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Editorial

Left ventricular reverse remodeling prediction in non-ischemic cardiomyopathy: present and perspectives

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1. Left ventricular reverse remodeling: a milestone toward better outcomes in non-ischemic cardiomyopathy patients

The prognosis of Non-Ischemic Cardiomyopathy (NICM) has strongly improved over the last decades, thanks to the increasing knowledge in the disease pathophysiology and the subsequent development of new drugs and devices (i.e., Implantable Cardioverter Defibrillator [ICD] and Cardiac Resynchronization Therapy [CRT]) [1-3]. Left Ventricular Reverse Remodeling (LVRR), thought to represent mostly the response to optimal medical treatment or to CRT, emerged as a milestone process on the road to achieve better outcomes in NICM [4]. LVRR is usually defined as a Left Ventricular Ejection Fraction (LVEF) increase ≥10 points or its normalization (≥50%) associated with an indexed Left Ventricular Diameter decrease ≥10% or its normalization (≤33 mm/m²). By using this definition, in the populations so far examined, the average rate of LVRR reaches approximately 40% [4].

Despite such achievements, defining prognosis, mostly in the early phases of the disease, and therefore assessing the best management for NICM patients, continue to be arduous in clinical practice. This is proved by the fact that NICM is still the first cause of cardiac transplant worldwide and that some patients are still projected to a poor outcome, often in the short term. Given this, it clearly emerges that the modern approach to this disease and particularly to LVRR prediction must be implemented [1].

2. Etiological classification as early determinant of LVRR

NICM is a complex entity caused by different etiologies, from potentially reversible conditions to genetic mutations. Despite our increasing knowledge, in up to 30% of cases, no reason able to explain the clinical picture can be found, so the disease is labeled as ‘idiopathic’ [5]. In order to accomplish even better outcomes, an accurate etiologic definition appears to be mandatory for overcoming the heterogeneity concern and to better manage NICM patients in the early phase of the disease. After ischemic and primary valvular diseases have been ruled out, the challenge of etiology definition must be faced in order to find any possible reversible condition such as myocarditis, tachy-induced, and toxic Cardiomyopathy (e.g., Alcoholic, Drug induced), so that specific therapy or withdrawal can be started as soon as possible. This clinical approach appears critical in addressing subsequent LVRR and, consequently, higher survival rates in NICM patients.

3. Prediction of LVRR: the leading role of cardiac magnetic resonance (CMR)

Important issues remain still debated regarding LVRR. Among others, the best timing for its evaluation and the finding of early LVRR predictors seem to be the thorniest. Even though it appears to be crucial in NICM natural history, it has been described that LVRR usually completes after 2 years of evidence-based treatment. However, important clinical decisions are often required before that time. Unfortunately, at the time of diagnosis, it is not yet clear which patients would eventually experience the inverse remodeling, making early prognostic stratification challenging. Many markers have been proposed to early predict LVRR. These have been obtained by clinical information, biomarkers, genetic assessment, and imaging techniques.

Among clinical variables, the presence of Left Bundle Branch Block at the time of diagnosis has been described as associated with a lower LVRR probability [4]. Similarly, a higher arterial blood pressure at baseline is considered to be a pre-sage of subsequent LVRR, probably indicating a less deranged Left Ventricle (LV) [6]. No definitive classic echocardiographic findings measured before medical therapy implementation have been reported as associated to subsequent LVRR. However, early (i.e. 6-month evaluation) improvement in significant Mitral Regurgitation or Right Ventricular function can be considered as useful markers in predicting LVRR completion [7,8]. Contractile LV reserve assessment using stress imaging (for example, with dobutamine) has a possible pathophysiological rationale for LVRR prediction. Despite the heterogeneity of each study considered, the presence of contractile reserve seems to be associated with a significantly lower risk of cardiovascular events in NICM [9]. However,
improvements in this interesting field might be reached using CMR stress tests or with the application of strain measurements to echocardiographic stress tests.

Few studies have been conducted to evaluate the role of biomarkers in predicting LVRR. Low levels of soluble ST2 (a cardiac protein released in stress conditions), integrated with other clinical information, appeared to be useful in predicting LVRR in a cohort of 304 patients with Heart Failure with reduced Ejection Fraction [10]. Given the lack of knowledge in this field, greater attention should be pointed out to these variables in next future research.

Regarding genetics, Next Generation Sequencing have raised the opportunity to improve our knowledge on NICM genetic background. It is well known in literature that assessing the presence of gene mutations in NICM patients is important, especially for the conduction of pedigree studies on relatives [1]. Genotype–phenotype correlations might be pivotal for the management of probands toward a precision medicine tailored to the single patient. Unfortunately, even though such evidences are increasing, they remain largely lacking. In this setting, recent studies pointed out that patients carrying structural cytoskeleton Z-disk gene mutations (e.g. Filamin C [FLNC] and Dystrophin [DMD]) have lower probability of subsequent LVRR [11]. Finally, it usually takes several months to obtain a complete genetic study, compromising the efficacy of this information in the current management of NICM patients, especially in the short term.

The increasing accessibility of CMR and its limited operator dependency led clinicians to consider it the gold standard for cardiac function assessment. Beyond this, it permits to obtain information that cannot be appreciated by other imaging techniques, especially regarding cardiac tissue intrinsic features. Given those peculiar characteristics and the ongoing attempts to improve this technology, CMR has the possibility to obtain a leading role for LVRR early prediction. Absence of Late Gadolinium Enhancement (LGE) is currently a well-known parameter able to predict improved survival and response to therapies (i.e. betablockers or CRT) but, if considered alone, it seems not to be enough for an accurate LVRR prediction [12]. This is probably caused by the fact that fibrosis substitution is often diffuse in NICM, not confined to narrow ventricular regions and therefore not localizable by a simple contrast-enhanced study. Techniques such as LGE quantification and the more recent diffuse fibrosis assessment by Extra Cellular Volume and T1 mapping evaluation have been developed to go beyond this limitation. Such technologies must be perfected in order to improve reproducibility and standardization, but they are absolutely promising [13,14].

4. Prediction of LVRR: the limited power of LVEF and the need of multiparametric scores

As clearly emerged in recent clinical trials, another important concern regards the limited power of LVEF as a prognostic factor, particularly in NICM [15]. This consideration led to the research of new techniques able to study the intrinsic conduction (i.e. non-invasive CMR assessment of LV contraction patterns for early recognition of CRT responders) [16] and contractility function of the entire myocardial wall or segments of it, in order to identify subtle LV dysfunction. This background has brought to Speckle Tracking Echocardiography (STE) development and its rapid spread, giving the opportunity to test new parameters. Among them, despite the necessity of further studies to confirm its ascending role, Longitudinal Strain appears to be one of the most interesting variable for prognostic stratification of NICM patients [17]. Its main limitation derives by the high inter- and intra-observer variability that weakens its reliability.

Feature Tracking strain analysis obtained from CMR imaging represents a promising tool that has been recently designed to face this important issue, demonstrating lower inter- and intra-observer variability. Small evidence supports that contractility parameters obtained with post-processing CMR techniques (especially Circumferential Strain) might improve the information obtained with LGE in predicting LVRR, thus giving new insights for prognostic stratification of NICM [18]. It must be pointed out that, so far, this technology has not been approved for clinical purposes.

If considered alone, each of these parameters is probably too weak to rely on for an accurate LVRR prediction, but together they might be seen as tesserae of a mosaic. In this perspective, information obtained by CMR should not be considered alone but it represents an insight that, integrated with data obtained with clinical observation and the above-mentioned techniques, can lead to the elaboration of multi-parametric scores for a more accurate prediction of LVRR and, as a consequence, of long-term outcomes. As a matter of fact, multiparametric prognostic scores are available and reliable for other cardiomyopathies [19,20], but they are lacking specifically for NICM. An increasing body of evidence suggests that an early CMR study could be appropriate for the initial diagnostic work-up and for early prognostic stratification of NICM patients. In the next future, large prospective studies are advocated to confirm the pivotal role of a systematic, comprehensive morpho-functional CMR study in the early assessment and prognostication of NICM, in order to include it in dedicated guidelines.

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Declaration of interest

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References


   • An interesting work on genotype-phenotype correlation in Dilated Cardiomyopathy.


   • The DANISH trial, a work which raised the attention of cardiological community on the use of ICD in NICM.


   • An accurate review on a sneaky disease.