A game of light and shadow...

Maria Touloupaki
Clinical Research Fellow in Cardiomyopathies
Royal Brompton and Harefield NHS Foundation Trust, London
NOTHING TO DECLARE
Past Medical History

- 32-year old, male

- PMH: Raynaud’s phenomenon

- Episodes of dizziness lasting up to 10 secs and palpitations occasionally. No syncopal or presyncopal episodes.

- Episodes of chest pain radiating up to his left shoulder, mainly post exertion that could last up to 30 mins.

- Persistent Troponin I rise (at the range of 130-230 ng/L, normal range <40 ng/L)

- Coronary angiogram: normal coronary arteries
24 h ECG Holter monitors

- **24h Holter monitor –November 2014 (carvedilol 12.5mg bd):**
  Sinus rhythm throughout, 36–120 bpm. In total 2797 (3.5%) PVCs (isolated, couplets, bigeminy). No significant atrial arrhythmias. No pauses. No symptoms reported.

- **48h Holter monitor -March 2016 (propranolol 80mg + 40mg):**
  Sinus rhythm throughout, 40 – 141 bpm. In total 6641 (3.6%) polymorphic PVCs (isolated, couplets, bigeminy, trigeminy). No significant atrial arrhythmias- occasional mainly isolated SVEs. No pauses. No symptoms reported.

- **24h Holter monitor -August 2017 (bisoprolol 5mg):**
  Sinus rhythm throughout, 50 – 135 bpm. 650 monomorphic PVCs (isolated, couplets). No atrial arrhythmias. No pauses. No symptoms reported in the patient’s diary.
Medication

- Bisoprolol 7.5mg od
- Ramipril 1.25mg od
Cardiac MRI

- **Left ventricle:**
  - Mildly dilated (EDV 110ml/m², ESV 53ml/m²) with a mildly reduced EF 52%.
  - Global mild hypokinesia with severe hypokinesia in the apical anterolateral wall

- **Right Ventricle:**
  - Moderately dilated (EDV 140ml/m², ESV 82ml/m²) with mildly reduced RVEF 41%.
  - Dysynchronous RV with micro-aneurysms on the RV free wall. Dilated RVOT.

- **On the Late Gadolinium Enhancement imaging:** fibrosis of the basal and mid inferior wall extending into the RV free wall as well as mid-wall fibrosis of the mid LV septum and the apical lateral wall.
CMR - LGE
Would you request any further investigations?
18- FDG PET/CT scan

- Intense FDG uptake in mid to apical interventricular septum (SUV max of 8.0)
- Moderately increased uptake in the basal lateral wall (SUV max of 5.8)
- Focal increased uptake in the rest of the lateral wall and the papillary muscle (SUV max of 5.2)
- No abnormal uptake in other heart chambers.

- No other sites of abnormal FDG uptake are noted in the nodes, lungs, liver, spleen or in the skeleton. No significant incidental findings on the CT component of this study.

**Conclusion** There is evidence of active myocardial inflammation in the mid to apical IVS, basal lateral wall and in the papillary muscle of the LV myocardium which can explain increased troponin levels. There is no evidence of inflammation in other chambers of heart, especially in the RV. There are no other sites of inflammation in the imaged body.
18- FDG PET/CT scan
18F- FDGPET SCAN...how does it work?

- The heart is capable of switching between substrates for energy production as a response to various stimuli.

- Normal myocytes utilize glucose as one of their main energy sources. Active inflammatory cells have high glycolytic activity to satisfy their large energy demands.

- The idea is to shift myocardial metabolism to fatty acid and suppress glucose utilization and 18F-FDG uptake by the normal myocardium.

- 3 approaches have been tried: prolonged fasting (5-12h -> 18h), dietary modification (high-fat, high-protein, low-carbohydrate diet) and IV administration of unfractionated heparin (UFH) - activates lipoprotein and hepatic lipases -> increasing plasma free fatty acids -> reduction in glucose consumption of normal myocytes.

PET SCAN

- Patient preparation of high importance to avoid false positive results

- 18F-FDG accumulates in active lesions where inflammatory cells utilize glucose as an energy source.

- After crossing the cellular membrane via glucose transporters, both 18F-FDG and glucose are phosphorylated by hexokinase.

- While glucose is further metabolized, the phosphorylated 18F-FDG remains trapped in the cells and can be imaged.
CMR / 18- FDG PET
DIFFERENTIAL DIAGNOSIS

- Sarcoidosis
- Myocarditis
- Infiltrative disease
- Dilated Cardiomyopathy
- Arrhythmogenic Cardiomyopathy
- ...

...
Family history

- His maternal grandfather died suddenly at 38yo whilst running and the post-mortem histology showed significant scarring of the heart (no further details available).

- His mother (diagnosed with dilated cardiomyopathy) died waiting for transplantation aged 48, having ICD implanted. The post mortem examination suggested Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC).

- His brother has Arrhythmogenic Cardiomyopathy

- A novel DSP mutation was detected in both brothers.
Arrhythogenic Right Ventricular Cardiomyopathy

- Rare inherited genetic disorder (1:1000 to 1:5000)
- Fibrofatty replacement of the RV myocardium -> Electrical and structural abnormalities
- LV involvement occurs in >50% of patients
- Palpitations, syncope, VT and SCD usually develop between 2\textsuperscript{nd} - 4\textsuperscript{th} decade of life.
- Important cause of SCD in athletes and young adults.
- Mutations in genes encoding desmosomal proteins
- Autosomal dominant inheritance pattern in most cases

<table>
<thead>
<tr>
<th>Gene</th>
<th>Encoded Protein</th>
<th>Subcellular Localization</th>
<th>Chromosomal Locus</th>
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</thead>
<tbody>
<tr>
<td>JUP</td>
<td>Junction plakoglobin</td>
<td>Desmosome</td>
<td>17q21.2</td>
</tr>
<tr>
<td>DSP</td>
<td>Desmoplakin</td>
<td>Desmosome</td>
<td>6p24.3</td>
</tr>
<tr>
<td>PKP2</td>
<td>Plakophilin-2</td>
<td>Desmosome</td>
<td>12p11.21</td>
</tr>
<tr>
<td>DSG2</td>
<td>Desmoglein-2</td>
<td>Desmosome</td>
<td>19q12.1</td>
</tr>
<tr>
<td>DSC2</td>
<td>Desmocollin-2</td>
<td>Desmosome</td>
<td>18q12.1</td>
</tr>
<tr>
<td>TMEM43</td>
<td>Transmembrane protein 43 (lumina)</td>
<td>Nuclear envelope</td>
<td>3p25.1</td>
</tr>
<tr>
<td>LMNA</td>
<td>Lamin A/C</td>
<td>Nuclear envelope</td>
<td>1q22</td>
</tr>
<tr>
<td>DES</td>
<td>Dsmin</td>
<td>Intermediate filament</td>
<td>2q35</td>
</tr>
<tr>
<td>CTNNA3</td>
<td>Alpha-T-catenin</td>
<td>Area composita</td>
<td>10q21.3</td>
</tr>
<tr>
<td>PLN</td>
<td>Phospholamban</td>
<td>SERCA</td>
<td>6q22.31</td>
</tr>
<tr>
<td>TGFBR3</td>
<td>Transforming growth factor-3</td>
<td>Growth factor</td>
<td>14q24.3</td>
</tr>
<tr>
<td>TTN</td>
<td>Titin</td>
<td>Sarcomere</td>
<td>2q31.2</td>
</tr>
<tr>
<td>SCN5A</td>
<td>Sodium voltaged-gated channel alpha subunit 5 (Na\textsubscript{1.5})</td>
<td>Sodium channel</td>
<td>3p22.2</td>
</tr>
<tr>
<td>CDH2</td>
<td>Caderhin C</td>
<td>Area composita</td>
<td>18q12.1</td>
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ARVC- Pathophysiology

- Mechanical and electrical uncoupling

- Genetically defective desmosomes → disruption of intercellular junctions, with myocyte detachment and cell death

- A parallel pathogenic mechanism involves the canonical Wnt–β-catenin signaling pathway. Plakoglobin translocation to the nucleus→ antagonizes the effects of β-catenin→ suppresses Wnt–β-catenin signaling → gene transcriptional switch from myogenesis to adipogenesis, fibrogenesis.

- **Connexome:** Desmosomes, sodium channels and gap-junction proteins interact synergistically to regulate adhesion, excitability and coupling of myocytes

- Loss of expression of desmosomal proteins → gap-junction remodeling → decrease in the amplitude and kinetics of the sodium current→ potentially fatal arrhythmias.
Arrhythmogenic Cardiomyopathy

- The hallmark of AC is replacement of the ventricular myocardium by fibrofatty tissue.

- Patchy inflammatory infiltrates (mainly T lymphocytes) are often observed in association with dying myocytes, suggesting that the pathologic process may be immunologically mediated.

- The fibrofatty scar tissue progresses from the epicardium -> endocardium.

- Typically localized in the inflow tract (subtricuspid region), outflow tract (infundibular region), and apex - “triangle of dysplasia”.

- In the typical form of ARVC, the LV is affected to a lesser extent; however, there are disease variants with equivalent or even predominant LV involvement usually limited to the subepicardium or midmural layers of the free wall.

Corrado et al Circ Res. 2017;121:784-802
Histology – Inflammation

- **Myocardial inflammation** may be seen in **up to 75% of hearts at autopsy**. It has been associated to **worse structural changes** and it probably plays a role in triggering **ventricular tachyarrhythmias**.

- **Nobody knows** if inflammation is a **reactive phenomenon to cell death**, **or the consequence of an infection or immune mechanism**.

- **Viruses** have been detected in the myocardium of some ARVC patients and have been claimed to support an infective etiology of the disease but it is most likely that either viruses are **innocent bystanders** or myocardial **cell degeneration may serve as a milieu favouring viral attachment**.

- **The role of inflammation remains largely undefined**. Inflammatory infiltrates may extend injury to previously unaffected regions of the myocardium, a process associated with **episodic exacerbations** – **“hot phases”** may characterized by chest pain and life-threatening arrhythmias. Such a clinical picture may be misdiagnosed as myocarditis or MI with normal coronary arteries.

Gaetano Thiene, Orphanet Journal of Rare Diseases 2007, 2:45.
<table>
<thead>
<tr>
<th>Category</th>
<th>Major Criteria</th>
<th>Minor Criteria</th>
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<tbody>
<tr>
<td>Global or regional dysfunction and structural alteration†</td>
<td>Regional RV akinesia, dyskinesia, or aneurysm and one of the following (end diastole): PLAX RVOT ≥32 mm (±19 mm per square meter when corrected for body-surface area), PSAX RVOT ≥36 mm (±21 mm per square meter when corrected for body-surface area), or fractional area change of ≥33%</td>
<td>Regional RV akinesia or dyskinesia and one of the following (end diastole): PLAX RVOT 29 to &lt;32 mm (16 to &lt;19 mm per square meter when corrected for body-surface area), PSAX RVOT 32 to &lt;36 mm (18 to &lt;21 mm per square meter when corrected for body-surface area), or fractional area change of 34 to 40%</td>
</tr>
<tr>
<td>On two-dimensional echocardiography</td>
<td>Regional RV akinesia or dyskinesia or dysynchronous RV contraction and one of the following: ratio of RV end-diastolic volume to body-surface area ≥110 ml per square meter (male patients) or ≥100 ml per square meter (female patients), or RV ejection fraction ≤40%</td>
<td>60 to 75% residual myocytes, on morphometric analysis (or 50 to 65%, if estimated) and fibrous replacement of the RV free-wall myocardium, with or without fatty replacement of tissue, in at least one endomyocardial-biopsy sample</td>
</tr>
<tr>
<td>On MRI</td>
<td>Regional RV akinesia, dyskinesia, or aneurysm</td>
<td></td>
</tr>
<tr>
<td>Tissue characterization</td>
<td>&lt;60% residual myocytes on morphometric analysis (or &lt;50%, if estimated) and fibrous replacement of the RV free-wall myocardium, with or without fatty replacement of tissue, in at least one endomyocardial-biopsy sample</td>
<td></td>
</tr>
<tr>
<td>Repolarization abnormalities</td>
<td>Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in patients older than 14 yr of age (in the absence of complete right bundle-branch block, QRS ≥120 msec)</td>
<td>Inverted T waves in leads V1 and V2 in patients older than 14 yr of age (in the absence of complete right bundle-branch block) or in V6, V5, or V6; inverted T waves in leads V1, V2, V3, and V4 in patients older than 14 yr of age (in the presence of complete right bundle-branch block)</td>
</tr>
<tr>
<td>Depolarization and conduction abnormalities</td>
<td>Epsilon wave (reproducible low-amplitude signals from end of QRS complex to onset of the T wave) in the right precordial leads (V1, V2, and V3)</td>
<td>Late potentials on signal-averaged ECG in at least one of three parameters in the absence of a QRS complex duration of ≥110 msec on the standard ECG; filtered QRS complex duration, ≥114 msec; duration of terminal QRS complex &lt;40 μV (low-amplitude signal duration), ≥38 msec; root-mean-square voltage of terminal 40 msec, ≥20 μV; terminal activation duration of QRS complex, ≥55 msec, measured from the nadir of the S wave to the end of the QRS complex, including R' in V1, V2, and V3, in the absence of complete right bundle-branch block</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>Nonsustained or sustained ventricular tachycardia with a left bundle-branch block and superior axis pattern (negative or indeterminate QRS complex in leads II, III, and aVF and positive QRS complex in lead aVL)</td>
<td>Nonsustained or sustained ventricular tachycardia of RV outflow configuration with a left bundle-branch block and inferior axis pattern (positive QRS complex in leads II, III, and aVF and negative QRS complex in lead aVL) or unknown axis, or &gt;500 ventricular extrasystoles per 24 hr (on Holter monitoring)</td>
</tr>
<tr>
<td>Family history</td>
<td>ARVC confirmed in a first-degree relative who meets current task-force criteria, ARVC confirmed pathologically at autopsy or surgery in a first-degree relative, or identification of a pathogenic mutation categorized as associated or probably associated with ARVC in the patient under evaluation;</td>
<td>History of ARVC in a first-degree relative in whom it is not possible or practical to determine whether current task-force criteria are met, premature sudden death (at &lt;35 yr of age) due to suspected ARVC in a first-degree relative, or ARVC confirmed pathologically or by current task-force criteria in a second-degree relative;</td>
</tr>
</tbody>
</table>
Multidisciplinary team meeting

- PET scan and the persistent troponin elevation possibly suggest an inflammatory cardiomyopathy.

- A possible explanation can be a coexisting myocarditis, suspecting that the patient’s presentation may be beyond the inflammatory response involved in ARVC and of course we would like to rule out sarcoidosis.

- A **cardiac biopsy** would be indicated.
RV endomyocardial biopsy

- **Fibrofatty replacement of cardiomyocytes.** Multiple islands of remaining dystrophic cardiomyocytes (hyperchromatic small nuclei). Surrounding the islands of myocytes is fibrosis and adipose tissue.

- In the interstitium occasional lymphocytes are noted, however NO overt active inflammation, giant cells or eosinophils are noted. No evident lymphocytic aggregates.

- No evidence of acute ischaemic damage.

- Congo red and Perles staining shows NO evidence of deposition of amyloid or iron. PAS shows NO evidence of storage disease

- The histology is consistent with a diagnosis of **ARVC**. No evidence of sarcoidosis or myocarditis. No extensive significant inflammation.
Would you offer the patient an ICD?
2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death

Proposed Scheme for Prognostic Stratification of Patients with ARVC According to the Clinical Presentation.

### Major Arhythmic Events
- Cardiac arrest due to ventricular fibrillation
- Sustained ventricular tachycardia

### Major Risk Factors
- Unexplained syncope
- Nonsustained ventricular tachycardia
- Severe right or left ventricular dysfunction

#### Minor Risk Factors
- Proband status, male sex
- Frequent PVBs (≥1000/24 hr)
- Inducibility on electrophysiological study
- Extent of negative T waves
- Amount of right ventricular fibrofatty scarring
- Multiple desmosomal gene mutations

### No Events or Risk Factors
- Healthy gene carriers
- Patients with definite ARVC
### Risk stratification and management of patients with arrhythmogenic right ventricular cardiomyopathy

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoidance of competitive sports is recommended in patients with ARVC.</td>
<td>I</td>
<td>C</td>
<td>388</td>
</tr>
<tr>
<td>Beta-blockers titrated to the maximally tolerated dose are recommended as the first-line therapy to improve symptoms in patients with frequent VT.</td>
<td>I</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>ICD implantation is recommended in patients with a history of aborted SCD and haemodynamically poorly tolerated VT.</td>
<td>I</td>
<td>C</td>
<td>389</td>
</tr>
<tr>
<td>Amiodarone should be considered to improve symptoms in patients with frequent PVC or NSVT who are intolerant of or have contraindications to beta-blockers.</td>
<td>IIa</td>
<td>C</td>
<td>390, 391</td>
</tr>
</tbody>
</table>

ICD implantation should be considered in ARVC patients who have haemodynamically well-tolerated sustained VT, balancing the risk of ICD therapy, including long-term complications, and the benefit for the patient.

ICD implantation may be considered in patients with one or more recognized risk factors for VA in adult patients with a life expectancy > 1 year following detailed clinical assessment that takes into account the lifelong risk of complications and the impact of an ICD on lifestyle, socioeconomic status and psychological health.

Invasive EPS with PVS may be considered for stratification of SCD risk.
35-year-old man with **Arrhythmogenic cardiomyopathy**
- Palpitations and dizziness, GI viral infection, 2 weeks prior to presentation
- ECG: T wave inversion V1-V2
- 24h Holter monitor: 1000 multifocal VEs
- CMR: RV apical aneurysm, no LGE
- No family history of Cardiomyopathy
- Genetic test: heterozygous for pathogenic mutation in PKP2 gene

Persistent high troponin 150-250 ng/L **BUT**

No evidence of cardiac inflammation on PET/CT: Normal myocardial perfusion with LVEF 70%. No significant perfusion abnormality identified in the RV. No evidence of the abnormal metabolic activity in the RV or in rest of the myocardium to suggest inflammation in the context of ARVC.
ARVC...lower risk?...different management?
Take home messages...

▪ This case demonstrates troponin rise and FDG cardiac uptake in a patient diagnosed with ARVC without evidence of sarcoidosis or myocarditis.

▪ PET/CT plays valuable role in inflammatory heart conditions diagnosis. Its significance in Arrhythmogenic Cardiomyopathy is not clear.

▪ The myocardial activity noted in PET may be linked to increased burden of arrhythmia. It may suggest a “hot phase” of the disease.

▪ Inflammation has not been imaged and quantified adequately in ARVC and its significance in management and prognosis is uncertain...
ARVC
And the story goes....

- 26yo female, 3 day Hx of dizziness and palpitations, occasional chest pain and Ventricular Tachycardia

- Elevated troponin >9000ng/L.

- CMR: RV dilatation with severe biventricular systolic dysfunction and subendocardial late enhancement

- **PET: significant FDG uptake in patchy distribution within the left ventricular myocardium.** No significant FDG uptake is noted in the RV myocardium or in the other chambers of heart. No significant FDG uptake is noted in the lungs, liver, spleen, bones or in the other imaged organs.

- Single chamber ICD implantation

- **Endomyocardial biopsy Right Ventricle: giant cell myocarditis.**

- Treated with IV methylprednisolone and RATG (rat antithymocyte globulin)

- Serial Scans showed **biventricular function improvement**
Giant cell myocarditis mimicking ARVC
Among patients with suspected CS, combining CMR and PET provides complementary value for estimating the likelihood of CS and guiding patient management.

**Combine Use of Cardiac MRI and PET for Suspected Cardiac Sarcoisosis**

- **Cardiac MRI**
  - **- LGE**
  - Consider ICD

- **FDG PET**
  - **When CMR is inconclusive or high suspicious of CS remains**

- **No FDG uptake**
  - Possible scar from burnt out CS
  - No role for immunosuppressive therapy

- **Abnormal FDG Uptake**
  - Myocardial inflammation
  - Consider immunosuppressive therapy