Insights on the heart of patients with "lone" atrial fibrillation

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The Problem with Atrial Fibrillation

AF is common and its prevalence is predicted to double by 2060.

AF is associated with an increased risk of stroke, myocardial infarction, heart failure, and death.

Only antithrombotic drugs have been consistently shown to improve AF prognosis. Chug et al. Circulation 2014.
Atrial Fibrillation Begets Atrial Fibrillation

Wijffels et al, 1995
Drugs Affecting the Cardiac Action Potential

Class 1
Na⁺ channel blocker
1a (moderate):
Quinidine, Procainamide
1b (weak):
Lidocaine, Phenytoin
1c (strong):
Flecainide, Propafenone

Class 2
β-blocker
Propranolol, Metoprolol

Class 3
K⁺ channel blocker
Amiodarone, Sotalol

Class 4
Ca²⁺ channel blocker
Verapamil, Diltiazem

By Architha Srinivasan
University of Cambridge
AF recurs after ablation even in the absence of electrical remodelling

*(sinus rhythm does not beget sinus rhythm)*
...and is AF the cause of cardiovascular morbidity and mortality in patients with AF?
A Comparison of Rate Control and Rhythm Control in Patients with Atrial Fibrillation
The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators

Estimates of All-Cause Mortality Risk (ITT)

Ablation vs. Drug
Hazard ratio: 0.85 (95% CI, 0.60–1.21)
P = 0.377

Mortality rate (%)

Months since randomization

Number at risk
Drug: 1108, 1046, 1023, 992, 903, 783, 679, 606, 527, 445, 334
Ablation: 1108, 1058, 1035, 1013, 933, 814, 724, 632, 555, 455, 332

Graph showing mortality rates for Ablation and Drug over 60 months since randomization.
Hypothesis

AF is always the results of an underlying cardiomyopathy

What is the evidence?
Multi-Parametric Cardiac Magnetic Resonance

Cardiac Volumes & Function
Tissue Characterisation
Myocardial Energetics
Myocardial Perfusion
Patients with “lone” AF and controlled LV rate

- **“PRE”**
  - Visit 1
  - Ablation
  - $^{31}$P MRS LV function, fibrosis & perfusion
  - < 4 weeks

- **“EARLY”**
  - Visit 2
  - LV function

- **“LATE”**
  - Visit 3
  - $^{31}$P MRS LV function, fibrosis & perfusion
  - 7 ± 1 months

**Matched Controls in SR**
Pre-Ablation: AF Patients vs. SR Controls
Lone paroxysmal or persistent AF is associated with impaired LVEF
Lone atrial fibrillation is associated with impaired LV energetics

$^{31}$P Magnetic Resonance Spectroscopy

![Graph showing PCr/ATP levels in controls and patients](image)
Myocardial perfusion is impaired in patients with “lone” AF

Wijesurendra et al. JAHA 2018
Intra-scan rhythms

Visit 1 → Ablation → Visit 2 → Visit 3

Visit 1: SR 45%, AF 55%
Visit 2: AF 6%, SR 94%
Visit 3: SR 87%

“EARLY” 20 ± 4 hours
“LATE” 7 ± 1 months

7-day Holter

AF Burden 53%
[IQR 1.5% - 100%]

AF Burden 0%
[IQR 0 – 0.1%]
7 months post-ablation, LVEF improves modestly, but does not normalise.
LV energetics and perfusion are unchanged following restoration of sinus rhythm post-ablation and still impaired compared to controls.
Summary

1. “Lone” AF is associated with mildly impaired LV function and reduced myocardial perfusion and energetics, which fail to normalise after successful ablation.

2. Impaired myocardial energetics and coronary microvascular dysfunction may be important pathophysiological mechanisms and potential therapeutic targets in AF.

Might AF cause irreversible changes in myocardial energetics and microvascular function?
A frameshift deletion in the sarcomere gene MYL4 causes early-onset familial atrial fibrillation

Atrial Fibrillation is a Cardiomyopathy Biomarker that Causes both the Arrhythmia and the Increased Stroke Risk
AF genes act via cardiac structural remodelling

Evidence from large-scale genetic studies

Tissue-specific gene expression enrichment for 151 biological AF candidate genes (>1M people → 60K AF cases)

1) Gene variance is associated with changes in ECG parameters that are associated with increased risk of AF (e.g., P wave duration, PR and QT intervals) in individuals in sinus rhythm.

2) 32 of 151 biological candidate genes could be targeted by existing drugs; e.g., flunarizine, fosphenytoin, anti-inflammatory drugs, omecamtiv mecarbil...).
Risk for AF according to a genome-wide polygenic score involving 6,630,150 variants in ~500K people

Nielsen et al. Nature Genetics 2018
Khera et al., Nature Genetics 2018
After plaque stenting, statins and life-style modifications are used to target the underlying pathobiology of CAD.

We may also find that **adjunctive therapies are needed** in AF to target the ongoing drivers of the disease process.