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# Towards an Improved and Personalized Risk Stratification of Sudden Cardiac Death in Dilated Non-Ischemic Cardiomyopathy: Is the Time for Ejection Fraction Coming to an End?

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Dilated non-ischemic cardiomyopathy (NIDCM) is one of the most common cardiomyopathies with an estimated prevalence in the range of 1-2 in 400 individuals (1). Ventricular arrhythmias (VA) manifesting as sudden cardiac death (SCD) are one of the main causes of death in this population. Still, the accuracy of arrhythmia risk stratification for primary prevention of SCD in NIDCM remains suboptimal. Left ventricular ejection fraction (LVEF) is currently the key variable for identifying patients at higher risk. According to current guidelines, NIDCM patients with LVEF < 35% would be at high risk of SCD and would warrant an implantable cardioverter-defibrillator (ICD) (2). Unfortunately, this LVEF-based approach offers a low positive predictive value. In the recently published DANISH study (Danish Study to Assess the Efficacy of ICD in Patients With Non-Ischemic systolic Heat Failure on Mortality) the rate of appropriate ICD therapies over 5 years was only 11% (3). This low rate of VA could be partially explained by the presence of heart failure as a competing risk of death in a population with severe LV dysfunction. In fact, the DANISH study failed to confirm any additional benefit of ICD on survival in NICM patients, in whom implantation was merely based on LVEF. On the other hand, it is already known that many NIDCM patients suffering from an out-of-hospital cardiac arrest do not have a severely reduced LVEF (4). These findings emphasize the urgent need of a more precise and cost-effective risk stratification approach for this population. Myocardial reentry is the main underlying mechanism of ventricular arrhythmia in patients with structural heart disease (5). Irreversible myocardial injury leads to apoptosis of cardiac myocytes and the deposition of myocardial fibrosis, which is the histological substrate needed for reentry. Using late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) imaging, the prevalence of fibrosis in NIDCM patients is estimated to be around 30% but probably depends on the disease evolution state and the cause of NIDCM. Several studies in the last decade have shown an association between fibrosis and the likelihood to develop VA. Gulati and colleagues (6) previously reported a 5-year event rate of 30% among NIDCM

patients having fibrosis in the LGE-CMR, showing that the addition of fibrosis to LVEF could potentially improve SCD risk stratification. However, not only the presence, but also the extent of fibrosis can provide further prognostic information. Higher SCD risk (HR: 1.15) has been described for each 1% increase in the volume of fibrosis (7). Nevertheless, formation of myocardial fibrosis in NIDCM patients can occur in different areas of the LV following different patterns. In this regard, whereas fibrosis localized in the interventricular junction is usually considered an unspecific finding without prognostic implication, mid-wall fibrosis and septal fibrosis have been described as powerful predictors of SCD (8,9). Therefore, it seems that pattern recognition could be also important.

In this issue of the Journal (10), Chen et al. show the results of a single-center retrospective study including 157 NIDCM patients without previous episodes of VA undergoing LGE-CMR imaging. Authors performed a quantitative and qualitative analysis of fibrosis, classifying patients according to the pattern of fibrosis distribution: 1) no LGE; 2) focal LGE: at most two sub-segments with LGE in the same slice; 3) multi-focal LGE: at least three non-contiguous sub-segments with LGE in the same layer, or in different layers but the same slice; and 4) ring-like LGE: at least three contiguous sub-segments with LGE at the subepicardial or mid-wall layer in the same slice. Thirty-three (21%) patients presented a ring-like LGE pattern characterized by a mainly subepicardial LGE location involving the septal and lateral segments at basal and mid-cavity. After a median follow-up slightly longer that 1 year, 14 (42%) patients with a ring-like LGE pattern presented VA. The rate of events in this group was significantly higher than in patients with focal LGE (a group with a predominant (81.3%) septum involvement) but presenting ‘only’ a 10% rate of VA events. Patients with a ring-like LGE pattern had also a higher rate of VA events than patients with a multi-focal LGE pattern (42.4% vs. 25%), despite showing a similar total amount of LGE. Interestingly, the ring-like LGE pattern was a predictor of VAs independently of the global LGE burden.

Despite its limitations, the results of this study provide a further piece of the puzzle in SCD risk stratification among patients with NIDCM, identifying the ring-like LGE pattern as particularly arrhythmogenic, even in patients without severe LV dysfunction. This specific scar phenotype, that can be assessed using LGE-CMR, has been previously associated with a particularly high risk of malignant arrhythmic events in patients without a previous NIDCM diagnosis. Muser D and coworkers recently reported that 4% of patients with apparently 'idiopathic' non-sustained VA undergoing LGE-CMR presented a subepicardial/mid-myocardial ring-like fibrosis pattern that was associated with a 3-fold increase in the risk of life-threatening VA, when compared to other types of scar distribution (11). Likewise, these authors found that this risk increase was independent of the total LGE burden. Zorzi et al. also showed that athletes with a stria pattern in the LGE presented higher risk of malignant VA than those with a spotty LGE pattern (12).

Whether this ring-like pattern of fibrosis formation is a consequence of different NICDM phenotypes or different environmental insults is not completely understood yet. Still, some NIDCM-associated mutations seem to be related with this type of scar distribution. Ortiz-Genga and colleagues previously described an international series of 28 families with a truncating mutation in the FLNC, a gene encoding the filamin C protein (13). This mutation results in a NIDCM phenotype characterized by mild to moderate LV systolic dysfunction, subepicardial fibrosis with a characteristic concentric pattern (ring-like) and frequent SCD (40 cases in 21 of 28 families). Smith and coworkers (14) recently reported a deep description of 107 patients with pathogenic DSP (desmoplakin) mutations. They described that circumferential LGE with a primarily subepicardial distribution was present in 20% of these patients, who also showed intramyocardial fat adjacent to fibrosis. The presence of LGE frequently occurred in the absence of significant LV systolic dysfunction. Similar findings have been reported by Segura-Rodriguez and colleagues (15) in patients with arrhythmogenic right

ventricular cardiomyopathy (ARVC) with LV involvement and a pathogenic mutation in desmosomal genes, which frequently show a characteristic LV subepicardial circumferential LGE pattern, as opposite to carriers of non-desmosomal mutations. These findings suggest that the ring-like scar pattern is the phenotype of a specific NIDCM subtype characterized by a non-severe LV dysfunction but with a significant risk of malignant VA. Despite a classification of this NIDCM phenotype as 'arrhythmogenic LV cardiomyopathy' has been proposed, we do not have specific diagnostic criteria yet, or specific recommendations for how to protect this population.

For a correct interpretation of the article of Chen et al., however, some important limitations should be bear in mind. The precise prevalence of the ring-like LGE pattern in the NIDCM population is not well known. Chen et al. describe a selected population of patients with NIDCM undergoing a LGE-CMR study in a single tertiary center. In this population, 78% and 21% of patients presented any pattern of LGE and a ring-like LGE pattern, respectively. These proportions are higher than the previously reported prevalence of fibrosis in the rest of the series, and it could be explained in part by the presence of a selection bias; authors included only hospitalized patients, most of them having symptoms of heart failure and a poor functional class. This selection of patients within a more advanced stage of the disease could also explain the 20% incidence of VA after only 13 months of follow-up, an out-of-scale event rate in a population without previous arrhythmic events. As a consequence, the external validation of these results for the general population of patients with NIDCM is limited. Further prospective studies including non-selected patients would be welcomed to confirm the real prevalence of the ring-like LGE pattern among the NIDCM population and the VA events incidence at longer follow-up. Moreover, we are still far from understanding the genetic mechanisms underlying this particular NIDCM scar phenotype. Still, we believe that this study pushes our knowledge

one grain of sand forward, heading in the right direction: towards a personalized and accurate estimation of VA/SCD risk in NIDCM patients.

**Conflicts of Interest:** Nothing to Disclose

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