

# The Diagnosis of Cardiomyopathy: The Cost of Lost Opportunity

*El diagnóstico de la miocardiopatía: el costo de la oportunidad perdida*

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*To succeed, jump as quickly at opportunities  
as you do at conclusions*

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As clinicians, we are constantly engaged in a tug of war between our penchant to be accurate in the anatomic-pathological diagnosis of a disease and the limitations of the collective diagnostic technology available to us. The clinical diagnosis and classification of cardiomyopathy assumes that we can segregate the major diagnostic buckets into those that can allow for both better therapeutic and prognostic determination. As such, we tend to intuitively separate the causes into 3 large divisions that include those etiologies emanating from disease within the coronary circulation (amenable to revascularization), those caused by mechanical aberrations leading to a pressure or volume overload (valvular heart disease) and finally those originating within the myocardial compartments (defects or dysfunction within the cardiomyocyte or its extracellular matrix). Thus, the opportunity provided by an accurate classification of causality allows for the creation of appropriate therapeutic avenues for the identified targets and may serve to elucidate the reasons for progression of disease and its collective impact upon the natural history.

We now have a large armamentarium of available diagnostic techniques for more accurate discrimination of the underlying causes, but it can be quite daunting in its panoply of possibility. Thus, we can use multi-modality non-invasive imaging (echocardiography, magnetic resonance imaging, positron emission tomography and computerized tomography), invasive diagnostic techniques (coronary angiography, sophisticated coronary imaging methods, endomyocardial biopsy), and now, genetic studies. Despite these advanced diagnostic platforms, we remain clinically limited in our approach by a combination of imposing barriers: a) feasibility (e.g. interaction of magnetic resonance im-

aging with implanted devices), b) availability and cost, and c) inherent inaccuracy nested within each technique with low sensitivity (endomyocardial biopsy) or poor specificity (echocardiography). In other cases, the sheer magnitude of complexity, cost, and inadequate knowledge of appropriate use serve as major limitations as in the case of genetic testing.

Several investigators have attempted to enhance our appreciation of these limitations, as well as offer solutions to the observed inaccuracy in clinical definitions and diagnosis. Early studies from pathological examination of hearts suggested that there is vast opportunity, even in the optimal discrimination between ischemic and non-ischemic causes of heart failure and more specifically, in determining the cause of death of these patients. At least 2 studies have demonstrated that coronary thrombosis, which is mostly silent and consequently misdiagnosed, may explain the high rate of sudden death in non-ischemic heart failure. (1, 2) Others have suggested that strategies which include a high use of endomyocardial biopsy may help in uncovering otherwise elusive causes of cardiomyopathy. Felker and colleagues (3) performed endomyocardial biopsy in over 1200 patients with cardiomyopathy and were able to yield a specific diagnosis in only 50% of these patients. Yet, they determined that separation of the etiology was indeed relevant in predicting prognosis and thereby guiding advanced therapy. Another study by our group led to the identification of a high rate of misclassification of significant coronary artery disease in the setting of heart disease clinically diagnosed as a "non-ischemic" cardiomyopathy.(4) In this analysis of 112 patients with a pre-transplant diagnosis of non-ischemic cardiomyopathy, 21% were reclassified pathologically as ischemic cardiomyopathy. Of the remaining accurately classified, a third had at least moderate-severe coronary disease in 1 vessel territory, with or without infarction. In addition, 18% had areas compatible with recent ischemia, as noted by occlusive thrombus or ischemic infarction.

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In this issue of the journal, Constantin and colleagues (5) take an important step forward by delineating the opportunities in the clinical identification of the primary causes of a myocardial defect. They examined 100 patients that received a heart transplant over a 10-year period for advanced heart failure, and found critical opportunities lost in 2 specific domains in the diagnosis of a non-ischemic heart failure. First, there was a small cohort of patients with ischemic etiology on pathology that had been inappropriately misidentified as not having a coronary etiology. This is in line with prior studies in this field and point to the inaccuracy of coronary angiography, poor interpretation of the findings, or failure to reevaluate over time when conditions change. The second area where there was improved reclassification from idiopathic to a specific cause comprises 3 diagnoses including hypertrophic cardiomyopathy, lymphocytic myocarditis, and infiltrative sarcoid heart disease. One could argue, of course, that the frequency of these observations or the cost of this lost opportunity were not excessive, since the patients' clinical course may not have been altered in terms of the trajectory and need for heart transplantation. However, a closer look at the data may argue otherwise. In many cases of hypertrophic cardiomyopathy, the disease burden is not just shared by the patient but also by the family and early detection of disease in siblings or family members may be particularly rewarding. In others, therapy directed to the primary etiology may attenuate the progression (steroids in sarcoidosis).

One area of opportunity is in familial cardiomyopathy, now determined to be a more common diagnosis than previously considered. (6) Although this was not directly evaluated in the Constantin study, it is very possible that many "idiopathic" cardiomyopathy patients had a specific genetic cause that was clustered in their families. To this end, Arbustini and colleagues (7) have proposed the MOGE(S) classification for phenotype-genotype associations in an effort to better classify the underlying disorders. This classification system encourages the combined clinical use of the Morphology (M), Organ involvement (O), Genetic defects (G), specific Etiology (E) and the Stage of heart failure (S). We would posit that a substantial number of patients in the current study might have been classified into this category had a detailed family history been obtained, genotyping for selected cases been conducted, and pathological assessments using higher resolution systems such as electron microscopy been employed.

What then are the lessons to be learned from this important study? First, we believe that a detailed 3-generation family history should be obtained in all patients presenting with idiopathic cardiomyopathy; second, we endorse the more frequent use of multimodality non-invasive imaging and, when indicated,

an endomyocardial biopsy should be performed. In this regard, it is essential for central core labs that have experience and technical expertise in the pathological assessment of cardiomyopathy, including electron microscopy, to be available. Furthermore, genetic testing may be appropriately applied in highly selective cases, though we admit the literature is still uncertain for non-hypertrophic forms of myocardial disease in this regard. Finally, we also believe that anchoring to a dated older evaluation is a pitfall that should be avoided. In such cases, one should not assume that a previously "normal" angiogram should deter reevaluation. We note that only half of the patients in the Constantin series underwent an angiogram within 6 months of the transplant operation, which points to a lower frequency of use of this otherwise worthwhile testing modality, especially when the clinical condition takes a steep decline.

While these solutions will not entirely rectify the problem(s) of misclassification, we believe that these are steps in the right direction to develop organized and standardized approaches for the identification and assessment of disease diagnosis. As Albert Einstein remarked, "Once we accept our limits, we go beyond them."

#### Conflicts of interest

Dr. Mehra has served as a consultant for Thoratec, St. Jude, Johnson and Johnson, Stealth Biotherapeutics, Boston Scientific and the National Institute of Health (USA)

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