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CURRENT PERSPECTIVES

Hypertrophic cardiomyopathy: Paradigm shifts in the last 30 years (Part 1)

Miocardiopatia hipertrófica: mudanças de paradigma nos últimos 30 anos (Parte 1)

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''Half of what you are taught in medical school will be wrong in 10 years' time.''

– Sydney Burwell, 1944

Although provocative and speculative, this statement by Dr Sydney Burwell, cardiologist and Dean of Harvard Medical School, may not be far from the truth. It reflects the rapid and constant nature of research, innovation, and technological advances in modern medicine, which often lead to the modification of concepts over time.

The radical right-wrong dichotomy of the sentence is exaggerated and open to criticism. It is desirable to look at the evolution of knowledge not as a sequence of abrupt scientific transitions,[1] but as a building constructed piece by piece, modified over the years by the addition of new portions. However, its basic concept – the change of scientific truths over time – remains true, even now, in the 21st century, more than 80 years later.

Sarcomeric hypertrophic cardiomyopathy (HCM) is a genetic disease of autosomal dominant transmission with incomplete penetrance and variable expressivity. It results from mutations in genes encoding cardiac sarcomere proteins and is defined by inappropriate ventricular hypertrophy (LVH), independent of loading conditions, in the absence of other cardiac or systemic disease or metabolic or multiorgan syndromes associated with LVH.[2]

The anatomic and pathologic features of HCM were described 60 years ago by Sir Donald Teare, a pathologist at St. George's Hospital in London,[3] and its clinical importance by Eugene Braunwald's group in the USA.[4] Major advances in the knowledge of HCM have modified early concepts and beliefs, representing paradigm changes in our understanding of the disease.

Hypertrophic cardiomyopathy is a relatively rare disease of young adults

The generally accepted prevalence of HCM (1:500 individuals [0.2%]) is mainly based on the analysis of echocardiographic data from the CARDIA study, published in 1995.[5] CARDIA examined 4111 young adults (aged 23–35 years) from different families, randomly selected from the urban population, using two-dimensional (2D) echocardiography. The diagnostic criterion was the presence of LV wall thickness ≥15 mm.

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Despite the unquestionable importance of the CARDIA study, it underestimates the real prevalence of HCM for several reasons[6]:

1. The CARDIA study only assessed patients with the classic HCM phenotype. It ignored the natural history of the disease, including the existence of mutation carriers and of early, non-hypertrophic phenotypes. In a 2012 study[7] that investigated mutations in genes encoding sarcomere proteins in 3600 individuals from different families, 0.6% of the subjects showed pathogenic mutations, tripling the estimated HCM prevalence to 0.6% (or 3:500 individuals). These data should be viewed with caution, as constant advances in genetics have shown us that some of these variants are of uncertain significance or non-pathogenic/probably non-pathogenic mutations.
2. CARDIA only included patients from different families. Given its autosomal dominant transmission, each offspring of a patient with HCM has a 50% chance of inheriting the disease-causing mutation. Accordingly, only one patient per family was included, underestimating the real prevalence of HCM.
3. CARDIA only included young adults, in accordance with the scientific consensus at the time that HCM was a disease of young adults. Accordingly, CARDIA excluded patients with HCM at puberty and in adolescence. Additionally, CARDIA also excluded individuals >35 years old; however, it is widely known today that due to late penetrance, the phenotype often develops beyond the age of 35.[2,8] For this reason also, CARDIA underestimated the prevalence of HCM.
4. Finally, CARDIA used echocardiography with fundamental frequency (the only type available at the time). Due to its suboptimal spatial resolution, fundamental imaging has low sensitivity for the diagnosis of LVH.[9] For this reason, CARDIA again underestimated the real prevalence of HCM.

The number of false negatives has been reduced by advances in echocardiography, as second harmonic technology is now incorporated into all machines, and as a consequence of the use of LV cavity opacification contrast agents, which enable accurate measurement of wall thickness.

Finally, the advent of new imaging techniques with excellent morphological definition, such as cardiac magnetic resonance imaging (CMR) and cardiac computed tomography (CCT), has further reduced the number of false negatives.[9]

Is hypertrophic cardiomyopathy a relatively rare disease of the young? No, HCM is a relatively frequent disease of all ages, with a prevalence between 0.2% and 0.6%.

Diagnosis and non-invasive imaging assessment of hypertrophic cardiomyopathy are only performed by echocardiography

In patients with HCM, clinical evaluation is often poor and inadequate. Imaging techniques are thus essential to assess the disease.

In the 1960s, during the early stages of HCM research, non-invasive assessment of HCM was limited to chest X-rays and esophagography (assessment of left atrial dimension).

During the 1970s, echocardiography entered the clinical arena, initially in A- and M-mode, later with 2D and Doppler technology. Echocardiography became the exam of choice for the morphological and functional assessment of HCM. Today, more advanced tools and techniques have been incorporated, including tissue Doppler, three-dimensional imaging, and assessment of myocardial deformation.

Since the beginning of this century, new players, such as CMR, CCT, and advanced nuclear cardiology (NC) techniques, have entered the clinical arena.[9] Given the different characteristics, advantages, disadvantages, accessibility and cost of each imaging technique, medical imaging associations worldwide recommend an integrated multimodality approach.[9]

Echocardiography will continue to be the first-line imaging method in all patients with HCM, followed by CMR (indicated at least once in this disease). CCT and NC are less frequently indicated, in all cases to respond to specific clinical problems.[9]

Are diagnosis and non-invasive imaging assessment of the disease only performed by echocardiography? No, imaging assessment of HCM should be performed using multimodality imaging in which echocardiography, CMR, CCT and NC techniques have precise indications.

Hypertrophic cardiomyopathy is a malignant disease and sudden death is the main problem

Initial studies[4] described HCM as having high mortality and morbidity, with sudden cardiac death (SCD) being the main cause of death with a very high incidence, of up to 7% per year.

As knowledge increased, it became clear that these findings did not reflect the overall HCM picture due to major selection bias (the data came from tertiary centers, where only severe patients were assessed, distorting mortality- and morbidity-related data).

However, these ideas have changed. It is now known that HCM is often a benign disease.[10] Of the pool of HCM patients, around 75% are estimated to be asymptomatic, with normal quality of life and life expectancy, low risk of SCD, and no need for any treatment. Around 20% of HCM patients have mild to moderate symptoms that are easily controlled with medical treatment; their mortality is similar to that of the general population. Only around 5% of patients with HCM have very severe and highly symptomatic disease with poor prognosis, if untreated. SCD, heart failure (HF) and atrial fibrillation (AF)/stroke are today the major problems.[10]

It is useful to classify symptomatic patients according to their clinical profile: ventricular dysrhythmia/SCD, intraventricular obstruction, HF with preserved ejection fraction, AF/stroke, and HF with reduced ejection fraction. These profiles may exist in isolation or coexist in the same individual.

Is hypertrophic cardiomyopathy a highly malignant disease, in which sudden death is the main problem? No, HCM is mostly a benign disease, but it can be associated with multiple complications and serious clinical problems in addition

to SCD. HF, intraventricular obstruction and AF/stroke are major clinical issues.

Conflicts of interest

The author is an advisory Boarded member of Bristol Myers Squibb (Mavacamten) and of Cytokinetics (Aficamten).

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