THE NORTHERN HOSPITAL

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPAHY

"The Spinet Player", oil on canvas, Thomas Wilmer Dewing, 1902

"Oh, Starbuck! It is a mild, mild wind, and a mild looking sky. On such a day - very much such sweetness as this - I struck my first whale - a boy - harpooner of eighteen! Forty-forty-forty years ago! - ago! Forty years of continual whaling! Forty years of privation, and peril, and storm-time! Forty years on the pitiless sea! For forty years has Ahab forsaken the peaceful land, for forty years to make war on the horrors of the deep! Aye and yes, Starbuck, out of those forty years I have not spent three ashore.

When I think of this life I have led, the desolation of solitude it has been, the masoned, walled-town of a Captain's exclusiveness, which admits but small entrance to any sympathy from the green country without - oh, weariness! Heaviness! Guinea coast slavery of solitary command! - When I think of all this, only half-suspected, not so keenly known to me before - and how for forty years I have fed upon dry salted fare-fit emblem of the dry nourishment of my soul - when the poorest landsman has had fresh fruit to his daily hand, and broken the world's fresh bread to my mouldy crusts-

away, whole oceans away, from that young girl-wife I wedded past fifty, and sailed for Cape Horn the next day, leaving but one dent in my marriage pillow - wife? Wife? Rather a widow with her husband alive.

Aye, I widowed that poor girl when I married her, Starbuck; and then, the madness, the frenzy, the boiling blood and the smoking brow, with which, for a thousand lowerings old Ahab has furiously, foamingly chased his prey - more a demon than a man! - aye, aye! What a forty years' fool - fool - old fool, has old Ahab been! Why this strife of the chase? Why weary, and palsy the arm at the oar, and the iron, and the lance? How the richer or better is Ahab now? Behold. Oh Starbuck! Is it not hard, that with this weary load I bear, one poor leg should have been snatched from under me? Here, brush this old hair aside; it blinds me that I seem to weep. Locks so grey did never grow but from out some ashes! But do I look very old, so very, very old, Starbuck. I feel deadly faint, bowed, and humped, as though I were Adam, staggering beneath the piled centuries since Paradise. God! God! God! - crack my heart! - stave my brain-mockery! Mockery! Bitter biting mockery of grey hairs, have I lived enough joy to wear ye, and seem and feel thus intolerably old? Close! Stand close to me, Starbuck, let me look into a human eye. No, no stay on board! - lower not when I do, when branded Ahab gives chase to Moby Dick. That hazard shall not be thine. No, no! Not with the far away home I see in that eye!"

Herman Melville, Moby Dick, 1851

In the late 1790s and early 1800s, the small island of Nantucket, just south of Cape Cod, Massachusetts, New England was the epicentre of the world's Whaling industry. Herman Melville in his immortal masterpiece "Moby Dick" exclaimed, "Two thirds of this terraqueous globe are the Nantucketer's. For the sea is his; he owns it, as Emperors own empires". Nantucket became for a brief time, the world's leading producer of lamp oil and candles. These products were derived from Whales. A number of merchants needless to say became extremely wealthy. Whaling however for most was a bitterly hard, dangerous and above all, lonely life. Many would be lost at sea without a trace; many would have their lives shortened by hardship, disease and injury. Most tragically in many ways was the separation of husbands from wives that Whaling entailed. No sooner had a young man married; when he then set out on his career of Whaling, barely seeing his wife or family for years at a time.

In Moby Dick, Captain Ahab, stands on the deck of his Whaler, it is a "mild, mild" day, which reminds him of the first time he set sail as a young boy. He catches the eye of his young harpooner, Starbuck barely eighteen years old, and on his first voyage. He sees a "far away home" look in the young boy's eye and realises the boy is missing his home already. He searches his own memories and sees only the staring alien eye, of a monster of the deep. In young Starbuck, he sees himself forty years before and begins to reminisce to him about his long years at sea. He wonders if the years of hardship and deprivation have been worth it and most bitterly concludes that it has not. "Palsied" of arm, with a wooden leg and grey hair, his very soul dried out like the salted meat he has lived on for forty years, and driven on now only by his obsession to do battle one last time with his nemesis, the great White Whale, Moby Dick, he implores Starbuck not to waste his life, as he has done.

Part of the brilliance of Melville's work, lies in his poignant imagery of the loneliness of the seafaring life. But not only did the men folk suffer, but perhaps even more so, their wives. Ahab laments, "Aye, I widowed that poor girl when I married her, Starbuck…, leaving but one dent in my marriage pillow - wife? Wife? Rather a widow with her husband alive". In the words of author, Philip Hoare, "Whaling separated the sexes; and in this isolated place, as isolated as any ship, and yet bleaker in mid-winter, whaling "widows" had recourse to opium to cope with the loneliness. Others used plaster dildos known as "he's at homes".

Against this background however there was at least one whaling widow who stood out as the exception rather than the rule. Little remembered today, she deserves to be counted among one of the very earliest and heroic of champions of women's rights. Her name was Kezia Coffin. Rather than waste her life on opium (or other distractions) whilst her husband was away at sea, she decided to make a life of her own, and this was against all the odds in an isolated Quaker male dominated society that was Nantucket in the late Eighteenth century. Kezia became the "she-merchant" of Nantucket, starting out by selling all manner of whale products such as whale bone corset pins. She rapidly expanded her business. When the American Revolution broke out, she became rich by making a secret deal with a certain British admiral to ship Whale oil and candles to London as well as a host of other smuggled goods at greatly inflated prices, an act which would have earned her a place on the scaffold, had she been discovered at the time. She eventually became known as the greatest merchant smuggler in New England. She began to wear the very finest clothes, and much to the disgust of her Quaker elders, purchased a forbidden "instrument of music", a spinet, upon which she would perform at wild parties with other whale widows of the town.

Melville showed us the tragedy of a wasted life, but at least it was a life that got lived, how much worse the tragedy of a young life cut short and never lived at all. In the medical profession we face this possibility on a daily basis. We must be ever vigilant for the potential signs that may put a young life at risk. Like Kezia Coffin, we must grasp any opportunity that comes our way in life. An important one presents itself in the form of the ECG. Any young patient who presents with unexplained chest pain, dyspnoea, palpitations or syncope must have an ECG. We must seize this opportunity to scrutinize the recording, for any tell tale signs of future disaster, and by so doing we may just save a young life, before it is too late.

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPAHY

Introduction

Arrhythmogenic Right Ventricular Cardiomyopathy or **ARVC (**also known as arrhythmogenic right ventricular dysplasia or ARVD), is an uncommon inherited heart muscle disease.

It is a major cause of **sudden cardiac death in young people**.

The condition has probably been under recognized in the past, but is now being increasingly recognized.

Epidemiology

ARVC is an important cause of sudden cardiac death in young adults, and **athletes** in particular.

Presentation is most common between the ages of **10 and 50**, with a mean age at diagnosis of approximately **30 years.**

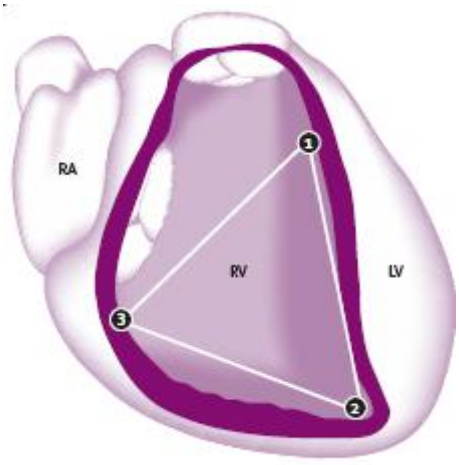
The disease is virtually never diagnosed in infancy and uncommonly before the age of 10.

Pathology

ARVC is considered to be a genetically determined myocardial dystrophy.

It is characterized by *fibro-fatty replacement of myocytes*, which predisposes to **cardiac arrhythmias**, the cause of sudden death.

The **right ventricle** is predominantly involved in ARVC; however the left ventricle may sometimes be involved also.



Dysplasia typically involves the inferior (3), apical, (2) and infundibular (1) walls of the right ventricle, (a so-called "triangle of dysplasia")

The fibrofatty replacement of the RV myocardium initially produces typical regional wall motion abnormalities.

With time these become global and result in RV wall thinning and chamber dilation.

Ventricular aneurysms may also develop, with its attendant complications.

Genetics

On a genetic level the dysplasia appears to be related to mutations in desmosomal genes. Desmosomes are important structures that mediate cell adhesion.

The most common pattern of inheritance of ARVC appears to be autosomal dominant with incomplete penetrance.

Autosomal dominant transmission means that a single copy of the abnormal gene is sufficient to cause the disease. On the other hand, a person with the abnormal gene will not necessarily develop any features of the disease. This latter phenomenon is termed incomplete penetrance.

Disease progression

Rather than being a smooth continuous process, disease progression can occur during periodic bursts in an otherwise stable disease. These disease exacerbations are clinically silent in most patients but sometimes can be characterised by the appearance of life-threatening arrhythmias and chest pain.

Environmental factors, such as exercise or inflammation, might facilitate disease progression by worsening cell adhesion.

Left-sided ARVC

As mentioned above, the pathologic process in classic ARVC predominantly involves the RV and sometimes extends to the LV.

In contrast, however, some patients will have a *left-dominant* arrhythmogenic cardiomyopathy (LDAC, also known as left-sided ARVC or arrhythmogenic left ventricular cardiomyopathy). These patients have pathological changes that predominantly involve the LV.

Differential diagnosis

The baseline ECG may resemble Brugada's syndrome with a right bundle branch morphology seen in the early precordial leads.

The main differential diagnosis of a VT will be with that caused by **Idiopathic RV tachycardia VT** with LBBB morphology and an inferior axis which may originate from the RV outflow tract in patients *without structural heart disease*. This idiopathic VT, which is a form of repetitive monomorphic VT, generally has a *much more*

benign prognosis than ARVC and can be successfully treated with radiofrequency ablation

The differentiation of the two is impossible on ECG alone, and will require electrophysiological studies.

Complications

1. Arrhythmias:

   Ventricular tachycardia/ VF

   - Monomorphic Ventricular tachycardia, with a left bundle branch block morphology, (which indicates an origin from the right ventricle).
   - This may be the cause of sudden cardiac death.

     Both VT and sudden cardiac death in patients with ARVC can be **exercise-induced** and in selected populations ARVC is a frequent cause of sudden cardiac death in athletes.

   Frequent ventricular extra-systoles:

   - >1000/ 24 hours documented on a Holter monitor is suggestive.
   - Although > 200 per 24 hours, in anyone who is known to have a first degree relative with a confirmed diagnosis of ARVC, may also be significant according to some criteria.

   Supraventricular tachyarrhythmias:

   The following may be seen:

   - Atrial fibrillation
   - Atrial tachycardia
   - Atrial flutter.

2. Dilated cardiomyopathy:

   - This will result in increasing symptoms of heart failure.

3. Ventricular aneurysms:

   - These may again induce arrhythmias
   - They may predispose to clot, with subsequent embolization
   - They may rupture, resulting sudden cardiac tamponade

- They may predispose to bacterial endocarditis.

Clinical Features

Presentation symptoms will usually be related to **arrhythmias** or to **heart failure.**

Symptoms in order of decreasing frequency include: [2]

- Palpitations
- Syncope
- Atypical chest pain
- Dyspnoea

Unfortunately **sudden cardiac death in a young person**, particularly an athlete, may be the first manifestation of the disease.

It is important to obtain a history of any close relatives who died unexpectedly at a young age.

Making the diagnosis

This will be done on a range of factors, including clinical, ECG, imaging, cardiac biopsy, and most importantly electrophysiology studies.

Standardized criteria for diagnosis have been developed, but will probably evolve further in the future, **(see appendix below).**

Investigations

Blood tests:

- FBE
- U&Es/ glucose
- Troponin I
- Mg/ Ca in the case of arrhythmias

CXR:

Evidence of dilated cardiomyopathy should be looked for, as well as of cardiac failure.

ECG:

Characteristic ECG features include:

Depolarization abnormalities, (resulting from delayed right ventricular activation):

- Prolongation of right precordial QRS duration > 110 ms or roughly 3 small squares, (which is 120 ms)
- There may be a RBBB type pattern in the early precordial leads
- There may be dominant R waves in the early precordial leads
- **Epsilon waves**

  These are a key characteristic ECG finding of ARVC.

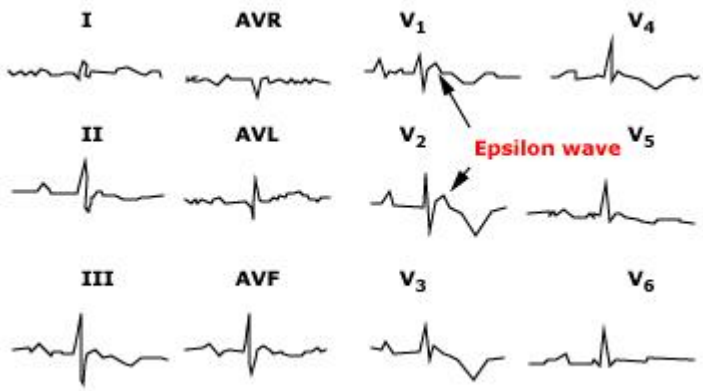
  They are defined as, **a small amplitude upward deflection, occurring after the QRS complex and before the onset of the T waves.**

  These may possibly be confused with the J waves (or Osborne) waves seen in cases of hypothermia, however J waves tend to be fused to the downstroke of the QRS complex, whilst Epsilon waves occur *after* the QRS. Clinical context is obviously also important when interpreting these deflections.

  Epsilon waves are "post-excitation" potentials, (as opposed to pre-excitation, or delta, potentials, as seen in WPW syndrome. Fontaine, who discovered, the epsilon wave, named it so because it *follows* delta in Greek in addition to being a mathematical symbol for smallness. These waves are usually quite small deflections and so the indication of ARVC can be subtle on the ECG. [4]

Repolarization abnormalities:

- **T wave inversion** in the right precordial leads, V1-V3, (in those > 12 years of age).



Epsilon waves seen in leads V1 and V2

Echocardiography:

This will be useful for confirmatory evidence which may include:

- Right ventricular chamber wall dilation and / or thinning
- Reduced ventricular ejection fractions
- Ventricular wall motion abnormalities
- Other secondary complications such as ventricular aneurysms.

MRI:

This can assess:

- Ventricular volumes
- Ventricular function, via ejection fractions, and wall motion abnormalities.
- It may also directly visualize myocardial fibro-fatty changes.

Electrophysiological studies:

Definitive diagnosis will most often be achieved by electrophysiological studies.

Myocardial biopsy:

Endomyocardial biopsy samples taken from the right ventricle will typically show fibro-fatty degeneration.

This is not commonly performed however because it lacks specificity and sensitivity, as well as being very invasive.

Management

1. Arrhythmias:
    - Arrhythmias can be treated along conventional lines.
2. Heart failure:
    - Heart failure can be treated along conventional lines.
3. Admission for monitoring:
    - Patients who present with symptoms of syncope, atypical, chest pain or dyspnoea and who have a suspicious ECG or who have direct family members with a confirmed diagnosis of ARVC should be admitted for

cardiac monitoring and review by a cardiologist, (preferably by a specialist in cardiac electrophysiology).

4. AICD:

   - Once ARVC is diagnosed, prevention of sudden death will be the most important management strategy

   - Current guidelines recommend AICD implantation for prevention of sudden cardiac death, particularly in patients with documented sustained VT or VF and for primary prevention in selected high risk patients without this.

5. Antiarrhythmic drugs:

   - Antiarrhythmic drugs are suggested only for patients who are not candidates for an ICD or as an adjunct to an ICD

6. Radiofrequency ablation:

   - Radiofrequency ablation is **not** adequate as a primary or sole therapy for the treatment of ventricular arrhythmias in patients with ARVC.

   - It can successfully treat some of the arrhythmogenic foci in ARVC, but due to the patchy and progressive nature of the disease, radiofrequency ablation is not a *definitive* therapy.

7. Sports participation:

   - Because of the increase in risk of sudden cardiac death, patients with ARVC should not participate in competitive sports.

   - Indeed any activity, competitive or not, that causes symptoms of palpitations, presyncope, or syncope should be avoided.

8. Assessment of direct family members:

   - Direct family members of a patient with diagnosed ARVC should also be assessed by a cardiologist, expert in this condition.

   - Genotyping may help to select those patients and families at highest risk of sudden cardiac death

Appendix

Task Force Criteria for diagnosis of ARVC [3]

I. Global and/or regional dysfunction and structural alterations*

Major

- Severe dilatation and reduction of right ventricular ejection fraction with no (or only mild) left ventricular impairment
- Localised right ventricular aneurysms (akinetic or dyskinetic areas with diastolic bulging)
- Severe segmental dilatation of the right ventricle

Minor

- Mild global right ventricular dilatation and/or ejection fraction reduction with normal left ventricle
- Mild segmental dilatation of the right ventricle
- Regional right ventricular hypokinesia

II. Tissue characterisation of wall

Major

- Fibrofatty replacement of myocardium on endomyocardial biopsy

III. Repolarisation abnormalities

Minor

- Inverted T waves in right precordial leads (V_2 and V_3) (people aged >12 years, in absence of right bundle branch block)

IV. Depolarisation/conduction abnormalities

Major

- Epsilon waves or localised prolongation (>110 ms) of the QRS complex in right precordial leads (V_1–V_3)

Minor

- Late potentials (signal-averaged ECG)

V. Arrhythmias

Major

- Arrhythmias listed below plus T-wave abnormalities—see III Repolarisation abnormalities

Minor

- Left bundle branch block type ventricular tachycardia (sustained and nonsustained) (ECG, Holter, exercise testing)
- Frequent ventricular extrasystoles (>1000/24-h) (Holter).

VI. Family history

Major

- Familial disease confirmed at necropsy or surgery

Minor

- Family history of premature sudden death (<35 years) due to suspected ARVC
- Family history of ARVC (clinical diagnosis based on present criteria)

ARVC=arrhythmogenic right ventricular cardiomyopathy. *Detected by echocardiography, angiography, magnetic resonance imaging, or radionuclide scintigraphy.

Diagnosis is established when two major, one major plus two minor, or four minor criteria from different groups are fulfilled

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