Diagnosing excessive trabeculation cardiomyopathy: in pursuit of the “holy grail”

Fabrizio Ricci^{1,2,3} • Mohammed Y. Khanji^{4,5,6} • Steffen E. Petersen^{5,6}

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Left ventricular non-compaction (LVNC) is a rare myocardial disorder classified as a primary genetic cardiomyopathy by the American Heart Association in 2006 and as an unclassified cardiomyopathy by the European Society of Cardiology in 2008. LVNC is characterized by a specific morphological appearance of the myocardium with prominent trabeculae, deep intertrabecular recesses, an inner spongy hypertrabeculated layer and an outer compacted epicardial layer, usually thinner than the endocardial one, potentially leading to heart failure, thromboembolism and life-threatening ventricular arrhythmias. Previously thought as a consequence of early arrest of the normal compaction process during embryonic development, new evidence suggests that the hypertrabeculation might be an aberration of mammalian cardiogenesis, that the compact wall grows by intrinsic proliferation rather than by compaction of the pre-existing trabecular layer and that hypertrabeculation can be dynamic, changing with disease progression, developing during the course of the disease, and potentially reversible [1]. Accordingly, the term “non-compaction” has been proposed to be replaced by “excessive trabeculation” (ET) [2].

In the absence of an established genotype-phenotype association and large-scale family segregation studies, it is unclear whether ET cardiomyopathy is a distinct disease or a morphological trait (epiphenomenon) shared by different cardiac diseases and extra-cardiac conditions. Arbustini et al described six different ET phenogroups, namely (i) asymptomatic subjects with normal left ventricular (LV) size and function, e.g. athletes and pregnancy, (ii) patients with genetic cardiomyopathies, including hypertrophic, dilated, restrictive and arrhythmogenic phenotypes, (iii) congenital heart disease, (iv) renal or haematologic disorders, (v) chromosomal disorders and (vi) isolated right or biventricular variants, providing rich areas for future clinical research [1].

Identification of ET alongside a thin layer of compacted myocardium on noninvasive imaging is essential to diagnosis; however, the key element in the diagnostic decision is not the burden of ET itself, but rather the associated dilation, dysfunction, hypertrophy, arrhythmias, conduction disease and/or tissue abnormalities, eventually prompting genetic counselling, testing and cascade family screening. Cardiovascular magnetic resonance (CMR) has become popular for the diagnosis of ET cardiomyopathy due to high spatial resolution and excellent signal-to-noise ratio by state-of-the-art cine imaging. CMR not only enables accurate and reproducible measurement of trabecular and solid myocardial layers [3] but also has unrivalled capacity of tissue characterization, quantification of biventricular function and volumes, and detection of thrombi within trabecular recesses. Based on currently suggested CMR criteria, ET cardiomyopathy can be diagnosed based on linear measurements (ratio between non-compacted and compacted myocardium) at end-diastole (Petersen method in long-axis views), or end-systole (Stacey method in short-axis views), or measurement of LV trabecular mass as the ratio between total and trabecular mass (Jacquier method in short-axis stack) or by fractal dimension—a quantitative measure of endocardial complexity (Capture method in short-axis views), with overall high diagnostic accuracy when used in the setting of high pre-test probability of disease, i.e.

✉ Fabrizio Ricci
fabrizio.ricci@unich.it

¹ Department of Neuroscience, Imaging and Clinical Sciences, “G. d’Annunzio” University of Chieti-Pescara, Via dei Vestini, 33 -, 66013 Chieti, Italy
² Department of Clinical Sciences, Lund University, Malmö, Sweden
³ Casa di Cura Villa Serena, Città Sant’Angelo, Pescara, Italy
⁴ Newham University Hospital, Barts Health NHS Trust, London E13 8SL, UK
⁵ Barts Heart Centre, Barts Health NHS Trust, London EC1A 7BE, UK
⁶ NIHR Barts Biomedical Research Centre, William Harvey Research Institute, Queen Mary University of London, London, UK

neuromuscular disorders, syncope, arrhythmia or thromboembolic event, family history of heart muscle disease[3]. However, lack of consensus on uniformly accepted standards of diagnosis and lack of a true gold standard to diagnose ET cardiomyopathy influence epidemiology and interpretation of imaging data. The widespread availability of improved cardiac imaging technologies and increased awareness of ET have driven an increasing number of ET cardiomyopathy diagnoses. However, major concerns about potential overdiagnosis remain, potentially leading to asymptomatic and healthy individuals being mistakenly labelled with the diagnosis of cardiomyopathy simply because they meet one of the diagnostic imaging criteria [1]. This can lead to anxiety for the individual and impact on their quality of life and have financial/insurance-related implications. There is indeed mounting evidence from multiple clinical studies, with different study designs and different patient populations, disputing the clinical significance of isolated ET in subjects with normal LV size and function, and questioning the causative relationship between the mere presence of ET and mortality, risk of arrhythmias and stroke, with unproven incremental prognostic impact over LV dilation, LV dysfunction and presence of late gadolinium enhancement (LGE) [4–8].

In this issue of *European Radiology*, Macaione et al [9] provide evidence that ET and LGE were both independent predictors of poor cardiovascular outcome in a prospective cohort of 78 middle-aged individuals with positive Jenni's echocardiographic criteria and high pre-test probability for LVNC clinically referred for a CMR scan in a high-volume centre. The extent of LV trabeculations was assessed with a two-step sequential analysis, including evaluation of Petersen's criteria (end-diastolic non-compaction [NC]/compaction [C] ratio > 2.3), which was fulfilled in the entire cohort, and global Grothoff's criteria, as defined by the simultaneous presence of 4 quantitative conditions: (i) percentage of trabeculated left ventricle myocardial mass (NC-LVMM) > 25%; (ii) NC-LVMM > 15 g/m²; (iii) NC/C ratio > 2.1 in at least one of LV segments 4–6; and (iv) NC/C ratio > 3.1 in at least one of the remaining segments, as per the AHA 16-segment model. Over a median follow-up of 41 months, 28 major adverse cerebro-cardiovascular events (MACCE) were recorded, including 2 cardiovascular deaths, 10 ventricular arrhythmias, 12 heart failure hospitalisations and 4 strokes. In multivariate analysis, both global Grothoff's criteria and presence of LGE predicted the MACCE endpoint, regardless of baseline LV dysfunction. Despite some limitations (small sample size, lack of important information like genetic characterization, strain and parametric mapping data, manual contouring for measurement of trabecular extent), this study adds to the current knowledge that sequential assessment of LV hypertrabeculation by the Petersen

method combined with more restrictive global Grothoff's criteria might convey independent prognostic information in the context of high pre-test probability of the disease, regardless of baseline LV function and LGE. Given the uncertainty regarding the definition of ET cardiomyopathy, this evidence further highlights the importance of improving the specificity of current diagnostic schemes, namely in the setting of isolated ET traits, in pursuit of a consensus on diagnostic criteria from scientific societies. The increasing availability of multi-modality imaging and affordable genomic data should facilitate the development of large, multi-centre, longitudinal cohort studies aimed to adequately address the prognostic power of more specific definitions of ET cardiomyopathy, to clarify the natural history of this condition, to establish clear genotype-phenotype correlation (including proband and relatives) and to identify genetic markers for early prediction of future development of overt cardiomyopathy.

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Methodology

• Not applicable/Editorial comment

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