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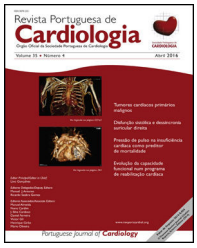

EDITORIAL COMMENT

Galectin-3: A simple tool for a complex clinical issue?

Galectina-3: uma ferramenta simples para uma questão clínica complexa?

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Advances in the pharmacological and non-pharmacological treatment of heart failure with reduced ejection fraction (HFrEF) have led to a substantial decline in the absolute rates of sudden cardiac death (SCD) over the past three decades.[1] Nevertheless, SCD still accounts for approximately 40% of all-cause mortality in contemporary HFrEF clinical trials, mostly attributable to ventricular arrhythmias.[1] Currently, the selection criteria of candidates for an implantable cardioverter-defibrillator (ICD) for primary prevention of SCD are based on left ventricular ejection fraction and New York Heart Association class, which have several limitations.[2] The majority of patients with HFrEF in whom an ICD is implanted for primary prevention according to current guidelines do not in fact receive appropriate therapies, and a non-negligible percentage of those who do not meet the criteria for ICD implantation are resuscitated from SCD.[3] Additional parameters are warranted to improve the selection of candidates for ICD implantation. At the same time, ventricular arrhythmias are a significant source of morbidity in patients with HFrEF and those with a larger arrhythmic substrate may benefit from more intensive treatment strategies.[3] Simple, noninvasive tools for stratifying the arrhythmic substrate in clinical practice would be useful for the tailoring of pharmacological therapy.[3]

Fibrotic myocardial tissue not only is a risk marker for the occurrence of ventricular arrythmias but also has a causal effect.[4] Myocardial fibrosis load, as assessed by cardiac magnetic resonance imaging (MRI), is strongly associated with the incidence of malignant ventricular arrythmias, although cardiac MRI may not be a feasible first-line screening test due to availability concerns and incompatibility with some implanted devices.[5]

Galectin-3 (Gal-3) is a beta-galactosid binding protein that promotes the conversion of inactive fibroblasts to active myofibroblasts and increases collagen and glycoprotein content in the myocardium.[6] Gal-3 thus promotes myocardial fibrosis and ventricular remodeling.[6] Gal-3 has been studied in clinical settings and higher Gal-3 levels are associated with a worse prognosis in patients with heart failure.[7,8] As Gal-3 promotes myocardial fibrosis, it may indirectly increase the risk of ventricular arrhythmias.[6]

In the study by Erdogan et al.[9] published in this issue of the *Journal*, the authors assessed a potential association between Gal-3 levels and the occurrence of ventricular fibrillation/ventricular tachycardia (VF/VT) episodes in patients with ischemic dilated cardiomyopathy and an implanted VVI-ICD. Nineteen healthy controls and 32

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patients with ischemic cardiomyopathy were included, in whom Gal-3 levels were quantified and a prior history of VF/VT episodes was assessed. Gal-3 levels were significantly higher in patients with ischemic cardiomyopathy than in controls. Among patients with ischemic cardiomyopathy, Gal-3 levels were significantly higher in those with a history of ventricular arrhythmia (VF/VT) who required ICD therapy compared with patients not requiring treatment, and Gal-3 levels were particularly high in patients with a prior arrhythmia storm. Of note, Gal-3 levels were reasonably accurate for discriminating patients with prior VF/VT episodes, with an area under the receiver operating characteristic curve of 0.823 (95% confidence interval [CI] 0.698-0.948). A cut-off of 7 ng/ml presented 84% sensitivity and 75% specificity for discriminating patients with prior VF/VT episodes. The authors concluded that Gal-3 may be used to improve risk stratification in patients with ischemic cardiomyopathy who are more prone to developing VF/VT episodes.

Gal-3 has potential advantages as a prognostic marker in clinical practice since it is an easily accessible and inexpensive tool, unlike imaging methods. Moreover, it directly reflects the underlying pathophysiology, as myocardial extracellular matrix remodeling leads to electrical heterogeneity that promotes VT/VF in patients with heart failure, and Gal-3 is a fibrosis marker that reflects the extent of the arrhythmogenic substrate.[4,6] The identification of biomarkers that simultaneously participate in pathophysiology and are predictors of clinical outcomes may be particularly valuable in clinical practice.[10] Published data on Gal-3 regarding risk stratification of arrhythmic events in patients with HFrEF, particularly in those with ischemic cardiomyopathy, are very scarce.[7] Erdogan et al.'s findings thus add to the knowledge of a potential biomarker for use in such a clinical scenario. Their results are consistent with a study by Pietro et al.,[7] who reported significantly higher Gal-3 levels in patients with sustained VT/VF episodes among heart failure patients undergoing ICD implantation. Moreover, higher Gal-3 levels were predictive of VT/VF episodes (hazard ratio 1.05, 95% CI 1.00-1.11, p=0.04).[7]

The findings of Erdogan et al.'s study[9] need to be interpreted with caution, considering its limited sample size. Moreover, the case-control design and the retrospective assessment of arrhythmic events may have led to overestimation of its results. Nevertheless, the findings are hypothesis-generating and identify Gal-3 as a potential complementary biomarker for predicting the risk of VF/VT episodes in patients with HFrEF of ischemic etiology. Larger studies prospectively assessing the accuracy of Gal-3 levels for predicting ventricular arrhythmias are warranted, as this parameter may improve risk stratification and could guide the decision whether to implant an ICD using a multiparameter approach.[11] In addition, indirect assessment of myocardial fibrotic burden using Gal-3 may be useful for tailoring pharmacological therapy in patients with HFrEF with a higher risk of ventricular arrhythmias.

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Conflicts of interest

The author has no conflicts of interest to declare.

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