Title Page

Full Title

Left Ventricular *Non*-Noncompaction:

The Mitral Valve Prolapse of the 21st Century?

All Authors

Gabriella Captur MD - Department of Cardiology (Division of Cardiovascular Imaging), The Heart Hospital part of University College London NHS Foundation Trust, UK

Andrew S Flett MBBS – Department of Cardiology (Division of Cardiovascular Imaging), The Heart Hospital part of University College London NHS Foundation Trust, UK

Daniel L Jacoby MD - Assistant Professor of Medicine (Cardiology); Director, Cardiomyopathy Program; Associate Program Director, Heart Failure and Heart Transplant; Co-Director, Adult Congenital Heart Disease Clinic, Yale School of Medicine, Connecticut, US

James C Moon MBBCh, MD - Reader/Honorary Consultant Cardiologist, Director of CMR Imaging Department, The Heart Hospital, part of University College London Hospitals NHS Trust, UK

Correspondence

Dr James C Moon

Address: 16-18 The Heart Hospital Imaging Centre, Westmoreland Street, London, W1G 8PH

Telephone: +44 (0) 020 3456 3081

Facsimile: +44 (0) 020 3456 3806

Email: james.moon@uclh.nhs.uk

Word Count

1,270 (and references/notes of 1,694)

Abstract

A spongiform epidemic is upon us – myocardial trabeculae are everywhere as left ventricular noncompaction (LVNC) ingratiates itself into modern day cardiology. Current understanding of the condition is evolving but remains incomplete, and brings to mind the chronicles of another great cardiac story: mitral valve prolapse. Anecdote suggests that many individuals with prominent trabeculae may be being falsely labelled with a disease - LVNC - using poor echocardiographic and cardiovascular magnetic resonance criteria. Until we have robust diagnostic criteria, etiology, clinicopathological significance and prognosis, the risk of casualties from ascertainment bias will remain.

We should look to history and learn from past mistakes - specifically from the mitral valve prolapse story to show the way forward for LVNC. Meanwhile, clinicians (and patients) should be wary, bearing in mind the possibility that they might be seeing LV*N*NC - left ventricular *non*-noncompaction.

Keywords

Heart failure

Cardiomyopathy

Left ventricle

Mitral valve insufficiency

Mitral valve prolapse

Main Text

Left Ventricular *Non*-Noncompaction:

The Mitral Valve Prolapse of the 21st Century

Introduction

The last decade has seen the emergence of a new entity - most commonly described as left ventricular noncompaction (LVNC). It has a number of aliases: 'apical web', 'hypertrabeculation', 'spongy myocardium', 'spongiform cardiomyopathy', 'left ventricular abnormal trabeculation' 'noncompaction syndrome of the myocardium', 'isolated noncompaction of ventricular myocardium' and 'persistent myocardial sinusoids' to name a few. Variously described as a cardiomyopathy (acquired or congenital), an overlap cardiomyopathy, a feature of cardiomyopathies, an epi-phenomenon, or a normal/racial variant, agreement is clearly lacking.

Academic output on this topic has been growing steadily but to date LVNC remains an unclassified cardiomyopathy.[1,2] Much of what we know comes from case reports and observational cohort studies derived from tertiary referral centres with between-study variation in terms of recruitment, diagnostic criteria, imaging modality used, genetic analysis and follow-up duration. The result is a flawed dataset, corrupted by ascertainment, referral, recruitment and publication biases which limit the use of standard epidemiologic approaches to defining diagnostic criteria and assessing risk.[3-9] Existing criteria, whether echocardiographic or cardiovascular magnetic resonance (CMR)-based, are imperfect. They are based on standards defining apparent abnormality in highly refined tertiary referral cohorts, which are then reapplied in variegate settings like the clinically asymptomatic or the ethnically-diverse patient groups,

paying little attention to coexisting pathologies (dilatation/hypertrophy) which might influence ascertainment. Most echocardiographic criteria (Table 1) are reliant on a single one-dimensional (1D), subjective measurement performed on a 2D image in an attempt to interpret the 4D beating heart using different imaging planes and phases of the cardiac cycle. Not surprisingly results were somewhat discordant when tested prospectively[10] so attention shifted to CMR in the hope that it would perform better. CMR did provide a global, more comprehensive overview of the left ventricular trabecular load,[11-13] but the same 1D approach was pursued with similar flaws (Figure 1).[14,15] The result is that much LVNC is really LV*N*NC – Left Ventricular *Non*-Noncompaction – a spurious result derived from ascertainment bias and incomplete understanding of normality, made worse by the inappropriate transferance of criteria to low pretest-probability populations. Compounding this, cardiac imaging keeps developing (7.7% per capita growth in echocardiography from 1999-2004)[16] and improving (harmonics, computerised tomography, CMR) resulting in an apparent epidemic of LVNC (when it is actually LV*N*NC). The human and societal cost (actual and psychological) of this disease label is high[17-19]– how does a life insurance company deal with individuals having an "unclassified cardiomyopathy" – the latest category into which LVNC is placed? Patients, by definition, present to a health care service with symptoms, triggering investigation. The result has been in many cases a disease label of LVNC, perceived risk and even the use of the implantable cardioverter defibrillators. But this story is not new – it has happened before and will likely happen again. A classic example is the mitral valve prolapse (MVP) saga which is instructive for how we might deal with LVNC.

The MVP Saga

Mitral valve prolapse, like LVNC, started with an alphabet soup of synonyms: 'floppy valve syndrome', 'auscultatory-electrocardiographic syndrome', 'systolic murmur-click syndrome', 'Barlow's syndrome', 'mesosystolic click-telesystolic murmur syndrome' and 'late-systolic click

syndrome'.[20,21] A term first coined in 1966, MVP is in its 6th decade of clinical recognition compared with the 2nd for LVNC. MVP was initially considered a rare condition associated with unusual features (panic attacks, polythelia, palpitations, chest pain, syncope, dysautonomia) and diagnosis was reliant on auscultation and M-mode echocardiography. In tandem with advances in imaging, its documented prevalence increased until it became almost ubiquitous - fuelling frantic research interest (Figure 2). More than half of today's adult population would bear a MVP diagnosis if the 1970s criteria were to be applied to modern imaging – mainly because of the saddle shape of the mitral valve annulus. This means that it is normal that in half of all possible (2D) long axis views, the closed mitral valve appears on the atrial side of the annulus.[21] But over time, clinicians looked to surgeons and pathologists for answers. Population based studies were performed, newer diagnostic criteria and subtypes emerged based first on pathological mechanisms, and later on outcomes. With better imaging, radiologic appreciation of MVP matured into the current form.[21] Clinical aspects of the disease gained importance - mitral regurgitation severity, reparability and effects on cardiac chamber size. The ability to accurately relate radiological and examination findings to prognosis and therapy paved the way for a more robust differentiation of the clinically important abnormality from the reassuringly-normal variant.

The Future for LVNC

The analogy of the MVP story to LVNC is clear (Table 2), highlighting the need for caution. Rather than diagnosing LVNC, imaging reports should focus on describing relevant additional features (scarring, thinning, thrombus, regional wall motion abnormalities, left ventricular diastolic/systolic function etc.) and on any less controversial diagnoses if present (such as dilated or hypertrophic cardiomyopathy). Clinicians should consider case review and external referral and should provide patients with copies of their own imaging for future evaluation, in case criteria should change over the years. The question is whether LVNC deserves to be a disease

entity in its own right, a risk marker (like left ventricular mass, left atrial area and diastolic filling), or a phenotypic manifestation of inherited rather than acquired etiology. The answer lies in large, unbiased (or at least less biased), community-based, prospective multicentre studies aimed at tracking possible LVNC over time. These studies should include ethnic subgroups, in particular black individuals who appear to have more pronounced trabeculation, and are therefore more likely to be mislabelled.[10] We envisage using a tiered diagnostic algorithm – firstly, the use of multiple plausible diagnostic criteria (looking to pathology and embryogenesis), refined with the help of inter-study and inter-observer reproducibility data, to provide a solid and credible phenotype; secondly, genetic linkage of these results to candidate genes and re-testing of established criteria; and finally, the use of prognostic data over time with further refinement of criteria and sub-typing of LVNC based on the above observations. In parallel, a developmental view of LVNC should be taken. If a lack of ventricular wall compaction during cardiac embryogenesis is the mechanism for LVNC, then murine morphogenetic data may help.[22] There are at least four mouse 'LVNC' models.[23-26] A dialogue will be needed between developmental biologists (who have also been struggling with trabecular quantification) and clinicians, in order to perfect scientific understanding and establish common principles underlying criteria.[22,25] Only with such an approach can the conundrum of 'distinct cardiomyopathy'[27] versus 'non-specific myocardial attribute' versus 'group of conditions with subtypes' be suitably addressed. Certainly, the time seems right.[28,29] So let us learn from history (the MVP saga) in our clinical and research domains, and consider LV*N*NC, the other side of the coin, when faced with apparent LVNC.

Conflict of Interest

None.

References

1. Richardson P, McKenna W, Bristow M, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathies. Circulation 1996;93:841-842.

2. 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.

3. Chin TK, Perloff JK, Williams RG, Jue K, Mohrmann R. Isolated noncompaction of left ventricular myocardium: a study of eight cases. Circulation 1990;82:507-513.

4. Jenni R, Oechslin E, Schneider J, Attenhofer Jost C, Kaufmann PA. Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction; a step towards classification as a distinct cardiomyopathy. Heart 2001;86:666-671.

5. Petersen SE, Selvanayagam JB, Wiesmann F, et al. Left ventricular non-compaction: insights from cardiovascular magnetic resonance imaging. J Am Coll Cardiol 2005;46:101-105.

6. Pignatelli RH, McMahon CJ, Dreyer WJ, Lee VV, Vaughn W, Valdes SO, et al. Clinical characterization of left ventricular noncompaction in children: a relatively common form of cardiomyopathy. Circulation 2003:108;2672-2678.

7. Belanger AR, Miller MA, Donthireddi UR, Najovits AJ, Goldman ME. New classification scheme of left ventricular noncompaction and correlation with ventricular performance. Am J Cardiol 2008;102:92-96.

8. Stöllberger C, Blazek G, Wegner C, Finsterer J. Heart failure, atrial fibrillation and neuromuscular disorders influence mortality in left ventricular hypertrabeculation/noncompaction. Cardiology 2011;119:176-182.

9. McRae CA, Ellinor PT. Genetic screening and risk assessment in hypertrophic cardiomyopathy. JACC 2004;4:2326–2328.

10. 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.

11. 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.

12. Korcyk D, Edwards CC, Armstrong G, et al. Contrast-enhanced cardiac magnetic resonance in a patient with familial isolated ventricular non-compaction. J Cardiovasc Magn Reson 2004;6:569-576.

13. Fernández-Golfín C, Pachón M, Corros C, et al. Left ventricular trabeculae: quantification in different cardiac diseases and impact on left ventricular morphological and functional parameters assessed with cardiac magnetic resonance. J Cardiovasc Med (Hagerstown) 2009;10:827-833.

14. Germans T, Wilde AA, Dijkmans PA, Chai W, Kamp O, Pinto YM, et al. Structural abnormalities of the inferoseptal left ventricular wall detected by cardiac magnetic resonance imaging in carriers of hypertrophic cardiomyopathy mutations. J Am Coll Cardiol 2006;48:2518-2523.

15. Johansson B, Maceira AM, Babu-Narayan SV, Moon JC, Pennell DJ, Kilner PJ. Clefts can be seen in the basal inferior wall of the left ventricle and the interventricular septum in healthy volunteers as well as patients by cardiovascular magnetic resonance. J Am Coll Cardiol 2007;50:1294-1295.

16. Pearlman AS, Ryan T, Picard MH, Douglas PS. Evolving trends in the use of echocardiography: a study of Medicare beneficiaries. J Am Coll Cardiol 2007;49:2283-2291.

17. Finsterer J, Stöllberger C, Tymms T, Fazio G, Siejka S. Shall a pilot with left ventricular hypertrabeculation/noncompaction fly passengers? Int J Cardiol 2010;145:72–73.

18. Stöllberger C, Finsterer J. A diagnostic dilemma in non-compaction, resulting in near expulsion from the Football World Cup. Eur J Echocardiogr 2011;12:8.

19. Picano E. Economic and biological costs of cardiac imaging. Cardiovasc Ultrasound 2005;3:13.

20. Levine RA, Weyman AE. Mitral valve prolapse: a disease in search of, or created by, its definition. Echocardiography 1984;1:3-14.

21. Weisse AB. Mitral valve prolapse: now you see it; now you don't: recalling the discovery, rise and decline of a diagnosis. Am J Cardiol 2007;99:129-133.

22. Chen H, Zhang W, Li D, Cordes TM, Mark Payne R, Shou W. Analysis of ventricular hypertrabeculation and noncompaction using genetically engineered mouse models. Pediatr Cardiol 2009;30:626-634.

23. Shi W, Chen H, Sun J, et al. TACE is required for fetal murine cardiac development and modeling. Dev Biol 2003;261:371-380.

24. Lee Y, Song AJ, Baker R, Micales B, Conway SJ, Lyons GE. Jumonji, a nuclear protein that is necessary for normal heart development. Circ Res 2000;86:932-938.

25. King T, Bland Y, Webb S, Barton S, Brown NA. Expression of Peg1 (Mest) in the developing mouse heart: involvement in trabeculation. Dev Dyn 2002;225:212-215.

26. Shou W, Aghdasi B, Armstrong DL, et al. Cardiac defects and altered ryanodine receptor function in mice lacking FKBP12. Nature 1998;391:489-492.

27. Roberts WC, Karia SJ, Ko JM, et al. Examination of isolated ventricular noncompaction (hypertrabeculation) as a distinct entity in adults. Am J Cardiol 2011;108:747-752.

28. Finsterer J, Stöllberger C. Definite, probable, or possible left ventricular hypertrabeculation/noncompaction. Int J Cardiol 2008;123:175-176.

29. Shimamoto T. There should not be any "probable" or "possible" left ventricular noncompaction. Int J Cardiol 2008 18;128:275-276.

30. Saleeb SF, Margossian R, Spencer CT, et al. Reproducibility of echocardiographic diagnosis of left ventricular noncompaction. J Am Soc Echocardiogr 2012;25:194-202.

31. Finsterer J, Stöllberger C, Feichtinger H. Histological appearance of left ventricular hypertrabeculation/noncompaction. Cardiology 2002;98:162-164.

32. van Dalen BM, Caliskan K, Soliman OI, et al. Left ventricular solid body rotation in non-compaction cardiomyopathy: a potential new objective and quantitative functional diagnostic criterion? Eur J Heart Fail 2008;10:1088-1093.

33. Dellegrottaglie S, Pedrotti P, Roghi A, Pedretti S, Chiariello M, Perrone-Filardi P. Regional and global ventricular systolic function in isolated ventricular non-compaction. Pathophysiological insights from magnetic resonance imaging. Int J Cardiol. 2012 Jul 26;158(3):394-9.

34. Sénéchal M, Michaud N, Machaalany J, et al. Relation of mitral valve morphology and motion to mitral regurgitation severity in patients with mitral valve prolapse. Cardiovasc Ultrasound 2012;10:13.

35. Guy TS, Hill AC. Mitral valve prolapse. Annu Rev Med 2012;63:277-292.

36. Topilsky Y, Michelena H, Bichara V, Maalouf J, Mahoney DW, Enriquez-Sarano M. Mitral valve prolapse with mid-late systolic mitral regurgitation: pitfalls of evaluation and clinical outcome compared with holosystolic regurgitation. Circulation 2012;125:1643-1651.

37. Habib G, Charron P, Eicher JC, et al. Isolated left ventricular non-compaction in adults: clinical and echocardiographic features in 105 patients. Results from a French registry. Eur J Heart Fail 2011;13:177-185.

Table 1.

Summary of adult echocardiographic and CMR diagnostic criteria for LVNC to date.

Modality	Year	Author	Measurement	Timing	Plane	Reliability		Pathoanatomical Correlation
						Intra-observer	Inter-observer	
Echo	1990	Chin[3]	X/Y ≤ 0.5	ED	PLAX SC A4C	✗	✓ *	✓ †
	2000	Jenni[4]	N/C > 2	ES	PSAX A4C	✗	✓ [30]	✓ ‡
	2002	Stöllberger[8]	>3 trabeculations≈ 2-Layered wall	ED ES	PSAX mA2C	✗	✓ [30]	✓ [31]
	2008	Belanger[7]	Maximal N/C Planimetric area	ES ES	A4C A4C	✗	✗	✗
	2008	van Dalen[32]	LV twist	D&S	PSAX	✓	✓	✗
CMR	2005	Petersen[5]	N/C >2.3	ED	HLA VLA LVOT	✗	✓ ~	✗
	2010	Jacquier[11]	Trabeculated mass >20%	ED	SAX	✓ §	✓	✗

*Inter-observer variation for X/Y ratios significant at the LV apex (p<0.001).

†Necropsy (n=3) comparison of endomyocardial patterns visually to echo without formal quantification.

‡Echo and pathoanatomical correlation in 9 patients.

≈Stöllberger criteria also include synchronous movement of trabeculae with compacted myocardium and connection between ventricular cavity and intertrabecular recesses.

~A separate group[33] investigated reproducibility for these criteria reporting <10% variability (statistical methods and significance levels not provided).

§Intra-observer data previously published by another group.[13]

Echo= transthoracic echocardiography; CMR= cardiovascular magnetic resonance; X= distance from the epicardial surface to the trough of the trabecular recess; Y= distance from the epicardial surface to peak of trabeculation; ED= end-diastole; PLAX= parasternal long axis; SC= subcostal; A4C= apical 4-chamber; N= thick noncompacted endocardial layer; C= thin compacted epicardial layer; PSAX= parasternal short axis; mA2C= modified apical 2-chamber; D&S= diastole and systole; LV= left ventricular; HLA= horizontal long axis; VLA=

vertical long axis; LVOT= left ventricular outflow tract view; SAX= short axis stack; ✓ = data published; ✗ = no data published; LVNC= left ventricular noncompaction.

Table 2. Table summarising similarities and differences between our evolution of understanding with MVP and LVNC.

	MVP	LVNC
Subtypes	▪ Classic versus nonclassic[34] ▪ Symmetric versus asymmetric ▪ Flail versus non-flail	▪ None ▪ No ethnic-specific reference ranges
Diagnostic criteria	2/3D Echo & TOE ≥2mm billowing, ≥5mm thickening } Established	2D Echo (5 techniques), CMR (2 techniques) } Consensus lacking
Incidence	Historically[21]: M-mode 17% ➡ 2D Echo 35% ➡ Presently[35]: 2 – 3%	True incidence unknown
Associations	Myxomatous degeneration Marfan's syndrome Ehlers-Danlos syndrome Osteogenesis imperfecta Polycystic kidney disease } Well established	Genetic† e.g. Neuromuscular disorders Mitochondrial myopathies Barth syndrome Zaspopathy Cardiac† e.g. Dilated cardiomyopathy Hypertrophic cardiomyopathy Restrictive cardiomyopathy Congenital heart disease Conduction disease } Recognition of 'new' associated conditions still ongoing
Complications	▪ Severe mitral regurgitation ▪ Atrial fibrillation ▪ Heart failure ▪ Ishaemic neurological events ▪ Infective endocarditis ▪ Mitral prolapse syndrome†	▪ Arrhythmias ▪ Heart failure ▪ Thromboembolic events ▪ Sudden cardiac death } Reported frequencies vary (based on single-centre case series)
Prognostic determinants	Specific to MVP ▪ Chordal rupture/flail leaflet Related to associated pathology ▪ Severity of MR and ERO[36] ▪ LV systolic dysfunction	Specific to LVNC ▪ None known Related to associated pathology ▪ LV systolic dysfunction ▪ Atrial fibrillation ▪ Coexistent neuromuscular disorders } Data from one single-centre case serie[8]
Study methodology	Case reports ➡ Case series ➡ Population-based case-control studies ➡ Randomised control studies	Case reports ➡ Case series { Single-centre: largest *n*= 162[8]; Multi-centre registry: largest *n*=105[37]
Treatment	▪ Sequential refinements in mitral valve repair procedures[35] ▪ Mitral valve replacement	▪ Consensus lacking

†All of the following have been described in relation to the mitral prolapse syndrome: atypical chest pain, palpitation, syncope, exertional dyspnoea, anxiety, low blood pressure, electrocardiographic abnormalities, autonomic nervous system dysfunction, renin-angiotensin-aldosterone system abnormalities, adrenergic hyperfunction and hypomagnesemia.
*List is not exhaustive.
MVP=mitral valve prolapse; LVNC= left ventricular noncompaction; 2/3D= 2 or 3-dimensional; echo= echocardiography; TOE= transoesophageal echocardiography; CMR= cardiovascular magnetic resonance; MR= mitral regurgitation; ERO= effective regurgitant orifice; LV= left ventricle.
[Rev. 1, comment 5]

Figure Legends

Figure 1.

Diastolic CMR cine image of the mid-ventricular short axis view (A) with superimposed pilot planes. Poor piloting results in (B) suggesting a hypertrabeculated left ventricle (arrow). The correct long axis view (C) is just 2mm offset to the false view.

CMR= cardiovascular magnetic resonance.

Figure 2.

Timeline of evolution of MVP. The histogram summarises PubMed citations dealing with MVP uncovered during an advanced Boolean search carried out in April 2011. Search limits set (serially) at year of publication starting January 1965 through till December 2010.

3D= 3-dimensional; TOE= transoesophageal echocardiography; MR= mitral regurgitation; MVP= mitral valve prolapse.