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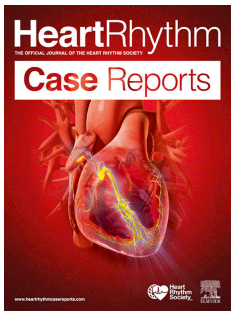

A case of Dressler's Syndrome after pulsed field ablation for atrial fibrillation.

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Title: A case of Dressler's Syndrome after pulsed field ablation for atrial fibrillation.

Short title: PFA-induced Dressler's Syndrome.

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Conflicts of interest

Jaspal S Gill declares no of conflict of interests
Mark M Gallagher declares no conflict of interests
Viral Sagar declares no conflict of interests
Manav Sohal declares no conflict of interests
Mark Specterman declares no conflict of interests
Lisa WM Leung declares no conflict of interests

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Introduction

Catheter ablation for atrial fibrillation (AF) is superior to pharmacological rhythm control in certain patient populations, and there is evidence that early rhythm control improves patient outcomes and results in decreased disease progression [1]. The safety of AF ablation should be the priority with advances proposed in recent years ranging from refining the method and energy delivery of ablation to various device-related strategies to improve esophageal protection.

Pulsed field ablation (PFA) has been presented as a non-thermal method of ablation, with high voltage electrical pulse waveform energy delivery being cardiomyocyte tissue-selective. The mechanism of irreversible cellular membrane disruption is by electroporation leading to cellular apoptosis [2]. This is in contrast to the tissue necrosis caused by radiofrequency and cryo-ablation energies. The cited safety advantage of PFA is tissue selectivity, sparing of the esophagus and phrenic nerve in addition to shorter left atrial dwell times [2]. Due to the rapid adoption of PFA since its introduction, operators are encouraged to report any PFA related adverse events as experience is gained. This case report is to our knowledge the first to describe Dressler's Syndrome induced by PFA for AF ablation.

Case Report

A 55-year-old gentleman presented with symptomatic persistent AF and evidence of AF associated cardiomyopathy. He underwent elective direct current cardioversion (DCCV) 4 months after the clinical diagnosis and onset of symptoms. The left ventricular function normalized after restoration of sinus rhythm. Left atrial volume index via echocardiographic evaluation was 37ml/m^2 in sinus rhythm. The baseline ECG demonstrated a chronic right bundle branch block (RBBB). He was listed for urgent elective AF ablation given the diagnosis of tachycardia mediated cardiomyopathy.

He had a past medical history of hypertension, hypercholesterolemia, non-alcoholic fatty liver, and a raised body mass index (35.9kg/m^2; weight 113kg). His medications were apixaban 5mg twice daily, bisoprolol 1.25mg once daily, atorvastatin 20mg at night, ramipril 1.25mg once daily, spironolactone 12.5mg once daily.

The patient attended for elective ablation for persistent AF in November 2024. The procedure was performed under general anaesthesia with transoesophageal echo (TOE) guidance. The patient was in AF at the outset and a DCCV was performed before mapping the left atrium under pacing from a decapolar catheter placed in the coronary sinus. A single transeptal puncture was performed using a Brockenbrough-1 Needle (BRK-1, Abbot Medical) guided by fluoroscopy and TOE. Electroanatomic mapping was performed utilizing the Orion multipolar catheter and Rhythmia^{TM} mapping system (Boston Scientific). There was normal pulmonary venous anatomy. Normal left atrial voltages were observed, and the volume was calculated at 156 ml. Pulmonary vein isolation was performed using pulsed field ablation with a pentaspline catheter (Farawave, Boston Scientific). A total of 34 applications were administered. The standard 32 applications (4 each of basket and flower configurations to each vein) and 2 extra applications in flower configuration to the left sided veins more anteriorly at the carina. Pulsed field lesions were delivered as per proprietary waveforms, with minimum time between lesions dictated by the proprietary Farapulse signal generator. Left Atrial dwell time was 72 minutes and activated clotting time (ACT) target was 350s. ACT values during left atrial dwell between 300-375s were achieved, with no measurements significantly above ACT target and a single measurement at 241s. Acutely successful pulmonary vein isolation was confirmed by mapping with the Farawave catheter. There was no effusion visible on TOE at the end of the procedure and no significant pericardial fat was identified. No acute complications were identified, and he was discharged home the next day in sinus rhythm.

4 days post-ablation, the patient presented to the emergency department with pleuritic central chest pain without accompanying symptoms. Examination was unremarkable and ECG showed sinus rhythm with RBBB as per baseline. Blood tests showed a troponin T of 252ng/L (Normal range <16), D-dimer of 69ng/L (normal range 50-300), and Haemoglobin 139g/L (120-170), Creatinine 67µmol/L (eGFR >90), and C-reactive Protein (CRP) of 16mg/L (Normal range <5). Bedside echocardiography showed

preserved biventricular function and trivial pericardial effusion. The Troponin T level was down trending from the value on discharge post ablation (281ng/L). He was discharged from the emergency department with a presumed diagnosis of procedure-related pericarditis. The patient was prescribed a tapering course of colchicine and ibuprofen with a proton pump inhibitor for gastroprotection.

At day 11 post ablation the patient re-presented with symptoms of general malaise, fevers with rigors and night sweats. The CRP was now 138mg/L. There was now a significantly increased circumferential pericardial effusion at 1.6cm maximum depth without echocardiographic features of tamponade. He was admitted to the cardiology ward and the suspicion of esophago-pericardial fistula prompted a cardiac gated computed tomography (CT) scan of the thorax (figure 1). This revealed the moderate sized pericardial effusion and a small left sided pleural effusion but no evidence to support cardiac perforation or atrio-esophageal fistula. Respiratory polymerase chain reaction (PCR) swabs did not detect any pathogen. Urinalysis and microscopy were negative. Blood cultures were negative for any growth.

Serial echocardiography over the subsequent days demonstrated further increase in size of the pericardial effusion to a maximum of 2.6cm with features of increased tricuspid and mitral inflow doppler respiratory variability but no evidence of overt chamber collapse (figure 2).

The patient was started on amoxicillin/clavulanic acid because of ongoing fevers, pleural effusion, and consequent possibility of a lower respiratory tract infection. A pericardiocentesis was considered but given the lack of haemodynamic compromise or concerning echo features, it was deemed unnecessary. Blood cultures repeatedly found no growth. Troponin T levels were never elevated beyond the acute post ablation period. The CRP remained elevated at 154mg/L by day 12 post ablation when the patient's presentation was treated as a post ablation Dressler's syndrome recalcitrant to non-steroidal/colchicine therapy and a switch was made to oral corticosteroid therapy with prednisolone 40mg daily. Liver function tests were found to be transiently deranged (peak ALT 258 U/L, GGT 357 U/L, ALP 430 U/L, Bilirubin 5 µmol/L)) and liver ultrasound demonstrated hepatic steatosis, as previously known (figure 3). The transient derangement in LFTs was attributed in part to

amoxicillin/clavulanic acid antibiotics and also a systemic inflammatory response. Autoantibodies showed a weakly positive anti-nuclear antibody (ANA - 1/80 Speckled pattern), negative smooth muscle antibody, negative mitochondrial antibody, and negative double stranded DNA. Immunoglobulins were recorded in the normal range and no paraprotein was detected on plasma electrophoresis. Alpha-1 anti-trypsin levels were mildly elevated at 2.1g/L (Normal range 1.1-2.1g/L) consistent with a systemic inflammatory response. Hepatitis A, B and C serology were negative.

Corticosteroid therapy was met with absence of further fevers, down trending inflammatory markers to normal, and a significant decrease in effusion size when assessed with echocardiography. The patient was subsequently discharged on day 16 post ablation. A follow-up echo 2 weeks post discharge (day 30 post ablation) showed a trivial amount of pericardial fluid, and the CRP was normal. In all corticosteroid therapy was weaned after 1 week of full dose by then 10mg per week over 4 weeks. He has been off all anti-inflammatory therapy since stopping corticosteroid therapy on day 47 post ablation. He now remains well and has maintained sinus rhythm off anti-arrhythmic drugs since ablation. A further transthoracic echo performed 159 days post discharge showed no pericardial effusion.

Discussion

To our knowledge this is the first recorded case of Dressler's Syndrome post PFA ablation for the treatment of atrial fibrillation.

Post-cardiac injury syndrome (PCIS) is a grouping of autoimmune mediated responses to cardiac tissue necrosis and encompasses syndromes such as Dressler's. Inflammation of both the pericardium, myocardium, and pleura may be present, and they occur after a variable latency period post insult, on average 4-5 days. This inflammatory process typically occurs after myocardial infarction without revascularization, post pericardiotomy, or post trauma, reflecting a cascade of events from the initial ischaemic tissue necrosis. In this patient, the clinical symptoms of

fevers, sweats and chest pain mounted >5 days post ablation, indicating a delayed onset, which would be in line with the definition of Dressler's.

Dressler's has been reported after radiofrequency, cryoballoon or hybrid ablation for AF [3]. Some data suggests that the more extensive the ablation performed, the higher the risk of PCIS, although there are case reports of its occurrence in very limited ablation, suggesting that even focal cardiac tissue necrosis can cause this systemic reaction. [4]

In our case, there was a standard set of PFA applications with no procedural anomalies. It is theoretically plausible that the patient's presentation could be related to procedural related micro-perforation with slow bleeding into the pericardial space, however the significantly raised inflammatory biomarkers observed and its prompt resolution with steroids is more suggestive of an inflammatory response. It had previously been believed that the lack of thermal effect of PFA and the mechanism of electroporation led to the process of apoptotic cell death rather than necrosis and that this led to a dampened inflammatory response to ablation [5]. This case is significant as it supports the wider recognition that although PFA is considered to be relatively tissue-specific, there remains the possibility of a thermal effect and therefore some degree of indiscriminate tissue necrosis. It is not yet known if this means that the risk of esophageal injury still exists, though the data suggest the risk to be very low as to our knowledge there have been no reported cases in the largest series to date [6].

There is a possibility that PFA could cause direct pericardial injury and thereby activate pro-inflammatory pathways related to pericardial fat. Activation or mediation of pericardial fat inflammation could occur due to ablation of adjacent myocardial tissue, and give rise to this patient's presentation, however, there was an absence of significant pericardial fat identified on echo. Direct injury should cause a more acute or immediate inflammatory reaction but, in this case, it was delayed, similar to Dressler's. Underpinning the exact pathophysiological mechanisms would be difficult without further clinical research or investigation of similar cases if or when they arise.

This case shows that Dressler's syndrome can occur after AF ablation by PFA. This complication adds to the other reported PFA complications such as post-procedure neurological events, acute cardiac tamponade, delayed phrenic nerve palsy and haemolysis requiring renal support. This case underscores the need for more data or a detailed review to determine if patient-specific or technology-specific factors, such as the number of applications, tissue contact, or waveform of the PFA system, could increase the risk of direct or indirect collateral injury.

Teaching Points

1. Pulsed field ablation can cause post-cardiac injury syndrome (PCIS) in a delayed setting similar to Dressler's Syndrome, suggesting that PFA may cause clinically relevant thermal effects and tissue necrosis.
2. Thorough investigations including a CT thorax with contrast and serial echocardiography remain important to rule out more extensive injury such as esophago-pericardial fistulas.
3. Medical management is similarly effective compared to treatment of Dressler's Syndrome due to other causes.

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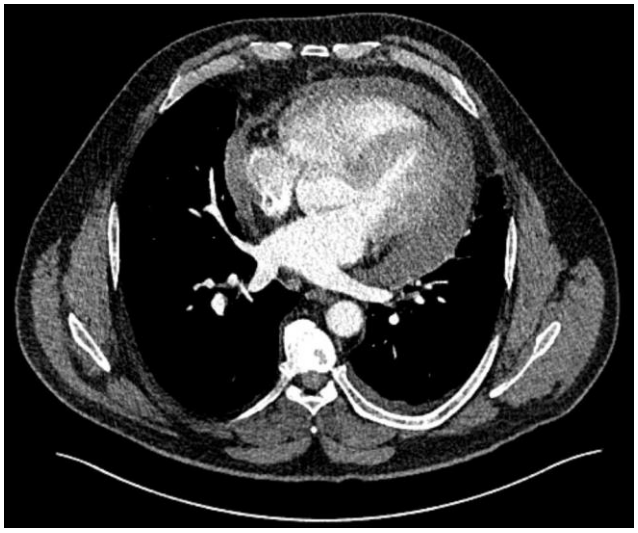
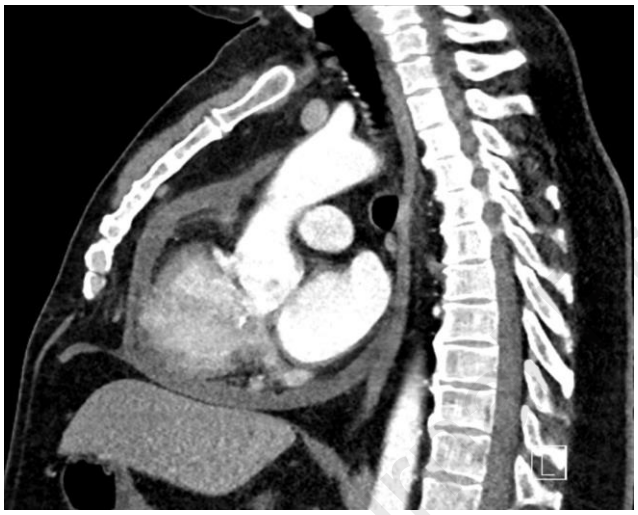
Figure legends:

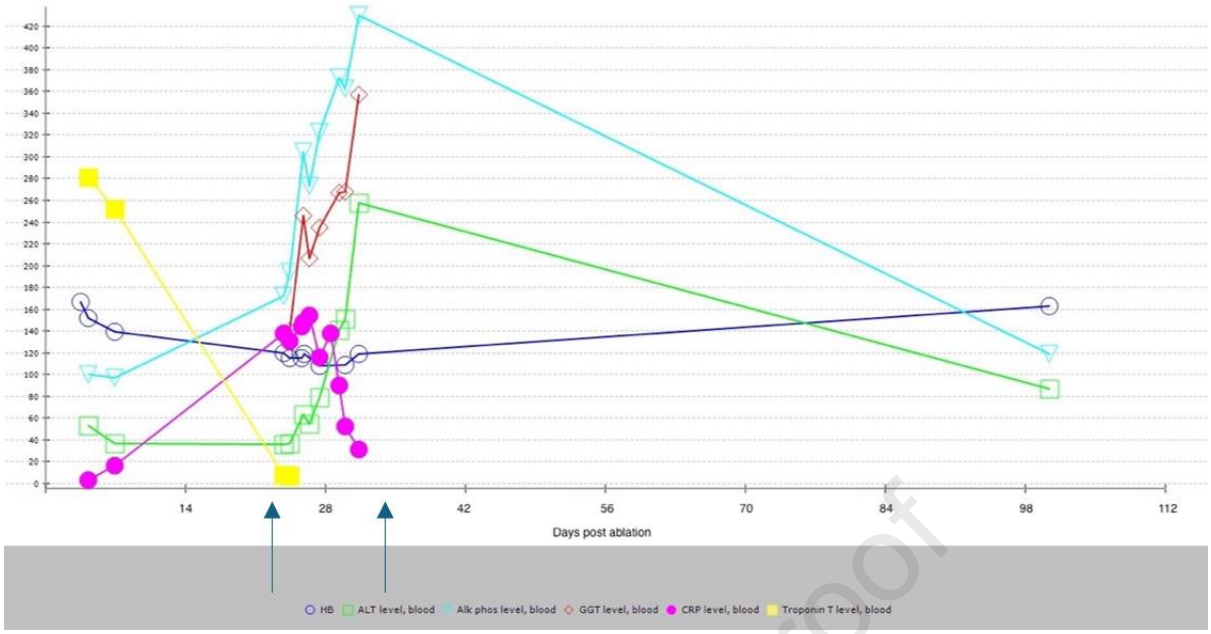
Figure 1: *Transverse plane (upper) Image of contrast enhanced CT showing moderate circumferential pericardial effusion measuring 15-30 Hounsfield units. There is a small left sided pleural effusion also seen. No evidence of contrast extravasation was demonstrated. Lower panel – a sagittal plan image showing circumferential pericardial effusion, contrast in the left atrium and no demonstrable communication with the esophagus.*

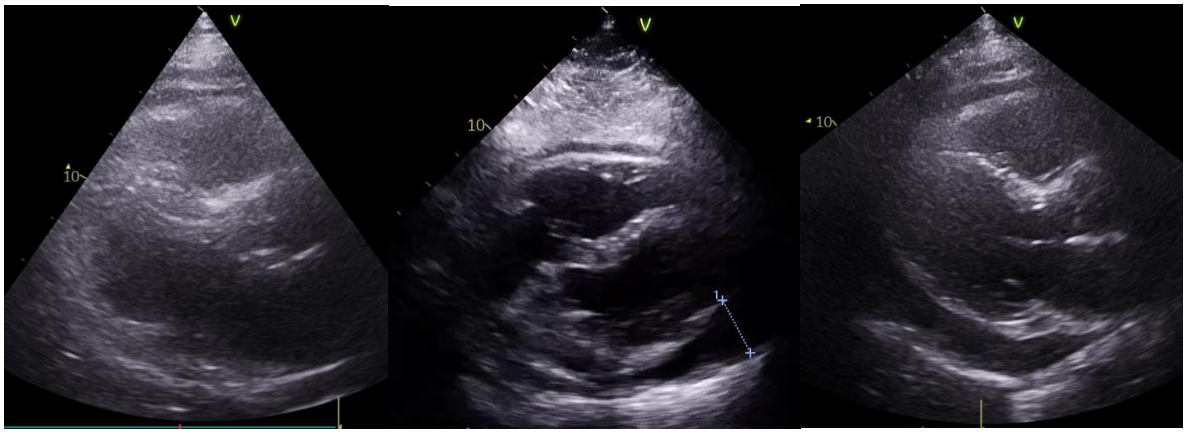
Figure 2: *Blood result trends over time demonstrating acute change and normalization. The arrows indicate when the patient was admitted and discharged*

Figure 3: *Transthoracic ECHO images showing progression of pericardial effusion. The leftmost image is a parasternal long axis view at Day 4. The middle image is a subcostal view at day 8. The rightmost image is a parasternal long axis view at day 14 with circumferential pericardial effusion measured at a max of 2.6cm. No significant pericardial fat was demonstrated on these echo images.*









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