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CASE REPORT
Inherited cardiac conditions/cardiomyopathies

Interatrial block as a first clinical presentation of atrial cardiomyopathy related to a novel LMNA variant: a case report

Michele Iavarone [1†], Simona Covino[1†], Roberta Petillo[2], and Vincenzo Russo [1*]

[1]Cardiology Unit, Department of Translational Medical Sciences, University of Campania 'Luigi Vanvitelli', AORN Ospedali dei Colli Monaldi Hospital, Via L. Bianchi 1 c/o Monaldi Hospital, AORN Colli, Naples 80131, Italy; and [2]Medical and Laboratory Genetics Unit, A.O.R.N. 'Antonio Cardarelli', Naples 80131, Italy

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Background Interatrial block (IAB) is a conduction delay in Bachmann's bundle with a well-described association with structural heart disease, supraventricular arrhythmias, and cardiovascular events.

Case summary We report the case of an asymptomatic 35-year-old man in whom the presence of IAB at electrocardiogram led to a comprehensive evaluation including speckle-tracking echocardiography, 24 h Holter monitoring, and genetic testing. Speckle-tracking echocardiography demonstrated a decrease in the longitudinal strain of interventricular septum, a typical feature of LMNA-related cardiomyopathy, and decreased indices of left atrial deformation. A diagnosis of cardiac laminopathy related to the frame shift variant c.1367 (p.Asn456Thrfs*24) of the LMNA gene was made. A dual-chamber implantable cardioverter defibrillator implantation was performed for the high risk of life-threatening ventricular tachyarrhythmias.

Discussion This case demonstrates that IAB could be a rare presentation of a life-threatening laminopathy. Strain echocardiography is an essential tool to evaluate the deposition of fibrosis tissue in subclinical cardiomyopathies. Our report describes a novel variant of LMNA gene associated with a high risk of sudden cardiac death.

Keywords Interatrial block • Strain imaging • Laminopathy • Arrhythmic risk • ICD • Case report

ESC curriculum 5.6 Ventricular arrhythmia • 5.10 Implantable cardioverter defibrillators • 6.5 Cardiomyopathy • 2.2 Echocardiography

Learning points

- Interatrial block (IAB) is an uncommon finding in young patients and may be the first presentation of atrial cardiomyopathy.
- Young patients with IAB should be evaluated by speckle-tracking echocardiography and, in case of abnormalities, screened for LMNA mutations.
- The LMNA-related cardiomyopathy is associated with early atrial myopathy, even in the absence of left atrial dilation and left ventricle dysfunction.

* Corresponding author. Tel: +39 0817062355, Email: vincenzo.russo@unicampania.it
† The first two authors contributed equally to the study.
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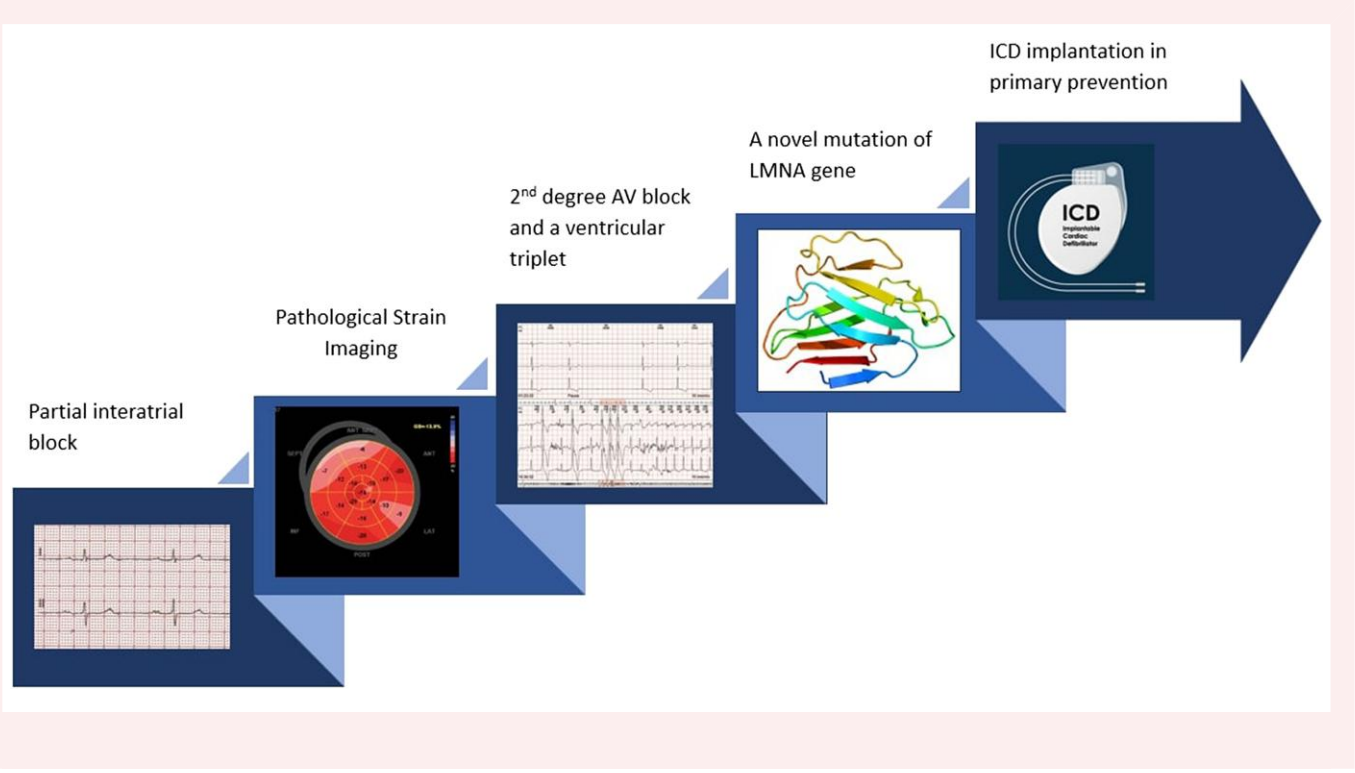
Introduction

Interatrial block (IAB) is a well-described, but poorly recognized, cardiac rhythm disorder caused by a delayed conduction across the Bachmann's region, which is located between the right and the left atrium.[1] Interatrial block has been associated with atrial cardiomyopathy,[2] other than being a predictor of atrial fibrillation (AF), ischaemic stroke, and cardiac death.[3] In this study, we describe the case of an asymptomatic young patient whose IAB was the first red flag of a subclinical life-threatening cardiomyopathy related to a novel Lamin A/C (LMNA) variant.

Summary figure



Case presentation

A Caucasian 35-year-old man was referred to our Cardiology Unit for a cardiac evaluation before non-competitive sport activity (gym), as required by a general practitioner, because of his highly abnormal family history. His mother underwent a heart transplant for end-stage dilated cardiomyopathy and his brother had just received a diagnosis of non-ischaemic cardiomyopathy with mildly reduced ejection fraction. At presentation, no family genetic or histological data were available. The patient was asymptomatic and his medical history was unremarkable. Physical examination showed no abnormalities. The 12-lead electrocardiogram (ECG) showed a sinus bradycardia at 50 b.p.m. The P-wave duration was 130 ms with a bimodal morphology in the inferior leads and a negative terminal component in the V1 of 60 ms (*Figure 1*). These findings suggested a diagnosis of partial IAB, potentially related to left atrium enlargement. The standard transthoracic echocardiography showed no significant abnormalities; however, strain imaging revealed a segmental longitudinal strain impairment involving the basal and medium segments of the interventricular septum (−7%) and determined a mild reduction of left ventricular global longitudinal strain (GLS; −13.9%; *Figure 2*). Both the peak atrial longitudinal strain and the peak atrial contraction strain reduced, compared with normal ranges (stratified for sex and age).

The 24 h ECG monitoring revealed a sinus bradycardia with a day-time mean heart rate of 56 b.p.m., 2 day-time episodes of Type 2 second-degree atrioventricular block with a maximum pause of 2.92 s, frequent premature ventricular complexes, and a ventricular triplet followed by a 4 min-long episode of AF at a high ventricular rate (*Figure 3*). With the clinical suspicion of a familiar cardiomyopathy, we performed a comprehensive genetic testing, which revealed the frame shift variant c.1367 (p.Asn456Thrfs*24) of the *LMNA* gene, a frame shift variant characterized by the replacement of asparagine at Position 456 for a threonine, terminating at Position 24 with a termination codon. The same variant was later found in the patient's brother. This clinical case was evaluated and discussed by a multidisciplinary team involving a medical geneticist, an electrophysiologist, and a cardiologist specialized in echocardiography. Considering a definite diagnosis of LMNA-related cardiomyopathy in the presence of conduction disturbances and an estimated 5-year risk of life-threatening ventricular arrhythmias (VAs) of 51.3% (based on the risk calculator on https://lmna-risk-vta.fr/), a dual-chamber implantable cardioverter defibrillator (ICD) was implanted.[4]

Discussion

The prevalence of IAB in the general population shows a slow increase over the lifetime, accounting for up to 59% of non-hospitalized participants aged >65 years with sinus rhythm.[5,6] Interatrial block was present

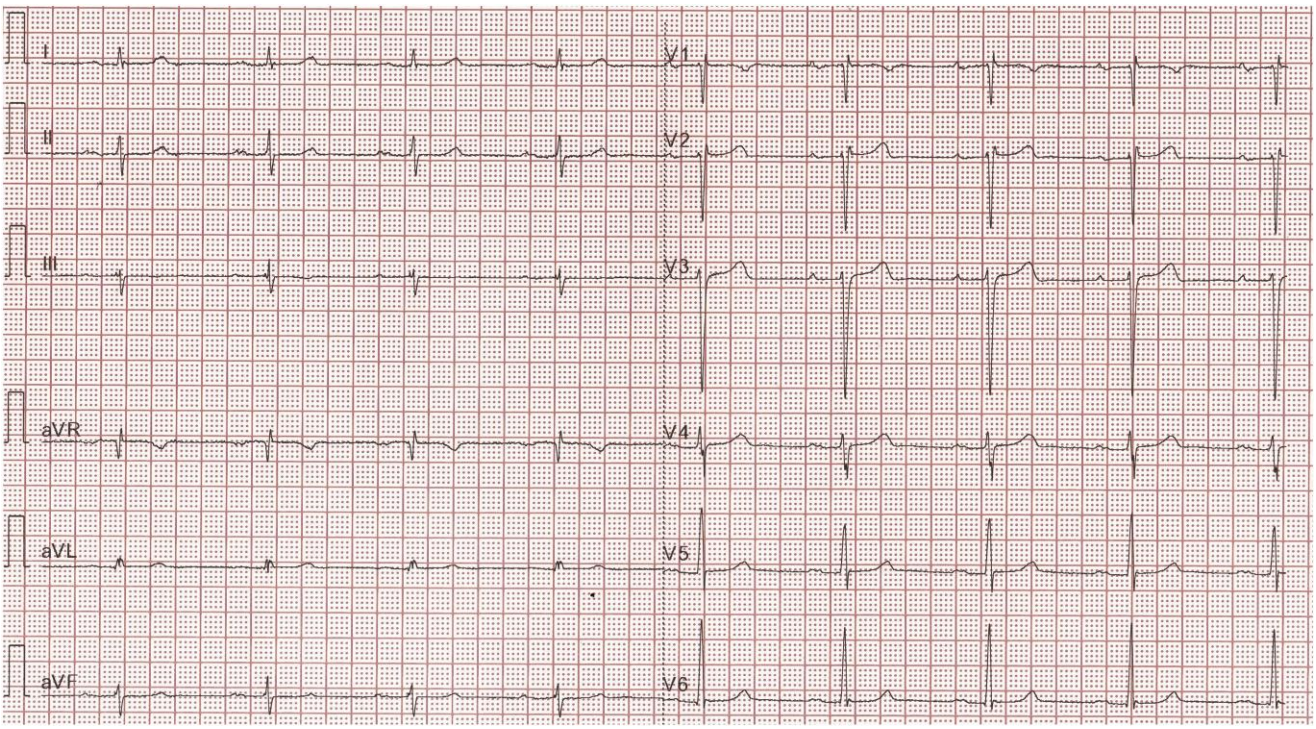


Figure 1 Partial interatrial block.

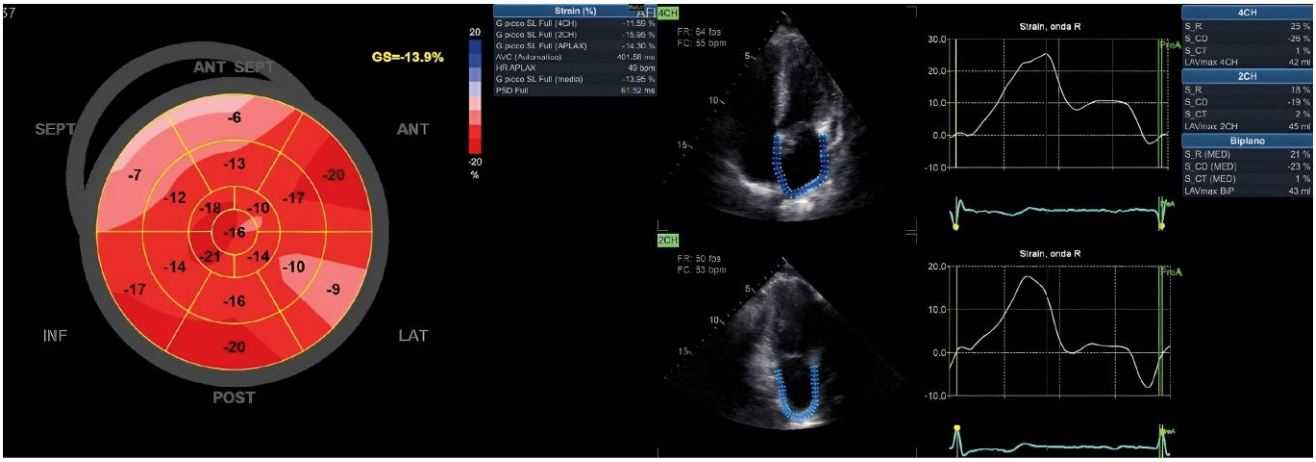


Figure 2 Echocardiographic findings showing a reduced global longitudinal strain (−13.9%), peak atrial longitudinal strain (−21%), and peak atrial contraction strain (1%). GLS, global longitudinal strain; PACS, peak atrial contraction strain; PALS, peak atrial longitudinal strain.

in 5 and 9% of healthy men younger than 20 and 35 years, respectively.[7] Interatrial block showed a high prevalence among patients with cardiomyopathy[8]; nevertheless, no case of IAB in patients with laminopathy has been described yet. Laminopathies are a group of rare genetic diseases, caused by variants in genes encoding proteins of the nuclear lamina, which encompass a wide spectrum of clinical manifestations involving alterations in electrical and mechanical cardiomyocytes. Thus, dilated cardiomyopathy, bradyarrhythmias, AF, or ventricular tachyarrhythmias leading to sudden cardiac death may occur alone or in combination.[9]

In our patient, IAB was the early marker of a subclinical atrial cardiomyopathy due to a novel frameshift non-sense LMNA variant and was characterized by left atrium (LA) strain impairment with normal LA dimension. The variant c.1367del (p.Asn456Thrfs*24) of the LMNA gene (NM_170707.4) is reported on the main bioinformatic prediction tools such as Varsome (https://varsome.com) and Franklin

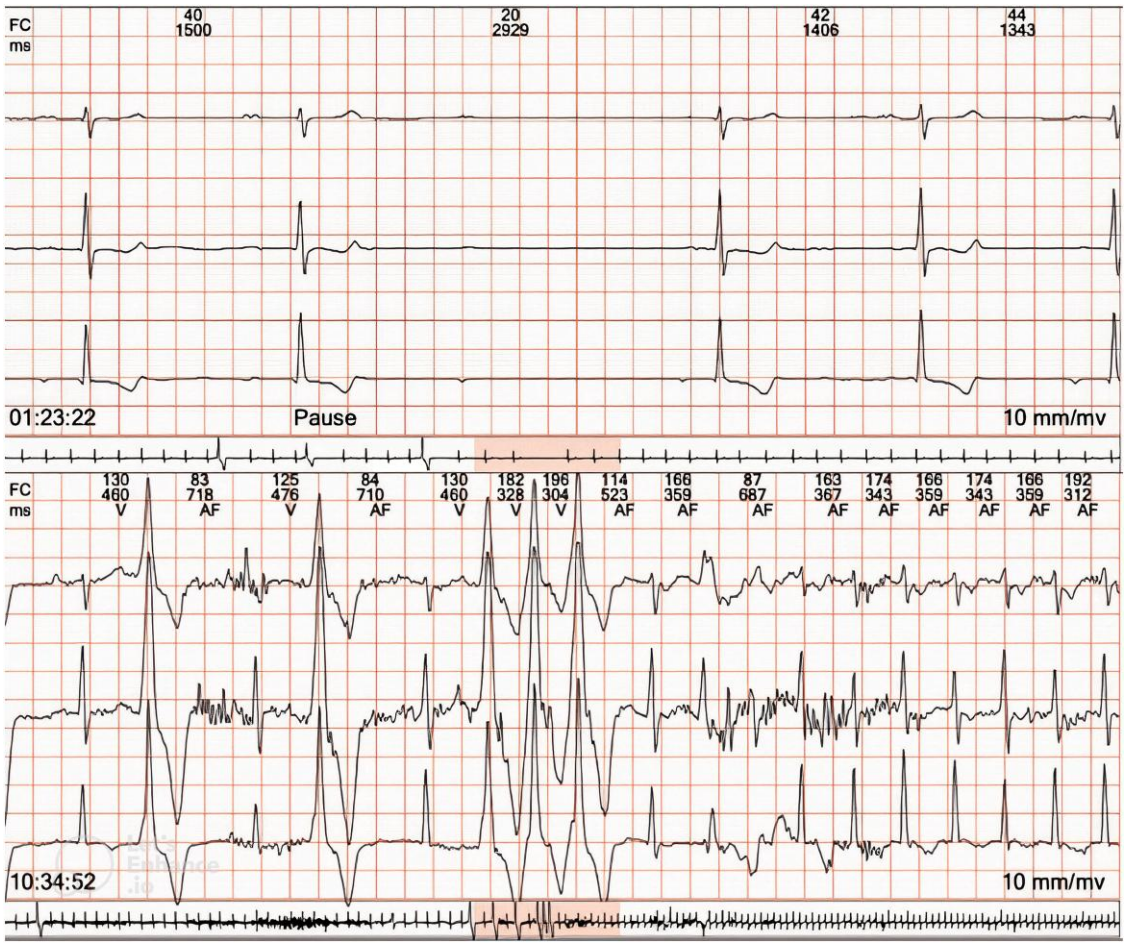


Figure 3 Second-degree AV block (upper panel) and ventricular triplet followed by atrial fibrillation (lower panel).

(https://franklin.genoox.com) as 'likely pathogenic' according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology variant classification criteria (PVS1, PM2 criteria).[10] PVS1 is considered a very strong pathogenic criterion; it refers to certain deleterious types of variants (e.g. frameshift, as for the present case) that can be assumed to disrupt gene function by leading to a complete absence of the gene product. This variant, indeed, is extremely rare, and therefore, it is not reported in the control databases (e.g. gnomAD genomes). If a variant is absent from the general population or control cohort >1000 individuals, it can be considered, when detected, a moderate piece of evidence for pathogenicity (PM2 criterion). The segregation analysis of the affected patient's relatives (mother and brother) supports the judgement of pathogenicity.

The association between IAB and LA wall deformation alterations, as an early expression of atrial remodelling, has been previously described in a cross-sectional study, including 56 unselected patients with partial or advanced IAB.[11]

The LMNA-related cardiomyopathy is associated with early intrinsic atrial myopathy reflected by high AF prevalence and reduced LA contractile strain, even in the absence of left ventricle dysfunction and LA dilation.[12] The reduced GLS in the basal segments of the interventricular septum is a frequent and early finding in LMNA cardiomyopathy; it has been related to fibrosis tissue deposition as much as an increased risk of severe arrhythmias and conduction defects.[13] Cardiac magnetic resonance (CMR) is considered the gold standard imaging technique to non-invasively identify and quantify myocardial fibrosis, with its natural ability for tissue characterization. The presence of late gadolinium enhancement in CMR may help identify LMNA patients at an increased risk of malignant VAs.[14]

A validated risk score for the prediction of 5-year life-threatening VAs in laminopathies identified male sex, non-missense LMNA variant, AV block, non-sustained ventricular tachycardia, and reduced left ventricular ejection fraction as significant predictors of sudden cardiac death.[15] In our patient, the maximum rate of risk of life-threatening ventricular tachyarrhythmias at 5 years was 51.3%, and therefore, a dual-chamber ICD implantation was performed. The present case offered us the opportunity to underline the role of a careful electrocardiographic analysis as the starting point of a multimodal approach leading to a diagnosis of genetic cardiomyopathy. A multidisciplinary team approach is necessary to achieve correct diagnosis, optimize patient management, and improve prognosis.

Conclusions

Interatrial block may be a red flag for LMNA-related cardiomyopathy in young patients. Young patients showing IAB should be evaluated by

speckle-tracking echocardiography and, in case of abnormalities, screened for the presence of the LMNA variant.

Lead author biography

Michele Iavarone, MD, graduated from the Medical School of the Luigi Vanvitelli University in Naples, where he is currently a resident of cardiology.

Consent: The authors confirm that the written consent for submission and publication of this case report, including images and associated text, has been obtained from the patient in line with COPE guidance.

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Data availability

The data underlying this article will be shared on reasonable request with the corresponding author.

References

1. Bayés de Luna A, Platonov P, Cosio FG, Cygankiewicz I, Pastore C, Baranowski R, et al. Interatrial blocks. A separate entity from left atrial enlargement: a consensus report. *J Electrocardiol* 2012;**45**:445–451.
2. Bayés-de-Luna A, Martínez-Sellés M, Elosua R, Bayés-Genís A, Mendieta G, Baranchuk A, et al. Relation of advanced interatrial block to risk of atrial fibrillation and stroke. *Am J Cardiol* 2020;**125**:1745–1748.
3. Martínez-Sellés M, Elosua R, Ibarrola M, de Andrés M, Díez-Villanueva P, Bayés-Genis A, et al. Advanced interatrial block and P-wave duration are associated with atrial fibrillation and stroke in older adults with heart disease: the BAYES registry. *Europace* 2020;**22**:1001–1008.
4. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, et al. 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J* 2022;**43**:3997–4126.
5. Ninios I, Pliakos C, Ninios V, Karvounis H, Louridas G. Prevalence of interatrial block in a general population of elderly people. *Ann Noninvasive Electrocardiol* 2007;**12**:298–300.
6. Russo V, Marano M. Letter to the editor—Prevalence of interatrial block during lifetime. *Heart Rhythm* 2016;**13**:e90–e91.
7. Gialafos E, Psaltopoulou T, Papaioannou TG, Synetos A, Dilaveris P, Andrikopoulos G, et al. Prevalence of interatrial block in young healthy men <35 years of age. *Am J Cardiol* 2007;**100**:995–997.
8. Russo V, Papa AA, Rago A, Ciardiello C, Marano M, Proietti R, et al. Interatrial block to predict atrial fibrillation in myotonic dystrophy type 1. *Neuromuscul Disord* 2018;**28**:327–333.
9. Crasto S, My I, Di Pasquale E. The broad spectrum of LMNA cardiac diseases: from molecular mechanisms to clinical phenotype. *Front Physiol* 2020;**11**:538082.
10. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;**17**:405–424.
11. Lacalzada-Almeida J, Izquierdo-Gómez MM, Belleyo-Belkasem C, Barrio-Martínez P, García-Niebla J, Elosua R, et al. Interatrial block and atrial remodeling assessed using speckle tracking echocardiography. *BMC Cardiovasc Disord* 2018;**18**:38.
12. Tremblay-Gravel M, Ichimura K, Picard K, Kawano Y, Dries AM, Haddad F, et al. Intrinsic atrial myopathy precedes left ventricular dysfunction and predicts atrial fibrillation in *Lamin A/C* cardiomyopathy. *Circ Genom Precis Med* 2023;**16**:E003480.
13. Hasselberg NE, Edvardsen T, Petri H, Berge KE, Leren TP, Bundgaard H, et al. Risk prediction of ventricular arrhythmias and myocardial function in Lamin A/C mutation positive subjects. *Europace* 2014;**16**:563–571.
14. Peretto G, Barison A, Forleo C, Di Resta C, Esposito A, Aquaro GD, et al. Late gadolinium enhancement role in arrhythmic risk stratification of patients with LMNA cardiomyopathy: results from a long-term follow-up multicentre study. *Europace* 2020;**22**:1864–1872.
15. Wahbi K, Ben Yaou R, Gandjbakhch E, Anselme F, Gossios T, Lakdawala NK, et al. Development and validation of a new risk prediction score for life-threatening ventricular tachyarrhythmias in laminopathies. *Circulation* 2019;**140**:293–302.