Title

Refractory coronary vasospasm and recurrent cardiac arrest.

Journal

BMJ Case Reports, 16(1)

Authors

Birs, Antoinette

Darden, Douglas

Adler, Eric

et al.

Publication Date

2023-01-11

DOI

10.1136/bcr-2022-253884

Peer reviewed

Refractory coronary vasospasm and recurrent cardiac arrest

Antinette S Birs , Douglas Darden, Eric D Adler, Gregory K Feld

Department of Cardiology, UC San Diego Health System, La Jolla, California, USA

Correspondence to
Dr Antoinette S Birs;
abirs@health.ucsd.edu

Accepted 5 January 2023

SUMMARY

We present a case of recurrent vasospasm as an uncommon cause of ventricular fibrillation in a young female patient who was found to have a genetic mutation of unknown significance in the desmoplakin (DSP) gene and ultimately required an implantable cardiac defibrillator and percutaneous coronary intervention. Refractory vasospasm as a cause of chest pain and cardiac arrest may be under-recognised. In this manuscript, we highlight the natural history of refractory vasospasm, treatment considerations including medical therapy, implantable cardiac defibrillator and percutaneous coronary intervention. Lastly, we explore the potential correlation between the DSP mutation and her clinical presentation and the growing importance of genetic testing in unexplained cardiac arrest.

BACKGROUND

Coronary artery vasospasm is a transient and typically reversible vasoconstriction of a major epicardial vessel that manifests with anginal attacks, ST elevation and myocardial ischaemia in the absence of atherosclerotic disease. Refractory coronary vasospasm is considered rare with an unknown prevalence in Western countries, in part due to the fact that patients with myocardial injury and non-obstructive coronary artery disease may be misdiagnosed with microvascular disease and in part due to fewer epidemiological investigations compared with Japanese and Far East regions.[1 2] A large multicentre Japanese registry of vasospastic angina described a small subset of patients who presented with out-of-hospital cardiac arrest; these patients were younger with a higher incidence of left anterior descending (LAD) spasm and a lower event-free survival.[2] Medical therapy with vasodilatory agents such as calcium channel blockers and nitrates is the cornerstone of treatment of vasospastic angina; however, there are no established guidelines for the management of patients with malignant coronary vasospasm and recurrent sudden death (SD), making this a highly interesting population to study.

Cardiac arrest in young patients is rare and multimodality evaluation may be necessary to elucidate a diagnosis in a population that lacks significant risk factors for atherosclerotic disease. Coronary CT angiography (CTA) and cardiac MRI may be employed to evaluate for inflammatory, structural and rare ischaemic causes of SD. Despite concerns regarding costs and difficulties in interpreting variants of unknown significance (VUS), there is a growing interest in obtaining genomic data in certain unexplained cardiac arrest populations.[3] While current guidelines do not recommend routine genetic testing in unexplained sudden cardiac arrest, it may be reasonable in cases with presumed genetic aetiology, or by phenotype-driven testing.[4] In this case, we will discuss desmoplakin (DSP) cardiomyopathy, a distinct form of arrhythmogenic cardiomyopathy with left ventricular predominance characterised by an inflammatory process with sporadic chest pain and high incidence of ventricular arrhythmia in the absence of coronary artery disease.[5]

CASE PRESENTATION

A healthy woman in her 30s with no medical history presented at 24 weeks' gestation with 1 day of episodic substernal chest pain and flank pain. She had no family history of early coronary artery disease or cardiomyopathy. She was hospitalised for the treatment of pyelonephritis and received azithromycin and antiemetics. During the first night of hospitalisation, she developed ventricular fibrillation (VF) and suffered a cardiac arrest requiring 45 min of cardiopulmonary resuscitation and emergent caesarean section. ECG demonstrated sinus tachycardia with QTc 510 ms (figure 1A). Troponin was 18 times above the normal limit. Echocardiogram demonstrated regional wall motion abnormalities in the anterolateral, mid-inferolateral and basal inferolateral segments with a mildly depressed ejection fraction of 47%. Coronary CTA was performed to evaluate for spontaneous coronary artery dissection (SCAD). She was found to have an anomalous left circumflex artery that had a retroaortic and non-malignant course, and no evidence of dissection or atherosclerosis (figure 2). Cardiac MRI was performed to evaluate for evidence of myocarditis, and other aetiologies including arrhythmogenic right ventricular cardiomyopathy, and cardiac MRI revealed mid-myocardial late-gadolinium enhancement (LGE) in the anterolateral wall (figure 3). Subsequent ECGs demonstrated a borderline QTc of 458 ms. She was discharged on nadolol for presumed long QT syndrome (LQTS) and counselled on avoiding QT-prolonging medications.

INVESTIGATIONS

Cardiac arrest in a young and healthy woman in the peripartum period is rare and when it occurs, there is often a high suspicion for SCAD, which is estimated to be the cause of one-quarter of acute myocardial infarctions that occur during pregnancies in the USA.[6] No evidence of SCAD was demonstrated on coronary CTA. Cardiac MRI was obtained to evaluate for evidence of inflammation,

To cite: Birs AS, Darden D, Adler ED, *et al*. *BMJ Case Rep* 2023;**16**:e253884. doi:10.1136/bcr-2022-253884

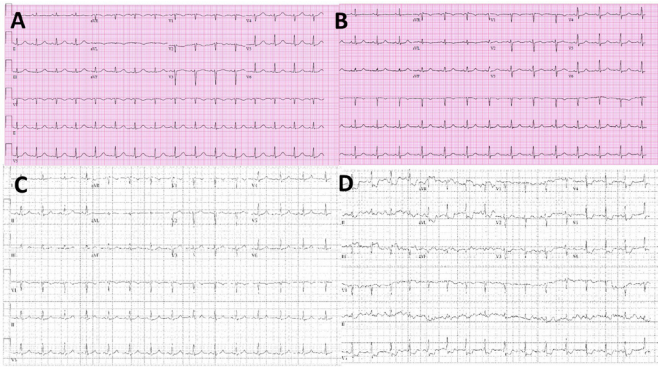

Figure 1 ECG tracings from (A) ECG following in-hospital cardiac arrest. (B) First ECG obtained following out-of-hospital arrest. (C) Presenting ECG following fourth anginal attack and NSTEMI. (D) Presenting ECG tracing from hospitalisation following fifth anginal attack and NSTEMI. NSTEMI, non-ST-elevation myocardial infarction.

scar, myocarditis, arrhythmogenic right ventricular cardiomyopathy, sarcoid or other structural abnormalities that could explain her presentation. Cardiac MRI demonstrated mid-myocardial anterolateral wall LGE consistent with ischaemia. Other primary inherited cardiomyopathies and channelopathies were considered. There was a high suspicion for an LQTS channelopathy given the prolonged QTc and a focused genetic panel was obtained which found only a VUS in the DSP gene, a protein integral in cardiac desmosome function and structure. In the absence of prolonged QTc on subsequent VF arrests, and no channelopathy identified on genetic testing, LQTS was no longer considered. A cardiac MRI was repeated 2 months following index hospitalisation demonstrating stable LGE with mid-myocardial anterolateral wall fibrosis and no evidence of evolving inflammatory pathology or myocarditis (figure 3C,D).

One year later, she suffered an out-of-hospital cardiac arrest. Notably, this arrest was preceded by episodic chest pain like her first presentation with no QT prolongation on ECG (figure 1B). She underwent cardiac catheterisation that demonstrated spasm in a diagonal coronary artery branch that resolved with intracoronary nitroglycerin. She underwent implantable cardioverter defibrillator (ICD) implantation for secondary prevention. The aetiology of her recurrent arrests was still unknown. The following year, she suffered a third anginal attack and out-of-hospital VF arrest, requiring seven shocks to restore sinus rhythm. ICD interrogation revealed that VF temporarily terminated after four shocks, but immediately recurred requiring an additional three shocks (figure 4). Non-invasive programmed stimulation (NIPS) was performed along with defibrillation threshold testing (DFT), which confirmed an adequate defibrillation safety

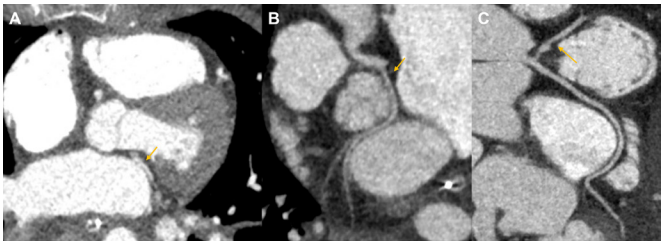

Figure 2 (A–C) Coronary CT angiogram of the left circumflex artery with anomalous takeoff from the right coronary cusp taking a retroaortic course in the transverse plane. Yellow arrow points to left circumflex artery.

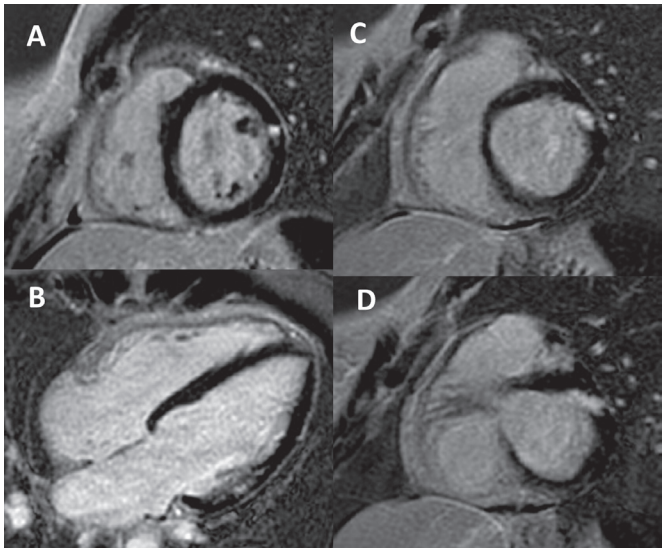

Figure 3 (A,B) Cardiac MRIs from index hospitalisation showing lateral wall mid-myocardial enhancement in short axis (A) and four-chamber view (B). (C,D) Repeat cardiac MRIs performed months later in follow-up. (C) Endomyocardial to mid-myocardial enhancement in lateral wall on short axis and (D) five-chamber view.

margin and appropriate ICD function. On review of prior coronary angiograms, refractory coronary vasospasm was suspected given observed vasospasm that was initially thought to be catheter induced. The results of the NIPS and DFT suggested that the refractory VF and multiple failed defibrillation attempts were likely a direct result of acute ischaemia from an occluded coronary vessel due to persistent vasospasm. Her preceding symptoms of classic spastic angina combined with vasospasm strongly supported the malignant coronary vasospasm diagnosis. Medical therapy with diltiazem, isosorbide dinitrate and atorvastatin was initiated and nadolol discontinued for the treatment of malignant coronary vasospasm.

Within 2 weeks of initiating the new medical therapy, she experienced another anginal attack. Angiography revealed severe vasospasm of the LAD artery with a focal 80% stenotic lesion refractory to intracoronary nitroglycerin and verapamil requiring percutaneous coronary intervention (PCI) with one drug-eluting stent (figure 5A–C). She was discharged on aspirin, clopidogrel, atorvastatin, diltiazem and isosorbide dinitrate. Days later, she presented with her fifth anginal attack and a non-ST-elevation myocardial infarction pattern on ECG (figure 1D). She underwent catheterisation, which revealed a patent LAD stent with diffuse vasospasm of the left circumflex coronary artery, which abated spontaneously (figure 5D).

TREATMENT

Initially, treatment with nadolol was initiated for presumed LQTS, but later discontinued after the patient's QTc normalised and genetic testing was negative for inherited LQTS. She received a secondary prevention ICD following her second cardiac arrest. Calcium channel blockers and nitrates were initiated for high suspicion of vasospastic disease, which was first considered after refractory VF was demonstrated despite appropriate ICD shocks. Despite treatment with calcium channel blockers and nitrates, she suffered recurrent coronary vasospasm with eventual placement of a percutaneous coronary stent for vasospasm refractory to intracoronary vasodilators. Although rare, in severe cases, PCI, coronary bypass grafting or heart transplant may

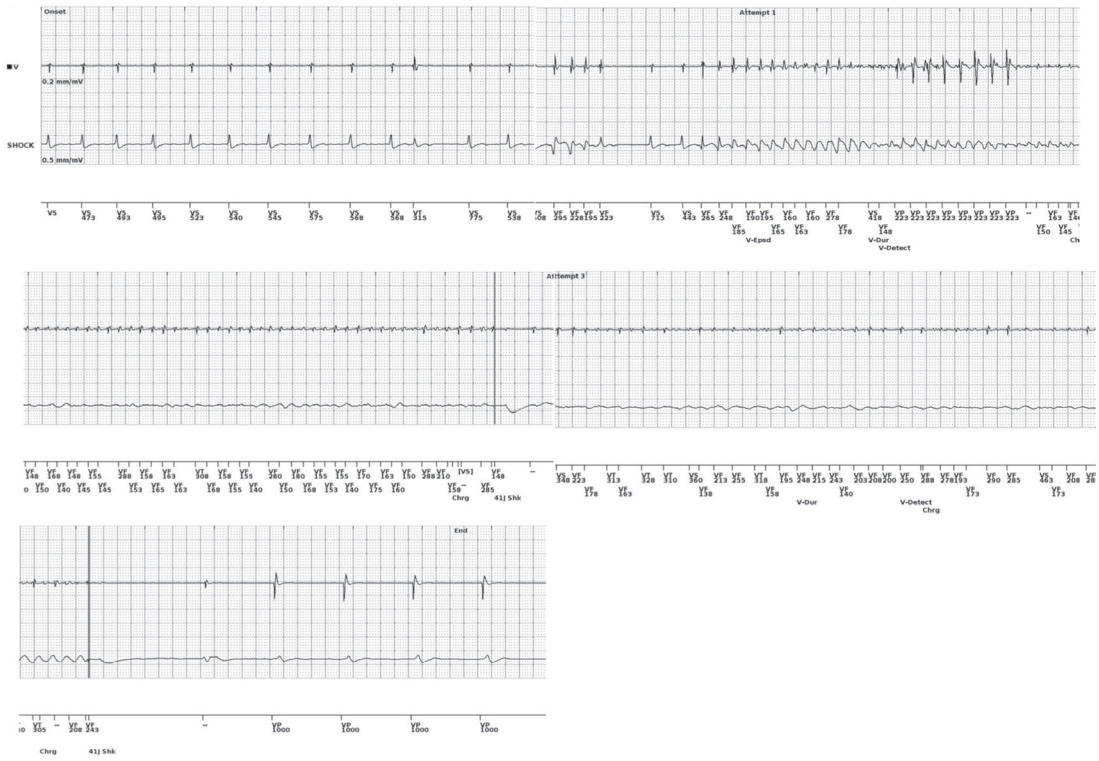

Figure 4 Tracings from out-of-hospital cardiac arrest. The first panel demonstrates initiation of ventricular fibrillation (VF) rhythm. The second panel demonstrates failure for shock to terminate VF and third panel demonstrates termination after fourth defibrillation.

be necessary.[7–10] As vasospasm is a diffuse process, sometimes involving multiple coronary arteries, it remains unclear what protective effect PCI has on morbidity or mortality. Interestingly, after mid-LAD PCI, our patient had no further VF. This suggests that PCI in an area that supplies a large myocardial territory may prevent further episodes of VF.[11] When considering PCI in patients with refractory vasospasm, the goal should primarily be to reduce the risk of further arrhythmic events, and benefits and risks of PCI need to be carefully weighed.

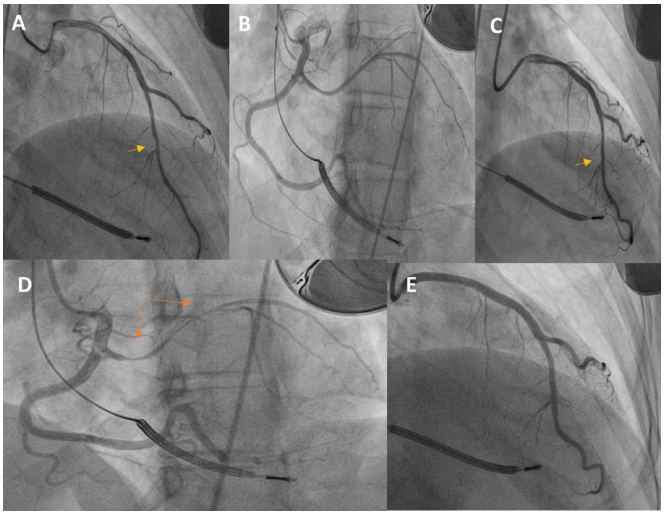

Figure 5 (A–C) First catheterisation demonstrating sustained spasm. (A) Yellow arrow demonstrates mid-left anterior descending (LAD) vasospasm. (B) Right coronary angiogram showing anomalous left circumflex coronary artery. (C) Angiogram showing percutaneous coronary intervention of mid-LAD lesion. (D,E) Recurrent non-ST-elevation myocardial infarction and catheterisation demonstrating vasospasm in left circumflex. (D) Severe narrowing (orange arrows) in proximal and middle left circumflex artery consistent with vasospasm and patent LAD stent with no evidence of vasospasm.

OUTCOME AND FOLLOW-UP

She has returned to her daily activities and has been angina free since last catheterisation, over 2 years prior. She remains on aggressive medical therapy with calcium channel blockers, nitrates, aspirin, clopidogrel and ranolazine. She has had no further ICD shocks or VF.

DISCUSSION

Refractory vasospasm should remain on the differential as a cause of chest pain, ventricular arrhythmia and sudden cardiac death in young individuals. Medical therapy, including calcium channel blockers, nitroglycerin, statins and hormone contraception therapy, has been shown to reduce episodes of vasospasm; however, select patients are refractory to medical therapy and require further intervention.[7 8 12 13] ICD therapy has proven efficacious for secondary prevention of SD[14]; however, the benefit of ICDs in those with refractory coronary vasospasm and SD is unknown. For our patient, VF was nearly refractory during episodes of ischaemia, despite several shocks. We postulate that severe vasospasm led to prolonged ischaemia and VF, and defibrillation was only successful after the vasospasm abated. Thus, ICD therapy may still be effective in these high-risk patients as VF induced by vasospasm was ultimately terminated with defibrillation.

This case highlights the similarities between vasospasm-induced episodic chest pain and ventricular arrhythmias with DSP cardiomyopathy, which is characterised by episodic myocardial injury, a high incidence of ventricular arrhythmias

and fibrosis leading to systolic dysfunction.[5] It is uncertain if this patient's VUS mutation is disease causing; however, in-silico tools predicted a damaging effect to the DSP gene. Although only hypothesis generating, the data from such in-vitro modelling provide a starting point for further investigation and require additional in-vivo study. Genetic testing may provide information regarding prognosis, follow-up recommendations and family screening for certain populations with idiopathic or unexplained cardiac arrest. In a pragmatic study of patients from the Canadian Cardiac Arrest Survivor with Preserved Ejection fraction Registry, patients with unexplained cardiac arrest following echocardiogram, ECG and coronary disease assessment, a disease-causing genetic variant was found in 10% of these patients.[3] Another study identified a 'concealed cardiomyopathy', by genetic testing in 22% of idiopathic sudden cardiac arrest survivors.[15] These studies demonstrate the increasing interest and attention to genetic testing in unexplained or idiopathic cardiac arrest survivors. For those with VUS, periodical contact with genetic testing vendors is recommended for updates of genetic testing results and for information regarding new or improved genetic tests.[16]

In conclusion, malignant coronary vasospasm can be highly morbid and even fatal. As medical therapy with vasodilatory agents such as calcium channel blockers and nitrates is critical for the treatment of angina, ICD therapy and coronary revascularisation may be considered in select patients with SD resulting from refractory coronary vasospasm. Lastly, the role of DSP mutation in those with refractory anginal attacks, vasospasm and ventricular arrhythmias warrants further investigation in this rare, high-risk cohort.

Learning points

- Ventricular fibrillation refractory to appropriate implantable cardioverter defibrillator (ICD) shocks should prompt investigation for vasospastic disease and inflammatory arrhythmogenic cardiomyopathy.
- Patients with recurrent cardiac arrests due to vasospasm require aggressive measures including ICD implantation in addition to medical management, and in rare cases require percutaneous stenting, bypass grafting or transplant. Patients should be evaluated at an experienced cardiac centre with a comprehensive multidisciplinary team.
- Desmoplakin (DSP) genetic mutation is associated with a fibrotic and inflammatory form of cardiomyopathy that has been characterised by left ventricular involvement, ventricular arrhythmias and poorly understood episodic chest pain. This case presentation proposes a possible relationship between vasospastic disease and some DSP variants.

Twitter Antoinette S Birs @AntoinetteBirs

Contributors ASB made substantial contributions to the concept and design of the study as well as carried out the data acquisition and analysis. She drafted the work and revised it for intellectual content. She agreed to all aspects of the work and gave a final approval for publication and agreed to be held accountable for all aspects of the work. DJD made substantial contributions to the analysis and interpretation of the data, and revised the work to enhance intellectual content. He gave final approval for publication and agreed to be accountable for the work in regard to its integrity and accuracy. EDA made substantial contributions to the concept and design of the work and was an integral part of revising the work for important intellectual content. He gave final approval of the version to be published and agreed to be accountable for all aspects of the work. GKF made substantial contributions to the conception and design of the work. He made contributions to revising the work for critical and intellectual content. He gave final approval of this version for publication and agreed to be accountable for all aspects of the work related to accuracy or integrity.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

ORCID iD

Antoinette S Birs http://orcid.org/0000-0001-7041-9075

REFERENCES

1 Ong P, Athanasiadis A, Hill S, *et al*. Coronary artery spasm as a frequent cause of acute coronary syndrome: the CASPAR (coronary artery spasm in patients with acute coronary syndrome) study. *J Am Coll Cardiol* 2008;52:523–7.
2 Takagi Y, Yasuda S, Tsunoda R, *et al*. Clinical characteristics and long-term prognosis of vasospastic angina patients who survived out-of-hospital cardiac arrest: multicenter registry study of the Japanese coronary spasm association. *Circ Arrhythm Electrophysiol* 2011;4:295–302.
3 Grondin S, Davies B, Cadrin-Tourigny J, *et al*. Importance of genetic testing in unexplained cardiac arrest. *Eur Heart J* 2022;43:3071–81.
4 Giudicessi JR, Ackerman MJ. Role of genetic heart disease in sentinel sudden cardiac arrest survivors across the age spectrum. *Int J Cardiol* 2018;270:214–20.
5 Smith ED, Lakdawala NK, Papoutsidakis N, *et al*. Desmoplakin cardiomyopathy, a fibrotic and inflammatory form of cardiomyopathy distinct from typical dilated or arrhythmogenic right ventricular cardiomyopathy. *Circulation* 2020;141:1872–84.
6 Vijayaraghavan R, Verma S, Gupta N, *et al*. Pregnancy-related spontaneous coronary artery dissection. *Circulation* 2014;130:1915–20.
7 Stern S, Bayes de Luna A. Coronary artery spasm: a 2009 update. *Circulation* 2009;119:2531–4.
8 Yasue H, Mizuno Y, Harada E, *et al*. Effects of a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, fluvastatin, on coronary spasm after withdrawal of calcium-channel blockers. *J Am Coll Cardiol* 2008;51:1742–8.
9 Kumar A, Chandna H, Santhanam V, *et al*. Refractory vasospasm with a malignant course. *Clin Cardiol* 2000;23:127–30.
10 Bär S, Perrin T, Räber L, *et al*. Diagnosis of malignant coronary vasospasm by 12-lead Holter electrocardiogram and optical coherence tomography. *Eur Heart J* 2019;40:3442.
11 Garan H, McComb JM, Ruskin JN. Spontaneous and electrically induced ventricular arrhythmias during acute ischemia superimposed on 2 week old canine myocardial infarction. *J Am Coll Cardiol* 1988;11:603–11.
12 Beltrame JF, Crea F, Kaski JC, *et al*. International standardization of diagnostic criteria for vasospastic angina. *Eur Heart J* 2017;38:2565–8.
13 Tezuka A, Shiina K, Fujita Y, *et al*. Efficacy of combined estrogen-progestin hormone contraception therapy for refractory coronary spastic angina in very young women. *J Cardiol Cases* 2020;21:200–3.
14 Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;337:1576–84.
15 Isbister JC, Nowak N, Butters A, *et al*. "Concealed cardiomyopathy" as a cause of previously unexplained sudden cardiac arrest. *Int J Cardiol* 2021;324:96–101.
16 Musunuru K, Hershberger RE, Day SM, *et al*. Genetic testing for inherited cardiovascular diseases: a scientific statement from the American heart association. *Circ Genom Precis Med* 2020;13:e000067.