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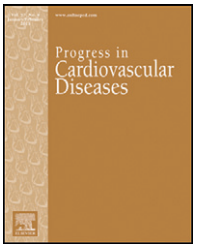

Atrial Structure and Function and its Implications for Current and Emerging Treatments for Atrial Fibrillation

Sandeep Prabhu[a,b,c,d], *Alex J.A. McLellan*[a,b,c,d], *Tomos E. Walters*[a,c,d], *Meenal Sharma*[a], *Alex Voskoboinik*[a], *Peter M. Kistler*[a,b,d,*]

[a]*Department of Cardiovascular Medicine, Alfred Hospital, VIC, Australia*
[b]*Baker IDI Heart and Diabetes Institute, VIC, Australia*
[c]*Cardiology Department, Royal Melbourne Hospital, VIC, Australia*
[d]*Faculty of Medicine, Dentistry, and Health Sciences, University of Melbourne, VIC, Australia*

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ABSTRACT

Left atrial (LA) structure and function are intimately related to the clinical phenotypes of atrial fibrillation (AF), and have direct implications for the success or otherwise of various therapeutic strategies. In conjunction with intrinsic structural characteristics of the LA, pathological remodelling to a large extent dictates the clinical course of AF. Remodelling is a product of the physiological and structural plasticity of the LA in disease states (including AF itself), and manifests as electrical, physical and structural changes that promote the substrate necessary for AF maintenance. The degree of remodelling impacts upon the efficacy of pharmacological, non-pharmacological and interventional treatments for AF. Evolving therapies seek to specifically target these processes although presently, several remain in the development phase. Catheter ablation (CA) is now firmly established as a highly effective treatment for AF, although increasing its efficacy in the remodelled LA of more severe AF phenotypes remains an ongoing challenge.

Atrial fibrillation (AF) is one of few cardiovascular (CV) conditions increasing in incidence across the world[1] conferring a considerable health, social and economic burden worldwide.[2] The treatment options for patients with AF have recently improved with the establishment of catheter ablation (CA) as a mainstream management option for a growing number of patients. In contrast, pharmacological treatments have been notably slow to develop and with the mainstay of therapy changing modestly only in recent times. The key to understanding the role and limitations of AF treatments is to appreciate the interplay of physiological and structural remodelling processes that occur in the setting of AF. This review seeks to examine the implications of left atrial (LA) structure and remodelling on current and evolving treatments for AF. In particular, we will focus on the treatment implications of electrical remodelling, intrinsic anatomical factors and structural remodelling on AF management.

LA remodelling

The LA is a complex entity displaying a considerable degree of physiological, electrical and anatomical plasticity in disease states.

"Remodelling" refers to electrical and structural alterations to the atrial tissue leading to impairment of normal atrial

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* Address reprint requests to Prof Peter M. Kistler, MBBS, PhD, Baker IDI Heart and Diabetes Institute, 75 Commercial Road, Melbourne, Victoria, Australia 3004.
E-mail address: peter.kistler@bakeridi.edu.au (P.M. Kistler).

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Abbreviations and Acronyms

3D = 3 dimensional

ACE = angiotensin converting enzyme

AF = atrial fibrillation

APD = action potential duration

AV = atrio-ventricular

CA = catheter ablation

CRP = C-reactive protein

CT = computer tomography

CV = cardio-vascular

ERP = effective refractory period

HF = heart failure

HTN = hypertension

I_{TO} = transient outward current (potassium)

I_{Kur} = ultra-rapid delayed rectifier current

I_{CaL} = L-type Ca^{2+} current

I_{Kr} = rapid delayed rectifier current

I_{Ks} = slow delayed rectifier current

I_{K1} = inward rectifier current

I_{KAch} = acetylcholine-activated inward rectifier current

LA = left atrial, left atrium, left atria

LAA = left atrial appendage

LV = left ventricle, left ventricular

MiRNA = micro-ribonucleic acid

MRI = magnetic resonance imaging

MMP = matrix-metallo proteases

NAC = N-acetyl cysteine

NF-κ-B = nuclear factor kappa light-chain-enhancer of activated B cells

NSR = normal sinus rhythm

PDGF = platelet derived growth factor

PPAR = peroxisome proliferator-activated receptor

function. Many disease processes lead to atrial remodelling, including hypertension (HTN), valvular heart disease (VHD) and cardiomyopathy, however, remodelling in the setting of AF is of particular interest as its occurrence appears to directly impact upon disease progression and the effectiveness of treatments. Electrical remodelling encompasses the electrophysiological changes promoting AF development and maintenance. These occur via changes in: ion channel function, intracellular calcium handling, autonomic activity and intercellular electrical conduction. Structural remodelling refers to alteration in atrial tissue composition (primarily by fibrosis) generally heralding irreversible microscopic (and often macroscopic) changes and a more severe disease phenotype. Both processes are intimately related and include overlapping disease pathways.

Electrical remodelling in AF and implication for treatments

Mechanisms of electrical remodelling

The mechanisms of electrical remodelling in AF are multifaceted. Electrical remodelling facilitates all three arrhythmia mechanisms: enhanced automaticity, triggered activity and re-entry.[3] Enhanced automaticity and triggered activity promote spontaneous rapid depolarisations of atrial myocytes. Re-entry is facilitated by processes which shorten atrial effective refractory period (ERP), reduce action potential duration (APD) and slow conduction velocity.[4] These changes increase the period of potential excitability (excitable gap) facilitating conditions favourable for AF.[5] Understanding the ionic currents involved in the normal atrial action potential is crucial to understating atrial function in AF and the potential sites for pharmacological intervention. Fig 1 provides a summary of the electrical remodelling processes occurring in AF, including summarising normal ion channel activity.

Analysis of isolated human atrial myocytes demonstrates that AF leads to a reduction I_{CaL} and I_{to} density, largely in response to increased intracellular calcium at rapid rates, promoting reduced APD and reduced rate response of atrial repolarisation. The inward rectifier I_{K1} current and I_{Ach} both display increased activity in AF at hyperpolarising potentials. These increase the excitability of atrial myocytes, promoting AF.[6,7]

Alterations in intracellular calcium handling have an important role in AF development and maintenance (Panel B). These result in increased intracellular Ca^{2+} from spontaneous sarcoplasmic reticular release of calcium via reduced I_{CaL} activity and via RyR2 and SERCA2a altered function[8] promoting triggered activity through early and delayed afterdepolarisations,[7] abnormal electric–mechanical coupling[9] and in ultra-structural changes and inflammatory cell and fibroblast modulation — providing an important mechanistic link between electrical and structural remodelling in AF.[8]

Sodium channel blockade

Flecanide is a class 1C antiarrhythmic medication which initially was thought to have primary activity against fast acting sodium channels and the rapid I_{Kr} current,[10] resulting in reduced conduction velocity and prolongation of APD. More recently the drug's activity on reducing intracellular calcium load has been appreciated, which also suppresses several pro-inflammatory pathways likely impacting upon structural remodelling — perhaps explaining flecanide's long term efficacy in AF control.[11]

Flecanide in AF has been evaluated in clinical trials as a short term reversion agent[12] and a long term antiarrhythmic.[13,14] In 3.5%–5% of cases, slowed conduction can facilitate organisation of AF to atrial flutter with the potential for 1:1 atrio-ventricular (AV) conduction and extremely rare and unstable ventricular rates.[15] Furthermore, its poor specificity for atrial activity and ventricular effects has limited its use particularly in those with structural heart disease. The Cardiac Arrhythmia Suppression Trial (CAST) study identified increased mortality in patients with prior myocardial infarction and left ventricular (LV dysfunction).[16] In heart failure (HF), flecanide has marked negative inotropic effects. Although flecanide remains an efficacious medication for use in AF, its lack of selectivity curtails its use in certain groups.

Given the proarrhythmic potential for non-selective sodium channel blockade, efforts have been made to specifically target the atrium. AZD 1035 is a compound displaying predominately atrial sodium channel blockade. Studies