Features of a covert cardiomyopathy are present in patients with unexplained syncope and incident ventricular tachycardia

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Syncope is defined as a transient loss of consciousness due to cerebral hypoperfusion and loss of postural tone with subsequent spontaneous recovery [1]. Broadly, its principal causes are neurally-mediated (e.g. vasovagal, situational, etc.), related to orthostatic hypotension, or cardiogenic (i.e. bradyarrhythmia, tachyarrhythmia, structural heart disease) [2].

In more than a third of patients, the cause of syncope remains unknown [1, 2] despite a complete initial work-up. Given that patients with unexplained syncope are at increased risk of premature death [1], more research is needed to detect possible unrecognized aetiological factors contributing to these syncopal events. In the presence of recurrent syncope of uncertain origin, Implantable Loop Recorders (ILRs) are recommended in order to unveil hidden arrhythmias [2]. Pooled data from nine studies show that at the end of a negative complete work-up for unexplained syncope, a correlation between syncope and tachyarrhythmia was found in 11% of patients [3].

In the current issue of *International Journal of Cardiovascular Imaging*, Musoni et al. reported a 13% incidence of Ventricular Tachycardia (VT) during 2.9 years of median follow-up after ILR implantation in patients with unexplained syncope. The relatively high incidence of VT in this cohort is in keeping with previous reports [3] and points towards the presence of an underlying ventricular condition; however, this is, by definition, in contrast with the baseline absence of an overt structural cardiac cause of syncope in this selected cohort. Theoretically, one could

hypothesise that there may be a *covert* cardiomyopathic process with arrhythmias and syncope being the first phenotypic manifestations.

In this new study, Musoni et al. analysed the association between baseline cardiac echocardiographic parameters with incident VT in unexplained syncope. The authors found that higher Left Ventricular (LV) wall thickness, increased LV mass index (LVMI) with eccentric remodelling, and reduced Global Longitudinal Strain (GLS) are associated with incident VT detected by ILR. These results may have important pathophysiologic implications as, despite the absence of an overt structural heart disease at baseline, these patients seem to display a subtle myopathic phenotype characterized by LV eccentric hypertrophy, LA dilation, and reduced longitudinal function (by GLS) [4] despite a normal LV ejection fraction, normal LV diastolic function (by Tissue-Doppler E'), see Fig. 1. Although standard echocardiography does not allow tissue characterization of the myocardium, one could even assume that a certain degree of LV fibrosis may play a role considering that reduced GLS is related to areas of LV fibrosis by Late Gadolinium Enhancement [5] and that the presence of LV fibrosis by Late Gadolinium Enhancement is associated with VT events [6]. After adjusting for known ischaemic heart disease, diabetes, and hypertension in multivariable models, the reported association between such echocardiographic abnormalities and VT events held statistical significance. These results imply that this newly identified abnormal cardiac phenotype cannot be fully explained by traditional clinical factors.

Given the limitations of this study design, it is difficult to ascertain directionality of effects and, as such, there is a possibility that repeated VT events may have induced the observed cardiac changes rather than being caused by them. Nevertheless, although both these possibilities are likely, previous studies revealed that patients with idiopathic VT display a completely normal cardiac profile [7] thus suggesting that VT events per se may be insufficient to cause cardiac abnormalities. Future studies are now needed to better

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Fig. 1 Proposed updated model of causes of ventricular tachycardia and syncope

characterise the directionality of such associations as well as to investigate possible unknown factors contributing to VT & syncope in patients without an overt structural heart disease. Based on the finding of LV eccentric hypertrophy, the search for possible aetiologic factors should focus on factors associated with volume overload (rather than pressure overload) as eccentric remodelling is usually accompanied by normal systemic pressure and normal peripheral resistance [8].

Among all the echocardiographic biomarkers of incident VT explored in this study, the authors reported that LVMI is the most robust independent predictor which is also specifically associated with sustained VT. The authors argue that echocardiographic predictors may be useful imaging biomarkers which may allow identification of individuals at high-risk patients among those investigated for unexplained syncope; this would have an ultimate potential to possibly reduce the number of (unnecessary) ILR implantation. Although the identification of predictors of malignant arrhythmias is of paramount importance for the clinical practice, the effect size of the reported associations in this study seems relatively small (Hazard Ratio = 1.03 per 1 g/m increase for LVMI in a multivariable model) yielding only a moderate overall predictive performance (C-stat for LVMI ranging from 0.51 to 0.75).

Finally, based on these exciting preliminary results, this editorial posits that a new form of subtle covert cardiomyopathy characterised by LV eccentric hypertrophy and reduced GLS, may underly syncope and VT events in previously unexplained syncope.

This model emphasizes the possibility that, in patients with unexplained syncope without overt structural heart disease, there may be a subtle covert cardiomyopathy underlying malignant arrhythmic events. The findings reported by Musoni et al. highlight that those patients with unexplained syncope who will develop Ventricular Tachycardia (VT), display a subtle LV eccentric hypertrophy, LA dilation, reduced GLS but normal LVEF and diastolic function (normal E' by Tissue Doppler). Future studies are needed to further define this new form of cardiomyopathy and to identify possible unknown factors playing an aetiological role. Such studies should also explore to what extent repeated VT events may affect the left cardiac chambers.

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