endocardial helical system.[19-20] Some case reports suggest that quinidine, a drug that restores transmural electrical homogeneity and aborts arrhythmic activity, may diminish the electrocardiographic pattern of ER and could possibly prevent or reduce recurrence of arrhythmias in these patients.[16] However, clinical trials with quinidine in these setting are lacking.

Malignant arrhythmias in noncompaction cardiomyopathy

NCCM is most probably a congenital cardiomyopathy with a poor prognosis for particular adult patients. The clinical presentation is highly variable, including asymptomatic subjects, end stage heart failure, life threatening arrhythmias, thrombo-embolic events and sudden death. [8] The first clinical case series described a high risk of ventricular tachy-arrhythmias and sudden cardiac death.[9] More recent reports however, show a more benign course, with lower incidences of (malignant) ventricular arrhythmias and better survival rates. [21] The precise substrate for malignant ventricular arrhythmias in NCCM patients is not completely understood. [12] In NCCM myocardial cells positioned around deep intra-trabecular recesses may serve as slow conducting zones for reentry.[22] Furthermore impaired flow reserve, causing intermittent ischemia, may play a role.[23] All in all, specific risk factors for sudden cardiac death in NCCM patients have not been identified. In particular, inducibility of sustained ventricular tachycardia during electrophysiological studies has little value as a tool for risk stratification in patients with NCCM.[24] Therefore, the (very) high prevalence of ER (75 %) found in this study in NCCM patients with malignant ventricular arrhythmias, could be important. Interestingly, early repolarization was also frequently (31%) observed in NCCM patients not presenting with ventricular arrhythmias, probably reflecting the assumed association of ER with excessive trabeculation.[7] Accordingly, the predictive value of ER for sudden death in patients with NCCM is limited. The calculated sensitivity in our study is only 75 % and the specificity 69 %. This might be improved by precise localization and pattern of ER (inferior or infero-lateral versus lateral localisation and horizontal/descending type versus rapidly ascending / upsloping type of ER). Indeed, inferior or infero-lateral ER was more prevalent in the VT/VF group than non VT/VF group**.** This is in concordance with recent findings that the inferior or infero-lateral ER but not lateral ER was associated with cardiac arrhythmic death.[13] Also,

there was a strong trend to higher prevalence of horizontal/descending type of ER, which is marked as a high-risk form of ER in recent papers.[5-6] These findings suggest that ER may be a risk factor for malignant ventricular arrhythmias and sudden cardiac death in general and in specific patient populations.

Clinical implications

The strong familial character of NCCM warrants further research towards appropriate risk stratification, especially in asymptomatic patients or relatives carrying NCCM genes. In particular the contribution of ER to risk stratification should be further elucidated as part of a multiple test strategy, in combination with known risk factors in other cardiomyopathies, like low LV ejection fraction, family history of premature SCD, non-sustained VT's and unexplained syncope.[25] Currently such risk stratification is not possible and further studies are urgently needed. In the mean time, current international guidelines for non-ischemic heart disease could be used for prophylactic ICD implantation [11]

Study limitation

This observational study was performed in a tertiary referral center to evaluate clinical presentations and outcome in patients with NCCM. This may cause selection bias and these patients may not be representative of the larger population with NCCM. Accordingly, no reliable estimate could be made of the prevalence of early repolarization and the real incidence of the malignant ventricular arrhythmias and sudden cardiac death in an unselected group of patients with NCCM. The study is also limited due to the relatively small cohort and the low number of events during follow-up. Nevertheless this represents the largest reported cohort evaluating the prevalence of early repolarization in this rare condition.

CONCLUSION

Among patients with NCCM a high prevalence of early repolarization was observed, especially in those patients who present with malignant ventricular arrhythmia, or sudden cardiac death. Therefore, early repolarization may be a useful risk marker for malignant ventricular arrhythmias and sudden cardiac death in NCCM. Larger, confirmative studies are required to investigate whether early repolarization can contribute to risk stratification in this group of patients and to identify those in whom ICD implantation is warranted.

ACKNOWLEDGEMENTS

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Cardiac β-myosin heavy chain defects in two families with non-compaction cardiomyopathy: linking non-compaction to hypertrophic, restrictive, and dilated cardiomyopathies

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INTRODUCTION

Endocardial myocardium and a thin compacted (C) epicardial myocardium (maximal end-systolic ratio NC/C 2atparasternal short-axis view) with documentation of perfusion of the deep intertrabecular recesses with colour Doppler ow. Non-compaction cardiomyopathy (NCCM), also called isolated ventricular non-compaction (IVNC) or left ventricular noncompaction (LVNC), has recently been recognized as a novel cardiomyopathy.[1–3] It is characterized by an excessively prominent trabecular meshwork and deep intertrabecular recesses, as seen early in human embryogenesis.[4,5] The diagnosis is established by imaging the ventricular walls and cavities, by two-dimensional transthoracic echocardiography with colour Doppler ow, contrast echocardiography, left ventricular (LV) angiography, computed tomography, or magnetic resonance imaging.[4,6–10] The diagnostic criteria, as proposed by Jenni et al.,4 are clinically most convenient and include abnormally thickened ventricular walls with a two-layered structure, consisting of thickened, non-compacted (NC) Clinical manifestations include the triad of heart failure, (potentially lethal) arrhythmias, and/or thrombo-embolism, mostly affecting patients at a relatively young age. NCCM is genetically heterogeneous and can be inherited as an autosomal-dominant or X-linked disorder. Thus far no common genetic determinants for NCCM have been identified.[11] A small proportion of familial autosomal-dominant NCCM can be explained by mutations in genes encoding cytoskeletal or cell junction proteins, LMNA/C, a-dystrobrevin, and Cypher/ZASP.[12–15] In some families with X-linked NCCM, an association was found with mutations in the TAZ gene, which is allelic with Barth syndrome.[16] Mutations in the alpha-cardiac actin (ACTC) gene are a rare cause for hypertrophic cardiomyopathy (HCM) or dilated cardiomyopathy (DCM). Recently, a mutation in this gene was identified in five families with HCM, LVNC, and atrial septal defects (ASDs), originating from the same region in Spain.[17] Additional NCCM loci have been identi ed on chromosomes 1q43, 5q, and 11p15.[18–20] At the Cardiogenetics Centre of the Erasmus MC, molecular screening of sarcomeric genes in NCCM patients resulted in the identi cation of mutations in the sarcomeric cardiac ß-myosin heavy chain gene (MYH7) in two separate families with autosomal dominantly inherited NCCM.

METHODS

Diagnosis

In this study, the internationally acknowledged echocardiographic diagnostic criteria for NCCM were used, consisting of (i) segmental, excessive thickening of the LV wall with a two-layered structure: a thin, compacted epicardial layer and a much thicker, non-compacted endocardial layer with the characteristic appearance of numerous prominent trabeculations (meshwork) and deep intertrabecular recesses, (ii) colour Doppler evidence of deeply per-

fused intertrabecular recesses, (iii) predominant localization of thickening in the LV apical, mid-lateral, and mid-inferior walls, and (iv) the absence of co-existing cardiac anomalies.4 A clinical diagnosis of NCCM required compliance to all the four criteria.

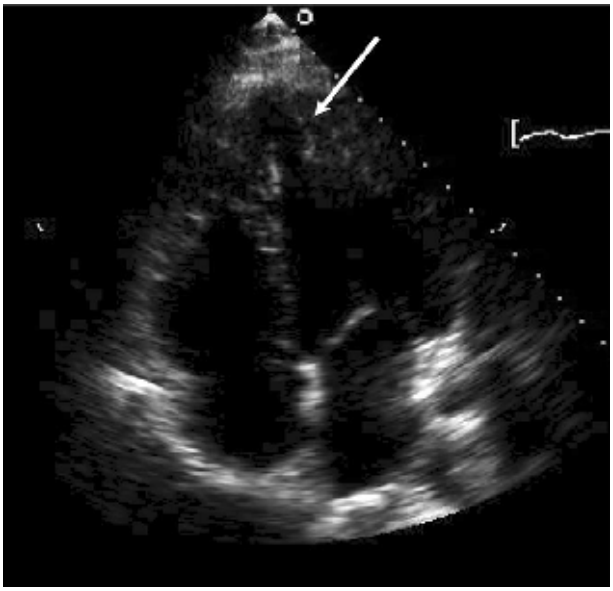

Figure 1 Two-dimensional echocardiographic four-chamber view of the 35-year-old asymptomatic sister of the proband of family A, showing excessive trabeculations of the apical (arrow) and mid-lateral left ventricular walls and mild left ventricular systolic dysfunction. The right ventricle was also excessively trabeculated.

Molecular analysis

Genomic DNA from index patients in autosomal-dominant NCCM families A and B was extracted from peripheral blood cells using standard techniques. Using a candidate gene approach, mutation analysis of the MYH7, TAZ, LMNA/C, MYBPC3, TNNC1, TNNT2, TNNI3, MYL2, MYL3, CSRP3, TCAP, ACTC, and TPM1 genes was performed using direct sequence analysis of all coding regions and intron–exon boundaries. Sequence analysis of M13-tagged PCR products was carried out on an ABI3730xl capillary sequencer using Big Dye Terminator v 3.1 chemistry (Applied Biosystems). (Details of the method and primer sequences are available on request.) Analysis of sequence data was performed using SeqScape analysis software (V2.5, Applied Biosystems). family, included screening of known genes associated with DCM and HCM and revealed a missense mutation in the p.Leu301Gln in exon 11 (nucleotide change c.902T.A) of the MYH7 gene in four NCCM patients of this family (Figure 2).[21] The p.Leu301Gln mutation segregated with the clinical features of NCCM in this family (Figure 3). The p.Leu301Gln mutation was not observed on 400 control chromosomes or in 300 HCM patients. p.Leu301Gln is in the functionally important globular head region (subfragment S1;

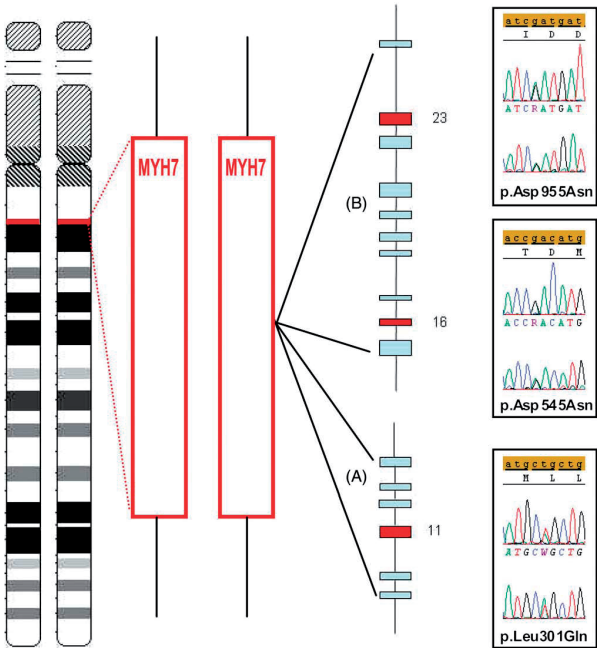

Figure 2. Schematic diagram showing chromosome 14 with the location of the MYH7 gene (14q12). Mutations were identified on one allele of the MYH7 gene in exon 11 in family A and in exons 16 and 23 in family B. Sequence traces show the mutations identified in families A and B.

the 'motor domain') of ß-myosin heavy chain, a region in which multiple pathogenic mutations have been described. Moreover, this mutation is pathogenic according to a prediction algorithm.[22] No mutations were found in the TA Z, LMNA/C,

Family A

In 2003, a 27-year-old woman presented with symptoms of severe congestive heart failure with progressive dyspnoea, fatigue, and oedema. Echocardiographically she had a moderately dilated LV with severe systolic dysfunction. The apical, lateral, and inferior walls were excessively thickened with prominent hypertrabeculation ('meshwork') with NC/C ratio .2. Her ECG showed sinus rhythm with left bundle branch pattern (QRS width 142 ms). Treatment with diuretics, ACE-inhibitors, b-blockers, and anticoagulants resulted in good clinical improvement. After 4 years of follow-up, she remains asymptomatic with NYHA functional class I. Her LV function also significantly improved with current LV end-diastolic and -systolic dimensions of 60/41 mm and fractional shortening of 32%. The familial history revealed a probably affected 27-year-old sister, who died 6 days after giving birth to her third child; LV function was severely impaired, with substantially dilated LA and LV. She developed clinical features of severe congestive heart failure with ventricular tachycardia and ventricular fibrillation, which could not be resuscitated. Her 73-year-old father was also known with con-

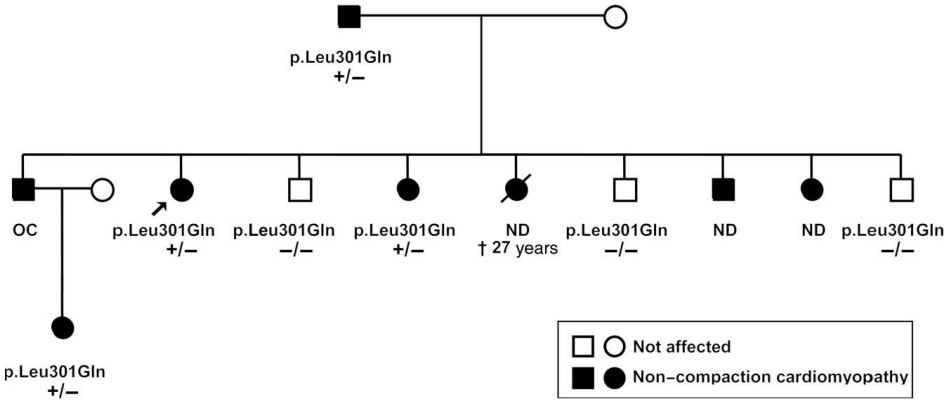

Figure 3 Pedigree of family A. The proband is indicated by the arrow. ND, not determined; OC, obligate carrier; þ/2, heterozygous for the p.Leu301Gln MYH7 mutation; 2/2, p.Leu301Gln absent.

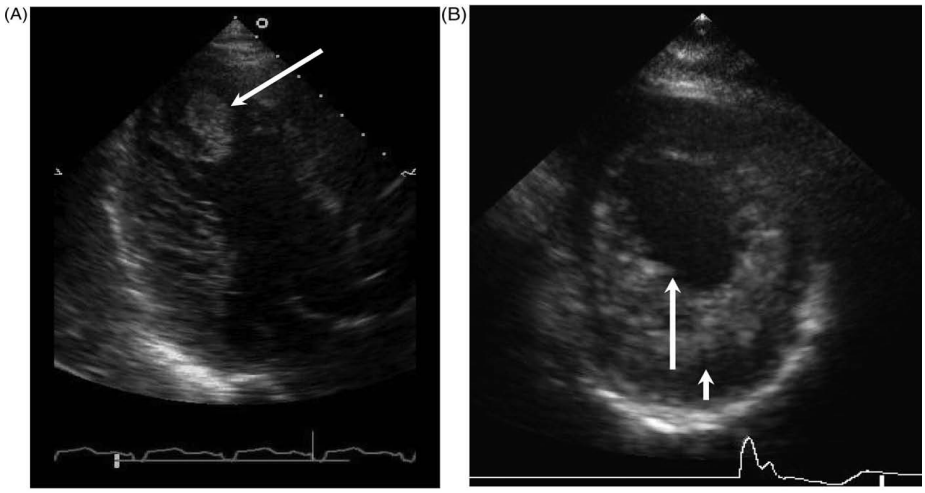

Figure 4 (A)Apicalthree-chamber and parasternal short-axis view of the index showing prominent thickened apical, lateral, and posteriorwalls of the left ventricle with loose meshwork of trabeculations; the arrow indicates the left ventricular thrombus; (B) arrows show the non-compacted to compacted ratio in systole is >2.

gestive heart failure, but also with coronary heart disease and diabetes. Echocardiography showed typical morphological features of NCCM, with excessively thickened myocardium of the apical, lateral, and anterior LV walls. Cardiological screening of seven asymptomatic siblings showed typical echocardiographic NCCM features in two sisters, aged 35 and 30, respectively, and two brothers, aged 34 and 49, respectively (Figure 1). The asymptomatic daughter of the eldest brother was also diagnosed with NCCM at age 24. Three brothers were free of cardiological features of NCCM. A candidate gene approach, to identify a genetic defect in this family, included screening of known genes associated with DCM and HCM and revealed a missense mutation in the p.Leu301Gln in exon 11 (nucleotide

change c.902T.A) of the MYH7 gene in four NCCM patients of this family (Figure 2).21 The p.Leu301Gln mutation segregated with the clinical features of NCCM in this family (Figure 3). The p.Leu301Gln mutation was not observed on 400 control chromosomes or in 300 HCM patients. p.Leu301Gln is in the functionally important globular head region (subfragment S1; the 'motor domain') of b-myosin heavy chain, a region in which multiple pathogenic mutations have been described. Moreover, this mutation is pathogenic according to a prediction algorithm.22 No mutations were found in the TAZ, LMNA/C, MYBPC3, TNNC1, TNNT2, TNNI3, MYL2, MYL3, CSRP3, TCAP, ACTC,and TPM1 genes.

Family B

In 2003, a 35-year-old man was hospitalized with severe symptoms of congestive heart failure. At the age of 3 years, he was treated for lymphoblastic leukaemia with chemoand radiotherapy (cytosine, arabinoside, methotrexate, and prednisone). Two months prior to hospitalization, he experienced progressive dyspnoea, orthopnoea, palpitations, fatigue, coughing, nausea, and vomiting. ECG showed sinus tachycardia with 123 b.p.m., a left bundle branch block (QRS width 154 ms), and biphasic P in V1. Echocardiographic examination revealed NCCM with severe systolic LV dysfunction (Figures 4A and B). Furthermore, a substantial thrombus was seen in the LV. Treatment with intravenous heparin and coumarine resulted in complete resolution of the LV thrombus after a few weeks (not shown). With diuretics, an ACE-inhibitor, and b-blocker therapy, an excellent clinical response was observed. After 2.5-year follow-up, he remains asymptomatic with moderate LV impairment. Cardiological screening of seven asymptomatic siblings showed typical echocardiographic NCCM features in two sisters, aged 35 and 30, respectively, and two brothers, aged 34 and 49, respectively (Figure 1). The asymptomatic daughter of the eldest brother was Although chemotherapy-induced cardiomyopathy was primarily considered, the typical echocardiographic features of NCCM warranted screening of rst-degree relatives, including both children Treatment with ACE-inhibitors, anticoagulants, and b-blockers was started. At follow-up, the ejection fraction improved and he remains free of symptoms. Neurological evaluation did not show features of limb girdle or progressive distal myopathy in this family. Cardiological evaluation of the father, suffering from Alzheimer's disease, similarly revealed NCCM at the apex of the LV. His ejection fraction was 45% at presentation.

His ECG showed sinus bradycardia. He is receiving treatment with ACE-inhibitors and anticoagulants. The asymptomatic 72-year-old sister of the father, with a history of diabetes mellitus type II and a coronary bypass, showed hypertrabeculation of the apical, inferior, and posterolateral LV walls, consistent with NCCM. A brother of the father died 2 years after being diagnosed with NCCM, at age 69. Neither of the parents of the father was known to have a heart condition; they both suffered a cerebro-vascular accident; the father died at age 78, the mother at age 75.

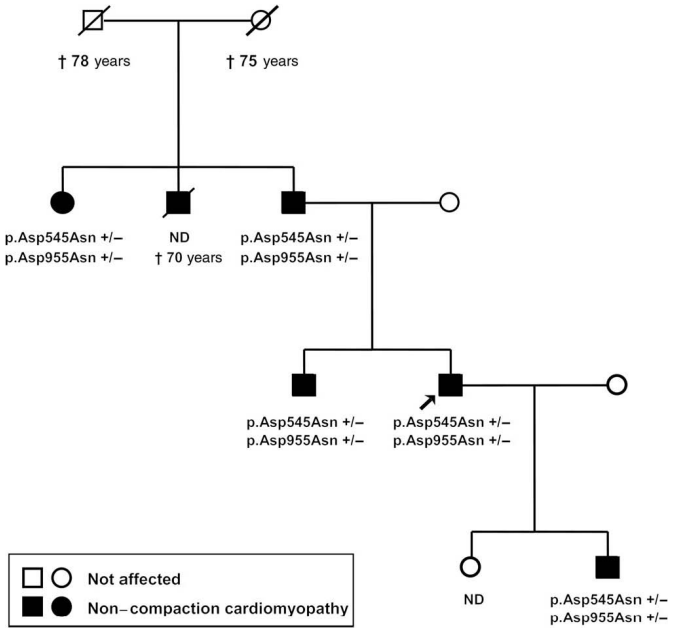

Figure 5 Pedigree of family B. The arrow indicates the proband. ND, not determined; þ/2, heterozygous for the p.Asp 545Asn and p.Asp 955Asn MYH7 mutations. † indicates deceased (death at this age).

DNA analysis of ve patients revealed the mutations p.Asp545Asn in exon 16 (nucleotide change c.1633G.A) and p.Asp955Asn in exon 23 (nucleotide change c.2863G.A) of the MYH7 gene (Figure 2).[21] Segregation analysis in this family subsequently demonstrated that these two MYH7 mutations were on the same allele (Figure 5). The p.Asp545Asn and p.Asp955Asn missense mutations were not observed on 400 control chromosomes or in 300 HCM patients. p.Asp545Asn is in the functionally important globular head region (subfragment S1; the 'motor domain') of the myosin heavy chain, a region in which multiple pathogenic mutations have been described. p.Asp955Asn is in the head–rod junction region (subfragment S2), a functionally important region for the interaction with the regulatory domain of myosin-binding protein C (MYBPC3).[23] Moreover, each of these mutations is pathogenic according to a prediction algorithm.[22] No mutations were identified in the TAZ, LMNA/ C, MYBPC3, TNNC1, TNNT2, TNNI3, MYL2, MYL3, CSRP3, TCAP, ACTC, and TPM1 genes.

DISCUSSION

Clinically, familial cardiomyopathies are classified as HCM, DCM, restrictive cardiomyopathy (RCM), and NCCM, also called isolated non-compaction of the left ventricle (IVNC) or left

ventricular non-compaction (LVNC) cardiomyopathy. The refinement of cardiac imaging techniques and more awareness among clinicians result increasingly in the recognition of the distinct features of NCCM, where in the past, misclassification may have occurred, particularly when suboptimal (i.e. older) imaging methods were used. Cardiological screening of relatives indicating familial recurrence of NCCM showed that genetic factors are important in the aetiology of this disease. In HCM, sarcomeric gene mutations are the predominant underlying genetic cause. Familial DCM is mainly associated with mutations in cytoskeleton and extracellular matrix genes, in addition to mutations in sarcomeric genes. Rare mutations, mostly in non-HCM/DCM genes, have been identified in a small proportion of familial NCCM. However, so far, no major genetic defect for NCCM has been identified. The identification of mutations in the MYH7 gene in two separate, large NCCM families suggests that MYH7 defects may be an important genetic cause for this form of cardiomyopathy. Defects in the MYH7 gene are a major cause of familial HCM and DCM, and, in addition, MYH7 mutations were recently shown to be associated with HCM with a restrictive phenotype (RCM).24 This article is the first to link MYH7 gene defects to familial NCCM. In family A, we found the single p.Leu301Gln mutation segregating with NCCM. In family B, we identified the missense double-mutation p.Asp545Asn/p.Asp955Asn on the same MYH7 allele segregating with the disease.

The majority of mutations in the MYH7 gene are missense mutations. Truncating mutations in MYH7, causing loss of function of one allele, are rarely observed. It is therefore unlikely that haploinsufficiency, i.e. the presence of only one intact allele of the gene, is the main underlying pathophysiological mechanism of MYH7-associated disease. This implies that the mutated MYH7 gene product acts as a 'dominant-negative' protein, perturbing the function of the protein formed by the normal MYH7 allele.25,26 This, so-called poison-polypeptide theory, easily accommodates the presence of double mutations on the same MYH7 allele, in which the second mutation further modifies the function of the mutated protein.27 Our findings show that a single mutated MYH7 allele, either carrying one missense mutation or a double missense mutation in cis, may result in dominantly inherited NCCM with a variable phenotype. The major cardiomyopathies are genetically heterogeneous diseases for which the causative genes are partially overlapping. The phenotypic variability of sarcomeric mutations is illustrated by MYH7 mutations, known to be involved in HCM, DCM, RCM, and NCCM (this study). Whether this means that these are different diseases or rather different manifestations (phenotypes) of the same pathological mechanism is presently not clear. The molecular basis of the phenotypic plasticity of MYH7 mutations remains unknown but it is likely to be multifactorial. It can be partially explained by the effect of different mutations on structural and regulatory components of the force generation and relaxation complex. Alternatively, effects of mutant proteins on energy homeostasis of the cardiomyocyte may influence disease outcome. The resulting phenotype is likely determined not only by the causal sarcomeric mutation but also by modifier genes, epigenetic factors, and environmental fac-

tors. Thus far it is thought that an intrauterine arrest of myocardial development with lack of compaction of the loose myocardial meshwork is the pathophysiological mechanism behind NCCM.28 MYH7 and other sarcomeric gene mutations are well known causes for late onset forms of HCM and DCM, presenting clinical features mostly at adult age. The identification of MYH7 mutations in familial NCCM and an ACTC mutation in HCM with NCCM and ASD,17 together with the observation of late onset NCCM in a Duchenne patient,29 suggests that the aetiology of NCCM extends beyond an arrest in embryonic cardiac development (i.e. the possibility of late onset NCCM). The current findings expand the genetic heterogeneity of NCCM, and the identification of MYH7 defects in familial NCCM suggests that NCCM may be part of a cardiomyopathy spectrum including HCM, RCM, and DCM. Regular cardiac follow-up of at-risk relatives is recommended in familial cardiomyopathies associated with sarcomeric defects. Similarly, periodic cardiological screening of unaffected at-risk relatives in familial NCCM could be necessary. Our observation also warrants molecular screening for MYH7 and possibly other sarcomeric defects in NCCM patients and has implications for cardiac screening for NCCM features in familial HCM, RCM, and DCM.

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The Importance of Genetic Counseling, DNA Diagnostics, and Cardiologic Family Screening in Left Ventricular Noncompaction Cardiomyopathy

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Background. Left ventricular (LV) noncompaction (LVNC) is a distinct cardiomyopathy featuring a thickened bilayered LV wall consisting of a thick endocardial layer with prominent intertrabecular recesses with a thin, compact epicardial layer. Similar to hypertrophic and dilated cardiomyopathy, LVNC is genetically heterogeneous and was recently associated with mutations in sarcomere genes. To contribute to the genetic classification for LVNC, a systematic cardiological family study was performed in a cohort of 58 consecutively diagnosed and molecularly screened patients with isolated LVNC (49 adults and 9 children).

Methods and Results—Combined molecular testing and cardiological family screening revealed that 67% of LVNC is genetic. Cardiological screening with electrocardiography and echocardiography of 194 relatives from 50 unrelated LVNC probands revealed familial cardiomyopathy in 32 families (64%), including LVNC, hypertrophic cardiomyopathy, and dilated cardiomyopathy. Sixty-three percent of the relatives newly diagnosed with cardiomyopathy were asymptomatic. Of 17 asymptomatic relatives with a mutation, 9 had noncompaction cardiomyopathy. In 8 carriers, nonpenetrance was observed. This may explain that 44% (14 of 32) of familial disease remained undetected by ascertainment of family history before cardiological family screening. The molecular screening of 17 genes identified mutations in 11 genes in 41% (23 of 56) tested probands, 35% (17 of 48) adults and 6 of 8 children. In 18 families, single mutations were transmitted in an autosomal dominant mode. Two adults and 2 children were compound or double heterozygous for 2 different mutations. One adult proband had 3 mutations. In 50% (16 of 32) of familial LVNC, the genetic defect remained inconclusive.

Conclusion. LVNC is predominantly a genetic cardiomyopathy with variable presentation ranging from asymptomatic to severe. Accordingly, the diagnosis of LVNC requires genetic counseling, DNA diagnostics, and cardiological family screening.

Key Words: noncompaction, cardiomyopathy, family study, genetics, hypertrophy, ventricles

Left ventricular noncompaction (LVNC) is a cardiomyopathy featuring segmental thickening of the LV wall with a thin compact, epicardial layer and an excessively thickened endocardial layer with prominent, deep intertrabecular recesses. Application of the echocardiographic diagnostic criteria for LVNC as postulated by Jenni et al[1] together with advances in cardiological imaging techniques have enhanced awareness and diagnosis of LVNC. Consequently, LVNC was incorporated in the most recent classification of cardiomyopathies as a genetic disease.[2] Prevalence of LVNC, estimated from retrospective studies, ranges from 4.5 to 26 per 10 000 adult patients referred for echocardiography.[3–5] LVNC was diagnosed in 3.7% of patients with an LV ejection fraction 45%, suggesting that LVNC might not be a rare disorder in adults.[5] In pediatric series, LVNC is the most frequent cardiomyopathy after dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM), comprising 9% of childhood cardiomyopathies.[6] Clinical features include heart failure, arrhythmias, and thromboembolic events.[3,7] Familial disease was estimated to occur in 18% to 50% of adults with isolated LVNC, mostly consistent with an autosomal dominant mode of inheritance.[3,8-13] Intra-familial phenotypic variability, including LVNC, HCM, and DCM, suggests that these cardiomyopathies may be part of a broader cardiomyopathy spectrum. The first association of isolated LVNC with mutations in the cardiac myosin heavy chain gene (MYH7) was reported in 2 unrelated Dutch families.[14]

LVNC also was associated with mutations in other sarcomere genes (cardiac troponin T [TNNT2] and cardiac α-actin [ACTC1]) in 17% of 63 adult patients with LVNC.[15–17] Linking LVNC to defects in the MYH7, TNNT2, and ACTC1 genes encoding sarcomere components that are frequent causes of HCM and DCM, provides additional evidence for a shared genetic susceptibility to LVNC, HCM, and DCM. Reports of mutations in lamin A/C (LMNA), α-dystrobrevin (DTNA), cypher/ZASP or lim domain binding 3 (LDB3), and sodium channel type V (SCN5A) expanded the genetic spectrum of LVNC.[18–20] Other genetic causes, characteristically in complex childhood LVNC with congenital heart defects or (metabolic) syndromes, include Barth syndrome with mutations in the Tafazzin gene (TAZ)[21,22] and rare chromosomal defects and loci.[23–30] The present study investigates the heredity of LVNC, the spectrum of clinical features, and the genetic causes of LVNC by combining systematic cardiological family studies with extensive molecular analysis.

METHODS

Study Population

The study comprised 58 unrelated patients with isolated LVNC; 53 were diagnosed consecutively from 2005 to 2008 in the cardiogenetics clinic of the Erasmus MC in Rotterdam and 5 in other tertiary referral centers in The Netherlands. All fulfilled the 4 echocardiographic diagnostic Jenni criteria: (1) excessively thickened LV myocardial wall with a 2-layered struc-

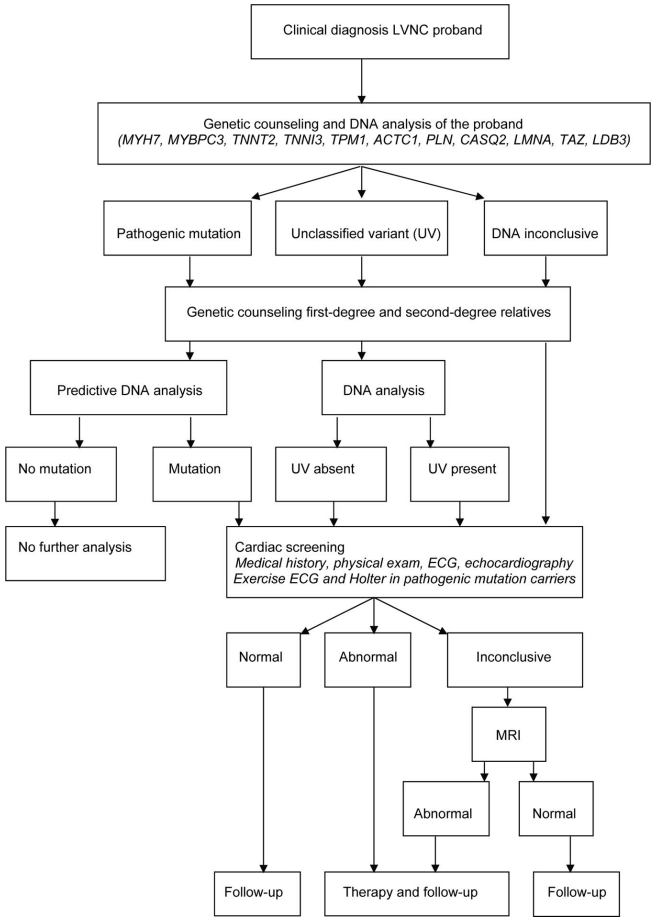

Figure 1. Flow chart for LVNC family screening.

ture comprising a compact epicardial layer (C) and a noncompacted endocardial layer (NC) of prominent trabeculations and deep intertrabecular recesses; (2) maximal end-systolic ratio of noncompacted to compacted wall 2 measured at the parasternal short axis; (3) color Doppler evidence of deep perfused intertrabecular recesses; and (4) absence of coexisting cardiac anomalies.[1] Subsequently, all patients were referred for genetic counseling and DNA analysis and to initiate family studies, as depicted in Figure 1.

Cardiological Family Study and Molecular Analysis

Family studies were initiated by ascertainment of family histories and inviting initially firstand second-degree relatives for genetic counseling. When possible, "cascade screening" for cardiomyopathies was pursued. Participation of 50 families of probands allowed inclusion of 194 relatives (Table 1). Relatives were referred for cardiological screening unless a familial pathogenic mutation had been detected. In that case, only mutation-positive individuals

Table 1. Descriptives of the LVNC Family Study

	Total	Men	Age of Onset/Screening Mean Years ± SD (Range)	Women	Age of Onset/Screening Mean Years ± SD (Range)
Probands	58	30	39 ± 17 (0 to 63)	28	37 ± 19 (0 to 66)
Adults	49	26	44 ± 12 (19 to 63)	23	43 ± 13 (19 to 66)
Children	9	4	7 ± 8 (0 to 17)	5	6 ± 6 (0 to 16)
Participating relatives	194	89	41 ± 21 (0 to 77)	105	43 ± 20 (0 to 78)
Parents	40	20	55 ± 15 (23 to 74)	20	56 ± 15 (23 to 78)
Siblings	64	27	38 ± 18 (3 to 66)	37	43 ± 17 (0 to 71)
Children	41	22	23 ± 15 (0 to 56)	19	33 ± 15 (11 to 47)
Second-degree relatives	43	18	51 ± 19 (15 to 76)	26	48 ± 21 (6 to 74)
Third-degree and more distant relatives	6	2	38 ± 1 (37 to 39)	4	41 ± 13 (5 to 55)

and relatives refusing DNA testing were examined cardiologically. Informed consent was requested to review medical records from 31 relatives who had cardiological examinations in other hospitals. Similarly, information was retrieved from the medical records of 13 deceased relatives reported to be affected. Details of the family studies of the probands identified with a genetic defect are presented in the Data Supplement.

Cardiological Family Study

Cardiological screening of relatives was performed by 2 cardiologists (K.C. and M.M.) and included a review of the medical history, physical examination, electrocardiography (Mortara Portrait, Milwaukee, Wis), and 2-dimensional echocardiography (iE33 system with a S5–1 transducer; Philips Medical Systems, Best, The Netherlands). If the imaging quality was poor, especially at LV apical or midventricular walls, MRI (1.5-T scanner; Signa CV/I, GE Medical systems, Milwaukee, Wis) was performed (n = 26). Measuring the maximal NC and C with electronic calipers in end-systolic parasternal short-axis or apical 4-chamber view assessed extent and severity of noncompaction. Relatives were diagnosed with LVNC when complying with the Jenni criteria and were diagnosed with DCM or HCM when meeting the current definitions.[31] When the ECG and echocardiogram were normal in relatives, LVNC or another cardiomyopathy was excluded. Other cardiological findings observed in relatives possibly associated with cardiomyopathy included ECG with pathological Q waves (>40 ms or >25% of R waves in at least 2 leads), LV hypertrophy, complete bundle-branch block, other intraventricular conduction, or repolarization abnormalities.

Molecular Study

DNA analysis in 56 probands was performed at the Department of Clinical Genetics and consisted of direct sequencing of all coding regions and intron-exon boundaries of the following

genes: MYH7, myosin binding protein C (MYBPC3), cardiac troponin C (TNNC1), TNNT2, cardiac troponin I (TNNI3), cardiac-regulatory myosin light chain (MYL2), cardiac-essential myosin light chain (MYL3), ACTC1,-tropomyosin (TPM1), cysteineand glycine-rich protein (CSRP3), theletonin (TCAP), calsequestrin (CASQ2), calreticulin (CALR3), phospholamban (PLN), TAZ, LDB3, and LMNA. One proband declined DNA analysis, and no DNA was available from 1 patient who died at 11 days of age. The parents of this patient were cardiologically unaffected and did not have a mutation. The mutations previously associated with cardiomyopathy (LVNC or HCM) were regarded as pathogenic. Novel mutations were considered to be pathogenic when they were truncating, splice-site, or de novo mutations or if they fulfilled the following 3 criteria: (1) segregation with disease in a family, (2) absence on 384 ethnically matched healthy control chromosomes, and (3) likely pathogenic according to prediction software (SIFT and PolyPhen).[32] DNA variants not fulfilling these criteria were considered unclassified variants.

Statistics

Statistical analyses were performed with SPSS for Windows 15.0 (SPSS Inc, Chicago, Ill). Unpaired Student t test analysis was used for continuous variables. Descriptive data for continuous variables were presented as mean 1 SD.[2] Analysis was used for categorical variables, and P values <0.05 were considered to be significant. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

The cardiological screening of relatives and the molecular analysis of probands and relatives combined showed that 67% (39 of 58) of LVNC is genetic (Table 2). The cardiological family study identified 64% (32 of 50) of isolated LVNC as familial. Genetic defects were identified in 50% (16 of 32) of cardiologically confirmed familial LVNC. In 50% (16 of 32) of familial disease, the genetic defect remained unknown. With extensive DNA screening,

Table 2. Cardiological Family Studies and Genotyping of 58 LVNC probands

	Cardiological Family Screening				
Proband	Positive	De Novo	Inconclusive	Not Performed	Total
With mutation	16*	1*	3*	3*	23
Without mutation	15*		13	5	33
Without DNA analysis	1*		1		2
Total	32		18†	8	58

*Genetic LVNC (total 39).
†Including the family of the de novo proband.

we found a mutation in 41% (23 of 56) of all tested probands. These results clearly indicate the importance of combining cardiological family screening for cardiomyopathy with genetic testing of patients with LVNC

Family histories reported by probands before DNA testing and cardiological family studies were performed failed to identify 44% (14 of 32) of familial disease. Only 9 (53%) of the 17 adult patients with a mutation reported familial disease before DNA testing and cardiological family evaluation. Familial disease was correctly reported by 8 of 14 (57%) adults without a mutation and by none of the parents of children with LVNC. Mutations were observed in 6 of 8 children with LVNC and in 17 of 48 (35%) of adult probands. LVNC was associated with defects in 6 sarcomere, 2 Ca^2 handling, and the LMNA, LDB3, and TAZ genes in this study. Mutations in sarcomere genes, in particular in MYH7, were the most frequent genetic defects: 9 of 57 adults and 2 of 9 children (Data Supplement; 1 through 9 and 18 and 19). None of the MYH7 mutation carriers had neuromuscular symptoms. Eighteen (32%) probands (14 adults and 4 children) had a single mutation consistent with an autosomal dominant

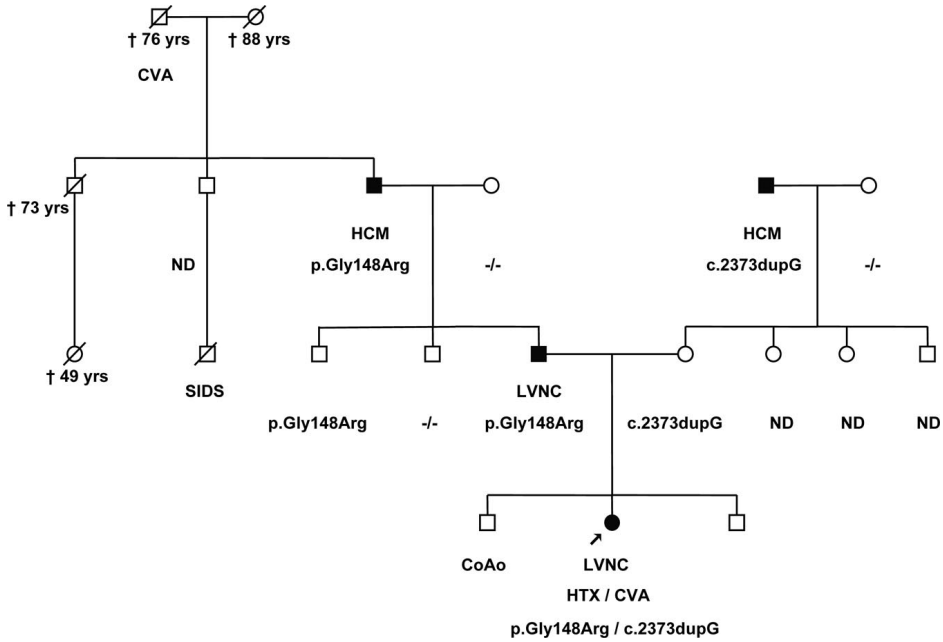

Figure 2. MYBPC3 p.Gly148Arg and c.2373dupG mutations in 1 family. Compound heterozygosity for 2 different MYBPC3 mutations in a patient with LVNC diagnosed at age 7 years from a family where 1 grandparent was previously diagnosed with HCM (Data Supplement; 23). Family studies identified a spectrum of cardiomyopathies: The asymptomatic parents were carriers, LVNC in the father and HCM in the paternal grandfather associated with the p.Gly148Arg mutation, and HCM in the maternal grandfather associated with c.2373dupG. Arrow indicates the proband; dagger, deceased. CVA indicates cerebrovascular accident; ND, not determined (ie, no cardiologic and molecular testing); SIDS, sudden infant death syndrome; CoAo, coarctation of the aorta; and HTX, heart transplant.

mode of inheritance. Two de novo mutations were observed: 1 in the asymptomatic father of an affected newborn and 1 in a young patient (Data Supplement; 20 and 21). Multiple pathogenic mutations occurred in 9% (5 of 56) of the probands. Two (22%) children (diagnosed at age 4 months and 7 years) had, respectively, mutations in TNNI3 and TPM1 and 2 different MYBPC3 mutations (Data Supplement; 22 and 23; Figure 2). Complex genotypes in adults constituted, respectively, of mutations TNNT2-LDB3 and LMNA-LDB3. One adult proband had 2 TNNT2 mutations and a CASQ2 mutation. In 5 families, unclassified variants were observed. Family studies are ongoing to determine the segregation in families and the phenotypic effect of multiple mutations or unclassified variants, especially in families where affected relatives were observed with single mutations (Data Supplement; 14, 16, and 22). DNA analysis was performed in 61 relatives from 20 families, confirming previous clinical diagnosis of 16 relatives: 12 with LVNC, 2 with HCM, and 2 with DCM. Foursymptomatic relatives (presenting with palpitations, fatigue, and shortness of breath) had a mutation and were diagnosed with LVNC by subsequent cardiological exams. Predictive DNA testing identified a mutation in 49% (17 of 41) asymptomatic relatives. Cardiological evaluation revealed that 53% (9 of 17) of the asymptomatic carriers had LVNC and 8 carriers showed nonpenetrance. Results of DNA analysis in relatives endorsed the pathogenicity of the mutation in 17 families. In 3 families with mutations, only unaffected carriers were identified; in 3 families, no cardiological or DNA family studies have been performed (Table 2).

Cardiological Studies

There was no difference in age at diagnosis in adult probands with respect to gender (P 0.4), between adults with 1 or multiple mutations and those without a mutation (P 0.4), or between the probands and affected relatives (P 0.2). In families with a mutation, unaffected adult carriers of a mutation were approximately the same age as the affected carriers (P 0.2). Fifty-six percent of unaffected carriers were older than 40 years, indicating nondependent or age-dependent penetrance of LVNC.

Similar proportions of adult probands with a single mutation and without a mutation were asymptomatic when diagnosed (29% and 16%; P 0.3; Table 3). All adult patients with multiple mutations presented with New York Heart Association class II and III. These differences cannot be attributed to a selection bias because clinical diagnosis of LVNC preceded DNA testing.

In 9 children, LVNC was diagnosed: in 4 before age 1 year, in 3 between 1 to 10 years, and in 2 between 10 and 18 years. The 2 children with multiple mutations were severely affected with cerebral infarctions, and 1 had a heart transplant at age 7 years (Figure 2). All the children were the first in their families to be diagnosed with cardiomyopathy; cardiological screening and DNA testing indicated familial LVNC in 89% (8 of 9) of their families; LVNC was diagnosed in 3 of 17 (18%) parents (as illustrated in Figure 3); and 3 of 15 (20%) were unaffected carriers. In total, cardiological screening was performed in 145 first-degree, 43

Table 3. Cardiological Features in LVNC Families

	Mutation*				No Mutation*			
	Probands (23)		Relatives (39)		Probands (35)		Relatives (49)	
	Adult (17)	Children (6)	Affected (34)	Other† (5)	Adult (32)	Children (3)	Affected (35)	Other† (14)
Age SD, y	41±11	6±6	41±21	43±15	46±13	6±10	43±15	48±16
Men	8	2	21	2	19	3	15	8
Presentation								
Asymptomatic	4		25	3	3		24	14
Heart failure	6	6	5		18	2	6	
Arrhythmias	5				6	1	1	1
Thromboembolism	1				3		1	
Other‡	1		2		3		1	
NYHA I	5		21	2	5		24	15
II	7		10	1	19		9	
III	5		2		8			
IV								
NC/C ratio 2	17		25		32		22	
NC/C ratio 1.0 to 1.9				3				9
ECG abnormal				1				8
LVH	1		4		4			9
Abnormal repolarization	4				8			
Abnormal Q	1		1		1			1
Bundle-branch block	4				9		2	
AV block			4					
T-wave inversion	1		1		4		1	
Diagnosis								
LVNC	17	6	25		32	3	22	
HCM			2				3	
DCM			6				9	
Congestive CM			1				1	
Family history of CM§	9	0			8	0		
Familial screening	15	5			27	3		
Familial CM	13	4			14	2		
Congenital heart defect in relative¶	2	2			3	1		

NYHA indicates New York Heart Association classification; NC/C ratio, ratio of noncompacted to compacted wall; LVH, left ventricular hypertrophy; and CM, cardiomyopathy. *Families with and without mutation. †Other includes NC/C ratio between 1.0 and 1.9 and/or ECG anomalies. ‡Chest pain (n 4), enlarged heart on x-ray, preoperative screening, prenatal sonography, and cardiac screening before Ritalin use. §Before cardiological family studies. Cardiological screening/DNA analysis. ¶Ebstein malformation, Fallot tetralogy, atrial septal defect type II and ventricular septal defect, or aortic coarctation in 4 families with a mutation. Valvular pulmonic stenosis; atrial septal defect type II, ventricular septal defect, or pulmonic atresia; or patent ductus arteriosus and aortic coarctation in 4 families without mutation.

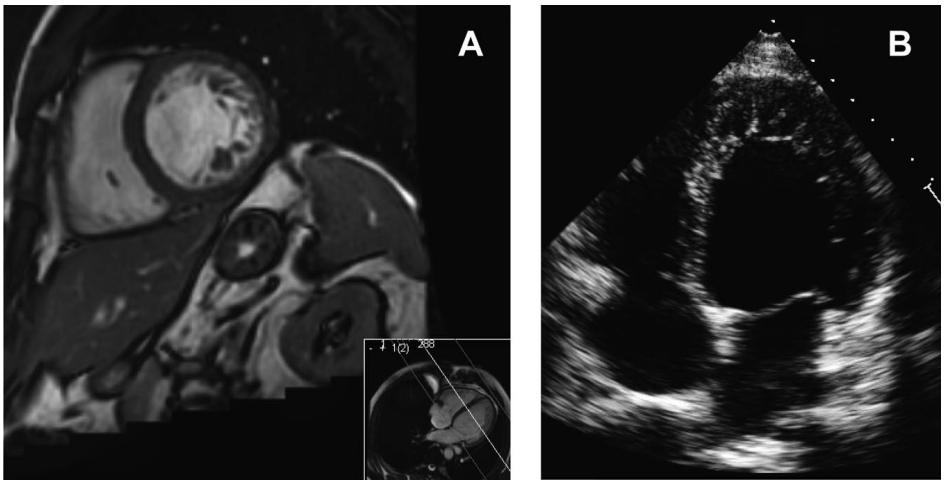

Figure 3. Cardiac MRI (A) and echocardiogram (B) illustrating a 2-layered myocardium with prominent intertrabecular recesses in the asymptomatic father with an MYBPC3 mutation (Figure 2).

second-degree, and 6 more distantly related relatives (Table 1). Of the 69 (35%) relatives diagnosed with cardiomyopathy 47 had LVNC, 5 had HCM, 15 DCM, and 2 congestive CM (Table 3). The majority (63%) of the relatives diagnosed with cardiomyopathy were asymptomatic. There was no significant difference in severe complications in affected relatives (heart failure, arrhythmia and thromboembolic events) in families without and families with a mutation (23% versus 13%; OR, 2.01; P 0.36). Two large families without mutation had recurrence of a severe phenotype; affected relatives in these families had been diagnosed prior to this study. In 34% (11 of 32) of familial disease, familial aggregation of LVNC, HCM, and DCM was observed. HCM and/or DCM was diagnosed in 4 families with a mutation (Data Supplement; 8, 10, 16, and 23; Figure 2) and in 7 families without a mutation (Table 3). In 7 families, congenital heart malformations were diagnosed. In 1 family with an MYH7 mutation, LVNC was associated with Ebstein anomaly, and in 2 families with MYBPC3 mutations, 1 relative with the mutation had Fallot tetralogy without LVNC and 1 had an aortic coarctation but did not have a DNA test (Data Supplement; 1, 10, and 22; Figure 2). In 3 families without a mutation, LVNC occurred together with valvular pulmonic stenosis, ventricular septal defect, atrial septal defect type II, pulmonic atresia, patent ductus arteriosus, or aortic coarctation in 6 relatives.

DISCUSSION

The approach of this study was to combine cardiological family studies with extensive genetic testing to establish a genetic classification of LVNC. The results showed that isolated LVNC is predominantly (67%) a genetic condition, including HCM and DCM in 11 families (34%).

The molecular screening of a large number of genes in this study allowed expanding the genetic spectrum of LVNC with novel genetic defects.

Genetic defects were identified in 41% of all patients and in 50% (16 of 32) of the cardiologically confirmed familial forms and consisted of 1 or more mutations in 11 different genes, indicating that further studies are needed to find causes for the remaining familial forms of LVNC. Molecular diagnosis of LVNC is important because it offers reliable identification of asymptomatic relatives at risk. In the absence of an identified genetic cause for LVNC, or when relatives decline DNA testing, cardiological screening remains the appropriate method to identify familial disease.

The proportion of familial disease in this study is higher than reported previously (18% to 50%) by studies investigating the prevalence of genetic defects in adult patients or ascertaining family histories of cardiomyopathy.[3,8-13] The systematic cardiological family screening showed that the majority (63%) of the affected relatives were asymptomatic, explaining that family histories without cardiological family studies failed to identify 44% of familial disease. Intrafamilial variability and incomplete penetrance, including asymptomatic disease, as well as small family size, may contribute to underestimation of familial disease. Therefore, cardiological evaluation of at-risk relatives of all patients with LVNC is recommended to enhance detection of familial disease, in accordance with the current expert consensus for family screening in HCM.[31] Familial screening for cardiomyopathies is important because early diagnosis in relatives may prevent severe complications. Nevertheless, predictive DNA testing and cardiological evaluation should only take place after relatives have been well informed about possible medical benefits of early diagnosis, including suitable treatment and lifestyle recommendations as well as psychological and socioeconomic consequences of predictive testing (particularly in countries where genetic discrimination by insurance companies or employers is not prohibited).

Similar to other familial cardiomyopathies, familial LVNC showed intrafamilial phenotypic variability, including HCM and DCM and reduced penetrance (ie, clinical symptoms not expressed or expressed to a lesser degree in some persons with the familial mutation).[3,12,33,34] In this study, nonpenetrance was observed in 8 relatives with a mutation ranging in age from 12 to 72 years. The risk of developing a cardiomyopathy in unaffected carriers is currently unknown and late onset cannot be excluded. Therefore, the implications of nonpenetrance include pursuing cardiological follow-up of unaffected relatives (as depicted in Figure 1). Nonpenetrance of LVNC calls for the continuation of cardiological surveillance of unaffected carriers. For families in which the genetic defect is unknown, continuation of cardiological follow-up of unaffected relatives and of family screening remains recommended until more families can be genotyped and the correct risk status of relatives can be established. Improved imaging by echocardiography and cardiac MRI has enhanced diagnosis and awareness of LVNC. However, establishing the extent to which physiological trabeculations are pathological remains difficult.[35]

Mutations in the sarcomere genes were found in 6 of 8 affected infants tested and in 17 of 48 adult probands. Although the number of children included in this study is too small to draw conclusions on the cause of childhood disease, molecular testing of sarcomere genes and systemic cardiological evaluation of first-degree relatives are recommended in early onset LVNC, especially in absence of dysmorphic features or metabolic defects. Congenital heart malformations in patients with LVNC should not refer from analyzing sarcomere genes. Our results endorse that co-occurrence of LVNC and congenital heart defects with and without sarcomere gene defect are not rare, warranting careful evaluation of the validity of the fourth of the Jenni diagnostic criteria.[15,17,36–38]

Two severely affected children and 3 adults were compound/double heterozygous, indicating that multiple mutations seem not to be significantly more prevalent in LVNC (22%) than in HCM (7%) (P=0.15).[39] In HCM, double heterozygosity for truncating sarcomere mutations have been associated with severe congenital forms of HCM, inherited in an autosomal recessive mode.[40–42] In this study, double mutations also were observed in adults with LVNC. The complex genetic defects in adults involved the combination of a sarcomere gene with another gene, suggesting that 2 sarcomere mutations may cause a more severe phenotype than the combination of a sarcomere mutation and a nonsarcomere mutation. The epigenic effect of multiple mutations may depend on the specific defects involved. Further studies are needed to investigate the role of additional mutations and determine whether they play a role in the phenotypic variability. For now, the evidence that sarcomere defects are an important cause for LVNC, together with the occurrence of LVNC, HCM, and DCM within families, suggests that these cardiomyopathies represent phenotypic variability within a spectrum and thus require comparable approach with respect to family screening.

The results of cardiological follow-up of families will help to understand the natural history of LVNC, to determine whether LVNC represents a congenital endomyocardial defect or may develop later in life, and eventually to attain recommendations for follow-up of relatives on the basis of accurate risk classification.[43] The perspective of new studies investigating modifying genetic effects or genome-environment interactions to explain variability and age-dependent penetrance of this phenotype is challenging.

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Frequency of Asymptomatic Disease Among Family Members With Noncompaction Cardiomyopathy

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ABSTRACT

Noncompaction cardiomyopathy (NCC) is a primary cardiomyopathy characterized by an excessively prominent trabecular meshwork and deep inter-trabecular recesses of the left ventricular walls. Most cases are inherited, with a dominant inheritance pattern. The aim of this study was to determine the prevalence and clinical characteristics of cardiomyopathies in close relatives of NCC patients. We evaluated 156, mostly 1st degree, family members of 44 adult NCC patients who consented for familial screening. A family history of cardiac disease was reported by 16 of the 44 patients (36%), including premature sudden death in 8 (18 %) families. A diagnosis of NCC (n=32) or DC (n=9) was made in 41 (26 %) relatives by echocardiography (n=38), contrast echocardiography (n=6) or MRI (n=10). Thirteen of these family members were already known with cardiac symptoms and signs, but the majority (28/41) were asymptomatic. Most subjects with NCC had mild to moderate LV dysfunction (n=29, 71%). After a median follow-up of 55 months [IQR 43-93]), the majority of them remained asymptomatic. Four family members were treated with prophylactic ICD implantation and 23 of those with NCC were treated with drugs, including ACE-inhibitors (41%), beta-blockers (34%) and anticoagulants (17%). In conclusion there is a high prevalence, mostly asymptomatic, of cardiac disease (26%) among 1st and 2nd degree family members of patients with NCC. This warrants screening and offers an opportunity for early intervention.

Keywords: noncompaction cardiomyopathy, familial screening, asymptomatic LV dysfunction, preventive treatment.

INTRODUCTION

Noncompaction cardiomyopathy (NCC) is a primary cardiomyopathy, originally described in 1984 and characterized by an excessively prominent trabecular meshwork and deep inter-trabecular recesses of the left ventricular (LV) walls.[1-3] NCC may present with heart failure, arrhythmias, embolic events or sudden cardiac death, but it may also be detected in asymptomatic individuals.[4] Most cases are familial with a dominant inheritance pattern.[5] As other cardiomyopathies, NCC is associated with different mutations of sarcomere genes. Some mutations have been found in patients with hypertrophic, dilated as well as noncompaction cardiomyopathy.[5-7] As cardiac disease can progress for years without any symptoms, preventive cardiac screening of the asymptomatic relatives may aid in the understanding of the pathogenesis of NCC. Furthermore, early diagnosis, before the onset of advanced symptomatic diseases, may improve patient management and prognosis. The aim of this study was to determine the prevalence and the clinical characteristics of cardiomyopathies in close relatives of NCC patients.

METHODS

Since 2005, adult patients with NCC and their family members are prospectively followed in our center, a tertiary referral center. Their data are collected and analyzed in accordance with hospital institutional review board policies. We obtained detailed family histories from all 80 patients in the registry to construct pedigrees. The family history was considered abnormal, if this was positive for non-ischemic heart failure, cardiomyopathies, documented supraventricular or ventricular arrhythmias, or pacemaker/ICD implantation. From 44 patients we obtained informed consent to contact family members and completed the screening and counseling as described below (see Table 1). Subsequently, the 44 patients were referred to a clinical geneticist for genetic counseling, to initiate family studies and to obtain further informed consent for DNA analysis. The results have been published recently.[5] All living first-degree relatives of these 44 patients were invited for cardiac examination after appropriate counseling. When possible, "cascade screening" for cardiomyopathies was pursued. From 231 first degrees relatives, 136 (59%) accepted the invitation for cardiac screening (median 60% IQR[20-83%].

Cardiac evaluation of 156 relatives was done by two experienced clinicians (KC and MM). Evaluation consisted of a review of the medical history, physical examination, electrocardiography (ECG) and two-dimensional echocardiography. From the ECG's heart rate, PQ, QRS and QTc intervals were measured. The QTc interval was calculated after correction for heart rate with Bazett's formula. The ECG was considered abnormal if it showed pathological Q's (>40 ms or >25 percent R waves in at least two leads) , left ventricular hypertrophy, complete

bundle branch block or nonspecific intraventricular conduction delay or (minor) repolarisation abnormalities.[8] LV end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD) were obtained by two-dimensional echocardiography, as well as the presence or absence of significant valvular abnormalities. Measurements of LV volumes and ejection fraction were not made because of the inherent problem to identify the endocardial border in the presence of extensive trabeculation. Global LV function was estimated by visual assessment by two experienced observers and classified as 1 = normal LV function, 2 = mild LV dysfunction, 3 = moderate LV dysfunction and 4 = severe LV dysfunction. Additionally, fractional shortening was measured: (LVEDD-LVESD)/LVEDD x 100%. The extent and severity of noncompaction was assessed by measuring the maximal non-compacted (NC) and compacted (C) wall thickness with electronic callipers in the parasternal short axis or the apical 4-chamber view, in end-systole. The *diagnosis of NC* was made if prominent trabeculations were present with a NC/C ratio > 2 at the end-systole, regardless of the LV function.[2] In case of MRI diagnosis, a non-compacted /compacted ratio of > 2.3 at end-diastole was taken.[9] Because of poor echo image quality, especially at the level of the LV apical or mid-ventricular walls, magnetic resonance imaging (MRI; n=10 (6%)) or contrast echocardiography (n=6 (4%)) was performed for firm diagnosis in 14 subjects (10%).[10] All echo and MRI images were reviewed by both clinicians and the diagnosis was made by consensus. Cardiac assessment was extended with 24 hours ECG monitoring and an exercise test (X-ECG) when NCC or other heart disease was suspected because of complaints, abnormal ECG, echocardiogram or MRI. The diagnosis of NCC was established according to stringent echocardiographic criteria, as described by Jenni et al: [2] a) an excessively thickened left ventricular (LV) myocardial wall with a two-layered structure comprising of a compacted epicardial layer and a non-compacted layer of prominent trabeculations on the endocardial side, b) a non-compacted/compacted myocardial thickness ratio > 2 measured at the moment of maximal thickness in end-systole at the parasternal short axis, c) color-Doppler evidence of deep inter-trabecular recesses in communication with the LV cavity, and d) absence of coexisting cardiac anomalies such (in the presence of isolated NCC)`. Dilated cardiomyopathy (DC) were diagnosed in case of myocardial abnormalities, not fulfilling the diagnosis of NCCM.

Continuous variables are summarized by mean ± SD or median and interquartile range (25th, 75th percentile) where appropriate. Categorical variables are presented as frequencies and percentages. Comparison of continuous variables between groups was made by unpaired Student's t-test. When comparing frequencies, the Chi-square or Fisher's exact test was used, where applicable. All tests were two-tailed and P-values less than 0.05 were considered statistically significant.

RESULTS

Baseline characteristics of index patients, with or without family screening, were fully comparable (Table 1). A total 156 close relatives of 44 unrelated NC patients accepted our invitation for cardiac screening and counseling (Figure 1 and Table 2). With cardiac screening, familial disease was present in 49%. Sudden cardiac death below the age of 60 years was reported in 8 (18%) families. In 1 sibling and 2 children, congenital heart diseases had been diagnosed before the family screening; including a combination of pulmonary valve stenosis and ASD in 2 subjects.

NCC or DC was found in 41 relatives (26%) by trans-thoracic 2D echocardiography (25), MRI (10) or contrast echocardiography (n=6) (see Figure 2 as an example; Table 3). It is of interesting that all relatives whom was defined as DC, had some form of prominent trabeculations (NC/C ratio between 1.0 -2.0), but not fulfilling the diagnostic criteria of NCC (NC/C ratio > 2.0). An abnormal ECG was observed in 51 subjects (33%). Of the 41 subjects with NCC or DC, 16 (39%) had a normal ECG. Thirteen (32%) of the subjects with NCC were already

Table 1. Clinical characteristics of noncompaction cardiomypathy index patients, with or without family screening.

Variable	Family screened (N=44)	Not screened (N=36)	P-value
Mean age at presentation (years)	39 ± 15	42 ± 13	ns
Men	20 (45%)	19 (53%)	ns
Family history of cardiomyopathies	16 (33%)	14 (39%)	ns
Family history of sudden cardiac death	10 (23%)	6 (17%)	ns
Heart failure	20 (45%)	16 (44%)	ns
Arrhythmias	11 (25%)	7 (19%)	ns
• Supra-ventricular	3 (8%)	1 (3%)	ns
• Sustained ventricular tachycardia or fibrillation	8 (18%)	6 (17%)	ns
Thrombo-embolic events	3 (7%)	3 (7%)	ns
Miscellaneous	10 (23%)	10 (28%)	ns
Left atrium (mm)	40 ± 10	42 ± 8	ns
LV end-diastolic diameter (mm)	60 ± 10	60 ± 10	ns
LV end-systolic diameter (mm)	48 ± 12	49 ± 12	ns
Fractional shortening, %	21 ± 8	20 ± 9	ns
% Noncompacted segments	58 ± 11	57 ± 12	ns
Noncompact/compact ratio	2.5 ± 0.3	2.5 ± 0.3	ns
Implantable cardioverter defibrillator	27 (61%)	18(50%)	ns
Heart transplantation	3 (7%)	1 (3%)	ns
Death	1 (2%)	2 (6%)	ns

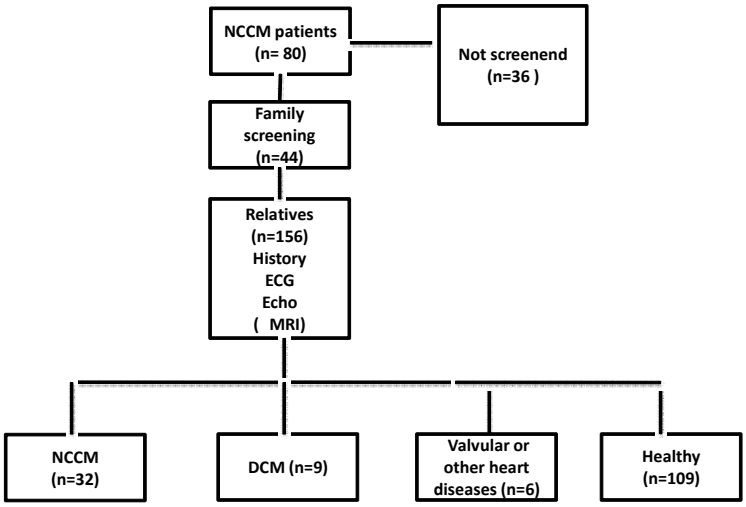

Figure 1. Summary of the evaluation of the close relatives of patients with NCC.

Table 2. Overview of the screened noncompaction cardiomyopathy relatives according to the family relations.

	Total	Parents	Siblings	Children	Second-degree
Numbers of patients	156	34 (22%)	58 (37%)	44 (28%)	20 (13)
Age at presentation, mean ±SD (years)	41 ± 19	60 ± 8	41 ± 13	24 ± 12	47 ± 15
Male	69 (44%)	16 (47%)	21 (36%)	24 (55%)	8 (40)
History of cardiac disease*	18 (12%)	5 (21%)	4 (7%)	6 (14%)	3 (15)
• Heart failure / DC	6	3	1	2	
• Supra-ventricular arrhythmias	7	2	1	2	2
• Thrombo-embolic events	2	1		1	
• Congenital heart disease	3		1	2	
• Chest pain	1				1
• Valvular heart disease	1		1		
• Coronary heart disease	1	1			
• Syncope	1			1	
Abnormal electrocardiogram	51 (33%)	13 (38%)	17 (29%)	13 (30%)	8 (40)
Abnormal echo	45 (29%)	10 (29%)	16 (28%)	15 (34%)	4 (20)
• Noncompaction	32 (21%)	7 (21%)	15 (26%)	12 (27%)	4 (20)
• Dilated cardiomyopathy	9 (6%)	1(3%)	5 (9%)	3 (7%)	
• Valvular heart disease	2 (1%)	2 (6%)			
• Congenital heart disease	3 (2%)		1 (2%)	2 (5%)	
Total NCC / DC	41 (26%)	8 (24%)	16 (28%)	13 (30%)	4 (20)

*=one or more combinations possible.

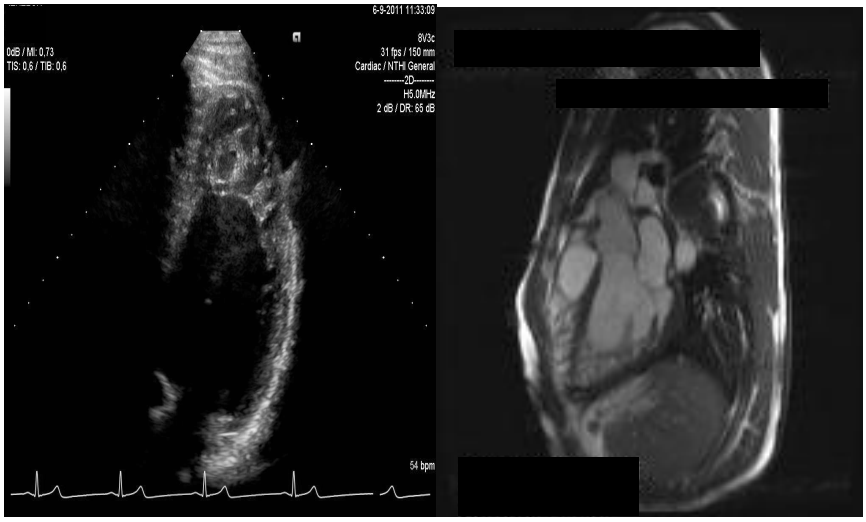

Figure 2. Close view of 4-chamber echocardiographic and 3-chamberMRI view of a 25 years old asymptomatic son of a female who was firstly presented in 2010 with paroxysmal atrial fibrillation and heart failure due to severe LV dysfunction at an age of 58 years. At the MRI, he had an ejection fraction around 40 % and prophylacticly treated with an angiotensin-converting enzyme inhibitor and a beta-blocker.

known with cardiac symptoms and signs, but the majority (n=28; 68%) was asymptomatic. The 6 patients, whom presented with heart failure and/or cerebrovascular accident, were previously regarded as DC, but at revision fulfilled the Jenni criteria for NCC. Most subjects with NCC had mild (n=21; 51%) or moderate to severe LV dysfunction (n=8; 20%).
After a median follow-up of 55 months [IQR 43-93]; Table 4), the majority (80%) of the 41 family members with NCC remained asymptomatic. Four patients were treated with prophylactic ICD implantation, because of significant LV dysfunction at the time of the screening and a positive family history of sudden cardiac death. Drug therapy was prescribed in 23 (56%) of the 41 subjects with NCC, including ACE-inhibitors (41%), beta-blockers (34%) and anticoagulants (17%).

DISCUSSION

The present study confirms a familial inheritance pattern in about half of patients with NCC. Indeed a positive family history (presence of nonischemic heart failure, cardiomyopathies, documented supraventricular or ventricular arrhythmieas, pacemaker / ICD implantation) may suggest a familial inheritance pattern in about half of the patients with NCCM. In the subset of 44 patients of whom relatives were screened cardiomyopathies were documented in 26%. Whether this proportion is correct remains unclear, because this may be result

Table 3. Clinical, electrocardiographic and echocardiographic characteristics of screened noncompaction cardiomyopathy relatives.

Variable	Affected (N=41)	Not affected (N=115)	P-value
Mean age at diagnosis, years	36 ± 19	43 ± 19	0.02
Male	23 (56%)	46 (40%)	0.10
Hypertension	2 (5%)	16 (14%)	ns
Diabetes Mellitus	2 (5%)	2 (2%)	ns
Coronary artery disease	1 (2%)	1 (1%)	ns
Congenital heart disease	2 (5%)	1 (1%)	ns
Asymptomatic	28 (68%)	110 (96%)	<0.0001
Heart Failure (NYHA)	5 (12%)	0	0.009
• I	2	0	
• II	3	0	
Supra-ventricular arrhythmias	4 (10%)	3 (3%)	0.08
Cerebro-vascular events	2 (5%)	0	0.08
Miscellaneous*	3 (7%)	2 (2%)	0.06
Abnormal electrocardiogram	25 (61)	26 (23)	0.0001
Atrial fibrillation	2 (5%)	1 (1%)	Ns
1st degree AV block	1 (2%)	2 (2%)	Ns
Bundle branch block	1 (2%)	0	Ns
Left ventricular hypertrophy	4 (11%)	6 (5%)	Ns
Nonspecific intra-ventricular conduction abnormality	5 (14%)	7 (6%)	Ns
T-wave inversion (lateral / inferior)	2 (5%)	0	0.08
Minor repolarization abnormality	10 (24%)	11 (10%)	0.03
Left atrium, mean ± SD (mm)	40 ± 8	39 ± 6	Ns
Intraventricular septum (mm)	9 ± 2	9 ± 2	Ns
Left ventricular end-diastolic diameter (mm)	56 ± 7	50 ± 5	<0.0001
Left ventricular end-systolic diameter (mm)	42 ± 8	31 ± 5	<0.0001
Fractional shortening , %	26 ± 7	36 ± 7	0.001
LV dysfunction	29 (71%)	1 (1%)	<0.0001
• Mild	21 (51%)	0	
• Moderate	4 (10%)	1 (1%)	
• Severe	4 (10%)	0	
Non-compacted segments (%, mean ± SD)	47 ± 14	0	
Non-compacted /compacted ratio (mean ± SD)	2.6 ± 0.3		
Valvular abnormalities	4 (10%)	3 (3%)	0.08

*=More than one item possible.

Table 4. Clinical management and outcome of the relatives with noncompaction or dilated cardiomyopathy.

Variable	Noncompacted	Dilated	Total
Number of patients	32	9	41
Follow-up, median [IQR], months	58 [38-97]	50[39-60]	55 [43-93]
• Lost to follow-up	3 (9%)	0	3 (7%)
Asymptomatic	24 (75%)	9 (100%)	33 (80%)
Heart Failure	3 (9%)	0	3 (7%)*
Supra-ventricular arrhythmias	2 (6%)	0	2 (5%)*
Thrombo-embolic events	0	0	0
Drug treatment	21 (66%)	4 (44%)	23 (56%)
• Anticoagulation	0	0	7 (17%)
• ACE-I /ARB	17 (53%)	3 (33%)	20 (49%)
• Beta-blocker	13 (40)	3 (33%)	16 (39%)
• Diuretics	5 (16%)	0	5 (10)
• Aldosterone antagonists	1 (3%)	0	1
• Digoxine	1 (3%)	0	1
Implantable cardioverter defibrillator	4 (13%)	0	4 (10%)
Death	1 (3%)	0	1 (cancer)

*= previously known; IQR=interquartile range; ACE-I= angiotensin converting enzyme inhibitor; ARB= angiotensin II receptor blocker.

of the sampling error due to premature death of some affected relatives or their refusal to participate or, perhaps, incomplete penetration. It should be appreciated that without systematic cardiac screening the majority (68%) of the diseased close relatives would have remained undetected, missing the opportunity for pre-symptomatic treatment. The absence of symptoms or signs of heart disease (68%), and of ECG abnormalities (39%) does not exclude the presence of NCC or another cardiomyopathy. Cardiac evaluation, including echocardiography or MRI is indispensable to reach a correct diagnosis.[2] Therefore, complete cardiac evaluation is essential in familial screening of NCCM patients.

The published cohorts of NCC patients are rather heterogeneous, reporting 18 to 51% prevalence of familial disease.[4,11-13] Although routine familial screening of first-degree relatives is generally recommended.[14] little is known about the distribution and spectrum of cardiac abnormalities in asymptomatic relatives of NCC patients. Using detailed history taking, ECG, echocardiography and MRI this study revealed frequent (26 %) disease in asymptomatic relatives. Furthermore 8% of all relatives had NCC with, already known, cardiac symptoms such as congestive heart failure, supra ventricular arrhythmias or cerebrovascular events. Interestingly, the prevalence of asymptomatic disease was equally distributed among closer and more distant relatives This finding supports the expansion of familial screening beyond the first degree family members as recommended in the recent guidelines, albeit there is a

high probability of selection bias in our study due to selective response on our invitation for familial screening .[15]

Screening of family members of patients with non-ischemic cardiomyopathy is advised because early diagnosis provides an opportunity for early treatment. Appropriate pharmacologic therapy, can significantly improve outcome in patients with asymptomatic LV dysfunction defined as an LV ejection fraction (LVEF) ≤ 35 to 40 %.[16-17] In addition implantation of an ICD may be appropriate, to prevent sudden cardiac death.[18-19] In this study LV dysfunction was present in 71 % of NCC or DC positive family members. Interestingly, there was also prominent trabecualtions in the DC group, probably suggesting a some sort of forme fruste of NCC like also known in other familial diseases like.[20] There are no large-scale trials that have specifically evaluated ACE inhibitors or beta-blockers in patients with non-ischemic, asymptomatic left ventricular dysfunction. Sufficient benefits however were observed in the SOLVD prevention trial to be able to justify the use of these medications.[16-17] In the SOLVD prevention trial in 4228 patients (83 percent post-MI) with asymptomatic LV dysfunction, prophylactic administration of enalapril reduced the probability of death or congestive heart failure by 29 percent. [16] In the placebo arm, patients with asymptomatic LV dysfunction not treated with an angiotensin converting enzyme inhibitor (ACE) progressed to symptomatic HF at a rate of 9.7 percent per year.

Screening of family members may help us to understand the pathogenesis and development of the disease. Genetic testing is useful in families where the genetic cause of the disease has been recognized.[21] Different mutations in different genes are reported, including sarcome gene mutations in about one third of the patients.[5,7] Some mutations related to NCC are also related to other cardiomyopathies suggesting common genetic pathways. In the majority of patients with a familial pattern of NCC, however, the genetic variations are as yet unknown. Therefore, the diagnosis depends on cardiac evaluation including cardiac imaging to recognize the prominent trabecular mesh and deep intertrabecular recesses of the LV walls. In addition, cardiac screening is appropriate in relatives of patients when the index patient or his / her relatives refuse genetic testing as well as in asymptomatic relatives with a documented NCC mutation. Recently, we described rigid body rotation as a new echocardiographic parameter with good predictive value for the diagnosis of NCC.[22] This could add an objective, quantitative functional criterion, aiding the correct diagnosis in NCC family members. In this study however, we did not yet implement such analysis.

In the current heart failure guidelines concluded that the weight of evidence supported screening first-degree relatives of patients with all non-ischemic cardiomyopathies with an electrocardiogram and echocardiogram. Families with a strong positive family history should be referred to a cardiovascular genetic center.[23] Indeed outcomes are expected to be impaired if effective therapy is delayed until patients develop overt heart failure, (potentially lethal) arrhythmias and /or embolic events. Regular cardiac follow-up of at-risk relatives is advised in familial cardiomyopathies associated with sarcomeric defects. The current data support

periodic cardiological screening of unaffected at-risk relatives in familial NCC.[24] However, because of possible psychological-, social-, legal-, insuranceor employment consequences, routine family screening should only been initiated after discussion of the possible medical benefits of early cardiac diagnosis of cardiac disease.[15]

The true frequency of familial disease in cardiomyopathies is probably underestimated. Increased awareness and ample use of imaging modalities, like echocardiography and MRI, will improve recognition of NCC. This should give new opportunities for timely intervention and increase our knowledge about the course of the disease.

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Bradycardiomyopathy: the case for a causative relationship between severe sinus bradycardia and heart failure

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ABSTRACT

A 28-year-old man presented with progressive fatigue. Physical examination and ECG revealed severe sinus bradycardia. Echocardiography showed features of non-compaction cardiomyopathy and moderate aortic valve regurgitation. We hypothesized that the chronic volume overload exaggerated by prolonged diastole due the bradycardia, resulted in heart failure and non-compaction cardiomyopathy look-a-like features. After implantation of an AAI pacemaker, his symptoms and signs of cardiomyopathy were fully recovered.

Keywords: bradycardiomyopathy; bradycardia; heart failure; pseudo-noncompaction cardiomyopathy

CASE

A 28-year-old man was referred because of progressive fatigue (functional NYHA class II). Physical examination revealed prominent bradycardia (40 bpm) and a blood pressure of 160/70 mm Hg. There was a systolic ejection and diastolic decrescendo murmur maximal at the 3rd left intercostal space. The ECG showed sinus bradycardia, normal AV conduction, and left ventricular (LV) hypertrophy. The 24hour Holter recording showed sinus rhythm with a mean heart rate of 44 bpm [range 2792 bpm] and frequent sinus node pauses lasting up to 2.7 secs during the night. Transthoracic echocardiography demonstrated severe dilatation of both the left atrium (LA 56 mm) and the left ventricle (end-diastolic dimension LVEDD: 76 mm, end-systolic dimension LVESD: 52 mm) with mild systolic LV dysfunction (LVEF: 48 %). There were prominently thickened apical, mid-lateral and mid-inferior LV myocardial wall segments, with a two-layered appearance; a thick non-compacted endocardial and a thin compacted epicardial layer with a ratio > 2, resembling non-compaction cardiomyopathy (NCCM; figure1). There was moderate aortic regurgitation due to prolaps of the non-coronary cusp (jet width/LVOT: 19 %, regurgitant volume 30 ml/beat). MRI confirmed the dilated LV with mildly diminished systolic function, and widespread trabeculations compatible with non-compaction cardiomyopathy. Bicycle exercise testing showed mildly diminished exercise tolerance (maximal 200 Watts or 81 % of predicted) with a heart rate increase from 38 bpm at rest to 136 bpm at maximal exercise and blood pressure rise from 160/80 to 250/100 mm Hg.

An electrophysiological study was performed to elucidate the mechanism of the severe bradycardia. No AV conduction disturbance and no arrhythmias could be induced. However, there was a significantly low intrinsic heart rate of 69 bpm after full vagal and sympathetic blockade (through infusion of 19 mg (0.2 mg/kg) propanolol and 3.8 mg (0.04 mg/kg) atropine intravenously; age / sex corrected norm: 101 bpm) indicating sinus node dysfunction.

Although the echocardiographic and MRI data indicated NCCM [1] , we considered the possibility of pseudo-NCCM, resulting from chronic volume overload caused by the combination of severe bradycardia (prolonged diastole) and moderate aortic regurgitation. It was thought that moderate aortic regurgitation alone could not explain the severe LV dilatation. The only major causative factor being severe bradycardia, we decided to implant an AAI pacemaker, and prescribe an ACE-inhibitor. After implantation of the AAI pacemaker, his symptoms rapidly improved, he returned to work as a telecommunication technician and restarted his favorite sport badminton. He became completely symptom free and a series of echocardiographic follow-up visits showed significant improvement of LV diameters.

At the last follow-up, 2.5 years after initial presentation, he was completely asymptomatic. Echocardiography showed complete recovery of the cardiac dimensions (LVESD 54, LVEDD 37 mm, LA 27 mm; figure 2) with a normal systolic LV function (EF 55 %). The aortic insufficiency had remained unchanged (ie moderate) over time. Although his abnormal LV

trabeculations were less prominent, his echo findings still were compatible with NCCM[1]. His exercise tolerance returned to normal (max. 240 W, 100 % predicted), with a heart rate increasing from 70 bpm to 164 bpm as a result of atrial pacing with rate response. Blood pressure rise from 140/75 mm to 239/60 mm Hg.

The association of sinus bradycardia and heart failure is a complex and multifactorial problem. Sinus bradycardia was reported to worsen the outcome of patients with heart failure; however, a causative relationship was never demonstrated.[2] To the best of our knowledge this is the first report demonstrating the causative relation between sinus bradycardia and a dilating "cardiomyopathy" causing heart failure. The unique nature of this case is that symptoms and ventricular chamber dilatation were effectively treated with AAI pacemaker implantation. It shows also nicely, that chronic volume overload may result in similar morphological features as in NCCM, which is a recently classified primary cardiomyopathy.[3] In fact, there is a known association between sinus node dysfunction and NCCM, which is attributed to the abnormal myocardial vascular supply or angiogenesis.[4,5] Therefore, the question remains if the noncompaction features in our patient are primarily due to chronic volume overload or due to primary myocardial disease.

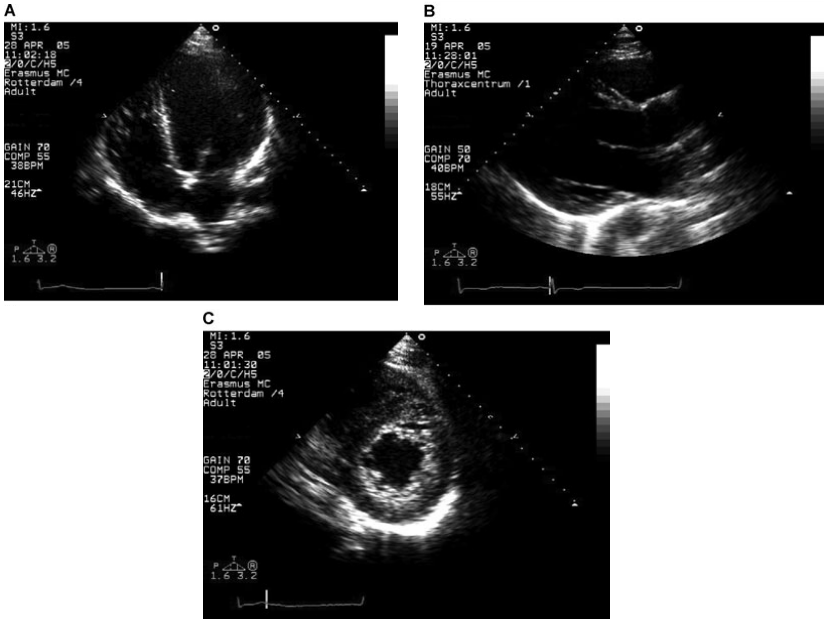

Figure 1. ***A, B, and C.*** *Echocardiographical left ventricular apical 4-chamber and parasternal long axis views in the end-diastole (A, B) showing severely dilated left ventricular (LV). The parasternal short axis view in end-systole shows excessive trabeculations (C) with 2-layered aspect: a thick noncompacted endomyocardial side and compacted epicardial side of the left ventricular myocardium (noncompacted/compacted ratio > 2).*

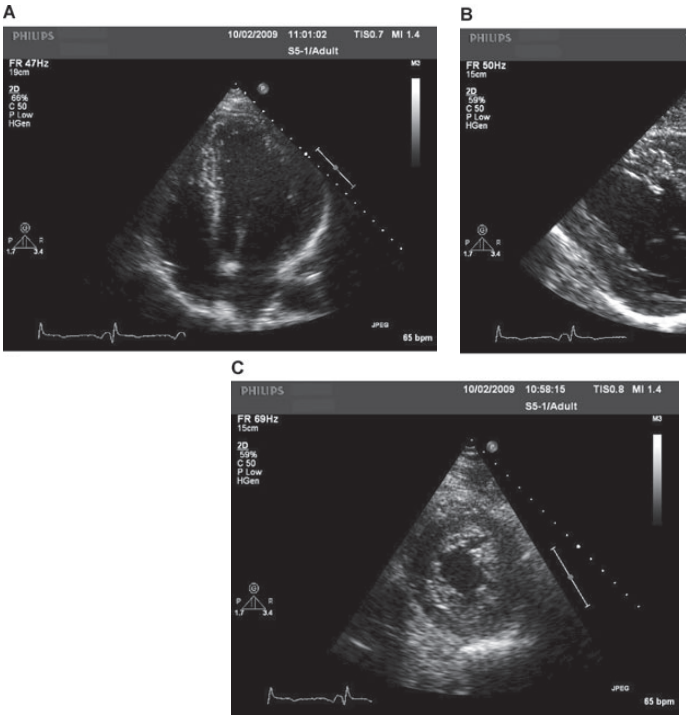

Figure 2. ***A, B, and C.*** *The echocardiographical views after 2.5 years' follow-up.*

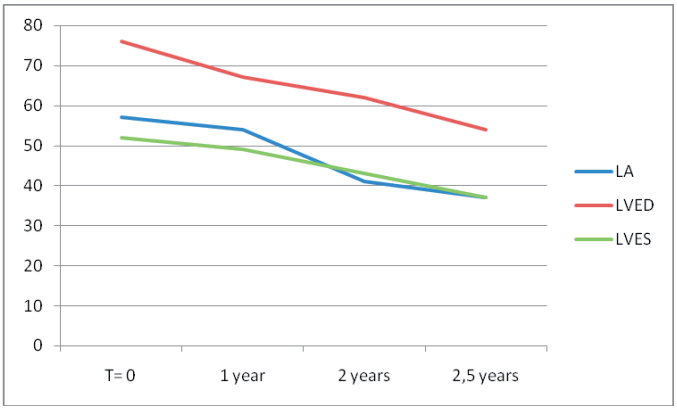

Figure 3. The left atrial (LA), left ventricular end-diastolic (LVED) and end-systolic (LVES) dimensions in millimeters, before (T=0) and after atrial pacing.

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How Should I Treat?

An Unusual Referral for Heart Transplantation

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Summary

Background: A 55 years old man was referred for cardiac transplantation because of intractable angina and fatigue.
Investigations: Physical examination, laboratory test, echocardiography, exercise ECG, MRI and coronary anteriography.
Diagnosis: multiple coronary artery fistulae.
Management: beta-blockers, angiotensin-converting enzyme inhibitor, ICD.

Keywords: refractory angina pectoris, coronary angiogram, coronary artery fistula, noncompaction cardiomyopathy, and cardiac transplantation.

HOW SHOULD I TREAT?

The presentation of the case

A 55 year old male was referred for cardiac transplantation because of intractable, incapacitating angina pectoris and severe fatigue. His medical history revealed syncope 3 years earlier, followed by slowly progressive fatigue and typical anginal chest pain. Angina pectoris was noted after 5 minutes of walking or one flight of stairs. His estimated functional capacity according the Canadian Cardiovascular Society and New York Heart Association Classification was class III. His family history was negative for atherosclerotic heart disease or cardiomyopathy and he had one healthy, 23-year old daughter. His cardiologist decided to refer the patient for cardiac transplantation, because evaluation in two other academic centers did not offer other treatment options.

The patient was a healthy appearing, lean Dutch male, who had no complaints at rest. Physical examination revealed a resting pulse rate of 70 b/m and blood pressure of 140/70 mm Hg. A "water-hammer" pulse was palpable till his distal lower extremity arteries. A 2/6 systolic and diastolic murmur was heard at the apex and left 4th inter-costal space. There were no signs of heart failure.

His electrocardiogram showed sinus rhythm 70 b/m, signs of left atrial dilatation and left ventricular hypertrophy with minor repolarisation abnormalities. A bicycle-exercise test revealed moderately severe impairement of exercise capacity (maximal load 95 Watt or 59 % predicted) with 2 mm horizontal ST segment depression at maximal exercise, normalizing at 7^{th} min of rest, consistent with significant myocardial ischemia (figure 1). A 24-hour Holter ECG showed sinus rhythm, without any arrhythmias.

Two-dimensional echocardiography demonstrated mild left ventricular (LV) dilatation (end-diastole 63 mm, end-systole 35mm), with prominent trabeculae of the left ventricular myocardial walls, not fulfilling the classical criteria for non-compaction cardiomyopathy [1]. Systolic biventricular function was normal (LV fractional shortening 44 %; movie 1). There were multiple fistulae seen with color Doppler, at the different levels of the LV walls (movie 2). Magnetic resonance imaging confirmed the echocardiographic findings, with good systolic LV (EF 73 %, cardiac output 8.8 l/min) and RV function and more pronounced abnormal trabeculations. The maximal noncompacted / compacted ratio was 4.4 (figure 3, movie 3). The coronary arteries were dilated to an estimated diameter of 8 mm. The flow in the left main coronary artery was 2.8 liters/min (normal: 90 ml/min) and the right coronary artery 1.2 liter/min. There were no signs of myocardial fibrosis on delayed enhancement acquisition. Coronary arteriogram showed severely tortuous and dilated coronary branches as well both the right and the left coronary artery with multiple coronary fistulae draining directly in the LV cavity (figure 4, 5 and movies 4, 5). The shunt fraction was calculated at 2.51. Left ventricular angiography confirmed globally good LV function and retrograde filling of the coronary arteries with partial opacification of the extensive coronary arterial fistulae (figure 6

and movie 6). There was poor opacification of the coronary sinus, probably due to shunting in to the LV cavity.

The patient's case was then discussed in our multidisciplinary team with respect to the correct diagnosis, prognosis and treatment options, including cardiac transplantation

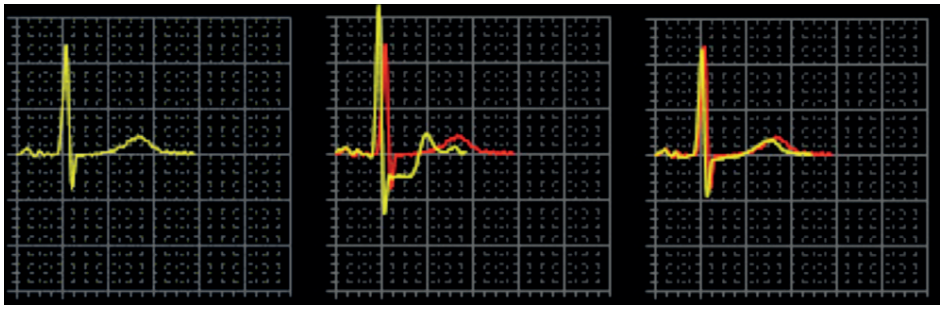
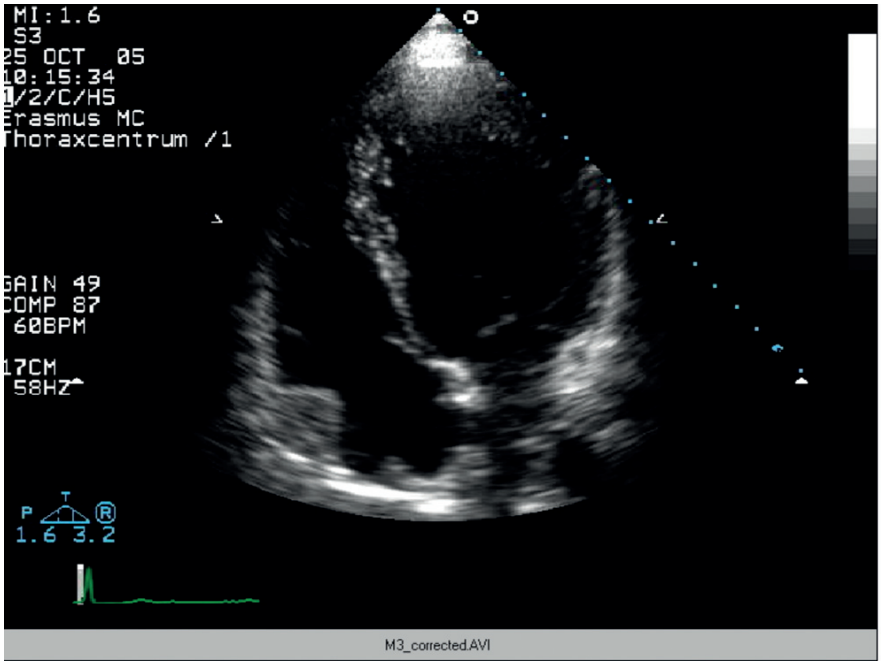
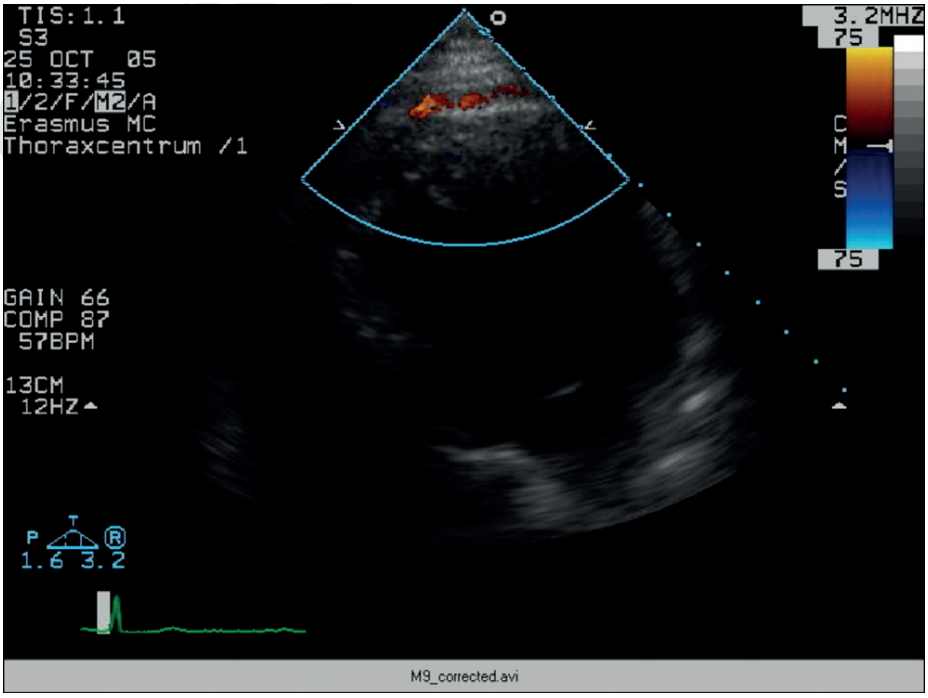


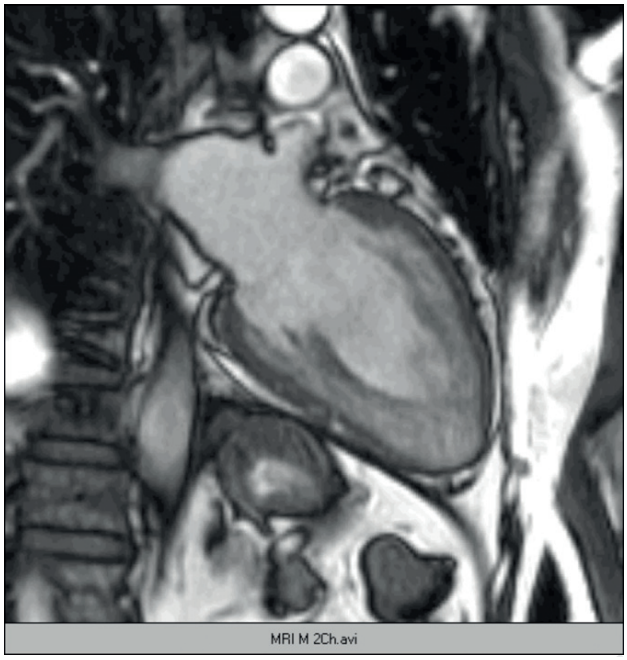
Figure 1. Exercise test showing the ECG at rest, maximal exercise and recovery.



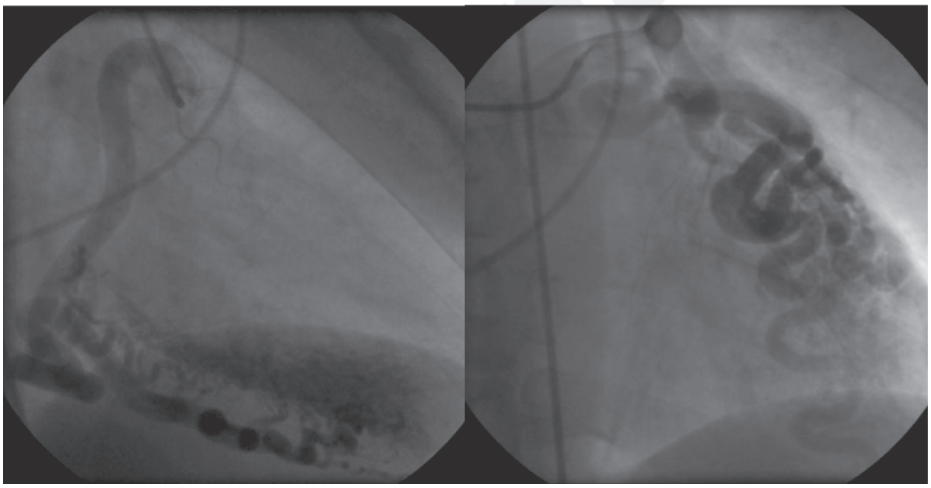
Movie 1. Apical 4-chamber view at the echocardiography, showing mild LV dilatation and good systolic LV function. There are prominent hypertrabeculation at the apical and mid-ventricular myocardial walls, mimicking noncompaction cardiomyopathy.



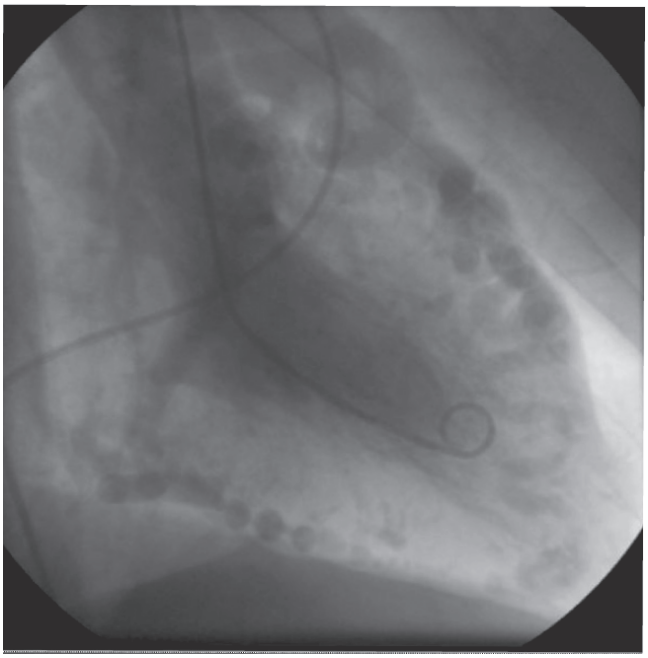
Movie 2. Echocardiographic apical 4-chamber view with color Doppler showing multiple fistulae, at the apical wall.



Movie 3. Two-chamber magnetic resonance imaging of the LV, showing extensive trabeculation with noncompacted / compacted ratio > 2, fulfilling the Jenni criteria for noncompaction cardiomyopathy [2]



Movie 4 and 5. Coronary angiogram of the RCA and LCA demonstrating multiple coronary-ventricular fistulae.



Movie 6. LV angiogram with retro-grade filling of the coronary arteries.

HOW COULD I TREAT?

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Typical patients referred to heart transplant (HT) units suffer from advanced heart failure due to severe left ventricular (LV) dysfunction. Major etiologic groups are idiopathic dilated cardiomyopathy and ischemic cardiomyopathy, accounting for 90% of HT recipients[1]. HT is considered when incapacitating symptoms do not respond to alternative therapies such as drugs, electrical therapies and percutaneous or surgical interventions. Prognosis in these cases may be estimated based on cardiopulmonary stress test and other methods[2], and consequently HT is usually indicated in relatively young (<65-70 y.o.) patients without significant comorbidities when the expected survival and quality of life caused by their cardiac disease are below those provided by HT.

Current survival of adult HT recipients 30 days, 1 year and 5 years after cardiac replacement is 90%, 80%, 70%, respectively. For patients surviving the first post-HT year, median survival is 13 years, and most of them enjoy good-to-excellent quality of life[1]. However, life after HT implies a number of drawbacks, including the permanent need of a combination of immunosuppressants for the prevention of acute graft rejection. This therapy is frequently accompanied by significant adverse effects (nephrotoxicity, arterial hypertension, dyslipidemia, diabetes, GI disturbances, myelodepression, osteoporosis and many others), and also by an increased risk of infection and neoplasia on the long-term. Allograft vasculopathy, a form of chronic rejection affecting both epicardial and microvascular coronary circulation, is the main cause of cardiac morbidity and death among late survivors[3,4].

Indication of HT in patients without refractory systolic heart failure is particularly difficult, because there are no validated methods for estimating their prognosis. In our series, only 16 out of 740 HT recipients (2%) had a LV ejection fraction >40%, and only one had refractory angina as the main reason for HT. In this setting, listing for HT is based on an imminent risk of death (e.g. arrhythmic storm), evidence of terminal phase (e.g. signs of cardiac cachexia) or severe, prolonged deterioration of the quality of life (e.g. inability to discharge from hospital, dependence of i.v. inotropes, etc.). Obviously, alternate therapies should always be attempted when judged feasible, and HT will still remain as the last choice.

The patient under consideration shows multiple coronary-cameral fistulae arising from all three major coronary arteries and emptying into LV cavity, a rare entity described as general-

ized coronary artery-left ventricular (micro)fistulae (GCLVF) by some authors[5]. In this case, a significant portion of the cardiac output (close to 50%) is diverted back to LV in diastole through multiple fistulae, thus mimicking the physiology of aortic regurgitation. Chronic volume overload has already caused LV dilation, and myocardial damage can be anticipated on the long term. Besides, there is objective evidence of myocardial ischemia on exertion, a finding previously described in many cases of GCLVF that is attributed to coronary steal phenomenon, with preferential shunting of coronary flow towards LV cavity in diastole[5,6]. The association of GCLVF with left ventricular non compaction (LVNC) found in this patient is unprecedented, and suggests the persistence of an embryonic pattern in LV wall, in which sinusoid gaps between muscular trabeculae do not disappear because of an impaired process of muscle compaction, thus turning into coronary-LV fistulae[6].

Therapeutic options in this case are certainly limited; however, every effort should be made before listing for HT in a patient with preserved LV function and no overt signs of cardiac failure. Our first move would be the initiation or increase of β-blocker therapy (an aspect not detailed in the case report), a measure that could be of help in a patient with exertional symptoms, hyperdynamic circulation and a heart rate of 70 bpm.

If β-blockade has no significant effect, we would consider the possibility of percutaneous closure of the main fistulous tracts. In the more common setting of a few, large coronary fistulae, many successful procedures with the use of detachable balloons, vascular plugs, covered stents, foam or coils delivered by different methods have been described[7]. In this case, the presence of numerous, intramyocardial, small size fistulous tracts poses a major technical problem; however, there are precedents of multistage procedures with delivery of coils into distal territories of all three major coronary arteries[8]. The aid of a vascular interventionalist with experience in the treatment of vascular malformations of the CNS (somewhat similar to this type of lesions) may prove invaluable in the planning and performance of these procedures.

If everything fails, HT would be an excellent option for this patient without obvious contraindications, with the benefits and risks exposed at the beginning of this comment.

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HOW SHOULD I TREAT? AN UNUSAL REFERRAL FOR HEART TRANSPLANTATION.

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Coronary artery fistulae are the most common form of hemodynamic significant coronary artery abnormalities. They can originate from anywhere in the coronary artery system and can terminate in any cardiac chamber, or a major vein or the pulmonary arteries. Significant coronary artery fistulas are rare as compared to minor or incidental coronary fistulas, which are seen over 75% of cases and almost all drain into the right side. Majority originate from the left coronary artery (~55%) with multiple fistulas occurring in only ~8% of cases[1]. Over 90% of fistulae drain into the right side with drainage into the left ventricle being the least common. Coronary fistulas that drain into the right side of the circulation create a left-to-right shunt of oxygenated blood back to the pulmonary circulation. Whereas coronary artery fistulas that drain into the left ventricle produce hemodynamic changes similar to aortic incompetence. Also, in addition to the volume overload on the heart, coronary artery fistula can result in coronary artery "steal" a phenomenon in which coronary blood preferentially passing through the fistula bypassing the more distal myocardium capillary beds that supply the myocardium (stealing blood). Clinical presentations are dependent on the type of fistula, shunt volume, site of the shunt, and presence of other cardiac conditions. Symptomatic patients present with angina, arrhythmia or other signs of congestive heart failure as was the case in the patient presented by Dr. Caliskan.

Caliskan et al. patient has bilateral coronary artery fistulae (left and right coronary arteries) draining into the left ventricle. The coronary arteries are diffusely dilatated and tortuous, reaching >8 mm in diameter. The left ventricle (LV) function is normal however, stress test is positive. The options that must be considered are could a percutaneous closure or a surgical closure be achieved. Because of the involvement of both coronary arteries and the tortuosity both options are not feasible.

There are several centers with extensive experience in catheter device closure. Different devices (balloons, plugs, coils and other occluding devices) have been developed but still struggle with vessel tortuosity, optimal catheter delivery and residual and or recurrent leaks. However, due to the presence of multiple drainage sites, the interventional option is impossible at this time. The surgical repair has a low mortality (<1%)[2] when a single coronary artery fistula is concerned, but in the patient presented, surgical correction would not be possible due to multiple sites of drainage and both coronary arteries being involved.

The clinical management is obviously challenging in this case, because of the large size of the fistulas, tortuosity, and both coronary arteries are involved, therefore we believe the best treatment is cardiac transplantation, which has a survival rate of 85% to 90% at one year[3, 4].

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HOW DID I TREAT?

Actual treatment and management of the case

Given the pan-cardiac character of the coronary-ventricular fistulae without a history of other diseases or trauma, we postulated that the etiology was congenital. Therefore, his 23-years old daughter was screened. She was asymptomatic, with normal exercise capacity, ECG, and normal two-dimensional echocardiography.

In early fetal development, the primitive loosely packed myocardium is nourished via sinusoids. As the myocardium becomes more compact, the sinusoids disappear and give rise to a network of veins, arteries, and capillaries. Persistence of these connections may result in coronary artery fistulae. Microscopic foci of persistent embryonic spongy myocardium may be seen, probably explaining the noncompaction cardiomypathy look -a-like in our case [1-3]. Congenital coronary fistulae communicating with the left ventricle are very rare and usually single. The right coronary artery seems to be affected more frequently than the left. Multiple coronary-ventricular fistulae affecting all three major coronary arteries are extremely rare [4]. Most coronary artery fistulae are small without compromising the myocardial blood flow and give no symptoms. However, with increasing shunting, and probably with increasing age (like in our case), a coronary artery steal syndrome develops with resultant ischemia and volume overload. Patients with a coronary artery fistulae are commonly identified because of the associated loud, continuous fistula murmur. Other clinical presentations include angina, arrhythmias, and heart failure due to chronic volume overload [6, 7].

In our case, since the coronary arterial fistulae were extremely numerous and affecting the whole heart, neither surgery nor trans-catheter coil closure seemed a reasonable option. As the patient also had excellent systolic left ventricular function, we felt that the option of cardiac transplantation was not the preferred treatment option at this time. We treated the patient with a beta-blocker, to slow his heart rate and decrease the oxygen demand of the heart. Thereafter, we started angiotensin converting enzyme-inhibitor, to unload the preand afterload of the LV, since we hypothesized that the numerous coronary-cameral fistulae

would give chronic left-sided volume overload. Finally, we hypothesized that the patient was at high risk for sudden cardiac death because of ischemia at exercise and a history of unexplained syncope. Therefore, an ICD was implanted prophylactically.

At three months of follow-up, angina was infrequent and exercise tolerance significantly improved. His estimated CCCS functional was class I and NYHA class II. The measured exercise capacity improved to 130 W (75 % predicted) with a peak VO^2 uptake of 24.7 ml/min/kg.

At 3½ years of follow-up, the patient was only mildly symptomatic, without any cardiac event or hospital admissions. His echocardiogram showed improved LV dimensions (end-diastolic 50 mm and end-systolic 36 mm) with excellent systolic function.

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Summary and conclusions

Noncompaction cardiomyopathy (NCCM) is recognized as a separate disease entity since the first report in 1984 of a rare case with persistent myocardial sinusoids and a series of 8 pediatric and adolescent patients in 1990 with increased trabeculation of the left ventricular endocardium. Given the cumulative evidence since then, NCCM is considered as a primary, predominantly genetic disorder of the myocardium.

The classic clinical presentation includes severe heart failure, malignant ventricular arrhythmias, thrombo-embolic events and sudden cardiac death. But the complete spectrum comprises also asymptomatic to minor cardiac complaints like atypical chest pain and nonspecific palpitations. The noncompacted myocardium is characterized by an excessively prominent trabecular meshwork and deep intertrabecular recesses, as seen early in human embryogenesis. Therefore, the primary patho-physiological hypothesis is that incomplete compaction of the loose myocardial meshwork during gestation results in a noncompacted, heart, prone to heart failure, arrhythmias and intracardiac thrombus formation. The diagnostic criteria proposed by Jenni et al. include abnormally thickened ventricular walls with a two-layered structure, consisting of thickened, noncompacted (NC) endocardial myocardium and a thin compacted (C) epicardial myocardium (maximal end-systolic ratio NC/C > 2 at parasternal short axis view). The diagnosis is established by imaging of the ventricular walls and cavities, classically by two-dimensional transthoracic echocardiography with color Doppler flow. The abnormal structures of NCCM could be identified as deep intertrabecular recesses with color Doppler flow as well as regional hypokinesia. Other imaging modalities like left ventricular (LV) angiography, computed tomography, contrast echocardiography and magnetic resonance imaging (MRI) have also been used to visualize these recesses.

Increased awareness of this disease entity made us recognize more and more cases of NCCM, especially with help of modern imaging modalities like contrast echocardiography and MRI allowing better visualization the left ventricular cavity. However, in daily clinical practice, many questions about several clinical aspects remained open, because the available literature consisted of several case reports and small case series only.

CLINICAL FEATURES

In **Chapter 1**, we present an overview of the current literature with emphasis on the clinical, familial and genetic features of NCCM in Chapter 1. Our conclusion is that NCCM is genetically heterogeneous cardiomyopathy with variable clinical presentation and prognosis, ranging form asymptomatic disease to severe disabling, progressive heart failure. The first clinical presentation of NCCM may occur from early childhood to advanced age. In childhood the clinical features are more often severe and frequently associated with congenital heart defects. In adults, the majority of the cases are isolated. The genetic etiology of NCCM requires that patients and their relatives are offered genetic testing and counseling.

At this moment, the diagnosis of NCCM relies fully on abnormal morphology as demonstrated by an imaging modality. In **Chapter 2**, we describe the use of left ventricular angiogram in the diagnosis of NCCM. Albeit the standard diagnostic procedure for NCCM is two-dimensional echocardiography with colour Doppler studies, a left ventriculography can be helpful in the diagnostic process in case of cardiac catheterization.
Early case series described a high morbidity and mortality with ventricular tachycardia and death or transplantation (47%!) at follow-up. In recent case series a better prognosis was found, albeit with limited follow-up time. In **Chapter 3**, we describe the clinical course and long-term (>5 years) outcome of NCCM patients in the current intensive treatment era. The main finding is that NCCM patients presenting without HF, have excellent long-term (8-years) survival provided that these patients are optimally treated with appropriate drug therapy and, in selected patients, prophylactic ICD implantation for primary or secondary prevention of sudden cardiac death. These findings have important implications for the counseling of the NCCM patients and their relatives, and provide a basis to propose a guideline for management of NCCM, which we present in a figure.

Echocardiographic features

NCCM is characterized by a prominent trabecular meshwork and deep intertrabecular recesses. Although systolic dysfunction is common, limited information is available on differences in wall motion of the normal compacted and noncompacted segments. We investigated with regional real-time three-dimensional (3D) echocardiographic analysis the specific contributions of noncompacted and compacted segments to global LV systolic dysfunction in patients with typical features of NCCM. The results, described in **Chapter 4,** indicate that noncompacted and compacted LV segments have comparable increased regional volumes and reduced systolic function. These results suggest that systolic LV dysfunction observed in NCCM is not confined to noncompacted LV segments.
In Chapter 5 we investigated the relation of left ventricular systolic function and the extent and severity of noncompaction with two-dimensional echocardiographic analysis and tissue Doppler images. We found that in NCCM patients, radial wall motion and longitudinal LV wall velocity was impaired but not related to the extent or severity of noncompaction cardiomyopathy. Both affected (noncompacted) and seemingly non-affected (compacted) segments contributed to reduced LV function in this cardiomyopathy. This suggests that the LV dysfunction in NCCM is not regional but a global problem.
The diagnosis of noncompaction cardiomyopathy (NCCM) remains subject to controversy. Current diagnostic criteria rely solely on the morphological features as seen by an imaging modality. Recently, speckle-tracking echocardiography has been introduced as a new method for angle-independent quantification of LV twist. Because NCCM is probably caused by an intrauterine arrest of the myocardial fiber compaction during embryogenesis, it may be anticipated that the myocardial fiber helices, normally causing LV twist, will also not develop

properly. The resultant LV rigid body rotation may strengthen the diagnosis of NCCM. In **Chapter 6** we studied LV twist characteristics in NCCM patients compared to patients with non-ischemic dilated cardiomyopathy (DCM) and normal subjects. In all controls and DCM patients, rotation was clockwise at the basal level and counterclockwise at the apical level. In contrast, in all NCCM patients the LV base and apex rotated in the same direction. These findings suggest that LV rigid body rotation (RBR), with near absent LV twist, may be a new sensitive and specific, objective and quantitative, functional diagnostic criterion for NCCM.
In **Chapter 7** we explored the diagnostic value of rigid body rotation in a large group of patients with prominent trabeculations, including healthy subjects, subjects with prominent trabeculations but not fulfilling the NCCM diagnostic criteria, typical NCCM patients and DCM patients. The majority of healthy subjects had completely normal rotation (98 %; initial counterclockwise basal and clockwise apical rotation, followed by endsystolic clockwise basal and counterclockwise apical rotation), whereas the subjects with hypertrabeculation not fulfilling diagnostic criteria for NCCM had predominantly partly normal rotation (71%; normal end-systolic rotation but absence of initial rotation in the other direction), and the patients with NCCM predominantly had abnormal rotation with the basal and apical level predominantly in the same direction (88%). None of the patients with DCM showed rigid body rotation. Sensitivity and specificity of rigid body rotation for differentiating NCCM from "hypertrabeculation" were 88% and 78%, respectively. Rigid body rotation is an objective, quantitative, and reproducible functional criterion with good predictive value for the diagnosis of NCCM as determined by expert opinion.
NCCM disputably believed to result from abnormal arrest in embryonic endomyocardial morphogenesis. During almost three decades of research on NCCM, more knowledge has developed alongside diagnostic uncertainties and precise definition. In **Chapter 8**, we present these uncertainties and provide perspectives on how to overcome these challenges. We discuss the uncertainties regarding the nomenclature, classification, pathophysiology, and limitations of the current diagnostic criteria. We reviewed the application of newer imaging modalities contrasted in relation to conventional assessments. Besides conventional echocardiography, imaging should include both *structural* (cardiac MRI, contrast and 3D echocardiography) and *functional* diagnosis using deformation imaging.

Arrhythmias and ICD therapy

The prevention of malignant ventricular arrhythmias and sudden cardiac death (SCD) is one of the major challenges in cardiomyopathies. Despite several decades of research, appropriate risk stratification to reduce SCD remains very difficult. In NCCM the prevalence of malignant ventricular arrhythmias, appropriate risk stratification and prevention of SCD is obscure. In **Chapter 9**, we comment on a study on the usefulness of invasive electrophysiological studies (EPS) in the risk stratification process of NCCM patients. We conclude that there is no evidence supporting routine EPS for risk stratification in patients with NCCM.

Until we have larger, prospective studies with long-term follow-up, EPS should be reserved for research protocols, including long-term FU studies. For appropriate risk stratification of SCD at long-term, we need large prospective clinical outcome data, which could only been realized in an international registry and follow-up studies.

Implantable cardioverter-defibrillators (ICDs) are frequently used for primary and secondary prevention in different cardiomyopathy patients, but data about ICD therapy in NCCM are scarce. In **Chapter 10**, we present the ICD indications and outcomes in our prospective NCCM cohort. It is shown that an ICD was frequently implanted (57%) for primary or secondary prevention of sudden cardiac death according the current ICD guidelines for non-ischemic cardiomyopathies. At follow-up, frequent appropriate ICD therapy was observed in both groups, supporting the application of current ICD guidelines for primary and secondary prevention of sudden cardiac death in NCCM.

In recent years, there is increasing evidence that early repolarization (ER) is associated with malignant ventricular arrhythmias, including ventricular fibrillation and SCD. A possible mechanism is increased trabeculation with deep intramyocardial invagination (a hallmark of NCCM!) carrying the Purkinje system deeper into myocardium resulting in delayed depolarization and inhomogeneous repolarization. We studied the prevalence of ER in NCCM patients, especially in those primarily presenting with malignant ventricular arrhythmias or sudden cardiac death (**Chapter 11)**. A high prevalence of ER was observed in NCCM patients, especially in those patients presenting with malignant ventricular arrhythmias (75%). Interestingly, ER was also frequently observed (31%) in NCCM patients not presenting with ventricular arrhythmias. We concluded therefore, that ER might be a useful risk marker for malignant ventricular arrhythmias and SCD in NCCM. Larger, confirmative studies are required to investigate whether ER can contribute to risk stratification in this group of patients and to identify those in whom ICD implantation is warranted.

Familial and genetic features

Soon after the first case reports of NCCM, familial and genetic etiology has been suspected and different mutations in different genes have been described. Autosomal-dominant as well as X-linked inheritance for NCCM has been described and several loci have been associated with the disease. Nevertheless, a major genetic cause for familial NCCM remained to be identified. In **Chapter 12,** we describe, in two separate autosomal-dominant NCCM families, the identification of mutations in the sarcomeric cardiac ß-myosin heavy chain gene (MYH7), known to be associated with hypertrophic cardiomyopathy (HCM), restricted cardiomyopathy (RCM), and dilated cardiomyopathy (DCM). The current findings expand the genetic heterogeneity of NCCM, and the identification of MYH7 defects in familial NCCM suggests that NCCM may be part of a cardiomyopathy spectrum including HCM, RCM, and DCM.

As part of the search for a possible association of NCCM with mutations in sarcomere genes, we studied systematically a series of families of patients who were consecutively molecularly screened and diagnosed with isolated NCCM (**Chapter 13)**. Combined molecular testing and cardiological family screening revealed that 67% of NCCM is genetic. The molecular screening of 11 genes revealed 35% sarcomeric mutations in adult NCCM patients and 6 of 8 pediatric patients.

In C**hapter 14**, we show the results of systematic cardiac evaluation, the prevalence and clinical characteristics of cardiomyopathies in close relatives of NCCM patients. In about half of patients with NCCM, a familial inheritance pattern was found. Among the studied relatives, we found a high prevalence of asymptomatic disease. Without systematic cardiac screening, the disease would have remained undetected in the majority of cases, thereby missing the opportunity for pre-symptomatic treatment. The absence of symptoms or signs of heart diseases and of ECG abnormalities did not exclude the presence of NCCM or another cardiomyopathy. Cardiac evaluation, including echocardiography or MRI appears indispensable to reach a correct diagnosis.

Pseudo-noncompaction cardiomyopathies

More than two decades after the first proposed diagnostic criteria, the diagnosis of NCCM still relies on abnormal morphological features with excessive trabeculations. The occurrence however of a high incidence of prominent trabeculations in subjects with chronic pressure or volume overload remains a major diagnostic problem in the correct diagnosis of NCCM. In **Chapter 15** we describe a young male with echocardiographic NCCM look-alike features in the presence of severe sinus bradycardia and moderate aortic valve regurgitation. We hypothesized that the chronic volume overload exaggerated by prolonged diastole due to the bradycardia resulted in heart failure and noncompaction cardiomyopathy look-alike features. After implantation of an AAI pacemaker, his symptoms and signs of cardiomyopathy fully disappeared. In **Chapter16**, we described a 55 years old male referred for cardiac transplantation because of intractable angina and fatigue. Echocardiographic examination showed mild LV dilation with good systolic function. There were prominent trabeculations at the apical and midventricular myocardial walls, mimicking non-compaction. Coronary angiography showed severely tortuous and dilated coronary arteries with multiple coronary-ventricular fistulae. The persistent embryogenic sinusoids and spongy myocardium probably explains the noncompaction look-a-like along with the chronic volume overload of the LV.

CONCLUSIONS

NCCM is genetically heterogeneous cardiomyopathy with variable clinical presentation. The prognosis, ranges from asymptomatic disease to severe disabling, progressive heart failure.

In our NCCM cohort, we found that NCCM patients presenting without HF, have excellent long-term (8-years) survival provided that they are optimally treated with appropriate drug therapy and, in selected patients, prophylactic ICD implantation for primary or secondary prevention of sudden cardiac death.

Albeit the standard diagnostic procedure for NCCM is two-dimensional echocardiography with colour Doppler studies, a left ventricular angiogram can be helpful in the diagnostic process in case cardiac catheterization is performed.

Systolic LV dysfunction is common in NCCM, but limited information is available on differences in wall motion of the normal compacted and noncompacted segments. We showed with 3D-echo that noncompacted and compacted LV segments have comparable increased regional volumes and reduced systolic function, suggesting that systolic LV dysfunction observed in NCCM is not confined to noncompacted LV segments. Using tissue Doppler images we confirmed that LV dysfunction in NCCM is not regional but a global problem.

Current diagnostic criteria rely solely on the morphological features as seen by an imaging modality but we showed that rigid body rotation cloud be an objective, quantitative, and reproducible functional criterion with good predictive value for the diagnosis of NCCM.

The prevalence of malignant ventricular arrhythmias, appropriate risk stratification and prevention of SCD is NCCM is highly challenging. Frequent appropriate ICD therapy at long-term follow-up supports the application of current ICD guidelines for primary and secondary prevention of sudden cardiac death in NCCM for the time being.

As there is increasing evidence that early repolarization is associated with malignant ventricular arrhythmias the high prevalence of ER in NCCM patients presenting with malignant arrhythmias and SCD, ER can contribute to risk stratification in this group of patients and to identify those in whom ICD implantation is warranted.

Combined molecular testing and cardiological family screening reveals that the majority of NCCM is genetic. The genetic etiology of NCCM requires that patients and their relatives be offered genetic testing and counseling. In more than one third of the NCCM patients, sarcomeric gene mutations were demonstrable. Systematic cardiac evaluation reveals also high prevalence of asymptomatic disease with the opportunity for pre-symptomatic treatment.

Future perspectives

The prevalence of NCCM is largely unknown. More definite answers are needed, based on pathologic, clinical, and genetic analyses. Large international, multicenter prospective registries, and consensus statements like in other cardiomyopathies are crucial to clarify current uncertainties. A clear patho-anatomic (and histo-pathologic?) cut-off definition of NCCM should be the initial step towards an uniform imaging diagnosis and the differentiation from pseudo-noncompaction cardiomyopathy (or secondary / acquired NCCM?). The new classification should define the NCCM clearly as a separate disease entity, with is own

nomenclature, classification, pathophysiology, and outcome. Patho-anatomic correlation of the imaging data should be sought in larger series.

Due to the genetic heterogeneity and lack of clear view on the genotype-phenotype relationship of NCCM, more genetic counseling, DNA diagnostics, and cardiologic family screening should be encouraged. Current genetic testing reveals relevant mutation in about one third only. Further molecular research is needed to investigate the role of additional mutations and possible role in the phenotypic variability. Also, the perspective of new studies investigating modifying genetic effects or genome-environment interactions to explain variability and age-dependent penetrance of this phenotype is challenging.

Different forms of the disease should be recognized: an isolated, mainly adult form of the disease, NCCM associated with congenital heart diseases (mainly in childhood) and NCCM in association with neuromuscular disease. Parameters should not only include the presence or absence of other concomitant cardiac disease (congenital, valvular), the size, location and severity of excessive trabeculations, but also LV functional parameters (impaired LV function, rigid body rotation), and possible genetic mutations. In this context, correctly defining the LV function is highly challenging, due to very irregular endocardial delineation and therefore routine LV ejection fraction measurements; appropriate imaging modality and methods should be sought.

Prevention of SCD and therefore appropriate risk stratification remains highly challenging. Strategies to improve outcome of patients with this rare disease, come from large case series like the present study but really need multicenter registry-based studies to expand, confirm and refine findings.

Samenvatting en conclusies

De eerste beschrijving van noncompaction cardiomyopathie (NCCM), in 1984, betrof een zeldzaam geval waarin het myocard grillige nissen vertoonde die in verbinding stonden met de linker ventrikel. Vervolgens werd in 1990 een reeks van 8 kinderen en adolescenten gerapporteerd met versterkte trabekel vorming van de wand van de linker ventrikel. Een hele rij van publicaties daarna heeft er toe geleid dat NCCM nu wordt beschouwd als een aparte, primaire, voornamelijk dominant overerfelijke genetische aandoening van de hartspier.
De klassieke klinische presentatie van NCCM bestaat voornamelijk uit hartfalen, maligne ritmestoornissen, trombo-embolieën en plotse dood. De patiënten kunnen echter ook klachtenvrij zijn of milde cardiale symptomen hebben zoals (atypische) pijn op de borst of hartkloppingen. De noncompacte, losmazige hartspier wordt gekenmerkt door uitgesproken, versterkte trabekelvorming met diepe nissen tussen de trabekels, zoals ook worden gezien in de vroege embryogenese. Daarom wordt aangenomen dat de noncompacte, losmazige hartspier pathofysiologisch het gevolg is van de onvoldoende uitrijping van de embryonale hartspier, waardoor de embryonale situatie blijft bestaan. Op latere leeftijd, bestaat dan kans op hartfalen, ritmestoornissen en intracavitaire stolsel vorming.
De diagnose NCCM wordt meestal gesteld aan de hand van door Jenni et al. opgestelde criteria: een abnormaal verdikte hartspier die uit twee lagen bestaat, een abnormaal dik, noncompact (NC) endocardiaal myocard en een dun, compact (C) epicardiaal myocard, waarbij de NC/C ratio in eindssystole > 2 is. Voor de diagnose is beeldvormend onderzoek nodig, meestal twee dimensionale echocardiografie met Doppler flow metingen, eventueel aangevuld met toediening van contrast. Hiermee worden regionale wand beweging stoornissen van de linker ventrikel en de diepe intertrabekulaire nissen in beeld gebracht. Andere beeldvormende technieken zoals invasieve ventriculografie met jodiumhoudend constrast of niet-invasieve ventriculografie middels computer tomografie of MRI zijn uiteraard ook hiervoor geschikt.
Na attent te zijn gemaakt op het bestaan van NCCM en door het beschikbaar komen van betere afbeeldingstechnieken hebben wij, steeds meer gevallen van deze aparte, maar zeldzame hartspierziekte ontdekt. Ook werden patiënten met deze afwijking naar ons verwezen, omdat in het Thoraxcentrum al vele jaren een bijzondere expertise is ontwikkeld op het gebied van hartspier ziekten (cardiomyopathieën) en behandeling van hartfalen. In de dagelijkse klinische praktijk bleven echter nog vele vragen onbeantwoord, mede omdat de literatuur tot nu toe voornamelijk uit casus beschrijvingen of kleine series bestond. Het onderzoek beschreven in dit proefschrift was gericht op een aantal van deze vragen.

KLINISCHE ASPECTEN

In **Hoofdstuk 1,** wordt een overzicht van de huidige literatuur gegeven met nadruk op de klinische, familiaire en genetische aspecten van NCCM. Wij concluderen dat NCCM een

genetisch heterogene hartspierziekte is met variabele klinische presentatie en prognose, variërend van asymptomatisch tot ernstig invaliderend progressief hartfalen dat tot de dood leidt of plotse hartdood. De eerste presentatie van NCCM kan zowel op de kinderleeftijd als op gevorderde leeftijd zijn. Op de kinderleeftijd zijn de klinische verschijnselen meestal ernstig en vaak geassocieerd met andere aangeboren hartziekten. Bij volwassenen daarentegen komt NCCM meestal solitair voor. Gezien de erfelijke oorsprong van NCCM is genetische counseling en testen van patiënten en directe familieleden wenselijk.
Op dit moment is de diagnose NCCM volledig gebaseerd op de morfologische afwijkingen zoals gezien worden middels beeldvormend onderzoek. In **Hoofdstuk 2**, wordt het gebruik van invasieve ventriculografie met jodiumhoudend contrast voor de diagnose NCCM beschreven. Hoewel de diagnose meestal wordt gesteld middels transthoracale echocardiografie met kleuren Doppler, kan deze ventriculografie ook van waarde zijn wanneer er toch een hartcatheterisatie wordt verricht om andere redenen.
In publicaties over de eerste reeksen patiënten werd een hoge morbiditeit beschreven met frequente ventriculaire tachycardieën en overlijden of harttransplantatie (gezamenlijk tot 47%!). Recente series laten echter een beter prognose zien, weliswaar tijdens een beperkte follow-up. Van NCCM patiënten die met moderne hartfalen therapie worden behandeld beschrijven wij in **Hoofdstuk 3** het klinische beloop en de prognose op langere termijn (>5 jaar). Wij laten zien dat de prognose van NCCM patiënten, die zich zonder hartfalen presenteren, goed is mits zij adequaat medicamenteus behandeld worden en in een geselecteerde groep profylactisch een ICD wordt geïmplanteerd voor primaire of secundaire preventie van plotse dood. Deze nieuwe bevindingen hebben belangrijke implicaties voor de counseling van NCCM patiënten en hun familieleden en bieden ons de mogelijkheid om een behandelplan voor NCCM patiënten voor te stellen, dat wij hebben samengevat in figuur 4.

Echocardiografische bevindingen

NCCM is gekarakteriseerd door een opvallende netwerk van trabekels met diepe intertrabekulaire nissen. Alhoewel de systolische functie van de linker ventrikel vaak gestoord is, was er weinig bekend over de verschillen in wandbeweging tussen de compacte en de noncompacte segmenten. Daarom hebben wij de specifieke bijdrage van noncompacte en compacte segmenten aan de globale LV functie onderzocht met segmentele "real-time" 3D echocardiografie . De resultaten zijn in **Hoofdstuk 4** beschreven. Het blijkt dat, in NCCM, de compacte segmenten evenveel bijdragen aan de globale LV (dis)functie als de noncompacte segmenten. Dit suggereert dat systolische disfunctie in NCCM niet is beperkt tot alleen noncompacte segmenten.
In **Hoofdstuk 5** wordt het onderzoek beschreven dat wij, middels Tissue Doppler imaging, hebben verricht naar de relatie van de systolische LV functie met de ernst en uitbreiding van de noncompacte segmenten. We vonden dat bij NCCM patiënten weliswaar de radiale wandbeweging en de longitudinale weefsel snelheid zijn gestoord maar dat deze niet zijn

gerelateerd aan de ernst en uitbreiding van de NCCM. Ook met deze onderzoekmethode blijken zowel aangedane (noncompacte) als ogenschijnlijk normale (compacte) segmenten evenveel bij te dragen aan de disfunctie van de linker ventrikel.

De diagnose NCCM geeft nog aanleiding tot veel discussie. De huidige diagnostische criteria gaan voornamelijk uit van de morfologische afwijkingen zoals worden gezien bij beeldvormend onderzoek. Recent is "speckle-tracking" echocardiografie geïntroduceerd als een nieuwe methode om de hoekonafhankelijke rotatie van de linker ventrikel te kwantificeren. Omdat NCCM waarschijnlijk wordt veroorzaakt door het stil blijven staan van de intra-uteriene "compactering" tijdens de endomyocardiale embryogenese, kan worden verwacht dat de hartspiervezel helices, die de normale LV rotatie veroorzaken, zich ook niet goed ontwikkelen. De daaruit voortvloeiende "starre LV rotatie" (rigid body rotation) kan dan ook worden gebruikt voor de diagnose van NCCM. In **Hoofdstuk 6** laten wij de resultaten van ons onderzoek naar de LV rotatie in NCCM patiënten zien. Deze werd vergeleken met die bij patiënten van niet-ischemische gedilateerde cardiomyopathie (DCM) en met normale controle personen. In alle controles en DCM patiënten, was de LV rotatie op het basale niveau met de klok mee en op het apicale niveau tegen de klok in. Bij NCCM patiënten daarentegen zagen wij de LV basis en apex in dezelfde richting roteren. Deze bevindingen suggereren dat "rigid body rotation" mogelijk een nieuw objectief, kwantificeerbaar en functioneel diagnostische criterium voor NCCM kan zijn.

In **Hoofdstuk 7** hebben we de diagnostische waarde van "rigid body rotation" getest in een grote populatie met opvallende trabekels in de wand van de linker ventrikel. De populatie omvatte gezonde personen, patiënten met opvallende trabekelvorming die niet voldeed aan de Jenni NCCM criteria, typische NCCM patiënten en DCM patiënten. De meerderheid van de gezonde proefpersonen liet een volledig normale rotatie zien (98% initieel tegen de klok in aan de basis en met de klok mee apicaal, eind-systolisch gevolgd door rotatie basaal met de klok mee en apicaal tegen de klok in). De patiënten met veel trabekels die niet voldeden aan de diagnostische criteria voor NCCM, hadden een deels normaal rotatiepatroon (71%; normaal eind-systolische rotatie maar geen initiële rotatie in de andere richting). Patiënten met NCCM vertoonden overwegend een abnormale "twist" met rotatie van de basis en van de apex van de ventrikel in dezelfde richting (88%). Geen van de patiënten met DCM liet "rigid body rotation" zien. De sensitiviteit en specificiteit van "rigid body rotation" van de linker kamer voor de differentiatie tussen NCCM en anderszins sterke trabekelvorming waren respectievelijk 88% en 78%. "Rigid LV body rotation" is een objectief, kwantificeerbaar en reproduceerbaar functioneel criterium met een goede voorspellende waarde voor de diagnose van NCCM.

Men gaat er van uit dat NCCM het resultaat is van een stoornis in de uitrijping van de embryonale endomyocardiale morfogenese. Alhoewel er in de laatste drie decennia veel onderzoek op het gebied NCCM is gepubliceerd zijn een aantal onzekerheden blijven bestaan omtrent de juiste afbakening van het ziektebeeld. In **Hoofdstuk 8**, bespreken wij deze

onduidelijkheden en worden voorstellen gedaan om hiervoor oplossingen te vinden. We bespreken de onzekerheden ten aanzien van de nomenclatuur, de indeling, de pathosfysiologie en de beperkingen van de huidige diagnostische criteria. Wij hebben de toepassing van nieuwe beeldvormende technieken op een rij gezet en vergeleken met de bestaande. Geconcludeerd wordt dat voor de diagnose NCCM zowel een *structurele* beoordeling (via conventionele echocardiografie of via nieuwe modaliteiten als cardiale MRI, contrasten 3D-echocardiografie) als een *functionele* beoordeling via beeldvorming van de rotatie nodig is.

Ritmestoornissen en ICD-therapie

Het voorkómen van maligne ventriculaire ritmestoornissen en plotse dood is een van de grote uitdagingen bij patiënten met een cardiomyopathie. Ondanks tientallen jaren van onderzoek blijft het erg moeilijk bij individuele patiënten het risico voor plotse dood te schatten. Bij NCCM ontbreken cijfers over de prevalentie van maligne ventriculaire ritmestoornissen, is er geen adequate risicostratificatie en tasten we voor de preventie van plotse dood nog in het duister. In **Hoofdstuk 9** wordt commentaar geleverd op een onderzoek naar het nut van invasief elektrofysiologisch onderzoek in de risicostratificatie van NCCM patiënten. We concluderen dat niet is bewezen dat systematisch elektrofysiologisch onderzoek nuttig is voor de risicostratificatie bij patiënten met NCCM. Zolang er nog geen prospectieve studies met voldoende follow-up zijn, moet elektrofysiologisch onderzoek worden gereserveerd voor research protocollen. Wij zijn van mening dat grote, prospectieve klinische studies nodig zijn om te komen tot adequate risicostratificatie op lange termijn. Dit kan alleen worden gerealiseerd in een (inter-)nationale registratie met langdurige follow-up.

Implanteerbare cardioverter-defibrillatoren (ICD's) worden vaak gebruikt voor primaire en secundaire preventie van plotse dood in patiënten met verschillende typen cardiomyopathie, maar gegevens over ICD-therapie in NCCM patiënten zijn schaars. In **Hoofdstuk 10** presenteren we de indicatie voor en resultaten van ICD implantatie in ons prospectief gevolgde NCCM cohort. We laten zien dat een ICD geïndiceerd werd geacht bij 57% van onze patienten, voor primaire of secundaire preventie van plotselinge hartdood, waarbij de huidige ICD richtlijnen voor niet-ischemische cardiomyopathie werden gevolgd. Tijdens de follow-up werd, zowel in de primaire preventieals in de secundaire preventie groep, frequent terechte ICD therapie waargenomen, zodat wij mogen aannemen dat met deze therapie plotse dood werd voorkomen. Dit ondersteunt ons beleid van het gebruik van de huidige ICD richtlijnen voor de preventie van plotse dood van NCCM patiënten.
In de afgelopen jaren is in toenemende mate bewijs geleverd dat vroege repolarisatie (ER) geassocieerd is met het vóórkomen van maligne ventriculaire ritmestoornissen, waaronder ventrikelfibrilleren en plotse hartdood. Versterkte trabekelvorming met diepe intramyocardiale nissen (een kenmerk van NCCM!) waardoor het Purkinje systeem dieper in de ventrikelwand komt te liggen en de repolarisatie trager verloopt en inhomogeen wordt speelt hierbij

mogelijk een rol. Wij hebben de prevalentie van ER in NCCM patiënten bestudeerd, in het bijzonder bij patiënten die zich primair presenteerden met maligne ventriculaire ritmestoornissen en plotse hartdood (**Hoofdstuk 11**). Wij vinden inderdaad een hoge prevalentie van ER bij NCCM patiënten. Met name patiënten met maligne ventriculaire ritmestoornissen hadden in 75% ER. Opvallend is dat ER ook frequent wordt waargenomen (31%) bij NCCM patiënten die zich niet primair presenteren met ventriculaire ritmestoornissen of plotse dood. Onze conclusie is dan ook dat ER een waardevol risico factor kan zijn voor maligne ventriculaire ritmestoornissen en plotse dood bij patiënten met NCCM. Grotere, prospectieve studies zijn nodig om te bevestigen dat de aanwezigheid van ER inderdaad kan bijdragen aan risico stratificatie in deze groep van patiënten en met name die patiënten kan identificeren die baat zullen hebben bij een profylactische ICD-implantatie.

Familiaire en genetische aspecten

Al snel na de eerste rapportages over NCCM, werden aanwijzingen gevonden voor een familiare en genetische etiologie. Intussen zijn diverse mutaties in verschillende genen beschreven bij families met NCCM. Hierbij kwam met name een autosomaal-dominante en X-gebonden overerving naar voren en werden verschillende loci in verband gebracht met de ziekte. De bij NCCM gevonden erfelijke afwijkingen zijn heterogeen en een primaire genetische mutatie voor NCCM is niet geïdentificeerd. Wij hebben in twee afzonderlijke NCCM families, autosomaal-dominant overervende sarcomeer gen mutaties in het cardiale B-myosine zware keten gen (MYH7) geïdentificeerd, dat sterk geassocieerd is met hypertrofische cardiomyopathie (HCM), restrictieve cardiomyopathie (RCM) en gedilateerde cardiomyopathie (DCM) **(Hoofdstuk 12)**. De genetische heterogeniteit van NCCM is dus nog groter dan tot nu toe bekend was. De identificatie van MYH7 mutaties in NCCM patiënten suggereert dat NCCM deel uitmaakt van een spectrum van cardiomyopatieën: hypertrofische-, restrictieve-, gedilateerdeen noncompaction cardiomyopatie.

Als onderdeel van de zoektocht naar een mogelijke associatie van NCCM met sarcomeer gen mutaties hebben we systematisch familieleden van NCCM patiënten onderzocht (**Hoofdstuk 13**). Gebruik makend van de combinatie van moleculaire testen en cardiologische familie screening bleek dat 67% van NCCM van genetische origine is. Moleculaire screening van 11 genen liet zien dat bij 35% van de volwassen NCCM patiënten en bij 6 van de 8 (75%) pediatrische patiënten sarcomeergen mutaties aantoonbaar waren.

In **Hoofdstuk 14** laten we de resultaten zien van de systematische cardiale screening van familieleden van NCCM patiënten. In ongeveer de helft van de patiënten met NCCM werd een familiair, erfelijke patroon gevonden. Onder de onderzochte familieleden vonden we een hoge prevalentie van asymptomatische hartspierziekte. Zonder systematische cardiale screening, zou deze in de meeste gevallen ongemerkt zijn gebleven met daardoor missen van een kans op preventieve, presymptomatische behandeling. Het ontbreken van klachten, symptomen van hart -en vaatziekten of ECG-afwijkingen sloot een onderliggende hartspier-

ziekte niet uit. Cardiale beeldvorming, met echocardiografie of MRI blijkt onmisbaar om NCCM te detecteren of uit te sluiten.

Pseudo-noncompaction cardiomyopathie

Meer dan twee decennia na het eerste voorstel voor diagnostische criteria, steunt de diagnose van NCCM nog steeds in belangrijke mate op abnormale morfologische kenmerken: overmatige trabekelvorming. Erg opvallende trabekels komen echter ook voor bij personen met chronische druk of volume overbelasting van de ventrikel en deze kunnen worden verward met NCCM. In **Hoofdstuk 15** wordt een jonge man beschreven met echocardiografische bevindingen passend bij NCCM, ernstige sinus bradycardie en matige aortaklep insufficiëntie. Onze hypothese was dat chronische volume overbelasting als gevolg van de bradycardie en matige aortaklepinsufficientie resulteerde in hartfalen en een NCCM-achtig beeld (een "noncompaction look-alike"). Na implantatie van een AAI pacemaker ter bestrijding van zijn ernstige bradycardie waren zijn symptomen verdwenen en de LV dimensies genormaliseerd. In **Hoofdstuk16**, beschrijven we een 55 jaar oude man, verwezen voor harttransplantatie wegens invaliderende angina pectoris en vermoeidheid. Echocardiografisch onderzoek toonde echter een goede systolische LV functie met milde LV dilatatie. Daarnaast was er opvallende trabekelvorming te zien in de apicale en midventriculaire LV wandsegmenten, die NCCM suggereerden. Coronaire angiografie toonde sterk gekronkelde en sterk verwijde kransslagaders met multipele coronair-ventriculaire fistulae. Een mogelijke verklaring voor dit pseudo-NCCM beeld is dat persisterende embryonale sinusoïden en de sponsachtige hartspier een gevolg zijn van abnormale cardiale embryogenese naast de chronische volume overbelasting van de linker kamer als gevolg van de fistels.

CONCLUSIES

NCCM is een genetisch heterogene cardiomyopathie met variabele klinische presentatie. De prognose varieert van asymptomatische ziekte tot ernstig invaliderend en progressief hartfalen of plotse dood. In ons NCCM cohort vonden we dat NCCM patiënten zonder hartfalen een uitstekende lange termijns (8-jaar) overleving hebben als zij optimaal worden behandeld met de juiste medicamenteuze therapie en, conform de richtlijnen voor andere cardiomyopatiën, profylactisch een ICD krijgen ter preventie van plotse hartdood.

Transthoracale echocardiografie met kleuren Doppler onderzoek is de standaard diagnostische modaliteit voor NCCM. Daarnaast kan invasieve ventriculografie nuttig zijn in het geval dat om andere redenen toch een hartkatheterisatie wordt uitgevoerd.

Systolische disfunctie van de linker ventrikel komt vaak voor bij NCCM patiënten, maar er was weinig informatie beschikbaar over de (dis)functie van compacte en noncompacte segmenten. We toonden met regionale 3D-echocardiografie aan dat noncompacte en

compacte LV segmenten een vergelijkbare regionale daling van de ejectie fractie vertonen, wat suggereert dat systolische LV disfunctie in NCCM niet beperkt is tot noncompacte LV segmenten. Met behulp van Tissue Doppler beelden bevestigden we daarna dat LV disfunctie in NCCM inderdaad geen regionaal maar een globaal probleem van de hartspier is.
De huidige diagnostische criteria leunen uitsluitend op morfologische kenmerken maar we hebben laten zien dat "rigid body rotation" van de linker ventrikel een objectief, kwantificeerbaar en reproduceerbaar functioneel criterium is met een goede voorspellende waarde voor de diagnose van NCCM.
De prevalentie van maligne ventriculaire ritmestoornissen bij NCCM is niet bekend en een adequate risicostratificatie en preventie van plotse dood bij NCCM patiënten blijft een grote uitdaging. In deze context ondersteunt frequente, terechte ICD therapie tijdens de follow-up van onze patiënten toepassing bij NCCM patiënten van de huidige ICD richtlijnen ter preventie van plotse hartdood.
Omdat er steeds meer aanwijzingen zijn dat vroege repolarisatie (ER) sterk geassocieerd is met maligne ventriculaire ritmestoornissen en wij een hoge prevalentie van ER vonden in de NCCM patiënten met maligne ritmestoornissen en plotse dood kan ER waarschijnlijk bijdragen aan de risico stratificatie ten aanzien van plotse dood in de NCCM patiënten en ons helpen bij het stellen van de indicatie tot profylactische ICD-implantatie.
Gecombineerd DNA onderzoek en cardiologisch familie onderzoek laat zien dat de meerderheid van de NCCM gevallen genetisch bepaald is. Derhalve is het advies dat patiënten en hun familieleden genetisch onderzoek en begeleiding wordt aangeboden. In ongeveer een derde van de NCCM patiënten worden sarcomeer gen mutaties gevonden en bij systematische cardiale evaluatie komt vaak asymptomatische ziekte bij de familieleden aan het licht. Hierdoor wordt het mogelijk om presymptomatisch, preventieve behandeling te starten.

TOEKOMSTPERSPECTIEF

De prevalentie van NCCM is grotendeels onbekend en we moeten meer te weten komen over de pathologie, de klinische vormen en de genetica. Een grote, internationale, multicenter, prospectieve databank zou belangrijke informatie kunnen leveren. Daarnaast is er behoefte aan consensus uitspraken zoals bij andere vormen van cardiomyopathie. Een duidelijke patho-anatomische (en histo-pathologische) definitie van NCCM zou de eerste stap zijn naar een uniforme diagnose aan de hand van beeldvorming en een afbakening van de pseudodan wel secundaire (verworven) noncompactie ten opzichte van de werkelijke NCCM. Een nieuwe classificatie moet NCCM duidelijk als een aparte ziekte-entiteit beschrijven, met een eigen nomenclatuur, indeling, pathofysiologie en prognose.
Omdat NCCM genetisch zo heterogeen is en een helder genotype-fenotype relatie ontbreekt, moet genetische counseling, DNA-diagnostiek, en familie screening met aanvullend

genetisch onderzoek worden aangemoedigd. De huidige genetische testen laten maar in ongeveer een derde van de gevallen een relevante mutatie zien. Verder DNA onderzoek is nodig om de rol van additionele mutaties en de mogelijke rol hiervan in de fenotypische variabiliteit te onderzoeken. Ook nieuw onderzoek naar genotype-fenotype en omgevingsinteracties naast variabiliteit in leeftijdsafhankelijke penetrantie kan een nieuwe perspectief bieden.

Er zijn verschillende vormen van NCCM: een geïsoleerde, voornamelijk bij volwassenen voorkomende vorm, een vooral bij kinderen voorkomende vorm die sterk geassocieerd is met aangeboren hartziekte en een derde vorm van NCCM die bij neuromusculaire ziekten wordt gezien. Bij NCCM moeten niet alleen de aanof afwezigheid van een andere gelijktijdige cardiale ziekte (aangeboren, valvulaire), de uitgebreidheid, de locatie en de ernst van overmatige trabekelvorming worden beschreven, maar ook functionele LV parameters (systolische LV functie, "rigid body rotation") en mogelijke genetische mutaties. Hierbij is het op de juiste wijze bepalen van de LV functie (i.e. ejectie fractie) moeilijk omdat de endocard zijde zeer onregelmatig begrensd is, waaroor endocardiale "tracing" onbetrouwbaar wordt. Derhalve moet worden onderzocht met welke beeldvormende modaliteit de LV disfunctie het beste kan worden gekwantificeerd.

Preventie van plotse hartdood en adequate risicostratificatie blijft een grote uitdaging. Strategieën om de prognose van patiënten met deze zeldzame ziekte te verbeteren zijn tot op heden gebaseerd op gegevens uit beperkte reeksen patiënten (zoals in dit proefschrift) dus grote multicenter (inter-)nationale "registries" zullen nodig zijn om voldoende "evidence" te vinden ter ondersteuning van het beleid.

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een Turks gezegde: "een man leer je kennen door gezamenlijk militaire dienst te doen, door gezamenlijk (in de gevangenis) te zitten of door een reis te maken". Na een gezamenlijke reis ken ik je nu en dat is een goed gevoel. Beste Kamer, jongste zusje; je hebt het niet altijd gemakkelijk gehad, maar je hebt alle stormen van het leven getrotseerd en bent daar fier doorheen gekomen. Ik wens je heel veel geluk en een gezond en lang leven.

Mijn ouders, sevgili annem ve babam, bir seyler basarabildiysem, hepsi ipti Allah, sonra sizlerin sayenizde oldu. Insallah, nice saglikli, neseli ve huzurlu yillariniz olmasi dilegiyle. Bu arada butun kardeslerime, abilerime ve ablalarima, her zaman destek ve yardimci olduklari icin minnettarligimi bildimek dilegiyle.

Sevgili Hatice, derler ya, iyi bir hanim esini vezir yapar. Sen olmasan, yuvada saglam bir direk gibi durmasan, bu kadar zorluklari asmanin, hemen hemen imkansiz olacagini, senin nesen, sabrin ve her zaman destegin olmasa, bir yerlere gelemiyecegimi butun sukranlarimla belirtmek istiyorum. Sana ve cocuklarima, yillarca cok az zaman ayirabildigim icin, ne kadar ozur dilesem az olacagimi biliyorum. Insallah cocuklarimiz ve butun ailelerimizle, nice saglikli ve mutlu yillar dilegiyle. Sevgili kizim Pinar, jij wilt ook heel graag "dokter' worden. Als ik zie wat voor fantastische meid je bent, briljant in bijvoorbeeld wiskunde, denk ik dat je alles kunt bereiken wat je wilt. Sevgili Tolga, canim oglum, je bent echt een kanjer en ik ben benieuwd of je je droom om "bij de politie" te gaan zult verwezenlijken (maar het hele leven ligt nog voor je!).

Curriculum Vitae

Kadir Caliskan is op 3 mei 1967 geboren in Mucur te Turkije. In 1978 verhuisde hij naar Nederland in het kader van gezinshereniging. Na zijn eindexamen in 1987 aan het Zaanlands Lyceum te Zaandam, studeerde hij geneeskunde aan de Universiteit van Amsterdam. Na zijn afstuderen in 1994 heeft hij een aantal jaren gewerkt als arts-assistent (afdeling Longziekten, Academisch Medisch Centrum, afdeling Interne Geneeskunde en Cardiologie, Kennemer Gasthuis Haarlem, afdeling Cardiologie, VUMC en afdeling Cardio-thoracale chirurgie te Onze Lieve Vrouwe Gasthuis Amsterdam). Aansluitend begon hij in 1999 begon aan zijn opleiding tot cardiologie in het Erasmus MC in Rotterdam (opleiders prof. dr. J.R.T.C Roelandt en prof. dr. M.L. Simoons). Hiervoor volgde hij de vooropleiding Interne Geneeskunde in Medisch Centrum Alkmaar (opleider dr. W. Bronsveld). De opleiding cardiologie werd afgerond in 2005. Sindsdien is hij werkzaam als cardioloog in het Erasmus MC. Zijn aandachtsgebieden zijn hartspierziekten, gevorderde hartfalen, harttransplantatie en steunharten.

Het onderzoek dat geleid heeft tot dit proefschrift werd verricht op de afdeling Cardiologie van het Thoraxcentrum in samenwerking met de afdeling Klinische Genetica van de Erasmus MC (dr. D.F. Majoor-Krakauer).

Kadir Caliskan is getrouwd met Hatice Caliskan-Alkan en zij hebben twee kinderen: Pinar (15 jaar) en Kemal Tolga (12 jaar).

PhD Portfolio

Name PhD student: K. Caliskan	PhD period: 2005-2012
Erasmus MC Department: Cardiology	Promotor(s): M.L. Simoons
Research School: COEUR	Supervisor: J.W. Deckers

1. PhD training

		Year	Workload (hours)	ECTS
General courses				
-	Biostatistics for clinicians		24	
-	Research Integrity (BROK)	2011	24	
-	Leiderschapdagen	2011	24	
Specific courses				
-	COUER PhD course and research seminars	2005-2012		6
International conferences and abstract presentations				
-	European Society of Cardiology: 1 x oral, 2 x poster			
-	American Heart Association: 2 x oral, 1 x poster	2005-2012	195	
-	American College of Cardiology: 1 x poster			
-	HeartRhythm (abstract presentation): 1 x poster			
-	ESC Heart Failure (abstract presentation): 1 x poster			
-	Cardiostim: 1x poster			
-	ESC Myocardial and Pericardial disaeses: 1x poster			
-	NVVC: 2 x oral presentation			
Presentations				
-	6 presentations at seminars	2005-2012	36	
Didactic skills				
-	Teach-the-teacher	2007	13	
Other				
-	NVVC congresses	2005-2012	80	
-	ISHLT congresses	2005+2012	48	
-	ISHLT Mechanical support course	2012	9	
-	ACC Fuster course	2006	24	
-	Cardiology and Vascular Medicine Update	2005-2012	85	
2. Teaching activities				
Lecturing				
-	Tutoronderwijs co-assistenten	2009-2011	24	
-	PKV en RISK onderwijs	2005-2012	40	
-	Journal Club	2005-2012	6	
-	Klinische lessen verpleegkundigen	2005-2012	20	
Total			780	6

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