Detection of subclinical hypertrophic cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is defined by hypertrophy. However, the broader phenotype includes disarray, ischaemia, and electrical abnormalities. There is evidence these traits manifest before overt hypertrophy. With cascade genetic testing and emergent therapeutics the detection of subclinical HCM is a rapidly emerging priority. In this domain, we outline the role of novel biomarkers, particularly quantitative perfusion and diffusion magnetic resonance imaging.

Hypertrophic cardiomyopathy (HCM), defined clinically by unexplained hypertrophy, is a leading cause of heart failure and sudden cardiac death (SCD). Every one of the approximately 500,000 individuals with HCM in the US and 1.5 million in Europe (1 in 500 estimated prevalence) were at one stage "subclinical". Cascade screening is increasingly identifying carriers (1). The detection/exclusion of early phenotypic changes - subclinical HCM - may affect follow-up frequency, influence risk stratification and, importantly, may be a trigger in the future for the implementation of novel therapies (e.g. myosin inhibitors) to prevent phenotype development.

The HCM phenotype is broader than just hypertrophy alone and includes fibrosis, ischaemia, disarray and electrical abnormalities (2–4). The sequence of events comprising phenotype development, and the links of these to heart failure and sudden death are incompletely understood with limitations to current risk stratification and therapies. However, many changes occur before overt disease, a classification that depends clinically on imaging to measure maximum wall thickness. Around half (depending on the precise definition of HCM) of patients have a known causal DNA variant (1). Recent advances are enriching the understanding and detection of genotype-positive, hypertrophy-negative subclinical HCM. These depend on a reappraisal of existing tests (ECG), new imaging techniques (perfusion, diffusion tensor imaging) and candidate new blood biomarkers in the context of a high pre-test probability (3,5,6).

The heart and myocardium in subclinical HCM may be abnormal in three domains. Firstly, secondary to abnormal cardiomorphogenesis where there may be the persistence of embryological features (such as

myocardial crypts and trabecular complexity) (2). Secondly, underlying histological changes beyond macroscopic left ventricular hypertrophy (LVH) including myocyte hypertrophy, fibrosis, abnormal myocyte orientation (disarray) and small vessel disease (2,3). Thirdly, molecular changes including calcium mishandling, energetics and excessive myosin-actin binding, the latter now targeted by myosin inhibitors. All three domains likely contribute to adverse events and are incompletely understood (4).

12-lead ECG abnormalities (commonly pathological Q waves/ repolarisation abnormalities) occur in almost a third of subclinical HCM, conferring a fourfold increased risk of progression to overt disease, although interpretation can be confounded by ethnicity, athleticism or comorbidities (e.g. hypertension) (7). Novel ECG approaches such as ECG imaging where epicardial electrograms are computed from body surface ECGs (commonly 128-256) and cross-sectional imaging, may overcome confounders and increase sensitivity (8). Initial echocardiographic changes often detect features of a hypercontractile state (small LV cavity size, higher ejection fraction) (9). However, myocardial deformation and diastolic function markers have conflicting results. Elongation of the anterior mitral valve leaflet may also be observed, even before the detection of obstruction (2).

The magnetic resonance imaging (MRI) technique diffusion tensor imaging (DTI), successfully used in brain imaging, and now possible for the heart, measures diffusion of water within an imaging voxel. Human studies show alterations in DTI parameters in overt disease that are likely to reflect underlying myocyte disarray. A steeper orientation of laminar sheetlets (functional units of myocytes that re-orientate to facilitate wall thickening) has also been detected, reflecting further a hypercontracted myocardial state and increased cardiomyocyte tension. DTI abnormalities are found even in non-hypertrophied segments suggesting an early disease role, and some relationship to arrhythmogenesis has been reported, with studies ongoing in subclinical HCM (5).

Myocardial perfusion abnormalities have long been detected in overt HCM using nuclear medicine techniques or cardiac MRI, with causative roles hypothesised of compressive forces of hypertrophied myocardium, outflow obstruction, elevated intracavity pressures, small vessel wall smooth muscle thickening and capillary rarefaction. Impaired perfusion has been related to functional limitations, arrhythmia, and adverse events. For subclinical HCM, developments in cardiac MRI mean fully quantitative myocardial blood flow can be derived routinely in some centres without ionising radiation. Using this, very striking, focal, dense perfusion defects can be seen in the complete absence of any LVH or scar, typically occurring in areas (septum/RV insertion points) where early LVH or scar are commonly detected in HCM (3). These findings raise questions

about ischaemia being to secondary LVH, and focus attention on the myocyte-capillary pair as the fundamental unit of myocardium or the potential of myocardial mechanics (e.g. sustained myocardial contraction) to reduce perfusion. Other novel techniques provide supporting information but are further from clinical deployment: HCM (including subclinical) has impaired tissue oxygenation using oxygen-sensitive cardiac MRI whilst a higher energy cost of contraction using phosphorous magnetic resonance spectroscopy has been observed in overt disease (10).

Using blood biomarkers to detect the overt and early processes of HCM has high potential. Many of the proteins synthesised in the heart that alter in HCM, such as collagen biomarkers also have origins in other tissues so confounding is likely. Established cardiac specific biomarkers (troponin, NT-pro BNP) are typically elevated in more advanced disease and are non-specific markers (myocyte death, myocyte strain). Novel biomarkers are likely to be panels of cardiac specific and non-specific markers (e.g. RNA or proteomics) combined using advanced analytic techniques (principle component analysis/artificial Intelligence approaches). One recent study showed a five peptides panel is elevated compared to healthy controls in both overt and subclinical HCM with markers tracking disease severity features (6). As with every highly multiplexed testing approach, derived assays require independent cohorts validation before clinical deployment.

The above tests are promising in the detection and classification of subclinical HCM. We are now witnessing new drugs that impact the cardiac sarcomere directly such as the myosin inhibitors, and their transition into clinical practice, where initial results in overt disease show improvement in symptoms and myocardial function with at least some beneficial cardiac remodelling (4). With some mutations, it may however be possible to attempt the prevention of subclinical to overt HCM transition. Furthermore, there is evidence that positive myocardial remodelling is more amenable in subclinical disease than overt where hypertrophy and fibrosis are more difficult to reverse (4). Studies to explore this possibility would benefit from a comprehensive phenotypic description of subclinical HCM, with the potential for therapeutic targeting to those patients manifesting early phenotypic changes. An era where cascade screening becomes cascade prevention, gate-keepered by novel phenotyping, is a tempting prospect.

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REFERENCES

1. Ommen SR et al, 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy. Circulation. 2020 Dec 22;142(25):e558–631.

2. Garcia-Canadilla P et al. Myoarchitectural disarray of hypertrophic cardiomyopathy begins pre-birth. J Anat. 2019 Nov 1;235(5):962–76.

3. Hughes RK et al. Myocardial Perfusion Defects in Hypertrophic Cardiomyopathy Mutation Carriers. J Am Heart Assoc. 2021 Aug 3;10(15):e020227.

4. Lehman SJ et al, Targeting the sarcomere in inherited cardiomyopathies. Nat Rev Cardiol. 2022 Jun 1;19(6):353–63.

5. Ariga R et al. Identification of Myocardial Disarray in Patients With Hypertrophic Cardiomyopathy and Ventricular Arrhythmias. J Am Coll Cardiol. 2019 May 28;73(20):2493–502.

6. Captur G et al. Identification of a Multiplex Biomarker Panel for Hypertrophic Cardiomyopathy Using Quantitative Proteomics and Machine Learning. Mol Cell Proteomics MCP. 2019/06/26 ed. 2020 Jan;19(1):114–27.

7. Lorenzini M et al. Penetrance of Hypertrophic Cardiomyopathy in Sarcomere Protein Mutation Carriers. J Am Coll Cardiol. 2020 Aug 4;76(5):550–9.

8. Rudy Y. Noninvasive Mapping of Repolarization With Electrocardiographic Imaging. J Am Heart Assoc. 2021 May 4;10(9):e021396.

9. Ho CY et al. The Burden of Early Phenotypes and the Influence of Wall Thickness in Hypertrophic Cardiomyopathy Mutation Carriers: Findings From the HCMNet Study. JAMA Cardiol. 2017 Apr 1;2(4):419–28.

10. Raman B et al. Association Between Sarcomeric Variants in Hypertrophic Cardiomyopathy and Myocardial Oxygenation: Insights From a Novel Oxygen-Sensitive Cardiovascular Magnetic Resonance Approach. Circulation. 2021 Nov 16;144(20):1656–8.

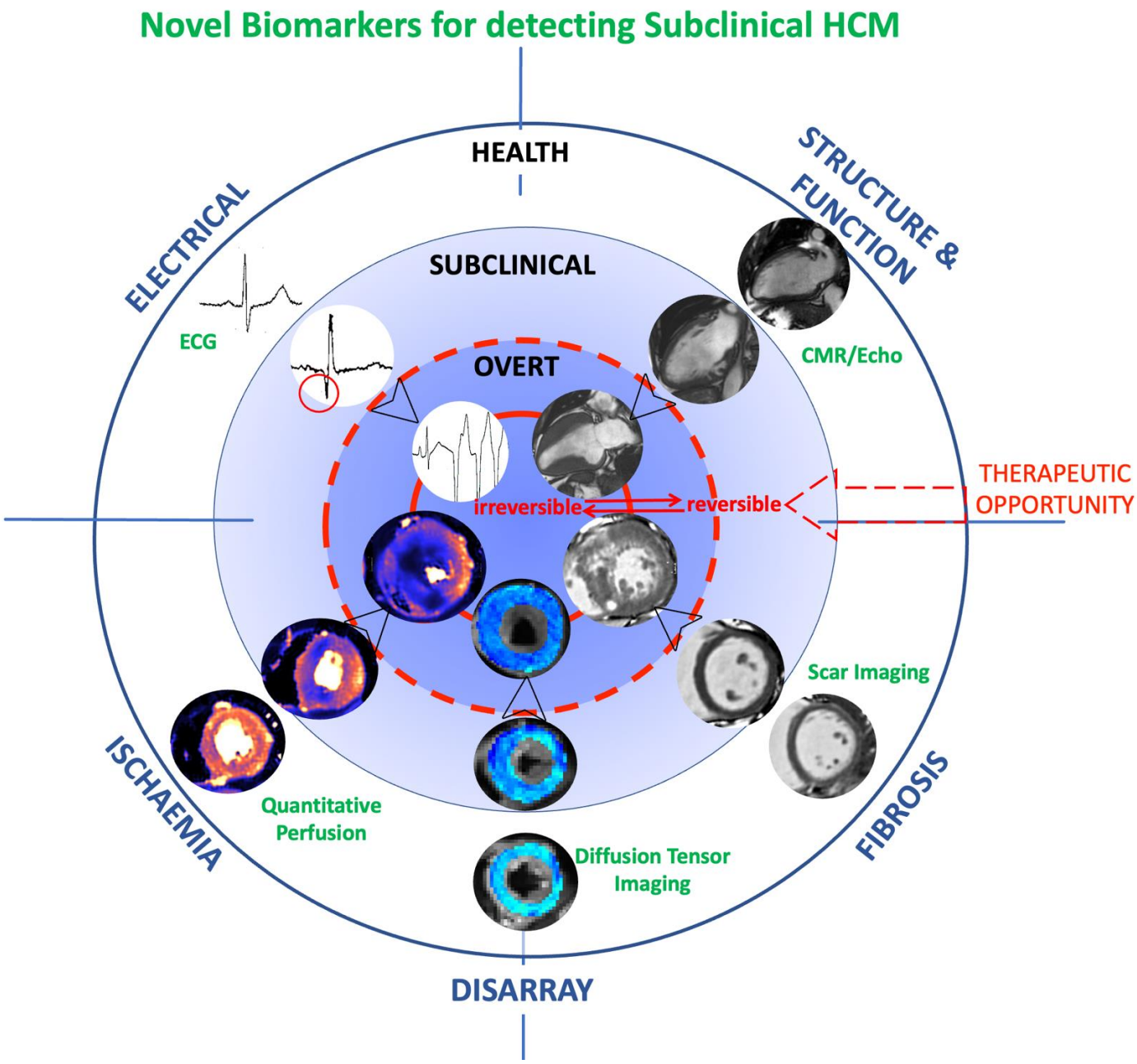

Figure: Novel biomarkers for the detection of subclinical disease. HCM, hypertrophic cardiomyopathy, CMR, cardiac magnetic resonance imaging