Is Left Ventricular Noncompaction a Trait, Phenotype, or Disease?

The Evidence Points to Phenotype

Ray E. Hershberger, MD; Ana Morales, MS, LGC; Jason Cowan, PhD

The question is is left ventricular noncompaction (LVNC) a trait, phenotype, or disease? By trait, we refer to a discrete and measurable characteristic like eye color. The term phenotype expands this definition to include multiple observable traits derived from diverse genetic factors (genotype) and to recognize additional roles for the environment in shaping visible expression of a genetically defined trait. Pathological phenotypes, with their myriad signs, symptoms, diagnoses, and prognoses, are recognized as diseases and are most often associated with adverse clinical manifestations or need for medical or surgical intervention.

So where in this conceptual framework do we place LVNC? This is a well-debated topic and one that has been recently systematically and expertly reviewed in much greater depth than afforded by this editorial. Although LVNC has increasingly been recognized as a cardiomyopathy—itself a term with clear disease connotations—mounting evidence now points to reclassification of LVNC as a distinct but not necessarily pathological phenotype. More specifically, the degree of compacted to noncompacted (NC) myocardium, by itself alone, does not seem to cause disease.

Why phenotype rather than trait? Traits are considered to be genetically driven and not malleable by the environment. As defined above, genetics interacting with environment are best labeled as phenotype. Left ventricular (LV) morphology is not fixed for certain characteristics, including LV wall thickness or LV size. The former is well known to increase with severe hypertension or aortic stenosis, and the latter increases with volume overload from aortic insufficiency. With medical or surgical therapy, both conditions will regress. A similar paradigm has been observed with dilated cardiomyopathy—a disease phenotype associated with heart failure and arrhythmia for which the dilated or remodeled left ventricle will reverse remodel with appropriate medical therapy. Characteristics such as these define phenotype, both physiological or pathological.

The key question is whether LVNC is a causal part of a pathological phenotype, its own distinct phenotypic entity, or merely a response element: a morphological change arising as a consequence of some other physiological or pathological signaling. In support of LVNC as a response element is the observation that NC versus compacted myocardium increases in highly trained athletes or in pregnancy, with reversion after delivery. Morbidity or mortality were not associated with the LVNC phenotype in either of these 2 studies. More importantly, no adverse effects have been observed in association with these morphological changes.

The initial clinical reports of LVNC, associated with substantial mortality, undoubtedly experienced an ascertainment bias—a systematic error in measuring the true frequency of an entity deriving from the manner in which the data are collected. As the adage goes: we find only what we look for—and what we find depends critically on the population in which we search. The development of the LVNC literature illustrates such an ascertainment bias. As reviewed, LVNC was initially observed as a phenotype in echocardiographic-based studies of symptomatic patients who had morbidity and mortality. In that setting, LVNC was attributed as a causal factor; however, subsequent imaging definitions for LVNC have differed. In a series of 199 patients with heart failure, 3 different echocardiographic definitions for LVNC gave concordance in only 30%. Two cardiac magnetic resonance approaches have used either the amount of NC to compacted myocardium >20% or the ratio of NC/compacted >2.3. Cardiac magnetic resonance imaging has become the gold standard for imaging LVNC because of its much greater resolution. Two contemporary population-based studies used cardiac magnetic resonance in individuals without known cardiovascular disease. Both studies observed that degree of LV trabeculation varied widely throughout the general population. The first study used baseline and follow-up data for 9.5 years from 2742 individuals recruited to the US-based and National Institutes of Health-funded MESA (Multi-Ethnic Study of Atherosclerosis). LVNC was divided into quintiles, with the NC/compacted ratio ranging from 2.46 to 5.41 in the fifth quintile. Only trivial differences were observed during the 9.5 years with LV ejection fraction or ventricular volumes. Importantly, no differences were observed in adverse cardiovascular outcomes, including atrial fibrillation, heart failure, stroke, or myocardial infarction, based on the quintiles of NC/compacted ratio. The second study conducted in

See Article by Miller et al

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Division of Human Genetics, Department of Internal Medicine (R.E.H, A.M., J.C) and Division of Cardiovascular Medicine (R.E.H), Dorothy M. Davis Heart and Lung Research Institute, Ohio State University College of Medicine, Columbus.

Correspondence to Ray E. Hershberger, MD, Division of Human Genetics, Department of Internal Medicine, Dorothy M. Davis Heart and Lung Research Institute, Ohio State University College of Medicine, Biomedical Research Tower Room 304, 460 W 12th Ave, Columbus, OH 43210. E-mail ray.hershberger@osumc.edu

(Circ Cardiovasc Genet. 2017;10:e001968. DOI: 10.1161/CIRCGENETICS.117.001968.) © 2017 American Heart Association, Inc.

Circ Cardiovasc Genet is available at http://circgenetics.ahajournals.org

DOI: 10.1161/CIRCGENETICS.117.001968
1480 individuals from the UK-Canadian TASCFORCE study (Tayside Screening for Cardiac Events), also identified LVNC as a common morphological finding (ranging from 14.8%–1.3% with increasing stringency of definitions in a population without known cardiovascular disease).

Might genetic background influence or modulate the development of NC myocardium? Might a genetic background, perhaps in association with a genetically mediated cardiomyopathy, lead to LVNC? It is now clear that LVNC has no specific gene ontology. LVNC has been reported in patients shown to have genetic cause in dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, the channelopathies, bicuspid aortic valve, aortopathy, and congenital heart defects. In the pediatric population, LVNC has been identified with rare genetic syndromes, including cardiomyopathy from mitochondrial disease and Barth syndrome—an X-linked condition.

What about clinical genetics? In earlier studies, patients or families were suggested to have isolated LVNC (iLVNC). Despite this attribution, the LVNC phenotype was commonly described in association with other conditions, especially other cardiomyopathies or heart failure. For example, Probst et al, referred to their cases as iLVNC only. The authors did not state how patients were ascertained, even though their report shows extensive cardiomyopathy, and other cardiovascular symptoms were common. Genetic findings were reported in 78% and 89%, respectively, and included variants in sarcomeric genes with MYH7 having the greatest number of variants. Among the probands with (n=18) or without (n=45) relevant variants identified, heart failure was present in 56% and 62% of each respective group. Similarly, of the 23 and 35 probands (mutation positive or negative) identified by Hoedemaekers et al, and reported as having iLVNC, 12 (52%) and 20 (57%) had heart failure. In that series, 67% were attributed as having genetic cause from 16 genes screened by Sanger sequencing.

Extending genetic information for LVNC, in this issue, Miller et al have contributed a study from the Cincinnati Children’s Hospital Medical Center. The authors aimed to test the hypothesis that the yield of genetic testing would be lower in those with iLVNC versus those with LVNC associated with cardiomyopathy. The authors concluded that only the co-occurrence of a cardiomyopathy with LVNC predicted positive genetic testing.

The Miller study, conducted from 2009 to 2012, was retrospective with LVNC identified by a chart review of patients referred for echocardiography. Of the 128 individuals identified from 120 families (8 siblings with LVNC), 59% were categorized as having idiopathic (nonfamilial) disease, 32% with familial, and 9% with syndromic or metabolic disease. The majority of patients (n=94; 73%) were identified with LVNC before 13 years of age. Patients were categorized into 3 groups: iLVNC (n=61; 48%), LVNC associated with a cardiomyopathy (n=42; 33%), or LVNC associated with other cardiovascular malformations (n=25; 20%). Genetic testing was undertaken in 75 of the 128, of which 65 of the 75 were tested with a gene panel. The authors applied current American College of Medical Genetics criteria (pathogenic, likely pathogenic, and variant of uncertain significance)—a strength of this work—for assignment of variant pathogenicity. Of the 75 tested patients, 13 (17%) had a pathogenic or likely pathogenic variant identified. The positive genetic test results were with LVNC/cardiovascular malformation (30%), of which 7 of the 10 in this group had a co-occurring cardiomyopathy, and LVNC/cardiovascular malformation (12%). None of those classified as iLVNC had positive genetic testing results. In addition to categories, the authors examined other clinical factors, including etiology, family history of cardiomyopathy, and myocardial dysfunction, but only the category predicted a positive genetic testing result. Beyond genetic analysis, because of the pediatric makeup of the patients studied, the study by Miller et al also expands the scope of LVNC observed in hypertrophic cardiomyopathy or dilated cardiomyopathy: 4 had mitochondrial disease and 3 had chromosomal abnormalities, including one 1p36 deletion syndrome.

Has the genetic evaluation of LVNC been completed? The answer to this question is clearly no. It is possible that understanding the genomics and cell biology of how NC myocardium grows and regresses might provide new insights into all of cardiovascular myocyte biology and the dynamics of ventricular morphology. It is also possible that a specific genetic background of common or rare variants may interact with environment to modulate, to a greater or lesser extent, the degree of LV trabeculation over time. To date, we are unaware of a genome-wide association study (with common variants) published with the LVNC phenotype. However, common or rare variant population-based studies, or large studies in specific cardiomyopathies where subjects with LVNC would be compared with the non-LVNC cohort, could provide the opportunity to identify genomic factors.

So where does this leave us? LVNC as a phenotype has been observed in varying degrees in population-based studies in ostensibly normal individuals, and no adverse outcomes have been observed; it has also been observed in response to physiological load, and it reverses (pregnancy and exercise). LVNC also has been observed in a wide variety of cardiovascular conditions, as listed above. Are the data fully complete to close the case that LVNC is not relevant for any cardiovascular pathological condition? This has been elegantly recently discussed. The question is whether LVNC observed in association with any other CV phenotype in any way facilitates or affects morbidity or mortality. To date, a rigorously designed study with a clearly articulated hypothesis has not been completed to determine whether LVNC does contribute to cardiomyopathy, arrhythmia, or stroke. Conceptually, such a study should leverage both population-based studies, already collected, and well-curated phenotypes, such as dilated cardiomyopathy (Figure). Until such data are in hand, we urge caution in closing the case. Although at the present, the data indicate that LVNC seems to be a phenotype with no direct causal relationship to adverse outcome, rigorous, well-designed studies will be welcomed to inform this debate.

The derivative of this conclusion, even if not yet fully confirmed, is agreement with the findings of Miller et al and their recommendations that genetic testing is unlikely to be useful for the LVNC phenotype itself but that rather it is best
Figure. A genetic study design for left ventricular noncompaction (LVNC) phenotype. Population studies have shown that the greatest number of individuals with an increased ratio of non-compacted to compacted myocardium have no other detectable cardiovascular disease, which is depicted by the blue circle (A), less the overlap of the dilated cardiomyopathy (DCM) population, shown in the red circle (C). The overlap of A and C is the LVNC observed with DCM (B). We speculate that LVNC may be controlled, in part, by a variety of genomic factors that might be detected by a genome-wide association study of all LVNC phenotypes, including DCM. We also suggest genome-wide sequencing studies to integrate rare variants into the analysis.

reserved for well-established disease phenotypes—for example, cardiomyopathy, channelopathy, and others where data for diagnosis, prognosis, and intervention are clearly established.

Disclosures

None.

References

1. Oechslin E, Jenni R. Nosology of noncompaction cardiomyopathy: the emperor still wears clothes? Can J Cardiol. 2017;33:701–704. doi: 10.1016/j.cjca.2017.04.003.
2. Anderson RH, Jensen B, Mohun TJ, Petersen SE, Aung N, Zemrak F, et al. Key questions relating to left ventricular noncompaction cardiomyopathy: is the emperor still wearing any clothes? Can J Cardiol. 2017;33:747–757. doi: 10.1016/j.cjca.2017.01.017.
3. 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. doi: 10.1016/j.jacc.2014.08.030.
4. Caselli S, Attenhofer Jost CH, Jenni R, Pelliccia A. Left ventricular noncompaction diagnosis and management relevant to pre-participation screening of athletes. Am J Cardiol. 2015;116:801–808. doi: 10.1016/j.amjcard.2015.05.055.
5. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, et al; American Heart Association; Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; Council on Epidemiology and Prevention. 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. doi: 10.1161/CIRCULATIONAHA.106.174287.
6. Gati S, Chandra N, Bennett RL, Reed M, Kervio G, Panoulas VF, et al. Increased left ventricular trabeculation in highly trained athletes: do we need more stringent criteria for the diagnosis of left ventricular non-compaction in athletes? Heart. 2013;99:401–408. doi: 10.1136/heartjnl-2012-303418.
7. Gati S, Papadakis M, Papamichail ND, Zaidi A, Sheikh N, Reed M, et al. Reversible de novo left ventricular trabeculations in pregnant women: implications for the diagnosis of left ventricular noncompaction in low-risk populations. Circulation. 2014;130:475–483. doi: 10.1161/CIRCULATIONAHA.114.008554.
8. Kohli SK, Pantazis AA, Shah JS, Adeyemi B, Jackson G, McKenna WJ, 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. doi: 10.1093/eurheartj/ehm481.
9. Zemrak F, Ahlman MA, Captur G, Mohiddin SA, Kavel-Boehm N, Prince MR, et al. The relationship of left ventricular trabeculation to ventricular function and structure over a 9.5-year follow-up: the MESA study. J Am Coll Cardiol. 2014;64:1971–1980. doi: 10.1016/j.jacc.2014.08.035.
10. Weir-McCall JR, Yecap PM, Pagapaorcupalo C, Fitzgerald K, Gandy SJ, Lambert M, et al. Left ventricular noncompaction: anatomical phenotype or distinct cardiomyopathy? J Am Coll Cardiol. 2016;68:2157–2165. doi: 10.1016/j.jacc.2016.08.054.
11. Agarwal A, Khandheria BK, Paterick TE, Treiber SC, Bush M, Tajik AJ. Left ventricular noncompaction in patients with bicuspid aortic valve. Am J Cardiol. 2014;64:1840–1850. doi: 10.1016/j.jacc.2014.08.030.
12. Ryan TD, Ware SM, Lucky AW, Towbin JA, Jefferies JL, Hinton RB. Left ventricular noncompaction cardiomyopathy and aortopathy in a patient with recessive dystrophic epidermolysis bullosa. Circ Heart Fail. 2012;5:e81–e82. doi: 10.1161/CIRCHEARTFAILURE.112.969675.
13. Postma AV, van Engelen K, van de Meerakker J, Rahman T, Probst S, Baars MJ, et al. Mutations in the sarcomere gene MYH7 in Ebstein anomaly. Circ Cardiovasc Genet. 2011;4:43–50. doi: 10.1161/CIRCGENETICS.110.957985.
14. Wessels MW, Willems PJ. Mutations in sarcomeric protein genes not only lead to cardiomyopathy but also to congenital cardiovascular malformations. Clin Genet. 2008;74:16–19. doi: 10.1111/j.1399-0004.2008.00985.x.
15. Barth PG, Valiampour F, Bowen VM, Lam J, Duran M, Vaz FM, et al. X-linked cardioskeletal myopathy and neutropenia (Barth syndrome): an update. Am J Med Genet A. 2004;126A:349–354. doi: 10.1002/ajmg.a.20660.
16. Probst S, Oechslin E, Schuler P, Greumann M, Boey P, Knirsch W, et al. Sarcomere gene mutations in isolated left ventricular noncompaction cardiomyopathy do not predict clinical phenotype. Circ Cardiovasc Genet. 2011;4:367–374. doi: 10.1161/CIRCGENETICS.110.959270.
17. Hoedemaekers YM, Caliskan K, Michels M, Frohn-Mulder I, van der Veer MR, et al. Mutations in the sarcomere gene MYH7 in X-linked cardioskeletal myopathy and neutropenia (Barth syndrome): implications for the diagnosis of left ventricular noncompaction cardiomyopathy. Circ Cardiovasc Genet. 2010;3:232–239. doi: 10.1161/CIRCGENETICS.109.903898.
18. Miller EM, Hinton RB, Czoxek R, Lorts A, Parrott A, Shikany A, et al. Genetic testing in pediatric left ventricular noncompaction. Circ Cardiovasc Genet. 2017;10:e001735. doi: 10.1161/CIRCGENETICS.117.001735.

Key Words: Editorials  cardiomyopathies  genetics  heart failure  pregnancy