Restrictive cardiomyopathies: The need for better characterization of a deadly disease

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Related article
by Szczygieł et al.

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An abrupt rise in filling pressure is the landmark feature of restrictive cardiomyopathies (RCM). Non-dilated but stiffened ventricles underpin diastolic dysfunction, atrial enlargement, and heart rate dependency due to fixed stroke volume. However, several knowledge gaps persist despite a thorough understanding of the underlying pathophysiology. The main reason is that pure RCM is the rarest cardiomyopathy phenotype, and its prevalence is still unclear [1]. In addition, a wide spectrum of diseases, both genetic and acquired, can manifest as RCM. Finally, to further complicate the RCM landscape, restrictive phenotypes can be transient or permanent; they even overlap with other phenotypes [2].

Nevertheless, this was a favorable year for management of cardiomyopathies, with the publishing of the first comprehensive cardiomyopathy guidelines by the European Society of Cardiology (ESC) [3]. The relevance of meticulous etiological research of RCM was emphasized since disease-modifying therapies are now available, especially for transthyretin cardiac amyloidosis (TTR-CA). On the other hand, only a few management recommendations were suggested, highlighting the lack of data on RCM. Indeed, except for TTR-CA, a few studies focused on RCM in recent years [4–7].

In this issue of *Kardiologia Polska*, Szczygieł and colleagues [8] provide interesting etiological, genetic, and prognostic insights (Figure 1) on a prospective cohort of patients enrolled in a single tertiary center. Thirty-six consecutive patients received a diagnosis of RCM from 2015 to 2016. Patients with hypertrophic cardiomyopathy features were excluded. Then, the entire cohort underwent cardiac amyloidosis screening, including medical history, physical examination, cardiovascular, digestive, and neurological assessment, laboratory tests, electrocardiography, echocardiography, and cardiovascular magnetic resonance. Novel non-invasive imaging features, such as impaired global longitudinal strain with the relative apical sparing pattern and increased T1 mapping, were not assessed in the entire population. A positive result of CA screening prompted amyloid typing through evaluation of serum-free light chains and immunofixation of both serum and urine.

According to recent position papers [9, 10], invasive tests are mandatory for the diagnosis of cardiac light chain amyloidosis (AL-CA), while a cardiac uptake on diphosphonate scintigraphy of at least grade 2 of Perugini score in the absence of a monoclonal protein allows non-invasive TTR-CA diagnosis. In non-amyloid RCM (na-RCM), genetic testing identified pathogenic or likely pathogenic (P/LP) variants in the majority of patients (86%), underscoring that RCM may be mostly a genetic disorder, especially after careful exclusion of infiltrative diseases. In this regard, similar results (60%) were found in a Spanish study including 32 patients with end-stage RCM [3]. All-cause mortality for the overall cohort was 56%. The poor prognosis was consistent with a previous multicenter Korean study, where five-year overall survival was 64% [5].

The recent EURObservational Research Programme Cardiomyopathy registry designed by the ESC provided further intriguing information [6, 7]. Patients with RCM showed the highest annual rates of major cardiovas-

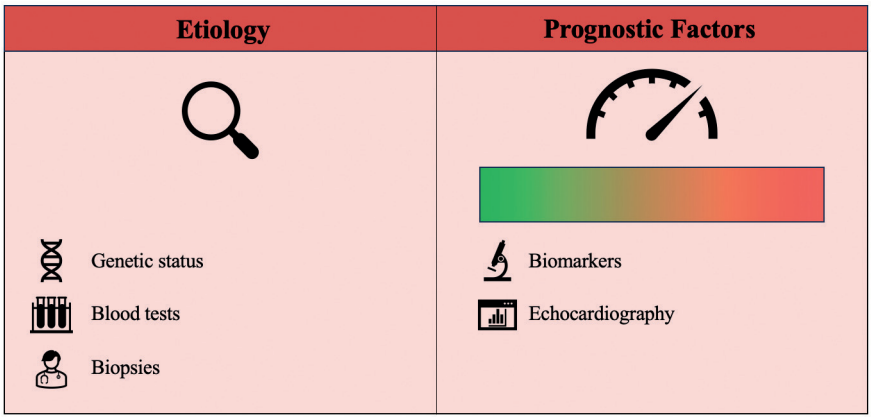

Figure 1. Key aspects of the study by Szczygieł et al. [7]. Left panel: etiologic evaluation. Right panel: assessment of biomarkers and echocardiographic findings as prognostic factors

cular events (P <0.001) as compared to those with other cardiomyopathies. Moreover, except for RCM, all cardiomyopathy phenotypes were more prevalent in males. Finally, RCM patients were more symptomatic, and their functional status was less likely to improve. Subsequently, biomarkers and echocardiographic findings were tested as predictors of outcomes. N-terminal proB-type natriuretic peptide (NT-proBNP) is included in every proposed prognostic staging score for both AL-CA and TTR-CA [3]. Interestingly, the authors evaluated NT-proBNP, high-sensitive troponin T (hs-TnT), soluble suppression of tumorigenicity 2 (sST2), and growth differentiation factor-15 (GDF15) in both amyloid and na-RCM. Univariate Cox models identified GDF15 as the strongest predictor among biomarkers (hazard ratio [HR], 1.45; confidence interval [CI], 1.12–1.88; P = 0.004). NT-proBNP and hs-TnT were also significantly associated with reduced survival (HR, 1.17; CI, 1.08–1.28; P <0.001 and HR, 1.10; CI, 1.04–1.16; P <0.001, respectively). Pericardial effusion was three-fold more frequent in AL-CA than na-RCM (P <0.001) and was the most important predictor of death (HR, 5.49; CI, 1.94–15.51; P = 0.001). It is important to note that the prognosis is still poor, as in previous reports [4, 6]. Additionally, the limited number of patients prevented further analyses.

In conclusion, while authors need to be congratulated for their effort to assess new biomarkers through a wide spectrum of well-characterized RCM, we believe that emerging targeted therapies are paving the way to a proactive approach aiming at precision medicine as a cornerstone of RCM management. We acknowledge that this is a difficult task to achieve, considering RCM epidemiology. Thus, further studies are required to improve the characterization and prognosis of such a deadly disease.

Article information

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