EDITORIALS

Left Ventricular Noncompaction: A Disease in Search of a Definition

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In the present issue of *Revista Española de Cardiología,* Stöllberger et al analyze the relation between gender and clinical, and morphologic characteristics in one of the broadest-ranging series of patients with left ventricular noncompaction in the literature.[1] From 36 933 transthoracic echocardiograms performed over a period of 10 years, they identified 100 patients who fulfilled pre-established diagnostic criteria. In their laboratory, left ventricular noncompaction was diagnosed in 2.7 per 1000 studies (which cannot be considered equivalent to the prevalence of the disease in patients undergoing echocardiography because it includes repeat studies of individual patients). Men accounted for 70% of patients, a figure similar to that reported elsewhere. Essentially, their findings are that the condition is more frequent in men, but hypertrabeculation is more prominent in women. Based on this observation, they formulate the following hypotheses to explain this greater frequency of the disease in men: *a)* that hereditary forms linked to the X chromosome exist; *b)* that more women die in the early stages of the disease and more men develop acquired forms; *c)* that remission is more common in women; and *d)* that there is a selection bias towards less indication for echocardiography in women with heart failure.[1] Although all these hypotheses are valid, one further option should be seriously considered, namely that the diagnostic criteria used may be wholly inadequate, or inadequate for men, or for women.

In hypertrophic cardiomyopathy something similar occurs. Despite being an autosomal dominant disorder of hereditary genetic origin, men dominate practically all series, representing approximately 60%-70% of cases. However, women with hypertrophic cardiomyopathy present more symptoms than men do.[2] In hypertrophic cardiomyopathy, the problem stems from the fact that, with standard diagnostic criteria (wall thickness >15 mm and no justifiable cause), diagnosis in men is easier. In women, the same wall thickness represents a greater degree of hypertrophy but indexed measures that could partly correct this selection bias are uncommon. In the left ventricular noncompaction, the criteria used lack a precise, absolute value for wall thickness or trabecula size: they are based on the subjective appreciation of the existence of prominent trabeculae and the relation between trabecular and compacted zones. But, clearly, the greater the absolute value of these measures of thickness, the more apparent the hypertrabeculation, and a direct relation does exist between body surface and wall thickness, which is usually greater in men.

Stöllberger et al base their diagnosis of left ventricular noncompaction on Jenni et al's echocardiographic diagnostic criteria[3]: *a)* >3 trabeculae projecting from the left ventricular wall distal to the papillary muscles, visible in a single echocardiographic plane; *b)* intertrabecular spaces perfused from the ventricular cavity (visualized by color Doppler); and *c)* a >2 ratio of noncompacted to compacted layers in the segment presenting most hypertrabeculation at end systole. They also specify the need to distinguish between trabeculae of false tendons and aberrant bands (the latter go from the lateral wall to the septum and/or are consistent and differ from myocardium in appearance). Other authors have adopted similar criteria but used measurement of the compacted and trabecular zones at end diastole, with a >2 ratio of total thickness (compacted and noncompacted zones) and compacted layer.[4] In other cases, a combination of both criteria has been used for diagnosis.[5,6] With magnetic resonance, the most adequate criteria proposed is a >2.37 ratio of noncompacted to compacted zones.

Not for the first time, we encounter the problem of more or less arbitrary diagnostic criteria. When are trabeculae considered abnormal? How thick do they need to be? Should we consider gender, race, or other factors when making the diagnosis? What are these criteria based on? What is the standard underpinning a definition of diagnostic criteria? Finally, we have to ask a key question: Is left ventricular noncompaction a unique disorder or is

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it a morphologic expression appearing in different diseases?

As in hypertrophic cardiomyopathy, left ventricular noncompaction has been labeled with many names, reflecting different concepts of the entity. Currently, the most accepted English term is: "left ventricular noncompaction" or "isolated left ventricular noncompaction." This reflects the concept that the disease is due to an interruption of the embryonic myocardial compaction process, occurring at 5-8 weeks gestation. This process is characterized by the progressive disappearance of sinusoidal intertrabecular spaces in the embryonic myocardium, which transform into capillaries within the coronary circulation. It develops from epicardium to endocardium, from the base of the apex and septum to the lateral wall, which would explain the most frequent locations of noncompacted myocardium. Initial descriptions of left ventricular noncompaction were drawn from patients with congenital cardiopathies, like cyanotic cardiopathies, outflow tract obstruction of both ventricles, and coronary abnormalities. In most of these cases, intertrabecular sinusoids, as well as communicating with the ventricular cavity, communicate with the coronary circulation. The hypothesis is that, in certain cases, increased embryonic left ventricular pressure caused by the congenital cardiopathy impedes the compaction process.[3,4,8] The term "isolated left ventricular noncompaction" was coined by Chin et al[4] in 1990 when they described the noncompacted morphology in 8 patients with no associated cardiac abnormalities or communication between intertrabecular spaces. Following their description, isolated cases and series of patients with this disorder have been reported. Some authors prefer the term "spongiform cardiomyopathy," which avoids assuming the problem is caused by detaining the myocardial compaction process.[9]

In recent years, the disorder has become more and more popular. The improved quality of echocardiography equipment, use of contrast media and cardiac magnetic resonance have permitted a clearer visualization of the left ventricular apical zone. The equipment previously available provided a resolution that enabled us to see apical wall thickening or nothing; now, we can see trabeculae and more or less prominent invaginations. Often, the specialist is not sure whether this hypertrabeculation is pathologic or a normal variant. This is more frequent in black individuals and levels of hypertrabeculation considered pathologic in whites, seem relatively common in blacks.[10] We have found cases of particularly marked hypertrabeculation in elite, competitive sportsmen (unpublished observations). In other cases, hypertrabeculation associates with left ventricular hypertrophy, fulfilling criteria for hypertrophic cardiomyopathy.[6,11,12] In these cases, many authors prefer to use the term "hypertrabeculation of the left ventricle," which, to a certain extent, implies it is unclear whether we are dealing with a clinically independent entity. Thus,

diagnostic criteria based on morphology have brought confusion and uncertainty to the concept and diagnosis of this disorder.

Familial Occurrence and Genetic Origins of Left Ventricular Noncompaction

Just like other primary cardiomyopathies (hypertrophic, dilated, restrictive, and arrhythmogenic right ventricular dysplasia), left ventricular noncompaction is frequently a familial disorder.[5,6,8,13] In fact, family members affected can be identified in >50% of cases. The familial nature of the disorder often goes unnoticed unless a systematic study of family members is conducted. As in other cardiomyopathies, index cases include the most severe forms of the disease. The initial descriptions of isolated left ventricular noncompaction include cases of this type, with severe systolic dysfunction and advanced heart failure, a high rate of complications, and poor prognosis. When a systematic study of family members is conducted, individuals are identified in the early phases of the disorder and/or with milder or asymptomatic forms, and with better prognosis (at least in the mid-term).[5,6] Again, we can establish an analogy with what we have learned in other cardiomyopathies. Hypertrophic cardiomyopathy was initially considered a rare entity with a high incidence of sudden death but once it was better known, it was found to be a relatively frequent disease, with a favorable prognosis in most cases.[5,6]

Recognizing left ventricular noncompaction as an eminently familial disorder has led to the search for genetic causes. In a short period we have been able to show that, like other primary cardiomyopathies, left ventricular noncompaction is genetically heterogeneous too. The cause of the disorder has been identified as mutations in genes associated with the mitochondrial function, like *G4.5,* which encodes the protein tafazzin, genes related with the cytoskeleton, like those of alpha-dystrobrevin or dystrophin, genes that code proteins of the Z line of the sarcomere, like *LDB3,* which codes the protein Cypher/ZASP, genes of the internal nuclear membrane proteins (*LMNA,* which encodes lamin A/C) and even genes that code sarcomeric proteins like cardiac alpha-actin and the beta-myosin heavy chain.[5,6,8,9,13-17] This genetic heterogeneity explains the variability in hereditary patterns, morphology, and alterations associated with left ventricular noncompaction. The *G4.5* gene is found in the X chromosome, which explains why the disorder is hereditary and gender-linked in these cases. Mutations in this gene have been associated with different phenotypes, like the Barth syndrome (recurrent neonatal-onset neutropenia, retarded growth, dilated cardiomyopathy, or left ventricular noncompaction) and isolated dilated cardiomyopathy. Mutations in the dystrophin gene (also linked to the X chromosome) cause muscular dystrophies (Duchenne and Becker) and can produce dilated cardiomyopathy with subclinical skeletal

myopathy, like the mutations in dystrobrevin. Mutations in Cypher/ZASP and lamin A/C present autosomal dominant hereditary patterns. Mutations in these genes have been related with the development of familial dilated cardiomyopathy and, in the case of lamin A/C, with the development of conduction disorders, skeletal myopathies, and other phenotypes. The cardiac actin and beta-myosin heavy chain genes have been associated with the development of hypertrophic cardiomyopathy and dilated cardiomyopathy, with an autosomal dominant inheritance. So, it is not strange to find individuals and families with overlapping phenotypes of hypertrophic and/or dilated left ventricular noncompaction.[5,6,8,9,13-17]

Stöllberger et al indicate that left ventricular noncompaction associates with a high frequency of neuromuscular disorders that they report present in up to 80% of cases. Neither we nor other authors have found such a high frequency of associated neuromuscular alterations but this possibility should clearly be borne in mind. The age and origins of the patients studied in each series probably condition the frequency and type of associated disorders. The systematic performance of echocardiograms in patients with neuromuscular disorders in a center that has access to neurologists like Professor Finsterer, interested in the cardiologic evaluation of these patients, will lead to the identification of a larger percentage of individuals with left ventricular noncompaction and neuromuscular alterations. Patients like these will appear less frequently in the echocardiography laboratories of centers where these diseases carry less weight but may be referred for heart transplantation or hypertrophic cardiomyopathy, as is our case. Without doubt, neuromuscular disorders frequently form part of the clinical presentation of noncompacted cardiomyopathies secondary to mutations in genes like *G4.5,* dystrophin, or lamin A/C, which are related to this type of disorder, whereas they will be infrequent when the noncompaction may be secondary to mutations in other genes like that of cardiac actin.

We do not know whether all forms of left ventricular noncompaction are caused genetically but this is highly likely to be the case. Even in apparently acquired forms, the noncompaction phenotype may develop in response to certain stimuli only in genetically predisposed individuals or patients with a specific myocardial structure. There can be no doubt that, currently, in many patients the disease is secondary to the genetic alteration. In these situations, identifying the cause of the disease facilitates new diagnostic criteria: the presence of the causal mutation. In these cases, the genetic diagnosis is immediately used as a standard to validate clinical diagnosis criteria for the disease. In order to do so, the relation between the presence of the mutation and the disease needs to have been clearly established. Furthermore, we need to remember that the presence of a mutation is often not the only factor that determines the development of the disease and healthy carriers may exist.[17] These limitations should be borne in

mind, but the usefulness of the genetic diagnosis to validate arbitrarily-established diagnostic criteria is unquestionable. For example, in our group, from the genetic diagnosis of an index case with left ventricular noncompaction we were able to identify the variable morphologic expression of the disease in numerous carriers of the same mutation (E101K in the cardiac actin gene) from different families. Some fulfilled the strict criteria for left ventricular noncompaction; in others, although ventricular morphology was similar, the degree of trabeculation was less and the diagnosis was inconclusive. Other carriers presented distal hypertrophy and it was impossible to identify invaginations and trabeculae clearly. Consequently, these patients had been diagnosed with hypertrophic cardiomyopathy. In some cases, hypertrabeculation and mild hypertrophy with restrictive phenotype were present. Several carriers, in different families, presented septal defects (fundamentally of the interatrial septum).[6] These families were not affected by 4 or 5 different diseases but one, single disease with an identifiable cause and manifestations that are typical but not always present in all carriers. Clinical and morphologic expression vary in all genetic and acquired diseases. In our opinion, it is quite artificial and arbitrary to say that an individual does not have left ventricular noncompaction (or whatever we may want to call a particular instance of the disease) because the relation between the noncompacted and compacted zones in end systole is 1.7 and not >2. Familial studies in individuals with left ventricular noncompaction show that established diagnostic criteria have limited sensitivity and that overlap occurs between phenotypes identified with different names. This overlap, the genetic heterogeneity of left ventricular noncompaction and the variability of hereditary patterns and associated phenotypes support the view that left ventricular noncompaction should not be considered a single disease but a morphologic manifestation appearing in different diseases with different clinical, prognostic, and optimal treatment etiologies.

Modern medicine advances thru the correct identification of diseases, knowledge of their natural history, and the discovery of their causes and pathophysiological mechanisms. Based on this knowledge, we can establish the most adequate strategies to prevent, and treat each disease. Initially, symptoms were diagnosed and treated, later came syndromes, and today the physician's objective should be to diagnose, prevent and treat the individual patient's specific disease. A clear example of this process occurs in cardiomyopathies. In 50 years, we have moved from diagnosing and treating these diseases according to the symptoms to doing so as a function of the gene or causal mutations. This process has occurred or is occurring in hypertrophic, dilated and restrictive cardiomyopathies and in arrhythmogenic right ventricular dysplasia. And we have to go thru the same process for this recently defined entity, called left ventricular noncompaction, spongiform cardiomyopathy, or left ventricular hypertrabeculation.

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