

Beyond Hypertrophic Cardiomyopathy: Rethinking Ventricular Thickening in the Spectrum of Cardiomyopathies

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Accurate medical terminology is crucial to avoid diagnostic biases and improve patient care. Inaccurate terms may induce cognitive biases and delay critical diagnoses.¹ In the field of cardiomyopathies, the term “hypertrophic cardiomyopathy” has been widely but generically used to describe increased ventricular thickness, which can be misleading and delay essential diagnoses.

The 2023 European Society of Cardiology (ESC)² guideline for cardiomyopathies proposes a classification based on ventricular phenotype, dividing them into five groups: hypertrophic cardiomyopathy, dilated left ventricular cardiomyopathy, non-dilated left ventricular cardiomyopathy, restrictive cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy. However, the group “hypertrophic cardiomyopathy” still encompasses heterogeneous conditions such as sarcomeric hypertrophic cardiomyopathy, cardiac amyloidosis, and Fabry disease, with distinct pathophysiologies, which may lead to diagnostic confusion in clinical practice.

Hypertrophic cardiomyopathy: potentially misleading nomenclature

In pathology, hypertrophy is the increase in cell size.³ In the heart, this suggests hypertrophy of cardiomyocytes, which can induce an anchoring bias,¹ leading physicians to prioritize the diagnosis of sarcomeric hypertrophic cardiomyopathy, while diseases such as cardiac amyloidosis — where thickening is due to extracellular amyloid accumulation — are underdiagnosed.

This problem is exacerbated in echocardiographic reports, which often use “hypertrophic cardiomyopathy”

nonspecifically.⁴ Although echocardiography is useful, it does not differentiate between thickening due to cellular hypertrophy or interstitial accumulation (infiltrative or storage diseases), making the term inadequate and potentially harmful in guiding clinical investigation and decisions.

To make this discussion even more precise, it is essential to remember that, in current practice, ventricular hypertrophy is defined based on increased left ventricular mass, with cutoff values above 116 g/m² in men and 96 g/m² in women, indexed by body surface area.⁴ However, this indexing model has significant limitations: it does not account for ethnic differences, body proportions, or significant changes in body composition;⁵ therefore, indexing by height (g/m²) would be more appropriate in many cases. For a more accurate approach, it is also crucial to differentiate the causes of ventricular thickening.

Phenocopies and genocopies in ventricular thickening: unraveling the etiology

The distinction between phenocopies and genocopies is essential to understand the complex etiopathogenesis of ventricular thickening. This conceptual differentiation guides a deeper diagnostic investigation beyond simple morphological observation. The term phenocopy, introduced by R. B. Goldschmidt in 1935,⁶ describes a phenotype identical or very similar to one typically determined genetically, but whose cause is acquired, mimicking the effect of a genetic variant. In the context of ventricular thickening, there are several acquired causes that simulate the phenotype of hypertrophic cardiomyopathy, such as prolonged systemic arterial hypertension, aortic stenosis, non-genetic cardiac amyloidosis (wild-type transthyretin or light chain), acromegaly, and chronic anabolic steroid use.

The term genocopy, coined by H. Nachtsheim in 1957,⁷ refers to a specific genetic disease that results in a phenotype known to be caused by another genetic variant. This means that conditions with fundamentally different genetic bases may have similar clinical and morphological presentations, requiring molecular analysis for precise diagnosis. The main genocopies in the context of septal thickening — that is, genetic diseases that mimic sarcomeric hypertrophic cardiomyopathy — include Fabry disease (an X-linked lysosomal storage disorder), hereditary transthyretin amyloidosis (ATTR) cardiac amyloidosis

Keywords

Hypertrophic Cardiomyopathy; Terminology; Diagnosis

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Manuscript received January 7, 2026, revised manuscript April 13, 2026, accepted April 24, 2026

Editor responsible for the review: Wolney Martins

DOI: <https://doi.org/10.36660/ijcs.20250292>

(variant in the transthyretin gene leading to amyloid fibril deposition in myocytes), RASopathies (diseases caused by genetic variants in the RAS/MAPK pathway, Noonan syndrome being the best known), mitochondrial cytopathies (genetic diseases that affect mitochondrial function, such as Barth syndrome and Friedreich's ataxia), and glycogen storage diseases (genetic variants that lead to abnormal glycogen accumulation in the myocardium, such as Danon, Pompe, Forbes diseases and PRKAG2 syndrome).

The etiological distinction among these conditions is vital to mitigate diagnostic biases and to guide a more comprehensive investigation (Figure 1), which may include advanced imaging exams, specific biomarkers, and targeted genetic testing.

The importance of terminological revision

Thus, we propose that the group currently labeled "hypertrophic cardiomyopathy" in the ESC classification be redefined as "cardiomyopathies with ventricular thickening." This proposal does not aim to relabel individual diagnoses of hypertrophic cardiomyopathy, but rather to enhance the terminology used in classification frameworks. The suggested change is not merely semantic; it aims to improve diagnostic accuracy, reduce cognitive bias, and encourage a broader etiological investigation—better capturing the clinical and pathological diversity underlying ventricular thickening.

Clinical guidelines play a central role in standardizing medical practice. Updating concepts and nomenclatures is necessary to ensure more accurate diagnoses, more appropriate treatments, and more efficient, personalized care based on the true pathophysiology of heart diseases.

Contribuição dos Autores

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Potencial Conflito de Interesse

Declaro não haver conflito de interesses pertinentes.

Fontes de Financiamento

O presente estudo não teve fontes de financiamento externas.

Vinculação Acadêmica

Não há vinculação deste estudo a programas de pós-graduação.

Aprovação Ética e Consentimento Informado

Este artigo não contém estudos com humanos ou animais realizados por nenhum dos autores.

Uso de Inteligência Artificial

Os autores não utilizaram ferramentas de inteligência artificial no desenvolvimento deste trabalho.

Disponibilidade de Dados

Os conteúdos subjacentes ao texto da pesquisa estão contidos no manuscrito.

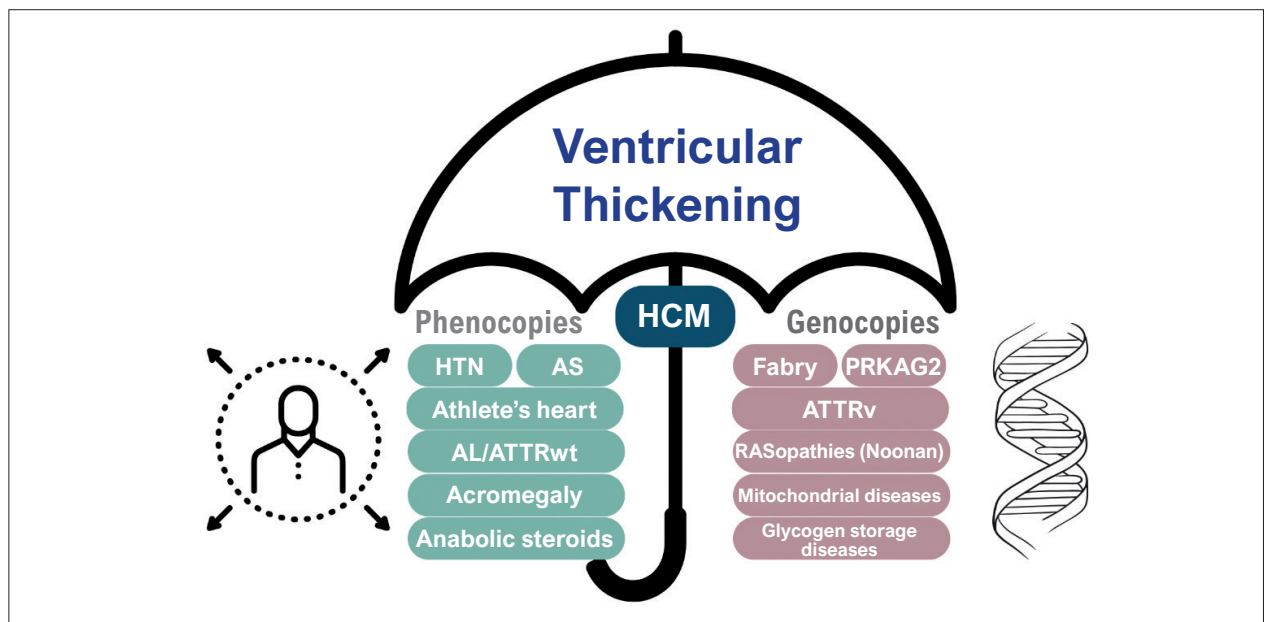


Figure 1 – Etiological spectrum of ventricular thickening: from phenocopies to genocopies. L: light chain amyloidosis; AS: aortic stenosis; ATTRv: variant transthyretin amyloidosis; ATTRwt: wild-type transthyretin amyloidosis; HCM: hypertrophic cardiomyopathy; HTN: hypertension; PRKAG2: protein kinase AMP-activated non-catalytic subunit gamma 2.

Brief Communication

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