

Case Report

J Vet Intern Med 2017;31:527–531**Naturally Occurring Biventricular Noncompaction in an Adult Domestic Cat**

M.D. Kittleson, P.R. Fox, C. Basso, and G. Thiene

A definitively diagnosed case of left ventricular noncompaction (LVNC) has not been previously reported in a non-human species. We describe a Maine Coon cross cat with echocardiographically and pathologically documented LVNC. The cat was from a research colony and was heterozygous for the cardiac myosin binding protein C mutation associated with hypertrophic cardiomyopathy (HCM) in Maine Coon cats (A31P). The cat had had echocardiographic examinations performed every 6 months until 6 years of age at which time the cat died of an unrelated cause. Echocardiographic findings consistent with LVNC (moth-eaten appearance to the inner wall of the mid- to apical region of the left ventricle (LV) in cross section and trabeculations of the inner LV wall that communicated with the LV chamber) first were identified at 2 years of age. At necropsy, pathologic findings of LVNC were verified and included the presence of noncompacted myocardium that consisted of endothelial-lined trabeculations and sinusoids that constituted more than half of the inner part of the LV wall. The right ventricular (RV) wall also was affected. Histopathology identified myofiber disarray, which is characteristic of HCM, although heart weight was normal and LV wall thickness was not increased.

Key words: Cardiomyopathy; Echocardiography; Feline; Hypertrabeculation; Left Ventricle; Noncompaction.

Case History

The echocardiographic morphology of the heart of a male, 4.2 kg Maine Coon cross cat born and raised in a research colony at the University of California, Davis was monitored over 5 years. Echocardiography was performed approximately every 6 months from 8 months of age using an echocardiograph machine with a 12 MHz transducer.³ The cat was heterozygous for the cardiac myosin binding protein C mutation (A31P) associated with HCM in Maine Coon cats.¹ This cat had no cardiac murmur, gallop sound, or arrhythmia and was in good health. At approximately 2 years of age, echocardiographic examination first identified a “moth-eaten” appearance to the LV wall in short-axis views and deep recesses in the inner LV wall on long-axis views representing hypertrabeculation (Fig 1). The distribution was most conspicuous at the mid- to apical LV. Color flow Doppler imaging was used to document that the recesses communicated with the LV cavity (Fig 2). Echocardiographic measurements were as follows: interventricular septum (IVS) thickness in diastole,

Abbreviations:

HCM	hypertrophic cardiomyopathy
IVS	interventricular septum
LVFW	left ventricular free wall
LV	left ventricle/left ventricular
LVNC	left ventricular noncompaction
RV	right ventricle
RVW	right ventricular wall

6 mm; LV free wall (LVFW) thickness in diastole, 6.2 mm; LV internal dimension in diastole, 13.4 mm; and LV internal dimension in systole, 6 mm. At approximately 6 years of age the cat developed an acute illness, sepsis, and died. Etiology was not established.

Necropsy was confined to cardiac examination. The heart was fixed in 10% neutral buffered formalin and sectioned in longitudinal, 4-chamber plane. Grossly, the LVFW had a coarse network of prominent trabeculations comprising more than half of the inner LV wall, whereas the right ventricular wall (RVW) had no grossly distinctive endocardial changes (Fig 3). The LV and RV wall thicknesses were measured perpendicular to the endocardial surfaces at the proximal LV papillary muscle level excluding trabeculae and papillary muscles. Tissues blocks were taken, imbedded in paraffin, sectioned, and stained. The heart weight was normal at 19.5 g (0.46% of body weight). Wall thicknesses were LVFW, 4.5 mm; IVS, 4.8 mm; and RVW, 2.1 mm—all within normal reference ranges.² Left ventricular papillary muscles appeared fused and were not distinctly formed. Chordae tendineae originated from the rounded, most proximal protuberance. The LV apex was focally thin, measuring 0.4 mm. Endocardial scarring was present at the juxtaposition of the papillary muscle and IVS as well as the thin apical segment.

Distinct hypertrabeculation involving the LV and RV walls was histologically apparent (Figs 3 and 4). These hypertrabeculated (noncompacted) inner regions were

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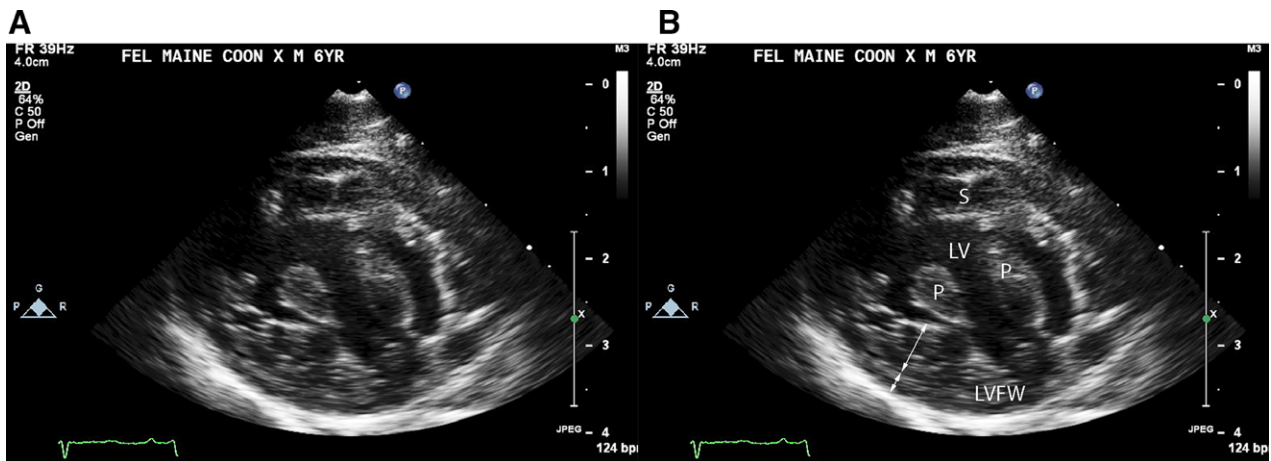


Fig 1. Two-dimensional echocardiograms of the heart. (A) Right parasternal cross-sectional LV view at the papillary muscle level shows a “moth-eaten” appearing, hypertrabeculated, caudo-lateral LV free wall. (B) A large, inner, noncompacted region (long arrow) appears adjacent to the thinner, external rim of normal myocardium (short arrow). P—Papillary muscle; LV—Left ventricular cavity; LVFW—Left ventricular free wall; S—Interventricular septum.

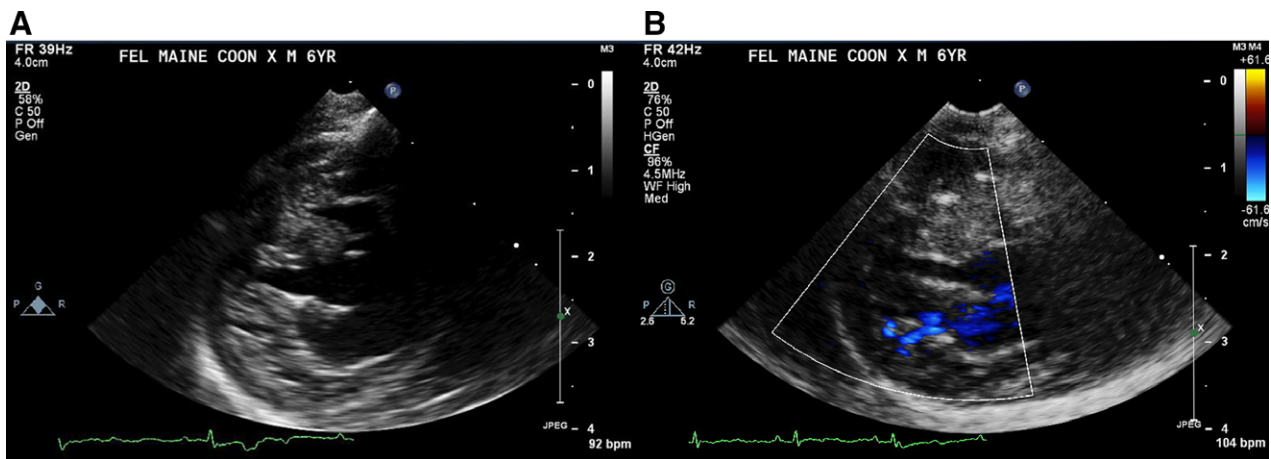


Fig 2. Right parasternal long-axis views of the LV. (A) Large trabeculations are noted below and in front of a papillary muscle, (B) color flow Doppler echocardiogram shows that the sinusoids (recesses) created by these prominent trabeculations (noncompacted LV wall myocardium) communicate with the left ventricular chamber.

substantially thicker than the outer compacted myocardium. The trabeculae were associated with endothelial-lined recesses that communicated with both the LV and RV chambers. The pattern of superficial noncompacted myocardial layer differed between the RV and LV walls. The LVFW had excessive, conspicuous, coarse trabeculae with deep intertrabecular recesses extending toward the outer wall. They were predominantly oriented perpendicularly or somewhat obliquely to the long axis of the LVFW, were present in long axis from the mitral valve annulus proximally to the LV apex distally, and were most prominent at the mid-LV regions. The RVW showed a noncompacted layer comprised of excessive networks of hypertrabeculation that included both anastomosing, polypoid structures and fine, small trabeculae (Fig 5). Collectively, these findings are consistent with biventricular noncompaction patterns reported in humans with LVNC.^{3,4} Sections from the basilar IVS

showed myofiber disorganization in which cardiac muscle bundles were arranged at oblique or perpendicular angles (myocyte disarray), as well as interstitial fibrosis (Fig 6). These findings are consistent with HCM.

Discussion

To the best of our knowledge, spontaneously occurring ventricular noncompaction in animals has only been purported from a single kitten affected with Purkinje fiber dysplasia.⁵ Ventricular noncompaction in humans is a rare, although increasingly described, heterogeneous myocardial disorder contemporarily classified as a form of cardiomyopathy.⁶ This disease was first described in 1926 in a child and was associated with other cardiac abnormalities.⁷ Fifty-eight years later it was reported in an adult woman as an isolated (primary) myocardial abnormality.⁸ Subsequently, it was

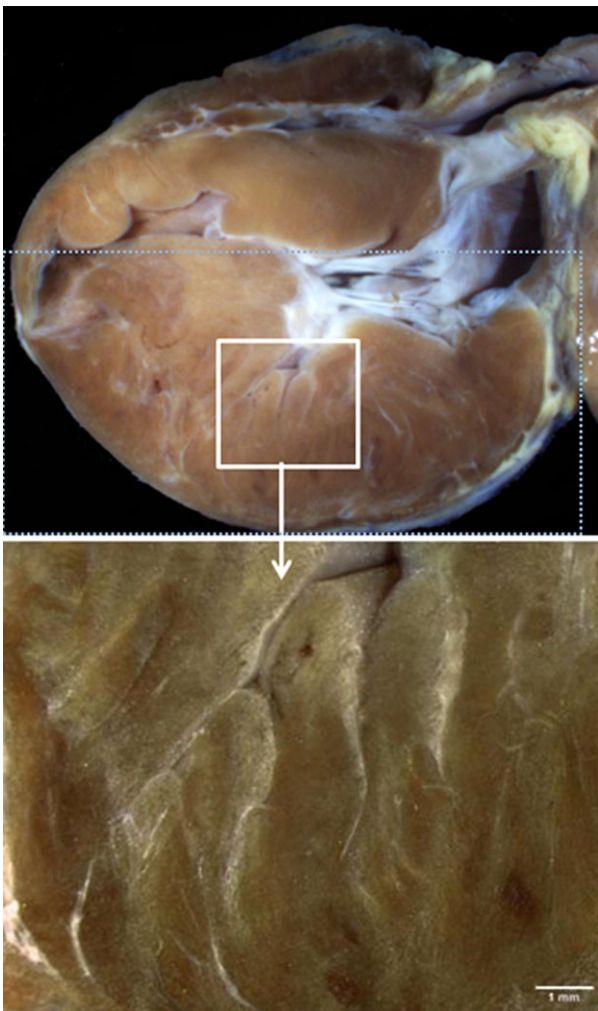


Fig 3. Necropsy specimen of the heart transected in a four-chambered section. Upper frame shows gross features of ventricular noncompaction associated with the left ventricular free wall (defined within the box). Papillary muscle formation is indistinct. Close-up view of the LVFW defined by the region within the box (lower frame) shows a coarse pattern of prominent, finger-like trabeculations with deep recesses confined to the inner portion of the LV wall.

reported in eight patients with a similar abnormality by Chin et al. who were the first to use the term “isolated noncompaction of LV myocardium.”⁹ Terminology for this condition has evolved.³ As with other cardiomyopathies during their emerging phase, this syndrome has gone by several names including but not limited to isolated ventricular noncompaction, noncompaction cardiomyopathy, noncompaction of the ventricular myocardium, hypertrabeculation, and spongiform cardiomyopathy. Classification and etiology of this condition continue to be deliberated.

The prominent morphologic feature of ventricular noncompaction is excessive, prominent trabeculae confined to the inner LV or RV walls and separated from each other by deep, intertrabecular sinusoids (recesses) that communicate with the ventricular cavity.^{3,4}

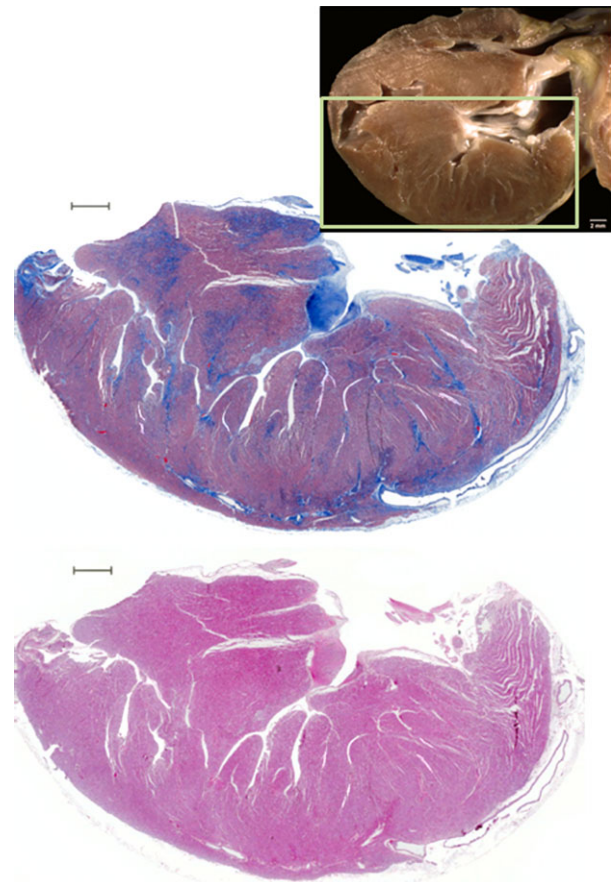


Fig 4. Histopathologic sections from the area of interest defined by the box (upper right frame, same specimen as Figure 3) demonstrate hypertrabeculated LV free wall myocardium. The inner, noncompacted portion is defined by the long trabeculae and is thicker than the outer, compacted portion of the wall. Central frame is a Masson's trichrome stain showing substantial replacement fibrosis (blue) in the papillary muscles and subendocardium and focal endocardial fibrosis affecting basal portions of sinusoids formed by excessive trabeculations. Bottom frame is hematoxylin and eosin stain. Bars are 1 mm.

Trabeculae are structures comprised of cardiomyocytes that are lined by endocardial cells which form in the ventricles toward the end of gestational week 4 in humans. Trabeculation increases the endocardial surface area to enhance gas exchange in developing myocardial tissue before the development of the coronary circulation.¹⁰ The coronary vasculature develops and invades the myocardium between human gestational weeks 5 and 8. Trabecular myocardium subsequently undergoes compaction, resulting in the disappearance of most of the intertrabecular recesses, leaving a relatively smooth ventricular endocardial surface. Trabecular compaction is normally more complete in left ventricular than in right ventricular myocardium.

Noncompaction may stem from arrested LV and or RV wall morphogenesis.^{10–12} This may result from intrauterine developmental arrest of normal myocardial compaction during the first trimester, leading to the formation of 2 myocardial layers: a compacted and a non-compacted layer. Recent evidence implicates the Notch

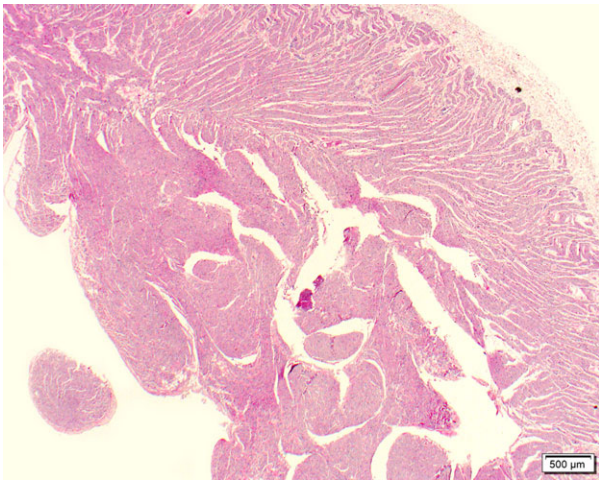


Fig 5. Histopathologic section from the RV wall showing coarse and fine networks of hypertrabeculation with anastomosing, poly-poid, broad, and fine trabeculae. These structures result in deep sinusoids and irregular, large spaces communicating with the RV chamber. Many small trabeculae, especially the compressed invaginations caused by intertrabecular invaginations, were not visible to the naked eye. Compared with the thick compacted inner zone in the LV, the RV compacted layer contained finer trabeculae and was relatively thin. Masson's trichrome stain.

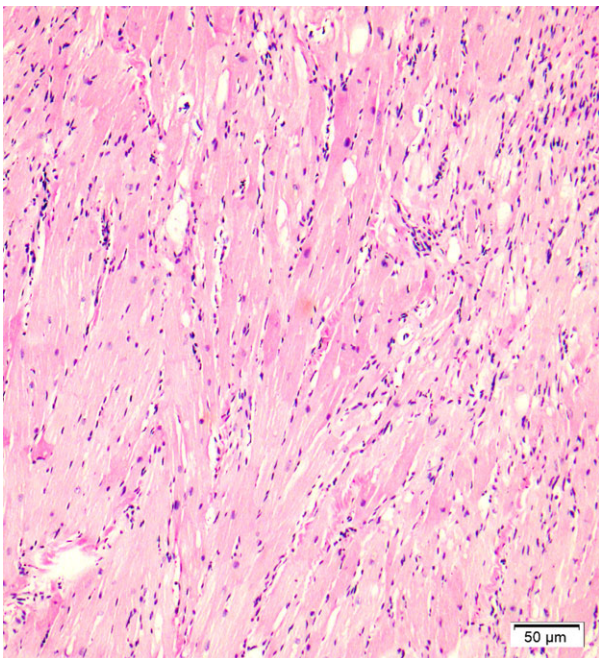


Fig 6. Histopathologic section from the interventricular septum showing myocyte disarray. Hematoxylin and eosin stain.

signaling pathway which regulates cell fate, differentiation, and patterning. This signaling system is controlled by ligands that are ubiquitinated by the E3 ubiquitin ligase MIB1. Inactivating mutations in the human MIB1 gene produces LVNC in transgenic mice.¹³ Nevertheless, the genesis of noncompaction in most patients remains uncertain, and some forms of noncompaction

occur in association with other diseases^{14,15} or with conditions such as systolic LV dysfunction.¹⁶

In humans, ventricular noncompaction can occur as an isolated abnormality or in association with various congenital heart diseases or other cardiac disorders or other cardiomyopathies.³ In isolated noncompaction, both familial and nonfamilial forms have been identified. Mutations in sarcomeric genes (beta-myosin heavy chain [MYH7], alpha-cardiac actin [ACTC], and cardiac troponin T [TNNT2]), Z-line genes, mitochondrial genes, the alpha-dystrobrevin gene, the lamin A/C gene, and the tafazzin gene have been identified in association with LVNC.¹⁷ Thus, it is increasingly recognized that certain gene mutations encoding for sarcomeric proteins can lead to a range of disease phenotypes including LVNC as well as hypertrophic, restrictive, and dilated cardiomyopathy.^{17–20} The present case of biventricular noncompaction in a cat lends credence to this concept. This cat had histologic findings of myocyte disarray and interstitial fibrosis, hallmark features of HCM. The presence of an HCM-producing gene mutation also was documented.

Echocardiographic IVS and LVW measurements suggested mild LV hypertrophy and when viewing the cut section, the LV appeared thickened. However, upon closer inspection, this impression was not supported. First, heart weight was in the upper range of normal and thus not consistent with LV hypertrophy which would markedly increase heart weight. The disparity between echocardiographic and gross wall measurements likely is attributable to overestimation of wall thickness by echocardiography which included the outer, noncompacted layer, whereas gross measurements aided by microscopy measured the inner, compacted myocardial layer. Furthermore, papillary muscle fusion contributed to the appearance of papillary hypertrophy, but these structures were not subjectively judged to be hypertrophied *per se*.

Ventricular noncompaction is characterized morphologically by three features—prominent trabeculae, deep intertrabecular recesses, and a thinner compacted layer of outer myocardium. The characteristic deep recesses (sinusoids) communicate with the ventricular cavity. However, the extent of each of these findings varies from patient to patient.^{3,4,21}

The diagnosis of ventricular noncompaction commonly is facilitated by echocardiographic criteria. These include assessment of the compacted (normal) outer myocardial layer toward the epicardium relative to trabeculated (noncompacted) myocardial layer comprising the inner myocardium. There is no consensus, however, and diagnostic criteria vary regarding echocardiographic views, number of trabeculations, and use of end-diastole versus end-systole for measurements. A study comparing three current diagnostic sets of criteria found that only 30% of patients believed to have LVNC achieved 100% agreement using reported criteria.¹⁶ Magnetic resonance imaging may improve upon the accuracy of diagnosing LVNC in the future.²²

The differential diagnosis for LVNC in humans includes apical forms of hypertrophic cardiomyopathy, a combination of both apical hypertrophic cardiomyopathy and

LVNC, hypertensive cardiomyopathy, endocardial fibroelastosis, abnormal chords, apical thrombus, and tumors.²³ None were present in this cat based on the pathological examination.

In conclusion, the present case demonstrated conspicuous and remarkable echocardiographic and pathologic features consistent with biventricular noncompaction that closely resemble those morphologic characteristics described in human patients with LVNC. Given the concomitant findings of left ventricular myofiber disarray and the presence of cardiac myosin binding protein C A31P mutation associated with HCM in Maine Coon cats, this may represent a mixed noncompaction—HCM case but without left ventricular hypertrophy. Thus, much like hypertrophic, restrictive, and arrhythmic forms of myocardial disease that occur in cats that strongly mimic those disorders in humans,²⁴ ventricular noncompaction may constitute a newly described form of cardiomyopathy in domestic cats. The presence of these findings in an HCM genotype positive, phenotype negative domestic cat is consistent with reports of ventricular noncompaction in human patients having other cardiac conditions.

Footnote

^a Philips iE33, Philips Healthcare, Foster City, CA

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Conflict of Interest Declaration: Authors declare no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

References

1. Meurs KM, Sanchez X, David RM, et al. A cardiac myosin binding protein C mutation in the Maine Coon cat with familial hypertrophic cardiomyopathy. *Hum Mol Genet* 2005;14:3587–3593.
2. Liu SK, Roberts WC, Maron BJ. Comparison of morphologic findings in spontaneously occurring hypertrophic cardiomyopathy in humans, cats and dogs. *Am J Cardio* 1993;72:944–951.
3. Towbin JA. Left ventricular noncompaction: A new form of heart failure. *Heart Fail Clin* 2010;6:453–469.
4. Burke A, Mont E, Kutys R, Virmani R. Left ventricular noncompaction: A pathological study of 14 cases. *Hum Pathol* 2005;36:403–411.
5. Gelberg HB. Purkinje fiber dysplasia (histiocytoid cardiomyopathy) with ventricular noncompaction in a savannah kitten. *Vet Pathol* 2009;46:693–697.
6. Elliott P, Andersson B, Arbustini E, et al. Classification of the cardiomyopathies: A position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2008;29:270–276.
7. Grant R. An unusual anomaly of the coronary vessels in the malformed heart of a child. *Heart* 1926;13:273–283.
8. Engberding R, Bender F. Identification of a rare congenital anomaly of the myocardium by two-dimensional echocardiography: Persistence of isolated myocardial sinusoids (noncompaction). *Am J Cardiol* 1984;53:1733–1734.
9. Chin TK, Perloff JK, Williams RG, et al. Isolated noncompaction of left ventricular myocardium. A study of eight cases. *Circulation* 1990;82:507–513.
10. Sedmera D, Pexieder T, Vuillemin M, et al. Developmental patterning of the myocardium. *Anat Rec* 2000;258:319–337.
11. Chen H, Zhang W, Li D, et al. Analysis of ventricular hypertrabeculation and noncompaction using genetically engineered mouse models. *Pediatr Cardiol* 2009;30:626–634.
12. Yang J, Bücker S, Jungblut B, et al. Inhibition of Notch2 by Numb/Numb like controls myocardial compaction in the heart. *Cardiovasc Res* 2012;96:276–285.
13. Luxán G, Casanova JC, Martínez-Poveda B, et al. Mutations in the NOTCH pathway regulator MIB1 cause left ventricular noncompaction cardiomyopathy. *Nat Med* 2013;19:193–201.
14. Stöllberger C, Finsterer J, Blazek G. Left ventricular hypertrabeculation/noncompaction and association with additional cardiac abnormalities and neuromuscular disorders. *Am J Cardiol* 2002;90:899–902.
15. Caliskan K, Ujvari B, Bauernfeind T, et al. The prevalence of early repolarization in patients with noncompaction cardiomyopathy presenting with malignant ventricular arrhythmias. *J Cardiovasc Electrophysiol* 2012;23:938–944.
16. Kohli SK, Pantazis AA, Shah JS, et al. Diagnosis of left-ventricular non-compaction in patients with left-ventricular systolic dysfunction: Time for a reappraisal of diagnostic criteria? *Eur Heart J* 2008;29:89–95.
17. Paterick TE, Umland MM, Jan MF, et al. Left ventricular noncompaction: A 25-year odyssey. *J Am Soc Echocardiogr* 2012;25:363–375.
18. Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies: An American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation* 2006;113:1807–1816.
19. Lopes LR, Elliott PM. A straightforward guide to the sarcomeric basis of cardiomyopathies. *Heart* 2014;100:1916–1923.
20. Klaassen S, Probst S, Oechslin E, et al. Mutations in sarcomere protein genes in left ventricular noncompaction. *Circulation* 2008;117:2893–2901.
21. Arbustini E, Weidemann F, Hall JL. Left ventricular noncompaction: A distinct cardiomyopathy or a trait shared by different cardiac diseases? *J Am Coll Cardiol* 2014;64:1840–1850.
22. Jacquier A, Thuny F, Jop B, et al. Measurement of trabeculated left ventricular mass using cardiac magnetic resonance imaging in the diagnosis of left ventricular non-compaction. *Eur Heart J* 2010;31:1098–1104.
23. Oechslin E, Jenni R. Left ventricular non-compaction revisited: A distinct phenotype with genetic heterogeneity? *Eur Heart J* 2011;32:1446–1456.
24. Maron BJ, Fox PR. Hypertrophic cardiomyopathy in man and cats. *J Vet Cardiol* 2015;17(Suppl 1):S6–S9.