Case Report

Arrhythmogenic Right Ventricular Cardiomyopathy Presenting with Intra-Operative Aborted Sudden Cardiac Death and Takotsubo-Like Left Ventricular Functional Abnormalities

Sarah Zaman[1], Nadarajah Ramesh[2], Pramesh Kovoor[1]

[1]Department of Cardiology, Westmead Hospital, Sydney, [2]Department of Emergency Medicine, Hawkesbury Hospital, NSW, Australia

Key words:
Takotsubo cardiomyopathy, arrhythmogenic right ventricular dysplasia, flecainide, arrhythmias, cardiac, anaesthesia, general.

A 46-year-old female under treatment with flecainide for atrial fibrillation developed cardiopulmonary arrest secondary to ventricular fibrillation during an elective laparoscopic cholecystectomy. The ECG after cardioversion demonstrated a prolonged QTc interval with elevated cardiac enzymes. A diagnosis of Takotsubo cardiomyopathy was made after angiography demonstrated normal coronary arteries with characteristic ballooning of the left ventricle seen on the left ventriculogram. However, right ventricular biopsy revealed significant fibrofatty infiltration of the myocardium. Treatment with flecainide and early features of arrhythmogenic right ventricular dysplasia may have predisposed the patient to ventricular fibrillation during the transient left ventricular dysfunction of Takotsubo cardiomyopathy.

Manuscript received:
January 2, 2009;
Accepted:
April 5, 2009.

Address:
Pramesh Kovoor

Director of Cardiovascular Services
Westmead Hospital
Westmead, NSW, 2145,
Australia
e-mail:
kovoor@westgate.wh.usyd.edu.au

First described in Japan in the early 1990s, Takotsubo cardiomyopathy is a syndrome characterised by transient left ventricular ballooning in the absence of coronary artery disease.[1] Believed to be triggered by an emotional or physiological stressor it mimics an acute myocardial infarct with chest pain and elevated cardiac enzymes.[2] Arrhythmogenic right ventricular dysplasia (ARVD) is a rare inherited cardiomyopathy characterised by fibrofatty replacement of the right ventricular myocardium, bringing with it an increased propensity for ventricular arrhythmias and sudden death.[3,4]

Case presentation

A 46-year-old Caucasian woman with no risk factors for coronary artery disease developed ventricular fibrillation (VF) requiring DC cardioversion during an elective laparoscopic cholecystectomy. Past medical history included paroxysmal atrial fibrillation (AF), initially treated with sotalol and changed to flecainide after recurrent AF and an episode of syncope. The echocardiogram had shown a structurally normal heart with a left ventricular ejection fraction (LVEF) of 67%. Surgical history included bilateral cataract extraction and appendectomy with no previous anaesthetic complications. Medications on admission for elective cholecystectomy included flecainide 100 mg twice daily and aspirin 100 mg daily. The patient's family history was significant for AF in her mother and sister, with no family history of sudden death or ventricular arrhythmias. Preoperative examination and ECG (Figure 1) were unremarkable, with no features of ARVD or Brugada syndrome.

Laparoscopic cholecystectomy was performed under general anaesthetic. VF oc-

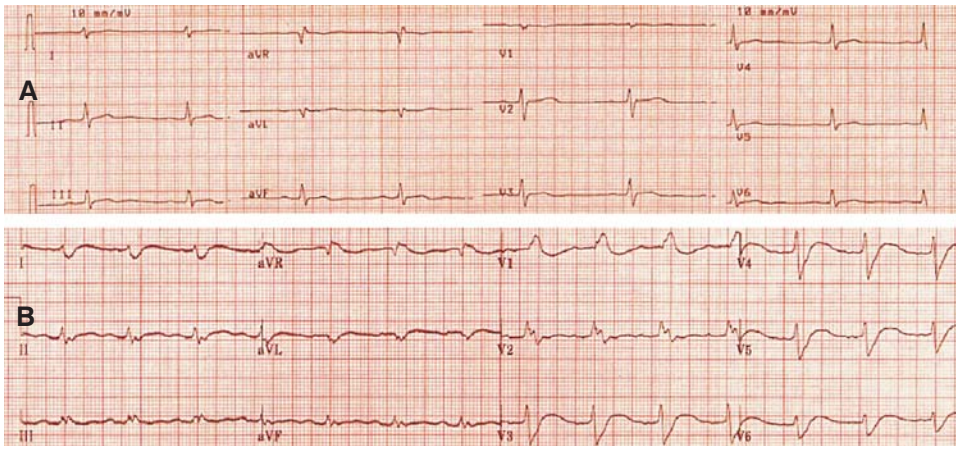

Figure 1. Electrocardiograms. A: preoperatively, showing normal sinus rhythm. B: on transfer to the intensive care unit, showing sinus rhythm with widespread broad QRS complexes, right bundle branch block and prolonged corrected QT interval.

curred at an early stage intraoperatively when only initial dissection had taken place. Following resuscitation and cardioversion the patient was transferred from the operating theatre to the intensive care unit where she remained intubated and mechanically ventilated. The ECG demonstrated sinus rhythm with widespread broad QRS complexes, right bundle branch block and a prolonged corrected QT interval of 560 ms (Figure 1). Arterial blood demonstrated metabolic acidosis (pH 7.24), elevated lactate (4.8 mmol/L) and normal electrolytes and creatinine. Creatinine kinase and troponin T were elevated at 280 IU/L and 0.35 μg/L, respectively. The patient developed pulmonary oedema and required haemodynamic support with intravenous inotropic and vasopressor medications. Emergency angiography revealed normal coronary arteries, while left ventriculography demonstrated severe akinesis of the apex and basal hyper-contractility during systole consistent with takotsubo cardiomyopathy (Figure 2). An intra-aortic balloon pump was inserted during cardiac catheterisation and flecainide was discontinued.

After 72 hours the patient was extubated and transferred to the coronary care unit. The ECG now demonstrated a normal QRS width with a normal corrected QT interval (440 ms) and new findings of widespread deep inverted T waves. Concern about ARVD contributing to ventricular arrhythmia in a young woman with a previous episode of syncope, together with the knowledge that ventricular arrhythmia was only rarely associated with takotsubo cardiomyopathy, led us to perform a right ventricular biopsy from the septal aspect on day 5. The biopsy demonstrated fibrofatty infiltration consistent with ARVD (Figure 3). Cardiac MRI with gadolinium showed a right ventricular size within the upper normal limits, decreased right

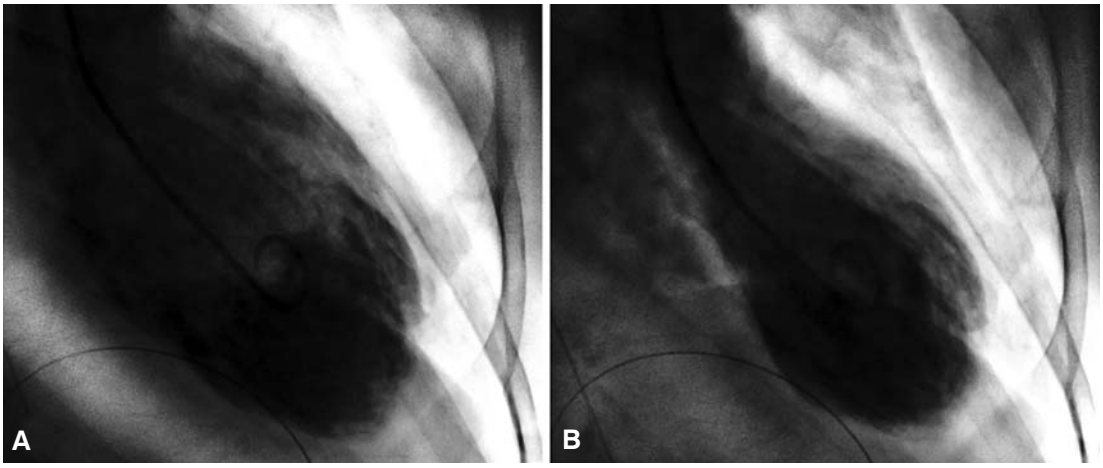

Figure 2. Left ventriculography (A – diastole, B – systole) showing akinesis of the apex, basal hyper-contractility and apical ballooning with systole.

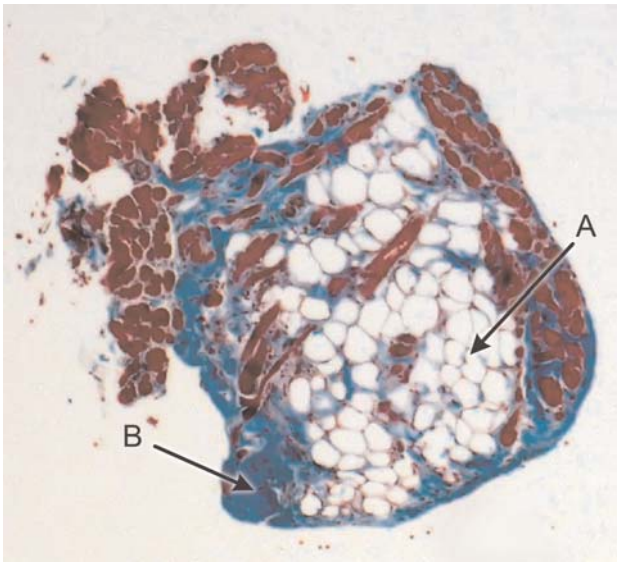

Figure 3. Right ventricular biopsy. There is 35-40% adipocyte infiltration (A) between the myocytes with surrounding fibrosis (B) and hypertrophy of the myocytes.

ventricular end-diastolic volume and left ventricular myocardial wall thinning. However, employment of a scan protocol for ARVD did not identify right ventricular transmural fatty infiltration. Gated heart pool scan on day 10 showed resolution of the left ventricular dysfunction with a normal left ventricular ejection fraction of 58%. After commencement of bisoprolol and implantation of a cardiac defibrillator the patient was discharged home. Follow up at 6 months in the defibrillator clinic revealed 3 episodes of non-sustained ventricular tachycardia lasting 5-7 beats with cycle length 340-350 ms.

Discussion

This patient's clinical presentation satisfies the Mayo diagnostic criteria for takotsubo cardiomyopathy, with new ECG changes, transient left ventricular ballooning, minimally elevated cardiac enzymes and the absence of atherosclerotic coronary artery disease.[5] The left ventriculogram in our case demonstrated the signature appearance of ballooning of the left ventricle with basal hyper-contractility resembling a *takotsubo*; a Japanese pot used for catching octopus. Takotsubo cardiomyopathy is commonly complicated by acute left heart failure requiring aggressive treatment, as seen in our patient, with intra-aortic balloon pumps, inotropic drugs and diuresis.[5] The left ventricular dysfunction in our case was transient, returning to normal by day 10, as has been reported as typical of the condition.[2] Takotsubo cardiomyopathy is thought to be precipitated by an acute physiological or psychological stressor. In our case it is postulated that the stressor was that of the general anaesthetic and operative procedure, as in several cases recently described in the literature.[6-8]

Other causes of arrhythmia and transient left ventricular dysfunction were initially considered. Flecainide is an antiarrhythmic frequently used in the prevention of AF. While a proarrhythmic effect is considered rare in the absence of structural heart disease, flecainide-induced QT prolongation with *torsades de pointes* has been described in the literature.[9,10] However, with a normal QT interval seen on the pre-operative ECG it is unlikely that flecainide was the sole trigger. The wide QRS and prolonged QT on ECG post-cardioversion could be consistent with diffuse cardiac ischaemia and lactic acidosis secondary to cardiac arrest. After successful defibrillation for VF, reversible myocardial stunning with normal coronary blood flow may occur. This myocardial stunning generally results in diffuse, global left ventricular dysfunction and is reversible in animal models within 72 hours.[11] In contrast, our case demonstrated isolated apical dysfunction that did not return to normal until day 10, consistent with takotsubo cardiomyopathy.

ARVD is an inherited disorder characterised by right ventricular dysfunction, with pathological examination demonstrating fibrofatty replacement of the myocardium of the right ventricle. ARVD is commonly associated with ventricular arrhythmias, syncope and sudden death.[3,4,12] In patients who are identified as high risk due to cardiac arrest, ventricular arrhythmias or left ventricular involvement with impaired ejection fraction, management of ARVD includes prophylactic ICD implantation.[13] In our case an ICD was inserted as secondary prevention after resuscitated cardiac arrest.

The diagnosis of ARVD is made according to the task force criteria for cardiomyopathy. Our case satisfied only one major criterion, that of fibrofatty replacement of the right ventricular myocardium, and one minor criterion, the presence of non-sustained VT on defibrillator interrogation. However, histological findings of 35-40% adipocytes combined with fibrosis and myocyte hypertrophy strongly argue for the diagnosis of ARVD in our patient.[14,15] While cardiac MRI did not demonstrate the classical ARVD hallmarks of transmural fatty infiltration and right ventricular aneurysms, the findings of left ventricular

wall thinning and borderline right ventricular enlargement may represent early disease with sub-epicardial location of the myocyte injury and repair process.[16] While frequently used in the investigation of ARVD, the use of MRI remains controversial, since misdiagnosis occurs in up to 73% of patients with MRI alone.[17] Endomyocardial biopsy remains the gold standard in detecting fibrofatty changes of the myocardium.

Other elements of this case support ARVD as an additional diagnosis to that of takotsubo cardiomyopathy. The episode of syncope in the patient's background history, at the time attributed to sotalol, may have represented an early feature of ARVD. VF cardiac arrest has only rarely been described in association with takotsubo cardiomyopathy, occurring in only 1-2% of patients.[18,19] In contrast, perioperative aborted sudden death is a common presentation of ARVD.[20] The ECG changes of QT prolongation with transient right bundle branch block, while described in takotsubo cardiomyopathy,[21] have also been seen as part of ARVD; sudden disease acceleration with acute transient ECG changes and myocardial enzyme release have been described in the literature.[16] These presentations are thought to be part of myocyte necrosis occurring as part of an early disease process, with episodic myocardial destruction and fatty replacement. Marked variability in the age of presentation of ARVD suggests that it can remain concealed for extended periods of time, during which individuals are asymptomatic but nonetheless are at risk of sudden death.[4,16] As a result the established diagnostic criteria lack sensitivity, particularly in detecting the disease at an early stage.[16,22]

This case is of a young pre-menopausal woman who, interestingly, had already developed bilateral cataracts. ARVD is typically inherited as an autosomal dominant trait with variable penetrance and expression with seven loci mapped to chromosome 14. A rare form of autosomal recessive ARVD secondary to a mutation in the plakoglobin gene has also been described.[23] A recent study describing a family with ARVD discovered a connection between ARVD and a rare hereditary form of anterior polar cataract which was also mapped to a gene locus on chromosome 14.[24] This case report provides a valuable second report of a potential connection between cataracts and a rare form of ARVD.

This case study highlights the unusual occurrence of aborted sudden cardiac arrest takotsubo cardiomyopathy in a pre-menopausal woman, triggered by general anaesthesia and cholecystectomy with the rare complication of VF arrest. While the case does not fulfil the task force criteria for ARVD, the unique finding of significant fibrofatty infiltration in the presence of cardiac arrest and bilateral cataracts adds to the expanding clinical knowledge regarding ARVD.

References

1. Dote K, Sato H, Tateishi H, Uchida T, Ishihara M. [Myocardial stunning due to simultaneous multivessel coronary spasms. A review of 5 cases.] J Cardiol. 1991; 21: 203-214. Japanese.
2. Akashi YJ, Nakazawa K, Sakakibara M, Miyake F, Koike H, Sasaka K. The clinical features of takotsubo cardiomyopathy. QJM. 2003; 96: 563-573.
3. Marcus FI, Fontaine GH, Guiraudon G, et al. Right ventricular dysplasia: a report of 24 adult cases. Circulation. 1982; 65: 384-398.
4. Dalal D, Nasir K, Bomma C, et al. Arrhythmogenic right ventricular dysplasia: a United States experience. Circulation. 2005; 112: 3823-3832.
5. Bybee KA, Kara T, Prasad A, et al. Systematic review. Transient left ventricular apical ballooning: a syndrome that mimics ST-segment elevation myocardial infarction. Ann Intern Med. 2004; 141: 858-865.
6. Consales G, Campiglia L, Michelagnoli G, et al. Acute left ventricular dysfunction due to tako-tsubo syndrome after induction of general anesthesia. Minerva Anestesiol. 2007; 73: 655-658.
7. Jensen JB, Malouf JF. Takotsubo cardiomyopathy following cholecystectomy: a poorly recognized cause of acute reversible left ventricular dysfunction. Int J Cardiol. 2006; 106: 390-391.
8. Jabaudon M, Bonnin M, Bolandard F, Chanseaume S, Dauphin C, Bazin JE. Takotsubo syndrome during induction of general anaesthesia. Anaesthesia. 2007; 62: 519-523.
9. Nogales Asensio JM, Moreno Sánchez N, Doncel Vecino LJ, Villar Mariscal C, López-Mínguez JR, Merchán Herrera A. Torsade-de-pointes in a patient under flecainide treatment: an unusual case of proarrhythmicity. Int J Cardiol. 2007; 114: sE65-67.
10. Thevenin J, Da Costa A, Roche F, Romeyer C, Messier M, Isaaz K. Flecainide induced ventricular tachycardia (torsades de pointes). Pacing Clin Electrophysiol. 2003; 26: 1907-1908.
11. Kern KB, Hilwig RW, Rhee KH, Berg RA. Myocardial dysfunction after resuscitation from cardiac arrest: an example of global myocardial stunning. J Am Coll Cardiol. 1996; 28: 232-240.
12. Mavrogeni S, Tolis V, Tolis C, Cokkinos DV. Arrhythmogenic right ventricular dysplasia with extensive myocardial fibrosis and concomitant coronary artery ectasia. Hellenic J Cardiol. 2007; 48: 42-43.
13. Wichter T, Paul M, Wollmann C, et al. Implantable cardioverter/defibrillator therapy in arrhythmogenic right ventricular cardiomyopathy. Single-center experience of long-term follow-up and complications in 60 patients. Circulation. 2004; 109: 1503-1508.
14. Basso C, Ronco F, Marcus F, et al. Quantitative assessment of endomyocardial biopsy in arrhythmogenic right ventricular cardiomyopathy/dysplasia. An in vitro validation of diagnostic criteria. Eur Heart J. 2008; 29: 2760-2771.
15. El Demellawy D, Nasr A, Alowami S. An updated review on

the clinicopathologic aspects of arrhythmogenic right ventricular cardiomyopathy. Am J Forensic Med Pathol. 2009; 30: 78-83.
16. Bauce B, Basso C, Rampazzo A, et al. Clinical profile of four families with arrhythmogenic right ventricular cardiomyopathy caused by dominant desmoplakin mutations. Eur Heart J. 2005; 26: 1666-1675.
17. Bomma C, Rutberg J, Tandri H, et al. Misdiagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. J Cardiovasc Electrophysiol. 2004; 15: 300-306.
18. Desmet WJ, Adriaenssens BF, Dens JA. Apical ballooning of the left ventricle: first series in white patients. Heart. 2003; 89: 1027-1031.
19. Gianni M, Dentali F, Grandi AM, Sumner G, Hiralal R, Lonn E. Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. Eur Heart J. 2006; 27: 1523-1529.
20. Tabib A, Loire R, Miras A, et al. Unsuspected cardiac lesions associated with sudden unexpected perioperative death. Eur J Anaesthesiol. 2000; 17: 230-235.
21. Denney SD, Lakkireddy DR, Khan IA. Long QT syndrome and torsade de pointes in transient left ventricular apical ballooning syndrome. Int J Cardiol. 2005; 100: 499-501.
22. Antoniades L, Tsatsopoulou A, Anastasakis A, et al. Arrhythmogenic right ventricular cardiomyopathy caused by deletions in plakophilin-2 and plakoglobin (Naxos disease) in families from Greece and Cyprus: genotype-phenotype relations, diagnostic features and prognosis. Eur Heart J. 2006; 27: 2208-2216.
23. Protonotarios NI, Tsatsopoulou AA, Gatzoulis KA. Arrhythmogenic right ventricular cardiomyopathy caused by a deletion in plakoglobin (Naxos disease). Card Electrophysiol Rev. 2002; 6: 72-80.
24. Frances R, Rodriguez Benitez AM, Cohen DR. Arrhythmogenic right ventricular dysplasia and anterior polar cataract. Am J Med Genet. 1997; 73: 125-126.