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Author/s:

Goette, A;Kalman, JM;Aguinaga, L;Akar, J;Cabrera, JA;Chen, SA;Chugh, SS;Corradi, D;D'Avila, A;Dobrev, D;Fenelon, G;Gonzalez, M;Hattem, SN;Helm, R;Hindricks, G;Ho, SY;Hoit, B;Jalife, J;Kim, YH;Lip, GYH;Ma, CS;Marcus, GM;Murray, K;Nogami, A;Sanders, P;Uribe, W;Van Wagoner, DR;Nattel, S

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EHRA/HRS/APHRS/SOLAECE expert consensus on Atrial cardiomyopathies: Definition, characterisation, and clinical implication

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EHRA/HRS/APHRS/SOLAECE expert consensus on Atrial cardiomyopathies: Definition, characterisation, and clinical implication^{☆, ☆ ☆}

Andreas Goette, (EHRA chair)^{a,*}, Jonathan M. Kalman, (APHRS co-chair)^{b,**}, Luis Aguinaga, (SOLAECE co-chair)^{c,***,1}, Joseph Akar^d, Jose Angel Cabrera^e, Shih Ann Chen^f, Sumeet S. Chugh^g, Domenico Corradi^h, Andre D'Avilaⁱ, Dobromir Dobrev^j, Guilherme Fenelon^k, Mario Gonzalez^l, Stephane N. Hatem^m, Robert Helmⁿ, Gerhard Hindricks^o, Siew Yen Ho^p, Brian Hoit^q, Jose Jalife^r, Young-Hoon Kim^s, Gregory Y.H. Lip^t, Chang-Sheng Ma^u, Gregory M. Marcus^v, Katherine Murray^w, Akihiko Nogami^x, Prashanthan Sanders^y, William Uribe^z, David R. Van Wagoner^{aa}, Stanley Nattel, (HRS co-chair)^{ab,ac,***}

Document Reviewers: Osmar A. Centurion (Paraguay), Karl-Heinz Kuck (Germany), Kristen K. Patton (USA), John L. Sapp (Canada), Martin Stiles (New Zealand), Jesper Hastrup Svendsen (Denmark), and Gaurav A. Upadhyay (USA)

Review coordinator: Alena Shantsila (UK)

^a Departement of Cardiology and Intensive Care Medicine, St. Vincenz-Hospital Paderborn, Working Group: Molecular Electrophysiology, University Hospital Magdeburg, Germany

^b University of Melbourne, Royal Melbourne Hospital, Melbourne, VIC, Australia

^c Centro Privado de Cardiología, Tucumán, Argentina

^d Yale University, New Haven, CT, USA

^e European University Quiron-Madrid, Madrid, Spain

^f Veterans General Hospital, Taipei, Taiwan

^g The Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA

^h University of Parma, Parma, Italy

ⁱ Mount Sinai School of Medicine, New York, NY, USA

^j Institute of Pharmacology, West German Heart and Vascular Center, University Duisburg-Essen, Essen, Germany

^k Federal University of Sao Paulo, Sao Paulo, Brazil

^l Penn State Heart and Vascular Institute, Penn State University, Hershey, PA, USA

^m Department of Cardiology, Assistance Publique – Hô pitaux de Paris, Pitié-Salpêtrière Hospital, Sorbonne University, INSERM UMR_S1166, Institute of Cardiometabolism and Nutrition-ICAN, Paris, France

ⁿ Boston University School of Medicine, Boston Medical Center, Boston, MA, USA

^o University of Leipzig Heart Center, Leipzig, Germany

^p Royal Brompton Hospital and Imperial College London, London, UK

^q UH Case Medical Center, Cleveland, OH, USA

^r University of Michigan, Ann Arbor, MI, USA

^s Korea University Medical Center, Seoul, South Korea

^t University of Birmingham, Birmingham, UK

^u Anzhen Hospital, Beijing, China

^v University of California, San Francisco, CA, USA

^w Vanderbilt University, Nashville, TN, USA

^x University of Tsukuba, Ibaraki, Japan

^y Centre for Heart Rhythm Disorders, South Australian Health and Medical Research Institute, University of Adelaide and Royal Adelaide Hospital, Adelaide, Australia

^z Electrophysiology Department at Centros Especializados de San Vicente Fundació n and Clínica CES. Universidad CES, Universidad Pontificia Bolivariana (UPB), Medellín, Colombia

^{aa} Department of Molecular Cardiology, Cleveland Clinic, Cleveland, OH, USA

^{ab} Université de Montréal, Montreal Heart Institute Research Center and McGill University, Montreal, Quebec, Canada

^{ac} Institute of Pharmacology, West German Heart and Vascular Center, Faculty of Medicine, University Duisburg-Essen, Essen, Germany

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*Correspondence to: Chefarzt Medizinische Klinik II, St. Vincenz-Krankenhaus, Am Busdorf 2, 33098 Paderborn, Germany. Fax: 05251/861652.

**Correspondence to: University of Melbourne, Royal Melbourne Hospital, Melbourne, VIC 3050, Australia. Fax: +61 3 9349 5411.

***Corresponding author.

****Corresponding author at: University of Montreal, Montreal Heart Institute Research Center, 5000 Belanger St. E., Montreal, QC, Canada H1T 1C8. Fax: +1 514 593 2493

E-mail addresses: andreas.goette@vincenz.de (A. Goette), jon.kalman@mh.org.au (J.M. Kalman), lsaguinaga@gmail.com (L. Aguinaga),

stanley.nattel@icm-mhi.org (S. Nattel).

¹ Presidente Sociedad de Cardiología de Tucumán, Ex-PRESIDENTE DE SOLAECE, Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología. Tel.: +54 381 4217676.

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1. Introduction and definition of atrial cardiomyopathy

The atria provide an important contribution to cardiac function [1,2]. Besides their impact on ventricular filling, they serve as a volume reservoir, host pacemaker cells and important parts of the cardiac conduction system (e.g. sinus node, AV node), and secrete natriuretic peptides like atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) that regulate fluid homeostasis. Atrial myocardium is affected by many cardiac and non-cardiac conditions [3] and is, in some respects, more sensitive than ventricular [4]. The atria are activated, besides the three specialised intermodal tracts [5,6], through working cardiomyocytes, so that any architectural or structural change in the atrial myocardium may cause significant electrophysiological disturbances. In addition, atrial cells (both cardiomyocytes and non-cardiomyocyte elements like fibroblasts, endothelial cells, and neurons) react briskly and extensively to pathological stimuli [3] and are susceptible to a range of genetic influences [7]. Responses include atrial cardiomyocyte hypertrophy and contractile dysfunction, arrhythmogenic changes in cardiomyocyte ion-channel and transporter function, atrial fibroblast proliferation, hyperinnervation, and thrombogenic changes [2]. Thus, atrial pathologies have a substantial impact on cardiac performance, arrhythmia occurrence, and stroke risk [1,8].

Ventricular cardiomyopathies have been well classified; however, a definition and detailed analysis of ‘atrial cardiomyopathy’ is lacking from the literature. The purpose of the present consensus report, prepared by a working group with representation from the European Heart Rhythm Association (EHRA), the Heart Rhythm Society (HRS), the Asian Pacific Heart Rhythm Society (APHRS), and Sociedad Latino Americana de Estimulación Cardíaca y Electrofisiología (SOLAECE), was to define atrial cardiomyopathy, to review the relevant literature, and to consider the impact of atrial cardiomyopathies on arrhythmia management and stroke.

1.1. Definition of atrial cardiomyopathy

The working group proposes the following working definition of atrial cardiomyopathy: ‘Any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically-relevant manifestations’ (Table 1).

Many diseases (like hypertension, heart failure, diabetes, and myocarditis) or conditions (like ageing and endocrine abnormalities) are known to induce or contribute to an atrial cardiomyopathy. However, the induced changes are not necessarily disease-specific and pathological changes often share many similarities [9,10]. The extent of pathological changes may vary over time and atrial location, causing substantial intraindividual and inter-individual differences. In addition, while some pathological processes may affect the atria very selectively (e.g. atrial fibrillation-induced remodelling), most cardiomyopathies that affect the atria also involve the ventricles to a greater or lesser extent. There is no presently accepted histopathological classification of atrial pathologies. Therefore, we have proposed here a working

histological/ pathophysiological classification scheme for atrial cardiomyopathies (Table 1; Fig. 1). We use the acronym EHRAS (for EHRA/HRS/ APHRS/SOLAECE), defining four classes: (I) principal cardiomyocyte changes [11–15]; (II) principally fibrotic changes [10,14,16]; (III) combined cardiomyocyte-pathology/fibrosis [9,11,12]; (IV) primarily non-collagen infiltration (with or without cardiomyocyte changes) [17–19]. This simple classification may help to convey the primary underlying pathology in various clinical conditions. The EHRAS class may vary over time and may differ at atrial sites in certain patients. Thus, this classification is purely descriptive and in contrast to other classifications (NYHA class, CCS class etc.), there is no progression in severity from EHRAS class I to EHRAS IV (Table 2). The classification may be useful to describe pathological changes in biopsies and to correlate pathologies with results obtained from imaging technologies etc. In the future, this may help to define a tailored therapeutic approach in atrial fibrillation (AF) (Figs. 1–3).

2. Anatomical considerations and atrial muscular architecture

2.1. Normal atrial structures

2.1.1. Gross morphology

Each atrium has a morphologically characteristic atrial body and appendage (Fig. 4). In the body, there is a venous component with the orifices of the systemic or pulmonary veins (PVs) and a vestibular component that surrounds the atrial outlet [20]. The interatrial septum (IAS) separates the atrial bodies. The venous component of the left atrium (LA) is located posterosuperiorly and receives the PVs at the four corners, forming a prominent atrial dome. The LA is situated more posteriorly and superiorly than the right atrium separated by the obliquity of the plane of the IAS [21].

The LA appendage (LAA) is smaller than the right atrium appendage (RAA). Narrower and with different shapes has a distinct opening to the atrial body and overlies the left circumflex coronary artery. Its endocardial aspect is lined by a complex network of muscular ridges and mem-branes [22,23]. Different LAA morphologies have been described, and it appears that LAA morphology correlates with the risk of thrombogenesis [24].

Bachmann's bundle is a broad epicardial muscular band running along the anterior wall of both atria (Fig. 4). The rightward arms extend superiorly towards the sinus node and inferiorly towards the right atrioventricular groove, while the leftward arms blend with deeper myofibres to pass around the neck of the LAA and reunite posteriorly to join the circumferential vestibule of the LA. The walls of LA are non-uniform in thickness (1–15 mm) and thicker than the right atrium [25].

2.2. Normal atrial myocardium

2.2.1. Atrial cardiomyocytes

Atrial cardiomyocytes are geometrically complex cylinders that sometimes bifurcate at their ends where they connect with adjacent fibres via band-like ‘intercalated discs’. This contractile syncytium is organised in well-defined bands that establish non-uniform anisotropic propagation of the atrial impulse [9,11,26]. The only clear light-microscopic morphological difference between atrial and ventricular cardiomyocytes is in size [27]. In paraffin-embedded human specimens, the cardiomyocyte transverse diameter is $\times 12$ mm in the LAs vs. 20–22 mm in the ventricles [11,28]. Atrial cardiomyocytes are mainly mononucleated; a

Table 1
Definition of atrial cardiomyopathy.

‘Any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically-relevant manifestations’.

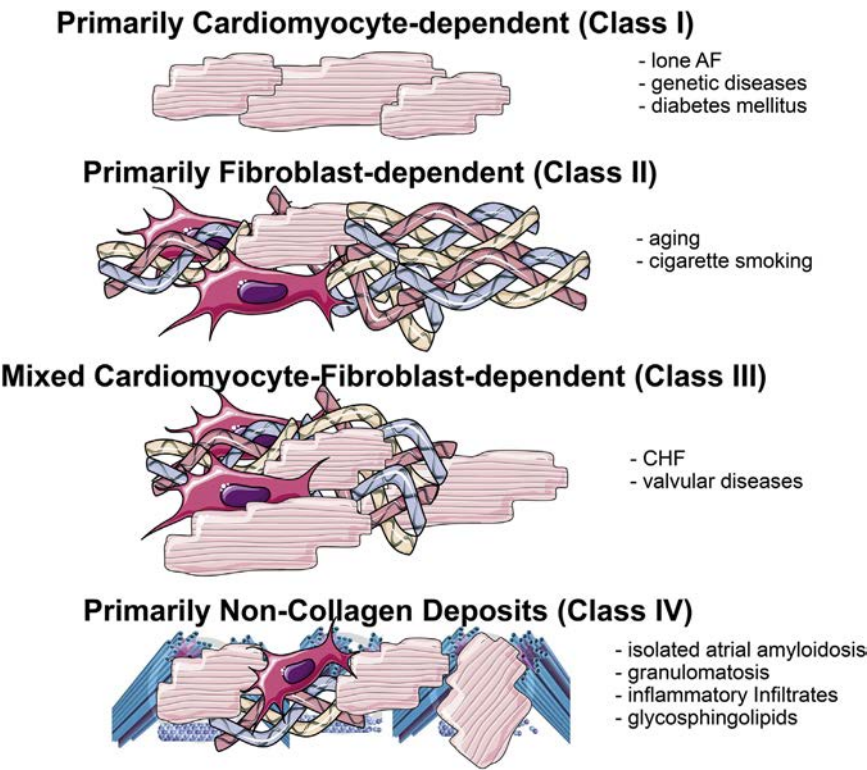


Fig. 1. Histological and pathophysiological classification of atrial cardiomyopathies (EHRA/HRS/APHRS/SOLAECE): EHRAS classification. The EHRAS class may vary over time in the cause of the disease and may differ at various atrial sites. Of note, the nature of the classification is purely descriptive. EHRAS I–IV is not intended to describe disease progression from EHRAS I to EHRAS IV.

Table 2
EHRAS classification of atrial cardiomyopathy.

EHRAS class	Histological characterisation
I [11–15,503]	Morphological or molecular changes affecting ‘primarily’ the cardiomyocytes in terms of cell hypertrophy and myocytolysis; no significant pathological tissue fibrosis or other interstitial changes
II [8,12,14,504–506]	Predominantly fibrotic changes; cardiomyocytes show normal appearance
III [9,11,12,217,266]	Combination of cardiomyocyte changes (e.g. cell hypertrophy, myocytolysis) and fibrotic changes Alteration of interstitial matrix without prominent collagen fibre accumulation
IV [17–19]	Accumulation of amyloid
Iva	Fatty infiltration
IVf	Inflammatory cells
IVi	Other interstitial alterations
IVo	

minor fraction possess two or more nuclei. The nucleus is usually centrally located, with granular and/or condensed chromatin. The nuclear shape is influenced by fibre contraction, becoming more fusiform with longitudinal cell stretch [29]. Biochemically, atrial cardiomyocytes have greater lipid content than ventricular muscle cells [30].

Atrial cardiomyocytes share many characteristics with ventricular in terms of nucleus, contractile apparatus, cytoskeleton, and organelles [27,29,31,32]. Unlike ventricular cardiomyocytes, atrial cardiomyocytes do not possess an extensive T-tubule network but they do have prominent sarcoplasmic reticulum (SR) elements known as Z-tubules [33]. Therefore, the atrial sarcolemma does not protrude into the cell, and voltage-operated Ca²⁺ channels mainly function at the cell periphery [34]. Atrial

cardiomyocytes display specific granules (100–400 nm) situated mainly in the paranuclear area adjacent to the Golgi apparatus, which contain ANP, the BNP, and related peptides [23,24].

2.2.2. Atrial interstitium

Atrial interstitium consists of cellular and extracellular components (see Figs. 2–5). The cellular elements include fibroblast/myofibroblasts, adipocytes, undifferentiated mesenchymal cells, and isolated inflammatory cells. The atrial wall has a significant number of medium-sized blood vessels, especially in the sub-epicardium. Mature adipose tissue is frequently found in atrial myocardium, especially the epicardium, and often permeates the layers around intramural coronary branches. The number of adipocytes is highly variable and increases with age [27]. The extracellular components consist of collagen fibres, which form most of the myocardial skeleton, proteoglycan particles, lipidic debris, spherical micro-particles, and matrix vesicles [27].

Collagen fibres, mainly type I, are both normal and essential components (Figs. 1–5). Atrial fibrous tissue may be sub-divided into pure interstitial and perivascular (or adventitial). Interstitial collagen fibres represent ~5% of the atrial wall volume. The atrial myocardium is also the site of sparse postganglionic nerve endings (from the ‘intrinsic cardiac nervous system’), mostly within discrete fat pads but also among cardiomyocytes [35].

3. Atrial-specific physiological and functional considerations

3.1. Atrial-selective electrophysiological properties

The atria have a number of electrophysiological features that distinguish them from the ventricles and govern their arrhythmia susceptibility.

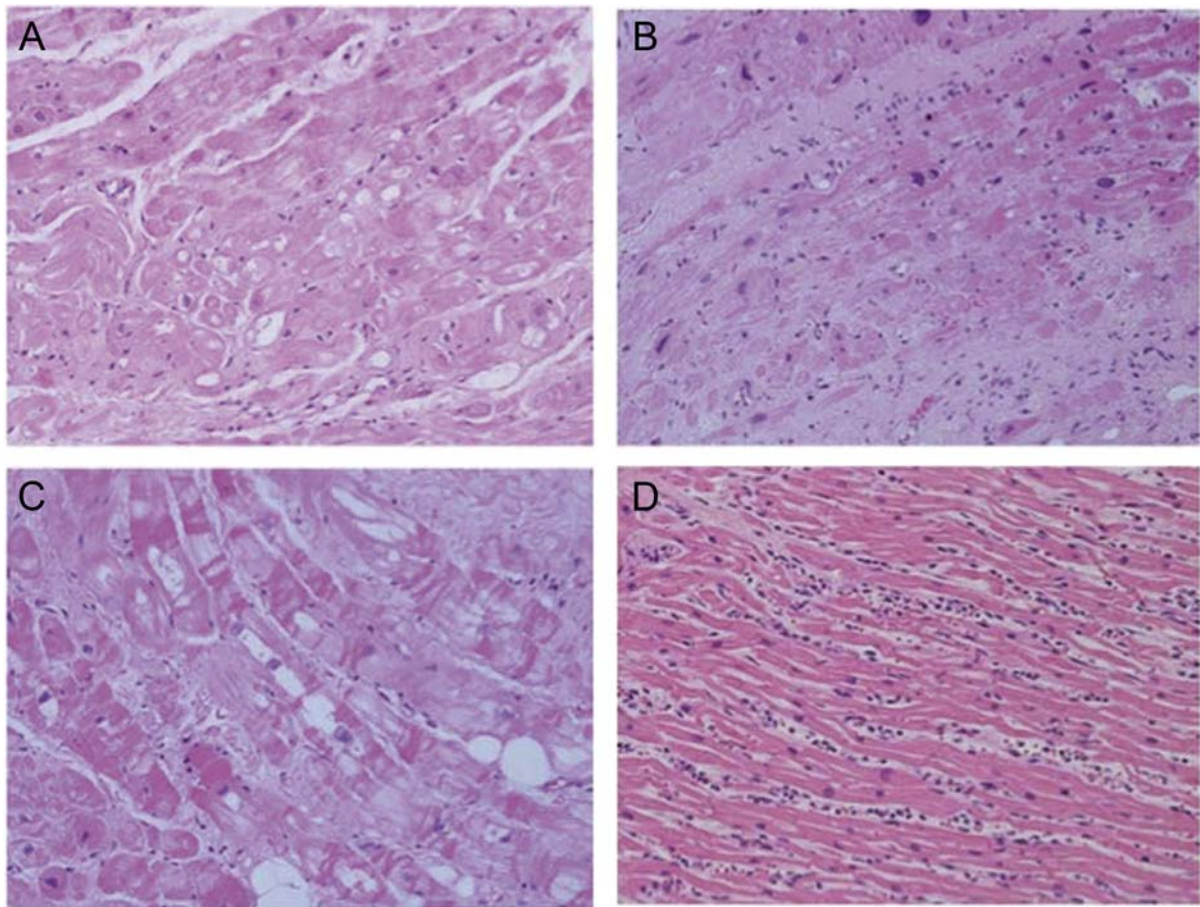


Fig. 2. (A) EHRAS Class I (biopsy): there are severe changes affecting 'primarily' the cardiomyocytes in terms of cell hypertrophy and myocytolysis; fibrosis is much less evident than myocyte modifications. (B) EHRAS Class II (biopsy): cardiomyocyte alterations are relatively modest compared with severe fibrotic changes; in this case, interstitial changes are much more prevalent than myocyte ones. (C) EHRAS Class III (biopsy): this is a combination of cardiomyocyte changes and collagen fibre deposition. (D) EHRAS Class IV (autopsy heart): primarily neutro-philic myocarditis.

3.2. Action potential/ion-channel properties

Atrial cardiomyocytes have distinct action potential (AP) properties from ventricular cardiomyocytes, resulting in a large part from distinct ion-channel properties and distribution (Fig. 6A) [36,37]. Atrial background inward-rectifier K^+ current (I_{K1}) is smaller than that of ventricular K^+ current, resulting in a less negative resting potential and more gradual slope of phase-3 repolarization. Atrial cells also have two K^+ -currents that are absent in ventricle cells: the ultrarapid delayed rectifier current (I_{Kur}) and the acetylcholine-regulated K^+ -current (I_{KACh}). In addition, there is evidence that atrial Na^+ -current has different properties compared with ventricular current [38]. As well as distinctions between atrial and ventricular APs, different atrial regions may have discrete AP and ion-channel properties [37,39]. These cellular electrophysiological characteristics have implications for antiarrhythmic drug action and design, and may also affect the responses to atrial arrhythmias and disease [36,37].

3.3. Intercellular coupling properties

The atria have a different pattern of cell-to-cell coupling protein (connexin) distribution compared with ventricular myocardium [36]. Whereas working ventricular cardiomyocytes express connexin-43 exclusively, atrial cardiomyocytes have significant expression of connexin-40 (Fig. 6B) [36]. Heterogeneities

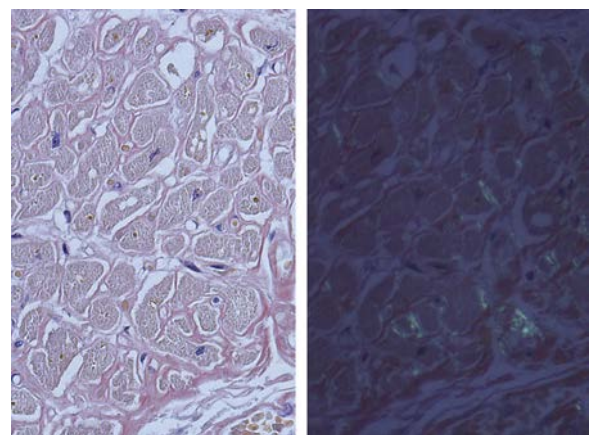


Fig. 3. EHRAS Class IV (autopsy heart): this image shows a myocardial interstitial with some fibrosis but prominent amyloid (AL type) deposition (left-hand side, congo red staining under regular light microscope; right-hand side, congo red staining under polarised light microscope).

in connexin-40 distribution are common in paroxysmal AF and may play a pathophysiological role [40], and gene variants affecting connexin-40 sequence and/or transcription predispose to AF occurrence [41].

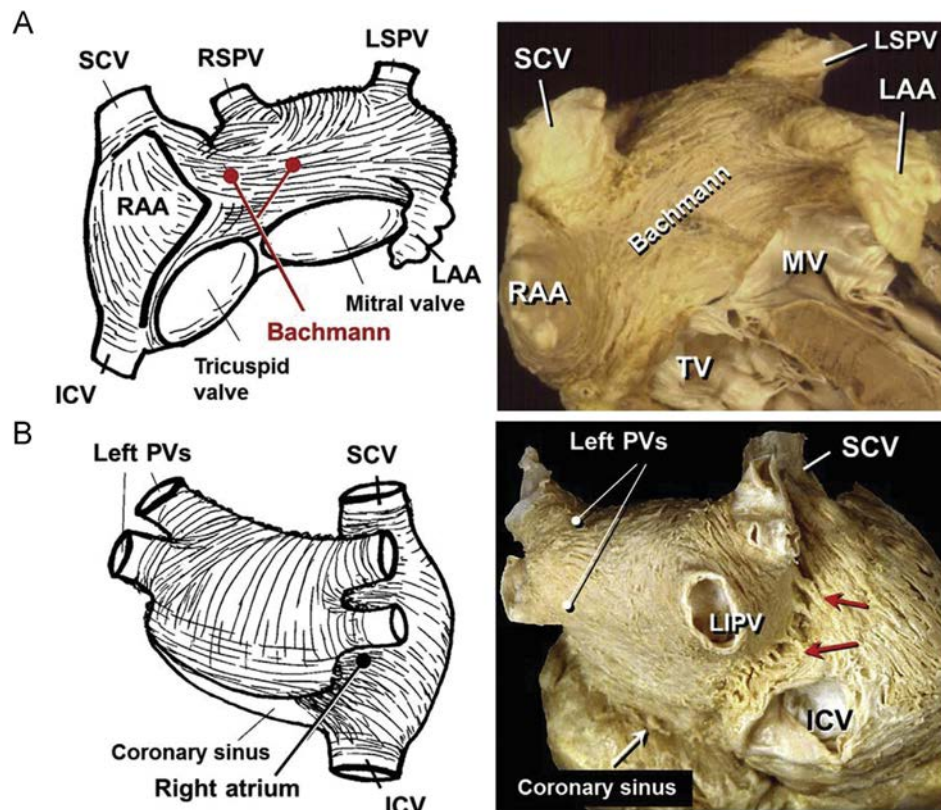


Fig. 4. Schematic representations and heart dissections to show the arrangement of the myocardial strands in the superficial parts of the walls. (A) The dissection viewed from the anterior aspect display the interatrial muscle Bachmann bundle and its bifurcating branches leftward and rightward. (B) A view of the roof and posterior wall of the left and right atriums. The right pulmonary veins (PVs) passes behind the intercaval area. The subepicardial dissection shows the abrupt changes in fibre orientation and the myocardial strands (septopulmonary bundle) in the region between the left and right PVs. The red arrows show multiple muscle bridges connecting the two atria. ICV, inferior caval vein; LAA, left atrial appendage; LSPV, left superior pulmonary vein; MV, mitral valve; RAA, right atrial appendage; RSPV, right superior pulmonary vein; SCV, superior caval vein; TV, tricuspid valve (see text for details).

3.4. Atrial structural properties

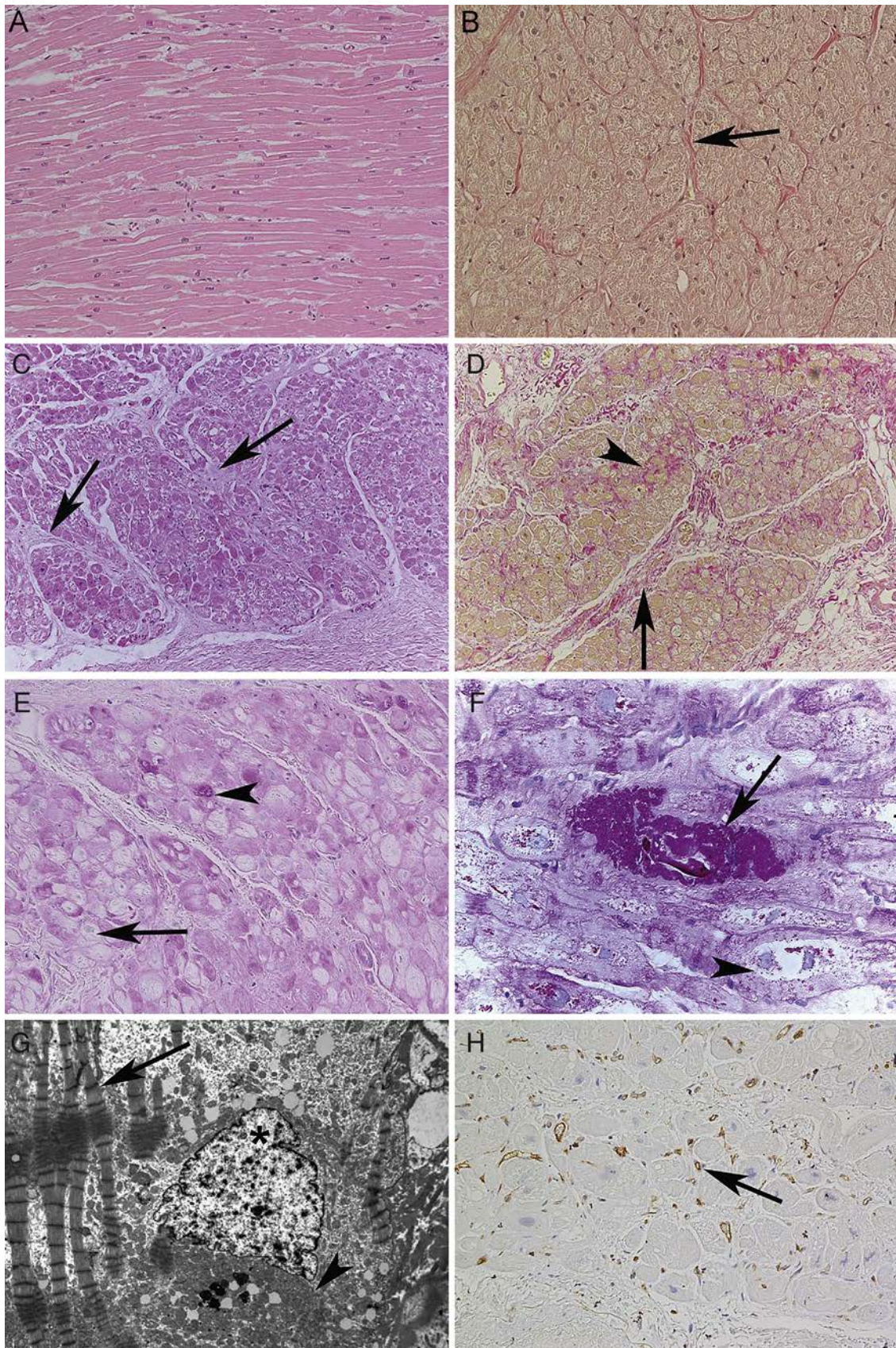
The atria have a very complex 3D structure (Fig. 6C) not found in the ventricles. These include interatrial connections limited to Bachmann's bundle, the septum, and the CS; pectinate muscles, the crista terminalis, and fibres surrounding the coronary sinus in the right atrium; and the PVs with complex fibre orientation around them in the LA. These structural complexities have important potential implications for atrial patho-physiology and management of atrial arrhythmias [42]. Extensive recent work has gone into the realistic mathematical reconstruction of such geometric complexities [43], and they have been incorporated into analytical approaches designed to implement patient-specific arrhythmia therapies [44]. Cable-like strands of atrial tissue like the pectinate muscles and crista terminalis are organised such that conduction within them is primarily longitudinal, with an 'anisotropy ratio' (longitudinal/transverse conduction velocities) as great

as 10, whereas in working ventricular muscle the ratio is typically more between 2 and 4 [45].

3.5. Autonomic ganglia

There are autonomic ganglia on the surface of the heart that are important way-stations for cardiac autonomic control [46]. Moreover, alterations in local cardiac innervation and intracardiac autonomic reflexes play an important role in physiology and arrhythmia control. Most of the cardiac autonomic ganglia are located on the atria, and in particular in the region of the PV ostia. Thus, they are well positioned to affect atrial electrical activity in regions particularly important in AF, and their alteration by therapeutic manoeuvres like PV ablation may contribute to antiarrhythmic efficacy [42,46,47].

Fig. 5. Normal histology of the left atrium and relevant pathological changes in mitral valve disease-associated atrial fibrillation. (A) Medium-power view of a normal left atrial myocardium which is composed of large bands of homogeneous cardiomyocytes. (B) In the same atrium as in (A), the Van Gieson staining show that collagen fibres (red colour) are primarily seen in the adventitial spaces of blood vessels (arrow). (C) Low-power view of a left atrium from a patient with mitral valve disease-associated atrial fibrillation. Large bands of cardiomyocytes are separated by significant amounts of pathologic fibrous tissue (arrows). (D) In the same atrium as in (C), the Van Gieson staining shows that the pathologic fibrous significantly thickens the perivascular spaces (perivascular fibrosis, arrow) and separates single or small groups of cardiomyocytes (interstitial fibrosis, arrowhead). (E) In atrial fibrillation, a variable number of cardiomyocytes undergo loss of contractile elements starting from the perinuclear area and resulting in so-called myocytolysis. These spaces may be empty (arrow) or filled with glycogen (arrowhead). (F) A higher-power view of myocytolysis with both glycogen rich (arrow) and optically empty (arrowhead) cardiomyocytes. (G) Ultrastructural view of a myolytic cardiomyocyte with significant loss of contractile elements around the nucleus (asterisk). In this empty area, there is very often accumulation of mitochondria (arrowhead) while the adjacent myofibrils display signs of abnormal contraction (arrow). (H) An LA from a patient with atrial fibrillation where the myocardial microcirculation (arrow) is slightly reduced and irregularly distributed. Stainings. (A and C) haematoxylin–eosin staining; (B and D) Van Gieson staining for collagen; (E and F) Periodic acid Schiff staining; (G) ultrastructural image; (H) immunohistochemical analysis with an anti-CD31 antibody. Original magnifications. (A, B, E, and H) $\times 20$; (C and D) $\times 4$; (F) $\times 40$; (G) $\times 2800$.



3.6. Left atrium mechanics

The left atrial contribution to overall cardiovascular performance is determined by unique factors. First, left atrial function critically determines left ventricular (LV) filling. Second, chamber-specific structural, electrical and ion remodelling alter left atrial function and arrhythmia susceptibility. Third, atrial function is highly relevant for the therapeutic responses of AF. Fourth, LA volume is an important biomarker that integrates the magnitude and duration of LV diastolic dysfunction. The development of sophisticated, non-invasive indices of LA size, and function might help to clinically exploit the importance of LA function in prognosis and risk stratification [1,48].

Fibre orientation of the two thin muscular layers (the fascicles of which both originate and terminate at the atrioventricular ring) introduce a complexity that challenges functional analysis. Ultrastructurally, atrial cardiomyocytes are smaller in diameter, have fewer T-tubules, and more abundant Golgi apparatus than ventricular. In addition, rates of contraction and relaxation, conduction velocity, and anisotropy differ, as does the myosin isoform composition and the expression of ion transporters, channels, and gap junctional proteins (see relevant sections).

3.7. Functions of the left atrium

The principal role of the LA is to modulate LV filling and cardiovascular performance by operating as a reservoir for PV return during LV systole, a conduit for PV return during early LV diastole, and as a booster pump that augments LV filling during LV diastole. There is a critical interplay between these atrial functions and ventricular systolic and diastolic performance. Thus, while LA compliance (or its inverse, stiffness), and, to a lesser extent, LA contractility and relaxation are the major determinants of reservoir function during LV systole, LV end-systolic volume and descent of the LV base during systole are important contributors. Conduit function is also governed by LA compliance and is reciprocally related to reservoir function, but because the mitral valve is open in diastole, conduit function is also closely related to LV compliance (of which relaxation is a major determinant). Atrial booster-pump function reflects the magnitude and timing of atrial contractility, but also depends on venous return (atrial preload), LV end-diastolic pressures (atrial afterload), and LV systolic reserve.

3.7.1. Left atrium booster-pump function

Left atrium booster-pump function represents the augmented LV-filling resulting from active atrial contraction (minus retrograde blood-ejection into the PVs) and has been estimated by measurements of (i) cardiac output with and without effective atrial systole, (ii) relative LV-filling using spectral Doppler of transmitral, PV, and LA-appendage flow, (iii) LA-shortening and volumetric analysis, and (iv) tissue Doppler and deformation analysis (strain and strain-rate imaging) of the LA-body [1]. Booster-pump function can also be evaluated echocardiographically by estimating the kinetic energy and force generated by LA contraction. The relative importance of the LA contribution to LV filling and cardiac output remain controversial. A load-independent index of LA contraction based on the analysis of instantaneous relation between LA pressure and volume, analogous to LV end-systolic elastance measurements, has been used as a load-independent measure of LA pump function, validated ex vivo and in the intact dog (Fig. 7) [49]. While LA pressure-volume loops can be generated with invasive and semi-invasive means in humans [50], these methods are cumbersome, time-consuming, and difficult to apply. Measurement of myocardial strain and strain rate, which represent the magnitude and rate of

myocardial deformation, assessed using either tissue Doppler velocities (tissue Doppler imaging, TDI) or by 2D echocardiographic (2D speckle-tracking or STE) techniques (Fig. 8) provide objective, non-invasive measurements of LA myocardial performance and contractility that overcome these limitations [1,51].

3.7.2. Left atrium reservoir function

Nearly half of the LV stroke volume and its associated energy are stored in the LA during LV systole. This energy is subsequently expended during the LV diastole. Reservoir function is governed largely by atrial compliance during ventricular systole, which is measured most rigorously by fitting atrial pressures and dimensions, taken either at the time of mitral valve opening/closure over a range of atrial pressures and volumes or during ventricular diastole, to an exponential equation [52]. Although this method requires atrial dimensions and pressures, the relative reservoir function can be estimated simply with PV Doppler: the proportion of LA inflow during ventricular systole provides an index of the reservoir capacity of the atrium. Reservoir function can also be estimated from LA time-volume relations as either the total ejection fraction or distensibility fraction, calculated as the maximum minus minimum LA volume, normalised to maximal or minimal LA volume, respectively.

Although largely neglected, the LA-appendage is more compliant than the LA-body [52], so the contribution of the appendage to overall LA compliance is substantial with potential negative implications for routine atrial appendectomy/ligation during mitral valve surgery.

Left atrium strain and strain rates during LV systole predict successful sinus rhythm restoration following DC cardioversion or AF ablation, and are surrogates of atrial fibrosis and structural remodelling; coupled with an estimate of atrial pressure (e.g. transmitral E/E'), strain has the potential to estimate atrial distensibility non-invasively [1,53].

3.7.3. Left atrium conduit function

Left atrium conduit function occurs primarily during ventricular diastole and represents the transport of blood volume that cannot be attributed to either reservoir or booster-pump functions, accounting for approximately one-third of atrial flow [54]. A reciprocal relation exists between LA conduit and reservoir functions; a redistribution between these functions is an important compensatory mechanism that facilitates LV filling with myocardial ischaemia, hypertensive heart disease, and mitral stenosis (MS). Conduit function is estimated by the early diastolic transmitral flow, diastolic PV-flow, and LA strain and strain rate during early diastole.

3.8. Atrial-selective Ca^{2+} handling

There are major differences in the expression and function of Ca^{2+} -handling proteins between atria and ventricles (Fig. 9) [55]. The atria have reduced cardiomyocyte contraction and relaxation times and shorter Ca^{2+} -transient duration [56–58]. In atria, protein levels [57,59] and activity [57,59] of the SR Ca^{2+} -ATPase2a (Serca2a) are two-fold higher, whereas the Serca2a-inhibitor phospholamban (PLB) is less abundant, vs. ventricles [57,59]. Atrial, but not ventricular, Serca2a is also regulated by sarcolipin (SLN) and SLN ablation increases atrial SR Ca^{2+} -uptake and contractility [60]. L-type Ca^{2+} -current [61] is similar in both chambers, whereas protein levels of ryanodine receptor type-2, calsequestrin, triadin, junction and Na^{2+} – Ca^{2+} exchanger are lower in atria than in ventricles [59,62,63]. In contrast to ventricular myocardium, T-tubules are less abundant in atrial cardiomyocytes [64]. In addition, atrial cardiomyocytes possess much more Ca^{2+} -buffering mitochondria than ventricular cardiomyocytes [56]. As a

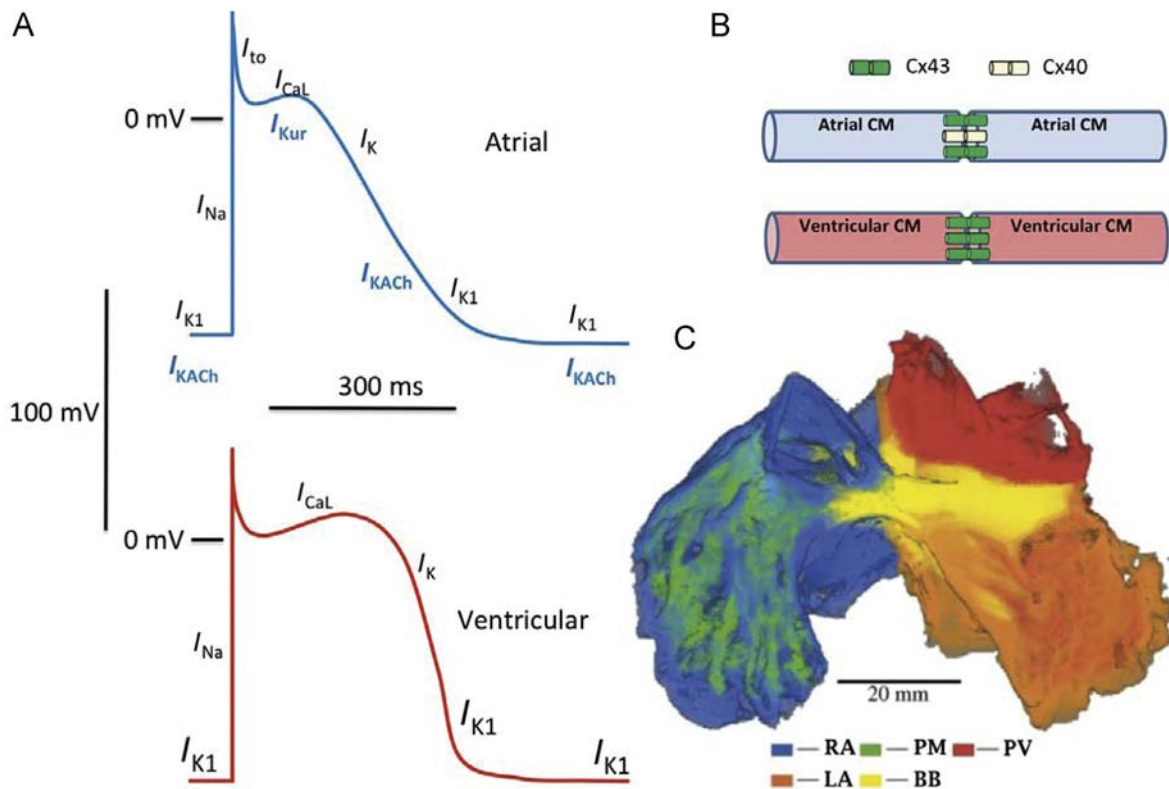


Fig. 6. (A) Comparison of atrial and ventricular action potential properties and underlying ionic currents. Resting potentials (2 mV) are more negative (averaging 280–285 mV) in ventricular vs. atrial (270–275 mV) myocytes. (B) Connexin distribution differs between atria and ventricles, with connexin-43 only expressed in ventricular cardiomyocytes (CMs) but atrial CMs having both connexin-40 and connexin-43. (C) Realistic reconstruction of the structure of sheep atria. The right atrium (RA), left atrium (LA), pectinate muscles (PM), Bachmann's bundle (BB) and pulmonary veins (PV) are colour coded. From Ref. [43] with permission.

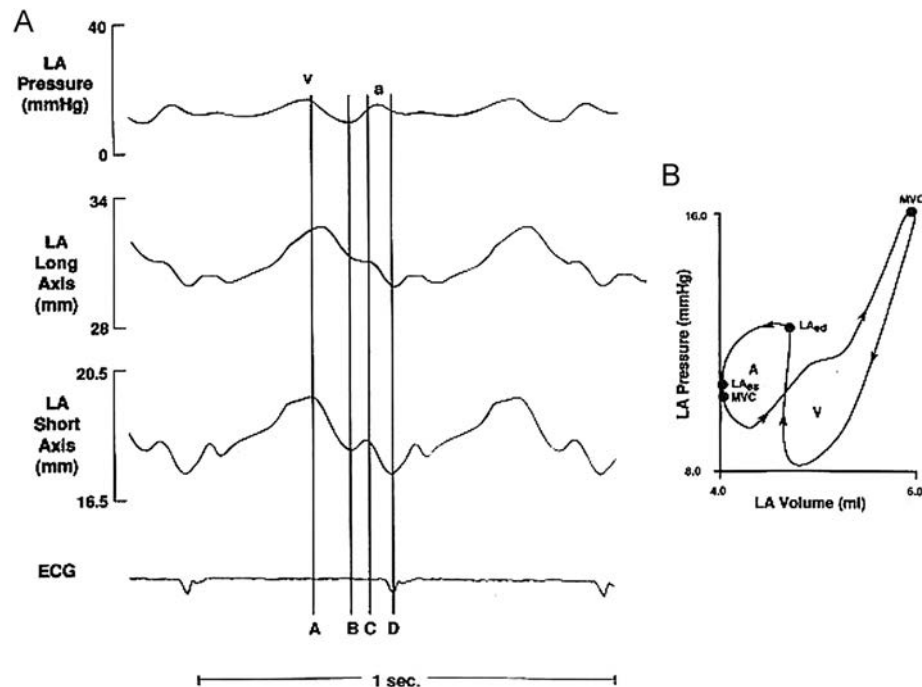
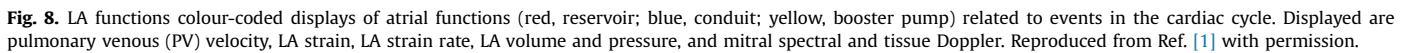


Fig. 7. Left atrial pressure–volume loop. (A) Analogue recordings of left atrial pressure and dimensions in the time domain. Vertical lines indicate time of mitral valve opening (A), end of passive atrial emptying and onset of atrial diastasis (B), atrial end-diastole (C), and atrial end-systole (D). a and v represent respective venous pressure waves. (B) Left atrial pressure–volume loop from a single beat illustrating characteristic figure-of-eight configuration. Arrows indicate the direction of loop as a function of time. A loop represents active atrial contraction. V loop represents passive filling and emptying of the LA. MVO, time of mitral valve opening; MVC, approximate time of mitral valve closure; LA, left atrial end-systole; and LAD, left atrial end-diastole. Reproduced from Ref. [49] with permission.



'Lone' atrial fibrillation (LAF) is diagnosed when no apparent explanation or underlying comorbidity can be identified [65,66]. Over the last few years, new epidemiological associations with AF have emerged and the number of true LAF cases has progressively decreased [67]. Like AF associated with comorbidities, LAF occurs more frequently in males than in females with a ratio of 3–4:1 [68]. Recent studies have shown that true cases of LAF can be diagnosed even in subjects older than 60 years, so that this age limit seems inappropriately conservative [69]. At the same time, it is unclear whether cases with left atrial enlargement should be excluded from the LAF category. In fact, LA enlargement might even be the consequence of the arrhythmia [70].

Frustaci et al [14]. explored the histological morphology of right atrial septal biopsies from patients with lone paroxysmal AF, finding chronic inflammatory infiltrates, foci of myocyte necrosis, focal replacement fibrosis, and myocyte cytoplasmic vacuoles consistent with myolysis. Of their 12 patients, 10 showed EHRAS class III changes and 2 showed EHRAS class II. Stiles et al [74]. found bi-atrial structural change, conduction abnormalities, and

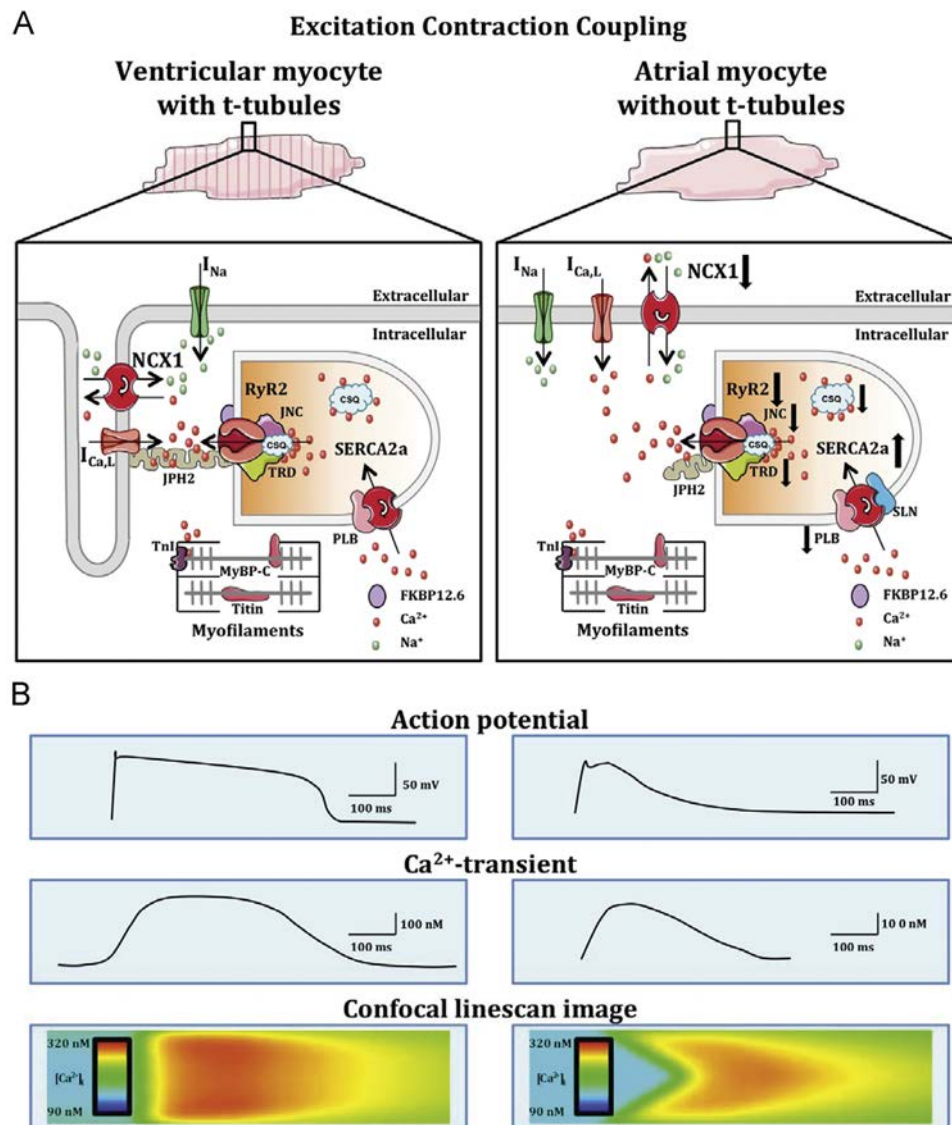


Fig. 9. Excitation–contraction coupling in atria vs. ventricles. Schematic representation of the cell structure and major Ca^{2+} handling proteins, along with related currents and ion transporters (A). Illustration of action potential (top), Ca^{2+} transient (middle) and confocal linescan image of intracellular Ca^{2+} wave propagation towards cell centre (bottom) in a ventricular (left) vs. atrial (right) cardiomyocyte (B). Arrows indicate differences in expression and/or function of Ca^{2+} handling proteins in atrial vs. ventricular cardiomyocytes. I_{Na} , Na^{+} current; FKBP12.6, FK506-binding protein 12.6; JPH2, Junctophilin-2; MyBP-C, Myosin binding protein C; TnI, Troponin-I; for further abbreviations, see text.

sinus node dysfunction in paroxysmal LAF patients. Skadis et al [75] demonstrated atrial perfusion abnormalities and coronary flow reserve impairment. Much more recently, morphometric assessment of atrial biopsies from the LA posterior wall of persistent or long-lasting persistent LAF patients demonstrated cardiomyocyte hypertrophy, myolytic damage, interstitial fibrosis, and reduced connexin-43 expression vs. controls [76].

4.2. Isolated atrial amyloidosis

The accumulation of insoluble, misfolded proteins is linked to an increasing number of age-related degenerative diseases [77]. Amyloidosis represent the deposition of insoluble, fibrillar proteins in a cross β -sheet structure that characteristically binds dyes such as Congo red. The most common form of age-related or senile amyloidosis is limited to the atrium, a condition known as isolated atrial amyloidosis (IAA) [17,78]. The incidence of atrial amyloidosis increases with age, exceeding 90% in the ninth decade [79].

Isolated atrial amyloidosis is also linked to structural heart disease. In atrial biopsies from 167 patients undergoing cardiac surgery, 23 of 26 amyloid-positive specimens were from patients with rheumatic heart disease (RHD), while the remaining 3 came from patients with atrial septal defects [80]. The overall incidence of 16% was greater than that was seen in control atrial autopsy specimens from trauma victims (3%). Histologically, IAA is classified as EHRAS IVa (Fig. 3; Table 2). Atrial natriuretic peptide is a fibrillogenic protein that forms IAA [81]. Amyloid deposits are immunoreactive for ANP in most patients [17], while transthyretin, a transport protein implicated in systemic senile amyloidosis, was also identified in 10% [4] (NT-pro-ANP has been identified in other studies [82]). As with fibrosis, amyloidosis can cause local conduction block and P-wave duration is increased in IAA. Atrial amyloid is found more commonly in patients with AF vs. sinus rhythm (Fig. 3). Both AF and IAA increased with advancing age and female sex, but the relationship between the two is independent of age and gender [83,84]. Isolated atrial amyloidosis is detected in

80% of PV sleeves of elderly patients [84]. For organ-specific amyloidosis such as Alzheimer's disease, there is no detectable correlation between quantity of fibrillar deposits and disease advancement [85]. Rather, disease phenotype correlates most closely with accumulation of soluble, prefibrillar protein aggregates [86]. Preamyloid oligomers (PAOs) are cytotoxic to cardiomyocytes [87]. They do not bind Congo red and thus are not visible by standard amyloid staining methods. Using a conformation-specific antibody, PAOs often co-localising with ANP were detected in atrial samples of 74 of 92 patients without AF undergoing cardiac surgery [88]. The preamyloid oligomer content was independently associated with hypertension. Additional studies are needed to further confirm this association and whether PAOs are increased in AF.

4.3. NPPA mutations

Atrial natriuretic peptide is released from the atria in response to atrial stretch or volume expansion, and produces natriuresis, diuresis, and vasodilation [89]. It also interacts with other endogenous systems, inhibiting the renin-angiotensin-II-aldosterone and sympathetic nervous systems, and regulates ion currents [90,91]. Atrial natriuretic peptide-knockout mice develop cardiac hypertrophy and exaggerated responses to hypertrophic stress [92]. The gene encoding the precursor protein for ANP, NPPA, encodes prepro-ANP, a 151 amino acid protein that includes a signal peptide cleaved off to form pro-ANP [93], which is stored in dense granules in the atria. Released pro-ANP undergoes proteolytic processing to generate N-terminal pro-ANP and ANP, 98 and 28 amino acids in length, respectively. N-terminal pro-ANP is cleaved into three hormones with biological activity similar to ANP: long-acting natriuretic hormone (LANH), vessel dilator peptide, and kaliuretic hormone.

Genetic studies have linked abnormal ANP production to familial atrial tachyarrhythmias and atrial cardiomyopathy. In a large family with Holt–Oram syndrome, a missense mutation in T-box transcription factor 5 (TBX5) resulted in an atypical phenotype with early-onset AF and the overexpression of multiple genes, including NPPA [94]. In a large family with multiple members having early-onset LAF, a 2-bp deletion was identified that abolishes the ANP stop codon, producing a mature protein containing the usual 28 amino acids plus an anomalous C-terminus of 12 additional residues [95]. The mutant ANP peptide is present in affected family members at plasma concentrations 5–10 times higher than wild-type ANP. Studies of the electrophysiological effects of ANP have been inconsistent [96].

Additional NPPA variants (S64R and A117V) have also been linked to AF [97,98]. The S64R variant occurs in vessel dilator peptide rather than ANP. A truncated peptide containing this mutation increased I_{Ks} several fold, an effect predicted to shorten action potential duration (APD) [97], but the variant has also been identified in unaffected elderly individuals without AF [96], and its functional pathological significance remains uncertain.

More recently, an autosomal-recessive atrial cardiomyopathy was described in patients harbouring an NPPA mutation (Arg150Gln) predicted to be damaging to protein structure [99]. The phenotype is characterised by biatrial enlargement, initially associated with atrial tachyarrhythmias such as AF and atrial flutter [100]. Biatrial enlargement progresses to partial and ultimately severe atrial standstill, associated with progressive decreases in atrial voltage and extensive atrial scarring. Whether atrial structural changes are primary, or secondary to atrial enlargement, is unknown. Loss of the antihypertrophic effects of ANP may cause the massive atrial enlargement seen in these patients.

4.4. Hereditary muscular dystrophies

A common finding in many inherited muscular dystrophies is cardiac involvement, related to myocyte degeneration with fatty or fibrotic replacement (Table 3) [101–103]. In some cases, this can be the presenting or predominant clinical manifestation. Multiple complexes and pathways are involved in the maintenance of myocyte integrity, and a defective or absent protein component can lead to progressive cell death. The large dystrophin–glycoprotein complex links the myocyte cytoskeleton to the extracellular basement membrane. For diseases of dystrophin, sarcoglycans, and other complex-related proteins, the most prominent manifestation is a dilated cardiomyopathy due to diffuse myocyte involvement, with arrhythmias and conduction abnormalities secondary to LV dysfunction [101–105]. Specific atrial involvement can lead to sinus node disease and/or atrial arrhythmias with associated thromboembolic events [106,107]. Myotonic dystrophy type I is the most common muscular dystrophy presenting in adults [108]. Up to 15% develop atrial arrhythmias during a 10-year follow-up [109]. The presence of conduction defects and atrial arrhythmias are independent risk factors for sudden death [103,110]. In Emery–Dreifuss and Limb–Girdle type IB disease, widespread atrial fibrosis can lead to atrial standstill [101]. In Emery–Dreifuss, AF and atrial flutter with slow ventricular responses and asystolic pauses can be observed, coupled with the occurrence of thromboembolism and stroke [111]. In facioscapulohumeral muscular dystrophy, arrhythmias are rare, with the most common being supraventricular tachycardia [112]. Histologically, the tissue composition may vary substantially, including all EHRAS classes (see Table 2).

4.5. Atrial cardiomyopathy due to congestive heart failure

Congestive heart failure (CHF) is a common cause (contributing condition) of AF [3]. The CHF-induced atrial phenotype is complex. A particularly important component is atrial fibrosis, which in experimental models occurs earlier in the course of CHF, and to a much greater extent, than in the ventricles, at least in part because of atrial-ventricular fibroblast–phenotype differences [4]. Congestive heart failure-related fibrosis slowly, if at all, and the AF-promoting substrate predominantly tracks fibrosis rather than other components of atrial remodelling like ion-current or connexin changes. Unlike the case for AF-induced remodelling, the atrial ion-current changes in CHF do not abbreviate APD or cause overall conduction slowing [113,114], so they do not contribute directly to arrhythmogenesis. On the other hand, CHF atria are prone to triggered activity due to abnormal Ca^{2+} handling [115]. The principle underlying abnormality appears to be increased cellular Ca^{2+} load. While the underlying mechanisms are not completely clear, they likely include phospholamban

Table 3
Hereditary muscular dystrophies with cardiac involvement.

Muscular dystrophy	Protein/gene	Primary cardiac disease
Duchenne	dystrophin	DCM
Becker	dystrophin	DCM
Myotonic dystrophy, type 1	DMPK	CSD
Emery–Dreifuss	Emerin	CSD
	Lamin A/C	(DCM)
Limb–Girdle	Lamin A/C	CSD
	Sarcoglycans	CM
	others	
Facioscapulohumeral	Dux 4	CSD (rare)

DCM, dilated cardiomyopathy; CSD, conduction system disease; DMPK, myotonic dystrophy protein kinase.

hyperphosphorylation (which increases SR Ca^{2+} up-take) and AP prolongation (which increases Ca^{2+} loading by enhancing the period during which L-type Ca^{2+} channels are open). The final phenotypic product of the CHF-induced Ca^{2+} -handling abnormalities is focal ectopic activity due to aberrant diastolic Ca^{2+} -release events from the SR, similar to abnormalities seen with paroxysmal and long-standing persistent AF [116].

Congestive heart failure also causes atrial hypocontractility, despite increased cytosolic Ca^{2+} transient, indicating reduced contractile sensitivity to intracellular Ca^{2+} , possibly because of reduced expression of total and phosphorylated myosin-binding protein C [115]. This hypocontractility may be important in contributing to the increased likelihood of thromboembolic events in AF patients who also have CHF. Of the atrial changes that occur in CHF, many are also seen in the ventricle. However, the highly atrial-selective fibrosis may contribute to atrial cardiomyopathy in the absence of clear signs of disturbed ventricular function, particularly in patients with prior CHF events who later become well-compensated under therapy or after resolution of the underlying cause. Collagen depositions are prominent in CHF, leading most commonly to EHRAS Class II and III properties. However, EHRAS Class IVi and IVf may also be found in certain areas of the atria (see Table 2).

4.6. Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is known to impair cardiac function and predispose to AF [117–119]. Obstructive sleep apnoea prolongs atrial conduction times, slows atrial conduction, reduces atrial-electrogram voltages and increases electrogram complexity [117,118]. Signal-averaged P-wave duration is increased by OSA, and decreases significantly with continuous positive airway pressure treatment [120]. In a rat model, repeated obstructive apnoea over a 4-week period increases AF vulnerability and slows atrial conduction by altering connexin-43 expression and inducing atrial fibrosis [121].

4.7. Atrial fibrillation-induced atrial remodelling

Atrial fibrillation itself induces atrial remodelling that contributes to the maintenance, progression, and stabilisation of AF [41,116]. The high atrial rate causes cellular Ca^{2+} loading. This induces a decrease in $I_{\text{Ca,L}}$ due to down-regulation of the underlying Cav1.2 subunits, and an increase in constitutively active $I_{\text{K,ACh}}$ [41,116,122,123]. MiR-328 up-regulation with consequent repression of Cav1.2-translation and Ca^{2+} -dependent calpain activation, causing proteolytic breakdown of L-type Ca^{2+} channels [41,116]. The rate-dependent up-regulation of I_{K1} results from a Ca^{2+} /calcein/NFAT-mediated down-regulation of the inhibitory miR-26, removing translational-inhibition of Kir2.1 [41,116]. Increased I_{K1} stabilizes AF by abbreviating and hyperpolarizing atrial cardiomyocyte Aps [41]. Small-conductance Ca^{2+} -activated K^+ (SK) currents (I_{SK}) also play a role in AF [41,116]. Computational modelling shows that increased total inward-rectifier K^+ current in chronic atrial fibrillation (cAF) is the major contributor to the stabilisation of re-entrant circuits by shortening APD and hyperpolarizing the resting membrane potential [41,116].

Atrial tachycardia remodelling reduces Ca^{2+} -transient amplitude by a variety of mechanisms, contributing to atrial contractile dysfunction [41,116,124]. Reduced atrial contractility causes atrial 'stunning' that may be involved in thromboembolic complications.

Long-term atrial tachycardia remodelling causes conduction slowing in several animal models, at least partly due to I_{Na} down-regulation [122]. Heterogeneously distributed gap-junction uncoupling due to connexin remodelling likely contributes to atrial conduction slowing [41,116]. Heterogeneity in connexin-40

distribution correlates with AF stability in goats with repetitive burst-pacing-induced AF [125]. Connexin-40 expression decreases in the PVs of dogs with AF-related remodelling, possibly due to tachycardia-induced connexin-degradation by calpains [41,116].

Long-term atrial tachycardia/AF may itself cause atrial fibrosis that contributes to long-term persistence [126]. Rapid atrial firing promotes fibroblast differentiation to collagen-secreting myofibroblasts through autocrine and paracrine mechanisms [32]. Atrial tachycardia-induced NFAT-mediated decreases in fibroblast miR-26 may also contribute to structural remodelling. Atrial fibroblasts have non-selective cation channels of the transient receptor potential (TRP) family that carry Ca^{2+} into the cell; the increased cell- Ca^{2+} then triggers increased collagen production. Since miR-26 represses TRPC3 gene expression, miR-26 reductions increase TRPC3 expression, promoting fibroblast Ca^{2+} entry that causes proliferation/myofibroblast differentiation [127]. TRPM7 may similarly contribute to fibrotic changes in AF [128].

APD shortening in cAF patients also results from increased inward-rectifier K^+ currents [129], both I_{K1} and a constitutive form of $I_{\text{K,ACh}}$ [41,116]. Agonist-activated $I_{\text{K,ACh}}$ is decreased in right atrium of AF patients because of a reduction in underlying Kir3.1 and Kir3.4 subunits [129], whereas agonist-independent current is increased [41,116].

Atrial cardiomyocytes from patients with long-standing persistent AF show spontaneous diastolic SR Ca^{2+} -release events (SCaEs) and delayed after depolarizations (DADs) [130]. CaMKII-dependent RyR2 hyperphosphorylation underlies the SR Ca^{2+} leak and SCaEs [32,106,130]. Protein kinase A-dependent RyR2 hyperphosphorylation also occurs [130], likely promoting the dissociation of the inhibitory FKBP12.6 subunit from the RyR2 channel. Larger inward NCX current may also contribute to the stronger propensity for DADs [130].

Although initial work pointed to unchanged I_{Na} or mRNA expression of the Nav1.5 α -subunit in AF patients, recent studies reported reduced peak I_{Na} [41,116]. There is also evidence for increased $I_{\text{Na,late}}$, although its functional consequences are less clear. Altered mRNA and protein levels of connexin-40/-43 may also contribute to re-entry-promoting conduction abnormalities in cAF patients. Reduced connexin-40 expression together with lateralization to the transverse cell membrane may cause heterogeneous conduction [41,116].

Overall, ion-channel changes contribute to AF stabilisation and early recurrence after cardioversion. Ca^{2+} -handling abnormalities are involved in atrial ectopy, and atrial fibrosis is important in the progression of long-term persistent AF to resistant forms. Atrial fibrillation-induced atrial myopathy has changes that depend on AF duration. Very short-term AF produces no ultrastructural alterations, while AF lasting several weeks causes EHRAS I alterations [13]. Long-term persistent AF produces EHRA III changes [126].

4.8. Drug-related atrial fibrillation

A large number of drug classes have been associated with the induction of AF either in patients without heart disease or in individuals with pre-existing cardiac disorders (Table 4) [131], but drug-induced AF (DIAF) has received less attention than that it might deserve. The overall incidence of DIAF is still unknown for several reasons: (a) the evidence associating specific drugs with AF has largely been based on anecdotal reports, with very few controlled prospective clinical trials, (b) DIAF is often paroxysmal and documentation may be difficult/poor, (c) while DIAF is easily recognised if it occurs just after i.v. drug administrations (e.g. adenosine or dobutamine), AF episodes can be missed if they appear after multiple exposures (e.g. chemotherapy), (d) patients often receive multiple drugs, making the specific culprit agent

Table 4
Drugs reported to induce atrial fibrillation.

Drug group	Drugs	Mechanism
Bisphosphonates	Alendronate, zoledronic acid	
Cardiovascular		
Inotropics	Dopamine, dobutamine, dopexamine, arbutamine, enoximone, milrinone, levosimendan	Adrenergic stimulation
Vasodilators	Isosorbide, losartan, flosequinan	Hypotension with probable adrenergic reflex
Cholinergics	Acetylcholine	Vagal stimulation
Diuretics	Thiazides	Hypokaliemia
Respiratory System		
Sympathomimetics	Pseudoephedrine, albuterol, oricyprenaline, salbutamol, salmetrol	Adrenergic stimulation
Xanthines	Aminophylline, theophylline	Adrenergic stimulation
Central Nervous System		
Anticholinergics	Atropine	Adrenergic stimulation
Anticonvulsants	Lacosamide, paliperidone	
Antidepressants	Fluoxetine, tranylcypromine, trazodone	Direct cardiodepressant effect, sympathetic tone
Antimigraine	Ondasetron, sumatriptan	coronary spasm
Antipsychotics	Clozapine, loxapine, olanzapine	Direct cardiodepressant effect, sympathetic tone
Cholinergics	Physostigmine, donepezil	Vagal stimulation
Dopamine agonists	Apomorphine	Vagal activity
Chemotherapeutics		Cardiac injury, coronary vasospasm, hypertension, reactive oxygen species, changes in mitochondrial calcium transport, electrolyte disturbances, inflammation
Alkylating agents	Cisplatin, cyclophosphamide, ifosfamide, melphalan	
Anthracyclines	Doxorubicin, mitoxantrone	
Anti-metabolites	Capecitabine, 5-fluorouracil, gemcitabine	
Antimicrotubule agents	Docetaxel, paclitaxel	
Tyrosine kinase inhibitors	cetuximab, sorafenib, sunitinib	
Topoisomerase inhibitors	amsacrine, etoposide	
Monoclonal antibodies Cytokines and immunomodulators	alemtuzumab, bevacizumab, rituximab, trastuzumab, azathioprine, interferon-gamma, interleukin-2, lenalidomide	
Genitourinary System		
Drugs for erectile	sildenafil, tadalafil, vardenafil	Hypotension with adrenergic reflex dysfunction
Tocolytic drugs	b2-adrenoceptor agonists (hexoprenalin, terbutaline), magnesium sulphate	
Hormones		
Anabolic-androgenic		Structural changes, changes in autonomic activity steroids

difficult to identify, (e) with non-cardiovascular drugs, DIAF is often diagnosed by non-cardiologists, often with an imprecise description of the arrhythmic event and clinical history [132]. Multiple mechanisms have been suggested to explain the pathogenesis of DIAF: (a) direct atrial electrophysiological effects like abbreviated refractoriness, slowed conduction, or triggered activity due to Ca^{2+} loading, (b) changes in autonomic tone, (c) myocardial ischaemia, (d) direct myocardial damage and other mechanisms such as release of pro-inflammatory cytokines, oxidative stress, hypotension, and electrolyte disturbances [131,132].

In the majority of cases, DIAF is a benign self-limited disorder. However, DIAF may be clinically serious in polymedicated patients with underlying comorbidities [132]. Discontinuation of the causative drug(s) usually leads to cardioversion in few minutes or hours. When AF persists, treatment is similar to that of non-DIAF patients [133,134]. Because of the wide range of mechanisms by which drugs cause AF, the histological changes associated with DIAF may vary substantially from EHRAS class I–IV (see Table 2 for reference). Future studies are warranted to assess specific effects of various drugs on atrial tissue.

4.9. Myocarditis

Myocarditis refers to an inflammatory disease of the heart, which occurs as a result of exposure to external triggers (e.g. infectious agents, toxins, or drugs) or internal ones like autoimmune disorders [135,136].

The incidence is difficult to ascertain since it depends on the diagnostic criteria. A likely estimate is 8 to 10 per 100 000 population, representing the third leading cause of sudden death after hypertrophic cardiomyopathy and coronary artery disease [137]. In autopsy series, the prevalence of myocarditis varies from 2% to 42% in young adults with sudden death [138,139]. Biopsy demonstrates an inflammatory infiltrate in 9–16% of patients with unexplained non-ischaemic dilated cardiomyopathy [140,141].

Myocarditis is defined by the ‘Dallas criteria’ as the presence of a myocardial inflammatory infiltrate with necrosis and/or degeneration of adjacent cardiomyocytes of non-ischaemic nature [142]. According to the type of inflammatory cell, myocarditis may be subdivided into lymphocytic, eosinophilic, polymorphic, giant-cell myocarditis, and cardiac sarcoidosis [136].

Atrial fibrillation is frequently part of the clinical presentation of myocarditis. In 245 patients with clinically suspected myocarditis, AF occurred in about 30% [143]. Myocarditis with lone atrial involvement is rarely diagnosed [144–146]. This may reflect the fact that atrial myocardium is not methodically sampled either at autopsy or in routine endomyocardial biopsy. In most such cases, AF dominated the clinical picture, suggesting a role for architectural remodelling that interferes with atrial conduction [9,147]. Giant-cell myocarditis is a distinct – and probably autoimmune – myocarditis characterised by diffuse infiltration by lymphocytes and numerous multinucleated giant-cells, frequent eosinophils, cardiomyocyte necrosis and, ultimately, fibrosis. The natural course is often fulminant and mortality is high if untreated. An isolated atrial variant of giant-cell myocarditis was

first reported in 1964 [148]. Since then, only a few cases have been described in the English language literature. The atrial variant appears to have a more favourable course compared with the classical form [149]. The atrial giant-cell myocarditis may represent a distinct entity, potentially attributable to atrium-specific auto-antigens [150]. EHRAS Class IVi is observed in patients with atrial myocarditis. As myocarditis persists and enters a chronic phase, characteristics may change to EHRAS Class III (see Table 2).

4.10. Atrial cardiomyopathy associated with genetic repolarization disturbances

Atrial standstill, a severe form of atrial cardiomyopathy, is associated with combined heterozygous mutations of SCN5A and Connexin-40 genes [151]. Gain-of-function mutations in K⁺-channel subunits (e.g. KCNQ1, KCNH2, KCND3, and KCNE5) or loss-of-function mutations in KCN5A have been identified in AF patients [152]. Thus, either gain or loss of K⁺-channel function can cause AF, indicating that repolarization requires optimal tuning and deficits in either direction can be arrhythmogenic. Recently, early repolarization or J-wave syndrome has been associated with AF although, in middle-aged subjects, early repolarization in inferior leads did not predict AF [153]. A gain-of-function mutation in KCNJ8, encoding the cardiac Kir 6.1 (KATP) channel, is associated with both increased AF susceptibility and early repolarization [154]. There is an established association between atrial arrhythmias and primary ventricular arrhythmia syndromes, which was first reported among conditions that manifest with obvious structural abnormalities [155]. Atrial fibrillation is relatively common in hypertrophic cardiomyopathy (prevalence $\times$ 20%) [156]. In arrhythmogenic right ventricular cardiomyopathy, an even higher proportion (up to 40%) of patients may manifest AF [157]. The association with AF also extends to primary arrhythmia syndromes without obvious structural heart disease. Supraventricular tachycardias, primarily AF/AFL, have been reported in Brugada syndrome [158,159]. Among long QT syndrome (LQTS) patients, prolongation of action potentials leading to atrial fibrillation has been suggested to be an atrial form of ‘torsades de pointes’ [152]. A subtle form of ‘cardiomyopathy’ that includes increased left atrial volumes occurs in $\times$ 12% of LQTS patients [160]. The reports available mostly implicate genetic variants in Na⁺-channel genes [161]. Patients with early-onset lone AF have a high prevalence of LQTS-associated SCN5A variants [162]. A mouse model of LQT3 is prone to atrial arrhythmias due to EADs [163]. There are sporadic reports of atrial arrhythmias in patients with CPVT [164]. Taken together, the associations between AF and sudden death syndromes likely reflect common mechanisms between atrial and ventricular arrhythmogenesis.

4.11. Ageing

In elderly dogs, premature impulses show markedly slowed conduction, associated with a doubling of fibrous-tissue content APD prolongation and spatial heterogeneity in repolarization [165,166]. Clinical mapping studies have also demonstrated similar findings of conduction abnormalities, prolonged refractoriness, reduced myocardial voltage, and a greater number of double potentials and fractionated electrograms [167,168]. Perhaps as a result of these atrial changes, alteration of wavefront propagation velocities has been described with an inverse correlation to age [169]. Histologically, fibrotic changes are the most obvious alteration (EHRAS Class II; see Table 2).

4.12. Hypertension

Hypertension accounts for at least one in five incident AF cases [170]. In hypertensive subjects, both left atrial enlargement and P-wave changes are predictive of AF occurrence [171,172].

In small animal models, mimicking hypertension by partial aortic clamping induces LA hypertrophy, fibrosis, connexin-43 down-regulation and slow/inhomogeneous conduction [173]. Prenatal corticosteroid exposure-induced hypertension in sheep causes atrial conduction abnormalities, wavelength shortening, and increased AF [174]. Lau et al. utilised a one-kidney one-clip model to investigate the impact of short- and long-term hypertension on the evolution of an atrial cardiomyopathy [175,176]. Utilisation of this model intrinsically is more reflective of a disordered renin-angiotensin axis. Short-term hypertension progressively enlarged the LA, reduced LA emptying fraction, prolonged atrial refractoriness, slowed conduction, and caused LA interstitial fibrosis and inflammatory cell infiltration [175,176]. In patients with established hypertension and LV hypertrophy, there is global and regional conduction slowing associated with fractionated electrograms and double potentials along the crista terminalis, along with an increase in low-voltage areas [177].

Importantly, population studies show increased AF risk even with ‘pre-hypertension’ (systolic blood pressure 130–139 mmHg) [178]. The ab-normal atrial substrate is reversible, with studies demonstrating improved electrical and structural parameters and reduced AF burden following treatment with renin-angiotensin-aldosterone system blockers [179–181]. In patients with resistant hypertension and improved blood pressure following renal denervation, there was a global improvement in atrial conduction and reduced complex fractionated activity. Histologically, pressure overload induces hypertrophy of atrial myocytes (EHRAS Class I). Collagen deposition may also occur (EHRAS II–III) with more severe hypertension causing LV hypertrophy and diastolic dysfunction (see Table 2).

4.13. Obesity

Several population-based studies have demonstrated a robust relationship between obesity and AF [182–184]. A recent meta-analysis estimates a 3.5–5.3% excess risk of AF for every one unit of body mass index increase [185].

Left atrium dilation and dysfunction are known consequences of the cardiomyopathy due to obesity [186]. In a sheep model of obesity, progressive weight gain over 8 months was associated with increased atrial volume, pressure, and pericardial fat volume along with atrial interstitial fibrosis, inflammation, and myocardial lipidosis [187]. This was associated with decreased conduction velocity, increased heterogeneity of conduction and a greater inducibility of atrial fibrillation. With more sustained obesity, animals not only demonstrate progressive atrial changes but also in areas adjacent to pericardial fat there is infiltration of the atrial myocardium by fat cells [188].

Obese patients have higher left atrial volume and pressure with lower left atrial strain associated with shorter refractoriness in the LA and the PVs [189]. A detailed evaluation of atrial changes associated with human obesity showed an increase in the left atrial epicardial fat, a global reduction in atrial conduction velocity, increased fractionation, and preserved overall voltage but greater low-voltage areas [190]. The low-voltage areas were observed in regions adjacent to epicardial fat depots.

Pericardial fat volume has been shown to be associated with AF incidence, severity, and adversely affects ablation outcome [191,192]. Epicardial adiposity is associated with altered 3D atrial architecture, adipocyte infiltration into the myocardium, and atrial

fibrosis that may contribute to conduction heterogeneity that promotes AF [193–195].

In the ovine model of chronic obesity, weight reduction is associated with reduction in total body fat, atrial dilatation, and interstitial fibrosis together with improved hemodynamics, atrial connexin-43 expression and conduction properties that result in reduced vulnerability to AF [196]. In humans, aggressive management of weight and associated risk factors is associated with favourable changes in pericardial fat volume, atrial size, myocardial mass as well as electrophysiological and electroanatomical changes along with reduced AF inducibility and burden [197]. Furthermore, weight loss in morbidly obese subjects is associated with reduced epicardial fat [198]. Weight reduction in obese individuals can result in regression of LV hypertrophy, reduction in left atrial size and reduction in AF burden/severity [199–201]. Histologically, fatty infiltrates (EHRAS Class IVf) as well as collagen depositions are present (EHRAS III; see Table 2).

4.14. Diabetes mellitus

Diabetes is an independent risk factor for development and progression of AF [202]. In a rat model of diabetes mellitus, atrial tissue fibrosis deposit is associated with decreased conduction velocity and greater AF inducibility [203]. Patients with abnormal glucose metabolism have larger left atrial size, lower left atrial voltage, and longer left atrial activation time compared with controls [204]. Insulin resistance is associated with increased left atrial size and structural heterogeneity [205,206].

Mitochondrial function is impaired, leading to oxidative stress, in diabetic atria [207]. Oxidative stress and activation of the advanced glycation end-product (AGE)-AGE-receptor (RAGE) system mediates atrial interstitial fibrosis up-regulation of circulating tissue growth factors and pro-inflammatory responses [207,208]. In addition, prolonged hyperglycaemic stress leads to accumulation of AGE-RAGE and nitric oxide inactivation, leading to endothelial dysfunction and myocardial inflammation [209].

Hyperglycaemia and AGE-RAGE ligand interactions lead to decreased phosphorylation of connexin-43, potentially impairing intercellular coupling [210]. Advanced glycation is also related to alterations in myocardial calcium handling and hence contractility [211]. These findings could explain the electrophysiological alterations that serve as a central mechanism of the vulnerability to AF in diabetes [212].

Aggressive treatment of diabetes and adequate glycemic control may prevent or delay the occurrence of AF, despite little direct evidence of the effects of anti-diabetic drugs on AF. Peroxisome proliferator-activated gamma receptor agonists may offer protection against AF beyond glycemic control, due to their anti-inflammatory, antioxidant, and anti-fibrotic effects [213]. However, caution should be taken in extrapolating these experimental findings to patients with diabetic cardiomyopathy. Histologically, changes in the atrial myocytes are the initial findings without significant fibrosis (EHRAS I). Later on the disease tissue appearance may change to EHRAS Class III and EHRAS Class IV (see Table 2).

4.15. Atrial cardiomyopathy due to valvular heart disease

Mitral valve disease (MVD) and aortic stenosis (AS) have been associated with atrial structural remodelling and a propensity for AF. Although secondary atrial cardiomyopathy is most often associated with age, hypertension, and heart failure in developed countries, RHD is responsible for over 40% of AF in the developing world [214].

4.15.1. Mitral stenosis

In atria from 24 patients with isolated MS and normal sinus rhythm undergoing mitral valvuloplasty, John et al [215]. reported unchanged or an increased effective refractory period (ERP), widespread and site-specific conduction delay, myocyte loss and patchy electrical scar, suggesting that structural changes and their electrophysiological consequences precede the development of AF. Factors associated with these structural changes include direct myocardial effects (pathognomonic inflammatory Ashoff bodies), ultrastructural changes, atrial fibrosis, immunoactive cytokines, and matrix metalloproteinase remodelling (decreased MMP-1 and MMP-3) [215–217]. Reverse atrial remodelling (an immediate reduction in LA pressure and volume and an improvement in biatrial voltage; and further increases in RA voltage 6 months later) was demonstrated in 21 patients with isolated MS undergoing commissurotomy [218]. In contrast, atrial remodelling did not reverse in patients with lone AF undergoing successful AF ablation; indeed, substrate abnormalities progressed (decreased voltage and increased regional refractoriness) over the subsequent 6–14 months [219].

Atrial enlargement and fibrosis are important determinants for the development and maintenance of AF. Increases in collagen I and collagen III (the latter which increase in cultured fibroblasts exposed to mechanical stretch) [220] were seen in patients with AF and MVD, but only type I was seen in patients with lone AF [221]. Cellular decoupling and myocyte isolation, tissue anisotropy, and conduction inhomogeneities were considered the substrate for local re-entry and arrhythmia.

4.15.2. Mitral regurgitation

Verheule et al [222]. found changes in atrial tissue structure and ultrastructure 1 month after creating severe mitral regurgitation (MR) by partial mitral valve avulsion. Effective refractory periods were increased homogeneously and sustained AF (.1 h) was inducible in 10 of 19 MR dogs; in this model, there were no differences in either atrial conduction pattern or velocities. Interstitial fibrosis, chronic inflammation, and cellular glycogen accumulation were noted in the dilated left atria, but myocyte hypertrophy, myolysis, and necrosis were absent. In contrast, myocyte hypertrophy, dedifferentiation, and degeneration and fibrosis are described in pigs with surgically created chronic MR [223] and patients with MR [12,224].

High-density oligonucleotide microarrays, enrichment analysis, and a differential proteomics approach were used to characterize the molecular regulatory mechanisms and biological processes involved in the atrial myopathy that is seen in pigs with moderate to severe chronic (6 and 12 months) MR [225]. Renin-angiotensin-system and peroxisome proliferator-activated receptor signalling pathways and genes involved in the regulation of apoptosis, autophagy, oxidative stress, cell growth, and carbohydrate metabolism were differentially regulated [225]. MLC2V (a marker of cardiac hypertrophy and important in the regulation of myocyte contractility) had the highest fold change in the MR pigs. Increased activity of a membrane-bound containing NADPH oxidase in atrial myocytes, which correlated with the degree of cellular hypertrophy and myolysis, was demonstrated in patients with isolated severe MR. The authors suggest that atrial stretch-induced NADPH oxidase activation and intracellular oxidative stress contributes to apoptosis, atrial contractile dysfunction, and atrial dilatation [226].

Correction of MR reverses many features of atrial remodelling and corrects functional abnormalities. Early LA reverse remodelling (45% reduction of mean LA maximal volume) and increased active atrial emptying was found in the early (30 day) post-operative period in 43 patients undergoing mitral valve surgery (successful repair or replacement) for chronic organic MR [227] and a similar improvement at 6 months was reported by Dardas et

al [228]. Histologically, EHRAS Class III is the most prominent finding in MVD, although the histological appearance of the tissue may vary substantially over time and interindividually and, therefore, all EHRAS classes may be found in the tissue (see Fig. 1; Table 2).

4.15.3. Aortic stenosis

Although AS is associated with chronic AF [229], animal models of AS and atrial remodelling are lacking. Kim et al [173], studied atrial electrical re-modelling in excised perfused hearts in a rat model of increased afterload simulating AS (ascending aortic banding), which produced LVH without systemic hypertension, heart failure, or neurohormonal activation. Banded hearts showed marked LA hypertrophy and fibrosis at 14 and 20 weeks post-operatively. The incidence and duration of pacing-induced AF was increased at 20 weeks and was associated with decreased mean vectorial conduction velocity and inhomogeneity of conduction, decreased expression of connexin-43, but without changes in ERP. Importantly, atrial remodelling was not present at 8 weeks, when the greatest degree of LVH was present [173].

Left atrium volumes are higher in patients with AS compared with controls and decrease significantly after valvuloplasty [230]. Plasma natriuretic peptide (ANP) levels are higher in symptomatic than asymptomatic patients with AS [231] and N-ANP levels predict atrial remodelling and late (2 month) post-operative AF after surgery for AS [232].

Taken together, these data support the notion that substrate-based AF is a consequence of the abnormal haemodynamics and atrial remodelling that accompany valvular heart disease. In this instance, atrial remodelling is the consequence of multiple biological processes that create structural and ultrastructural abnormalities and a change in conduction (as opposed to refractoriness) that favours the development and maintenance of AF. Histologically, EHRAS Class III is the most prominent finding, although the histological appearance of the tissue may vary substantially over time and interindividually (see Figs. 1–3; Table 2). Atrial pathology often also affects specialised conduction system tissues like the sinus and AV nodes. However, these changes are beyond the scope of the present consensus report, which focuses on atrial cardiomyocytes and tissue.

5. Impact of atrial cardiomyopathies on occurrence of atrial fibrillation and atrial arrhythmia

Controversy about the mechanism of AF has been alive for over 100 years, yet given the continued increase in worldwide burden of AF [233], ongoing investigation will drive improved treatment and prevention. Currently, there are two opposing sides in the debate about re-entrant mechanisms in AF. On one side are those who promote variants of the original idea of Gordon Moe that fibrillation, whether atrial or ventricular, results from the continued random propagation of multiple independent electric waves that move independently throughout the atria [234,235]. On the other side are those who adhere to the theory that fibrillation is a consequence of the continued activity of a few vortices (rotors) that spin at high frequencies, generating ‘fibrillatory conduction’ [236,237]. In either case, arrhythmia maintenance is favoured by abbreviated APD/refractory period [13,238,239]. Another pre-requisite of the multiple wavelet hypothesis is that there should be slow conduction, which is not the case for rotors. According to rotor theory, slowing of conduction is established dynamically by the curvature of the rotating wave front, which is steepest near the rotation centre, at which refractory period is briefest and conduction velocity is slowest [240]. Which of the

above two mechanisms prevails in human AF has not been fully established, yet [241].

Regardless of the mechanism that maintains it, AF leads to high-frequency atrial excitation, which if sustained, results in ion-channel remodelling that further abbreviates the APD and refractory period to boost its stabilisation. Such AF-induced electrical remodelling is reversible in the short term (minutes, hours, or days), but less so when lasting months or years. For a detailed discussion of AF-induced remodelling, see chapter 3. How these changes contribute to AF perpetuation in the long term has not been fully determined.

In a recent study using a sheep model of persistent AF induced by intermittent atrial tachypacing there was a progressive spontaneous increase in the dominant frequency (DF) of AF activation after the first detected AF episode [240,242]. The results suggested that, unlike the tachypacing induced electrical remodelling that can occur over minutes or hours, there existed a protracted, slowly progressing electrical and structural remodelling secondary to AF that sustains for days or weeks [240,242]. In addition, a consistent left-vs.-right atrial DF difference correlated with the presence of rotors, DF gradients, and outward propagation from the posterior LA during sustained AF in the explanted, Langendorff-perfused sheep hearts [242], and an underlying basis is seen in humans [243]. The DF of non-sustained AF increases progressively at a rate (dDF/dt) that accurately predicts the transition from episodic, non-sustained AF to persistent, long-lasting AF [126]. Although fibrosis developed progressively [126], it is unknown what role if any fibrosis played in rotor acceleration or stabilisation. Other studies using different animal models have also demonstrated that long-term atrial tachypacing results in atrial fibrosis [244], with concomitant release of cytokines that are known to modify atrial electrical function [245]. In the sheep model, atrial structural changes leading to PLA enlargement likely made rotors less likely to collide with anatomic boundaries, thus contributing to their stabilisation and AF persistence [242,246].

Distinct stresses of the atrial myocardium could contribute to the transformation of atrial cardiomyopathy into an arrhythmogenic substrate for AF. For instance, mechanical stress is a major regulator of cardiac electrical properties. The two atria are particularly sensitive to changes in mechanical coupling due to their ‘reservoir’ position and their function of ‘pressure sensor’ with a specific endocrine role, i.e. the secretion of natriuretic peptides. Many mechanosensors are expressed in the atrial myocardium and contribute to the interplay between membrane electrical properties, mechanical stresses, and myocardial wall deformation [247]. Recently, it has been reported that shear stress of atrial cardiomyocytes regulates the surface expression of voltage-gated potassium channels via the stimulation of the integrins that link myocytes to the extracellular matrix [248,249]. During atrial haemodynamic overload, the mechano-sensor signalling pathways, are constitutively activated, such that myocytes are no longer able to respond to shear stress. This process results in the acceleration of atrial repolarization and could contribute to AF vulnerability [249].

Oxidative stress is also thought to be important in AF-induced atrial remodelling leading to cardiomyopathy and AF perpetuation [250]. However, the manner in which reactive oxygen species (ROS) mediate atrial ionic remodelling is inadequately understood. NOX2/4 activity increases in fibrillating atria and is a potential source of ROS in AF. Mitochondrial ROS is potentially another important source of oxidative stress; mitochondrial dysfunction has been demonstrated in AF. It remains to be determined whether atrial oxidative stress directly affects atrial APD and refractoriness and thus contributes to rotor acceleration and stability in AF. Several sarcolemmal ionic currents are directly or indirectly

modulated by ROS [251], but the relevance of these mechanisms to human AF has not been demonstrated.

Sustained AF activates the release of pro-inflammatory cytokines and hormones related to cardiovascular disease and tissue injury, including angiotensin-II (Ang-II), tumour necrosis factor (TNF)- α , interleukin (IL)-6, and IL-8 [252]. Pro-inflammatory stimuli such as NOX-derived ROS, growth factors, and other hormones has been demonstrated to have a role in Ang-II function [253]. However, the precise molecular modifications of the putative signalling targets of ROS after Ang-II stimulation are yet to be identified. Knowing which NOXs are activated by Ang-II in the normal atria may help generate better interventions aimed at preventing AF associated with Ang-II activation. Ang-II is a well-known trigger of fibroblast activation and differentiation into myofibroblasts, which are key factors in the generation of fibrosis. Pro-inflammatory cytokines also promote ion-channel dysfunction, which together with myocyte apoptosis and extracellular matrix remodelling predisposes patients to AF.

Recently, atrial adipose tissue has emerged as a potential player in the pathophysiology of AF [3,254]. In addition to its paracrine effects [192], adipose tissue can infiltrate the subepicardium of the atrial myocardium and become fibrotic [255] contributing to the functional dissociation of electrical activity between epicardial layer and the endocardial bundle network, favouring wavebreak, and rotor formation. Lone AF or rapid atrial pacing promotes adipogenesis through the regulation of genes specific to metabolic adaptation. Therefore, it is possible that the accumulation and infiltration of adipose tissue reflects metabolic stress secondary to excessive work of the atrial myocardium [191]. Furthermore, adipose tissue can induce fibrosis and alter gene-expression patterns [195,256].

6. Atrial cardiomyopathies, systemic biomarkers, and atrial thrombogenesis

6.1. Atrial cardiomyopathies and systemic biomarkers

6.1.1. Atrial inflammation and inflammatory biomarkers

Infiltration of neutrophils, macrophages, and lymphocytes accompanies surgical injury or pericarditis, promoting the development of atrial fibrosis, resulting in heterogeneous and slowed conduction, a risk factor for re-entrant arrhythmia [257–261]. This provides a mechanistic link between inflammatory activation and atrial arrhythmogenesis. Anti-inflammatory interventions such as prednisone are effective in preventing neutrophil infiltration in sterile pericarditis and in suppressing pacing-inducible atrial flutter [262], and steroid pre-treatment has been found to reduce the incidence of postoperative AF in an appropriately powered randomized, clinical trial [263]. An ongoing trial studies the effect of colchicine (NCT 001128427).

In a mouse model of persistent hypertension, Ang-II infusion promotes increased atrial abundance of myeloperoxidase (MPO, a neutrophil and macrophage oxidant-generating enzyme) and promotes atrial fibrosis [261]. In MPO knockout mice, the profibrotic response to A-II infusion was eliminated. Angiotensin II and endothelin-1 are linked to inflammatory and proarrhythmogenic atrial remodelling [2,264–266]. This evidence suggests that inflammatory cell infiltration has an important role in promoting the creation of a substrate for AF, as a result of conduction heterogeneity and slowing, both in the setting of cardiac surgery and beyond.

6.1.2. Systemic inflammatory activation in atrial fibrillation

In addition to haemodynamic stress-induced cellular inflammation of the atria, a cross-sectional study demonstrated that AF

was associated with higher plasma levels of C-reactive protein (CRP), a sensitive but non-specific biomarker of systemic inflammation produced by the liver [267]. A follow-up secondary analysis of the participants Cardiovascular Health Study participants further revealed that elevated CRP predicted incident AF [268].

Subsequent studies have demonstrated relationships between several different serologic markers of inflammation and AF, including IL-6 [269], TNF- α [270], aldosterone [271] and simple white blood cell counts [272]. Analyses of multiple inflammatory biomarkers within the same study have suggested that IL-6 and osteoprotegerin [273] may be especially important. The relationship between IL-6 and AF may be mediated by left atrial enlargement [269].

While evidence that inflammatory markers presage the development of AF has been replicated [268,274], there are also multiple studies to demonstrate that atrial arrhythmias likely contribute to inflammation: specifically, cardioversion of AF [275] as well as ablation of either AF [276] or atrial flutter [277] has resulted in a decrease in inflammation. Indeed, Marcus et al. demonstrated that the rhythm at the time of the blood draw (AF vs. sinus) was an important determinant in detecting an elevated CRP or IL-6 level [278]. Taken together, these data suggest that the relationship between inflammation and AF may be bidirectional and progressive.

6.1.3. Intra-atrial sampling studies

As the enhanced risk of stroke in the setting of AF has been attributed to status of blood flow and in particular thromboemboli originating in the left atrial appendage, there has been an interest in determining whether peripheral blood can adequately reflect the hypercoagulability that may be present locally within the atria (see Fig. 10) [279]. The first intra-atrial sampling study failed to identify evidence of statistically significant differences between several markers of hypercoagulability in right and left atrial vs. femoral vein and arterial samples among persistent AF patients with MS [280]; of note, the same markers revealed statistically significant differences when compared with normal controls without AF [279]. In contrast, a subsequent study demonstrated that platelet activation acutely increased in coronary sinus blood in AF, while systemic platelet activation (obtained from the femoral vein) revealed no such change [281].

A similar approach to multi-site sampling has also been applied to better understand the relationship between inflammation and AF. Liuba et al. found higher levels of IL-8 in the femoral vein, right atrium, and coronary sinus than the left and right upper PVs among eight permanent AF patients (without any such differences 10 paroxysmal AF patients or 10 controls) [280].

6.1.4. Practical implications and use of systemic biomarkers

Systemic biomarkers have been used to predict development of AF and/or its complications (Table 5). Various studies have examined the role of inflammatory indices, natriuretic peptides, injury markers, etc. in predicting incident AF, especially in the post-surgery setting. Many of these bio-markers are non-specific, and high levels may reflect infection or sepsis, an acute phase reaction, etc [282–284].

Adding BNP and CRP to a prediction score derived from CHARGE-AF (which included data from the Atherosclerosis Risk in Communities Study (ARIC), Cardiovascular Health Study (CHS), the Framingham Heart Study, the Age, Gene/Environment Susceptibility Reykjavik Study (AGES), and the Rotterdam Study) and utilising age, race, height, weight, systolic and diastolic blood pressure, current smoking, use of antihypertensive medication, diabetes, history of myocardial infarction and history of heart failure [285] improved the statistical model [286]. Once again, the addition of CRP did not meaningfully improve the model.

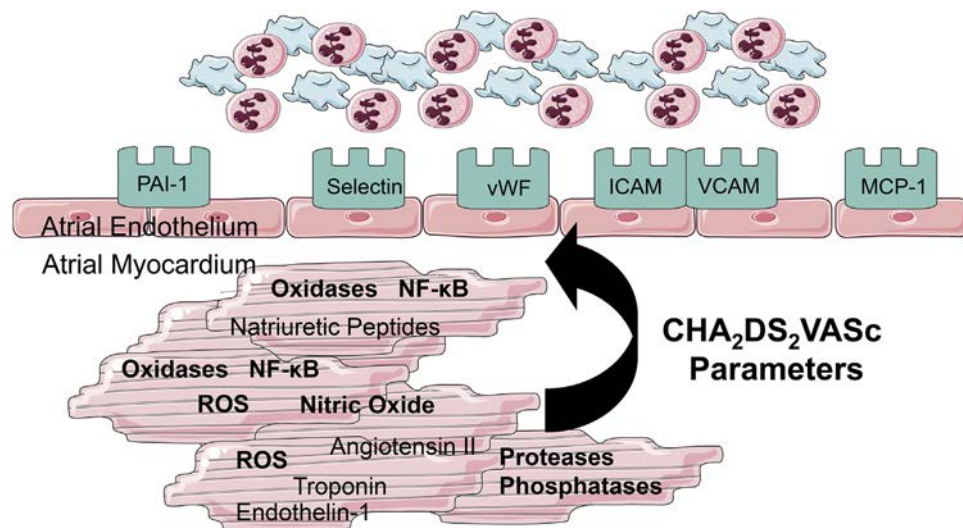


Fig. 10. Concept of 'endocardial remodelling' in fibrillating atria. In accordance to Virchow's triad hypercoagulability, flow abnormalities, and endothelial changes must co-exist to induce thrombogenesis at the atrial endocardium. Molecular studies have revealed substantial endocardial changes in left atrial tissue samples. Prothrombotic factors (vWF, adhesion molecules like VCAM-1, P-selectin etc; green) are expressed at the surface of endothelial cells causing an increased adhesiveness of platelets and leucocytes to the atrial endocardium. This initiates atrial thrombogenesis at the atrial endocardium. Several clinical factors like diabetes mellitus, heart failure ageing etc. (CHA₂DS₂VASc Parameters) increase molecular alterations (oxidative stress pathways etc.) within myocytes and endothelial cells, and thereby, increase the expression of prothrombotic factors. These alterations are not directly related to the presence of absence of atrial fibrillation in the surface ECG, and therefore, help to explain, why thrombogenesis is increased even during episodes of sinus rhythm.

Table 5
Coagulations markers in atrial fibrillation.

Study	AF group(s)	Control group(s)	Significant abnormalities found in AF (increase in coagulation markers) ^a
Gustafsson (1990) [507]	20 (with stroke) 20 (without stroke)	40 (normal without stroke) 20 (with stroke)	D-dimers, vWF irrespectively of history of stroke
Kumagai (1990) [508]	73	73	D-dimers
Asakura (1992) [509]	83	(normal)	PF1 + 2, TATIII complex
Sohara (1994) [510]	13 (paroxysmal)	(normal)	TATIII complex (no difference in D-dimers),
Lip (1995) [511]	87	158	D-dimers, vWF
Lip (1996) [512]	51	26 (healthy)	D-dimers
Kahn (1997) [513]	50 (without prior stroke) 25 (with prior stroke)	31 (without prior stroke) 11 (with prior stroke)	Fibrinogen in AF without stroke vs. controls without stroke (no difference was seen between groups with prior stroke)
Heppell (1997) [514]	19 with thrombus in LA 90 without thrombus in LA	not applicable	D-dimers, vWF, TATIII complex if LA thrombus
Shinohara (1998) [515]	45 (non-valvular)	not applicable	D-dimers, TATIII complex in patients with low vs. high LAA velocity
Feinberg (SPAF III) (1999) [516]	1531	not applicable	No association of PF1 + 2 with thromboembolism
Mondillo (2000) [517]	45	35 (healthy)	D-dimers, vWF, s-thrombomodulin
Fukuchi (2001) [518]	16	27 (cardiac without AF)	vWF in LA appendage tissue
Conway (2002) [296]	1321		vWF in high-risk group for stroke
Kamath (2002) [519]	93	50 (normal)	D-dimers
Vene (2003) [520]	113		D-dimers in patients having cardiovascular events vs. no event
Nakamura (2003) [521]	LA appendage tissue of 7 non-valvular	4 non-cardiac death	vWF, TF
Conway (2003) [297]	994	not applicable	vWF not associated of with risk of stroke, vWF independently associated with vascular events
Kamath (2003) [522]	31 (acute onset) 93 (permanent)	31 (healthy)	Haematocrit raised in acute AF
Sakurai (2004) [523]	28 (AFL)	27	D-dimers in permanent AF (but not in acute AF)
Inoue (2004) [524]	246 (non-valvular)	111	D-dimers if impaired LAA function
Kumagai (2004) [525]	16 (post mortem)		D-dimers in patients having risk factors, PF1 + 2 (NS)
Marin (2004) [526]	24 (acute onset) 24 (chronic)	24 (CAD patients in sinus rhythm) 24 (healthy)	vWF and protein in patients with enlarged atrium
Nozawa (2004) [527]	509	111 (healthy)	D-dimers, vWF, s-thrombomodulin (no longer different after cardioversion)
Freestone (2005) [528]	59	40 (healthy)	D-dimers, PF1 + 2 (NS)
Nozawa (2006) [295]	509 (non-valvular)		vWF
Ohara (2007) [294]	591 (non-valvular)	129	D-dimers (but not PF1 + 2) predictive for thromboembolic events
			D-dimers, PF1 + 2, platelet factor 4, b-thromboglobulin
			D-dimers, PF1 + 2 (correlated with presence of risk factors for stroke)

AF, atrial fibrillation; AFL, atrial flutter; CAD, coronary artery disease; LA, left atrial; LAA, left atrial appendage; NS, non-significant; vWF, von Willebrand factor; PF1 + 2, prothrombin fragment 1 + 2; TATIII, thrombin-antithrombin III; TF, tissue factor; s-thrombomodulin, soluble-thrombomodulin.

^a Significantly different in AF group, unless otherwise indicated.

In another study evaluating the relationship of extracellular matrix modulators (matrix metalloproteinases, MMPs, and their tissue inhibitors, TIMPs) and AF risk, only elevated MMP9 levels were significantly associated with AF risk [287]. Proteases having desintegrin and metalloprotease activities (ADAM) are related to atrial dilatation and thereby influence mechanical performance of the atria [288].

The clinical benefit of considering biomarkers associated with AF is questionable unless there is clear evidence of a direct benefit in AF risk prediction and management- this has not been achieved to date.

6.2. Prothrombotic indices – coagulation, platelets

Over 150 years ago, Virchow proposed a triad of abnormalities that contributed to thrombus formation (thrombogenesis), that is, abnormalities of vessel wall, abnormal blood flow and abnormal blood constituents (Fig. 10). In the setting of AF, abnormalities of vessel walls are evident by the association of thromboembolism with structural heart disease (eg. mitral valve stenosis) and complex aortic plaque, as well as endothelial damage/dysfunction, whether recognised by biomarkers (eg. von Willebrand factor (vWF), tissue plasminogen activator, tPA), immunohistochemistry studies of the left atrial wall, electron microscopy, or by functional studies (eg. flow mediated dilatation) [289]. Abnormal blood flow in AF can be visualised by spontaneous echocontrast in the LA, as well as low left atrial appendage Doppler velocities. Abnormal blood constituents in AF are evident from abnormalities of coagulation, platelets, fibrinolysis, inflammation, extracellular matrix turnover, etc. that are all directly or indirectly associated with thrombogenesis, or a predisposition to the latter. While abnormalities of platelets are often evident in AF, they may be more reflective of associated vascular disease or comorbidities than of AF per se [290,291]. Indeed, thrombus obtained in AF is largely fibrin-rich ('red clot') compared with arterial thrombus, which is largely platelet-rich ('white clot'), providing a mechanistic explanation for the role of anticoagulation therapy, rather than anti-platelet therapy for AF-related thromboembolism [291,292].

The concept of AF being a prothrombotic or hypercoagulable state was first proposed in 1995 [293]. Many prothrombotic indices in AF have been related to subsequent stroke and thromboembolism, whether in non-anticoagulated or anticoagulated subjects (Fig. 10). Initial studies showed that coagulation-related factors, such as fibrin D-dimer (an index of fibrin turnover and thrombogenesis) were related to stroke risk strata as well as an adverse prognosis from thromboembolism, whether or not patients were anticoagulated [294–297]. In contrast, there was no prognostic advantage of platelet indices [295,298,299].

6.2.1. Prediction of thrombogenesis

Addition of vWf refines clinical risk stratification in AF, first shown in the non-anticoagulated or suboptimally anticoagulated patients from the SPAF study [300]. More recently, vWf has been related to thromboembolism as well as bleeding risks in anticoagulated AF patients [301]. Ancillary studies from large Phase 3 anticoagulation trials have reported prognostic implications for increased levels of D-dimer, troponin, natriuretic peptides, and novel biomarkers (e.g. GDF15) [302–304]. Many of these studies have been performed in selected clinical trial cohorts, and the prognostic role in risk stratification requires prospective testing in unselected large 'real-world' cohorts with a broad range of stroke risk and renal function. As in the case of AF prediction, evidence for the additive value of biomarkers for stroke risk prediction from large prospective non-anticoagulated 'real-world' cohorts is limited [305]. Endocardial thrombogenic alterations in diseased atria, which appear to be related to oxidative stress, appear to contribute

to clot formation, particularly in the left atrial appendage [306–310]. Thus, the impact and the relation between EHRAS Classes and the extent of endocardial thrombogenic alterations have to be assessed in future studies. Interestingly, duration of AF does not correlate with the extent of observed endocardial changes [309].

7. Imaging techniques to detect atrial cardiomyopathies mapping and ablation in atrial cardiomyopathies

It is well established that an enlarged LA is associated with adverse cardiovascular outcomes [311–316]. In the absence of MVD, an increase in LA size most commonly reflects increased wall tension as a result of increased LA pressure [317–320], as well as impairment in LA function secondary to atrial myopathy [321,322]. A clear relationship exists between an enlarged LA and the incidence of atrial fibrillation and stroke [323–332], risk for overall mortality after myocardial infarction [321,322,333,334], risk for death and hospitalisation in patients with dilated cardiomyopathy [335–344], and major cardiac events or death in patients with diabetes mellitus [345]. Left atrium enlargement is a marker of both the severity and chronicity of diastolic dysfunction and magnitude of LA pressure elevation [317–320]. A recent consensus report on multi-modality imaging for AF patients summarizes the current status of atrial imaging in more detail [346].

7.1. Echocardiography

Echocardiography is the imaging modality of choice for screening and serially following patients with diseases involving the LA morphology and function [347].

For assessment of atrial size, most widely reported is the linear dimension in the parasternal long-axis view using M-mode or 2 delayed enhancement (DE) [324–339,345,347–349]. However, due to the complex 3D nature of the atrium and the non-uniform nature of atrial remodelling, this measurement frequently does not provide an accurate picture of LA size [350–354]. Thus, when assessing LA size and remodelling, the measurement of LA volume is a more powerful prognostic indicator in a variety of cardiac disease states [329,331,333–339,345,347–360]. Two-dimensional echocardiographic LA volumes are typically smaller than those reported from computed tomography or cardiac magnetic resonance imaging (CMR) [361–365]. Left atrium volume from 2D images is best measured using the disk summation algorithm because it includes fewer geometric assumptions [366,367]. The advent of 3-D ECHO has improved the accuracy of ECHO volume measurements which correlate well with cardiac computed tomography [368,369] and magnetic resonance imaging [370,371]. Compared with 2D assessment of LA volume, 3DE also has superior prognostic prediction [372,373].

The recommended upper normal indexed LA volume is 34 mL/m² for both genders which fits well with a risk-based approach for determination of cut-off between a normal and an enlarged LA [323,357–359].

7.2. Left atrial function by Doppler echocardiography

Left atrium function can be assessed by pulsed-wave Doppler measurements of late (mitral A) diastolic filling. Multiple studies have used this parameter as an index of LA function assessment, but it is affected by age and loading conditions [317,374–382]. The PV atrial reversal velocity has also been used as a measurement of LA function [317,377,379–382]. In the presence of reduced LV compliance and elevated filling pressures, atrial contraction results in significant flow reversal into the PVs [80,81]. Studies have also

demonstrated that Doppler tissue imaging can be used as an accurate marker of atrial function [383,384].

7.2.1. New echocardiographic techniques

Two-dimensional speckle-tracking echo has been used as a more sensitive marker to detect early functional remodelling before anatomical alterations occur [385–400].

Strain (S) and strain rate (SR) imaging provide data on myocardial deformation by estimating spatial gradients in myocardial velocities [385,388,392,393,401–405]. This technique has been used as a surrogate of LA structural remodelling and fibrosis [388–393]. Interestingly, LA dysfunction with changes in strain and strain rate has been observed in patients with amyloidosis in the absence of other echocardiographic features of cardiac involvement [402]. Abnormalities in atrial strain have been observed in diverse conditions, including AF, valvular pathology, heart failure, hypertension, diabetes, and cardiomyopathies [388,389,396–400]. Population-based studies have demonstrated the prognostic value of LA strain analysis for long-term outcome [388,394].

Less research and fewer clinical outcomes data are available on the quantification of RA size. Right atrial volumes are also underestimated with 2D echocardiographic techniques compared with 3DE [343,406,407].

7.3. Cardiac computed tomography

Cardiac CT may be used for accurate assessment of atrial volumes. Volumetric data from cardiac computed tomography (CCT) are comparable to data generated by CMR and 3D echocardiographic imaging and is superior to 2D echocardiography [371]. The LA volume prior to catheter ablation and the presence of asymmetry of chamber geometry predicts the likelihood of maintaining sinus rhythm post-procedure [408]. As the LA enlarges, the shape of the LA roof initially becomes flat and then becomes coved, and this progression may correlate with development of non-PV substrate in patients undergoing AF ablation [409].

CCT may also be used to screen for thrombus prior to AF ablation. The diagnostic accuracy of CT has been studied by multiple groups, with a systematic review of 19 studies and 2955 patients reporting a sensitivity and specificity of 96 and 92%, respectively, translating to a positive predictive value of 41% and a negative predictive value of 99% [410]. Diagnostic accuracy increased to 99%, with 100% specificity, when delayed imaging was performed. An advantage of using CT imaging to exclude thrombus is that CCT is frequently performed prior to AF ablation for integration into the electroanatomic mapping systems routinely used during AF ablation procedures. CCT can also provide accurate information about PV anatomy and variants and correlates well with CMR in that regard [411].

7.4. Magnetic resonance imaging of the atrium

Over recent years CMR has been used in clinical and research settings to provide gold standard volumetric assessments of chamber structure and function. Drawbacks are that CMR is expensive and has more limited availability than echocardiography. Recently, contrast-enhanced CMR with gadolinium has been used as a technique to detect atrial fibrosis [412]. Although these methods are still in relatively early stages and have not been extensively reproduced, the ability to identify early degrees of atrial structural change would no doubt enhance our ability to detect varying degrees of remodelling that may not be as clear from volumetric or functional assessment. In addition to late-gadolinium-enhanced (LGE) CMR to detect replacement fibrosis, post-contrast T1 mapping [413,414] has been used to quantify

diffuse interstitial fibrosis. Both techniques have been correlated with bipolar voltage measured during invasive mapping [412]. However, these techniques require specialised post-imaging processing. While they are commonly used for ventricular imaging, they have not been widely employed for atrial imaging because of the technical challenges in achieving adequate image resolution in the thin-walled atrium [415].

Using a systematic scoring system for the extent of delayed enhancement, a recently-published multicentre study has related the extent of LGE CMR detected fibrosis to the outcome of AF ablation [416]. The risk of recurrent AF increased from 15% for stage I fibrosis (<10% of the atrial wall) to 69% for stage IV fibrosis ($\geq 30\%$ of the atrial wall). The authors suggested that CMR quantification of fibrosis may play a role in the appropriate selection of patients most likely to benefit from AF ablation. Late-gadolinium-enhanced CMR has also been used to predict development of sinus node dysfunction [417], stroke risk [418], and progression of atrial fibrillation from paroxysmal to persistent [419]. However, various studies have highlighted the need to further improve the methods of accurately identifying replacement fibrosis and to improve reproducibility of data analysis before LGE CMR can be considered a routine clinical tool [420,421].

Recently, a number of studies have used CMR DE late gadolinium enhancement (LGE) in order to non-invasively characterize the extent and distribution of scarring present following AF ablation [422–424]. Several studies observed that patients with more extensive scar at 3 months (or greater percentage scar around the PV circumference) had a lower AF recurrence rate [423,425]. Another study showed a correlation between measured contact force at the time of ablation, and the extent of CMR determined scar development [426]. Other studies have shown a concordance between scar around the PVs and low-voltage regions on invasive electroanatomic mapping (EAM) [427,428]. Isolation of PVs at repeat procedures could be achieved guided by the imported MR image to identify the gaps [427,428]. However, other studies found no association between CMR scar gaps and mapped PV reconnection sites. A study in 50 paroxysmal AF patients undergoing either wide area or ostial ablation found that the proportion of patients in whom CMR could correctly identify the distribution of ablation lesions varied from as low as 28% to 54% depending on the technique used [429]. These authors concluded that LGE imaging of atrial scar was not yet sufficiently accurate to reliably identify ablation lesions or to determine their distribution. Whether CMR will have the resolution to detect such focal regions where scar is incomplete remains uncertain. Of note, Harrison et al. used an animal model to correlate lesion size on CMR with lesion volume at pathology. The correlation depended critically on the definition of pixel intensity used to define scar with small changes in definition leading to large changes in estimated scar volume [415].

7.5. Imaging with electroanatomic mapping

Electroanatomic mapping systems have become the standard for invasive substrate characterisation of atrial cardiomyopathies. Using various technologies, these systems allow for rapid characterisation and reproduction of atrial anatomy with 3-D display rendering. Anatomic variations in PV anatomy, including common ostium or additional veins, may be identified. Visualisation software allows for accurate measurements of atrial distances [430] and gross volumetric data but assessment of venous diameter may be suboptimal owing to venous susceptibility to distortion. Anatomic imaging of the atria may be enhanced with the co-registration of DICOM images from previously acquired cardiac MRI or CT or with the use of real-time contrast angiography or intracardiac echocardiogram.

While EAM allows for anatomic reproduction of the atria, it also enables the assessment of the atrial substrate through the geographic display of unipolar and bipolar signal amplitude data, as well as other signal characteristics, on rendered atrial surfaces. Regions of low-voltage, electrical silence, fractionation, or double potentials are reputed to correlate with underlying atrial fibrosis, surgical patches, or scar. In the same way, electrical activation of the atrium may be imaged allowing for assessment of regional changes in conduction velocity [431] that may be proarrhythmic and support the perpetuation of atrial fibrillation. The use of EAM for activation mapping of atrial arrhythmia will be discussed in the subsequent section on ablation techniques.

Electroanatomic mapping has been used to image the electroanatomic substrate of atrial cardiomyopathy associated with sinus node disease [432], rheumatic MS [215], atrial septal defect [218,431], CHF [433], obstructive sleep apnoea [117], and ageing [167]. It has been a powerful research tool that has enhanced our understanding of the atrial substrate in patients with paroxysmal and persistent atrial fibrillation and [74,434] those who have failed initial PV antrum isolation [435].

Unlike cardiac MR, CT, or echocardiography, EAM requires invasive catheterization and mapping. However, despite recent advances in MRI techniques that allow for imaging atrial scar, EAM imaging arguably has a great clinical feasibility and superior ability to image and to define the atrial substrate that leads to the development of atrial fibrillation. A recent consensus report on multi-modality imaging for AF patients is a useful detailed reference [346].

7.6. Ablation of atrial tachyarrhythmia

Numerous single-centre, randomized studies and larger multicentre observational registries have demonstrated the superiority of AF ablation over drug therapy for maintenance of sinus rhythm. However, late recurrences are common and associated with more advanced atrial substrate associated with structural heart disease [436–446].

It is in this context that it is important to consider the various types of underlying atrial cardiomyopathy and how they may affect ablation outcomes. This is timely, as it has recently been observed that lone AF is a rapidly disappearing entity as we recognise conditions such as sleep apnoea, obesity, endurance exercise etc. previously not suspected of being causally associated with atrial fibrillation [447]. In addition, emerging data suggest that treating these underlying causes may be central to improving long-term ablation outcomes [199,200,448,449]. In addition, LA ablation procedures may alter atrial size, structure, and mechanical atrial function. Catheter ablation may thus influence ongoing pathologies and atrial thrombogenesis [450,451].

Mapping studies have demonstrated a common electrophysiological endpoint for a range of such conditions affecting the atrium either primarily or secondarily, many of which have been shown to be associated with atrial remodelling characterised by conduction slowing and myocardial voltage reduction suggesting fibrosis [117,167,177,433,452,453]. Magnetic resonance imaging techniques attempting to characterize the extent of myocardial fibrosis have demonstrated that this appears to be the strongest independent predictor of AF recurrence after ablation [416,454]. Whether the EHRA classification has value for informing catheter ablation in human atria remains to be determined.

7.7. Age and atrial fibrillation ablation

Increasing age has been shown to be associated with increasing atrial fibrosis in both basic and clinical studies [167,455]. Numerous studies have evaluated ablation outcomes in ageing patients

(variously defined as .65 through to .80) [444,445,456–462]. Observational studies have consistently reported high multiple procedure success rates at 12 months of up to 80% in older patients. Conflicting data exist regarding outcomes in comparative studies with one study demonstrating a reduced success rate in patients over 65 years while another study showed similar efficacy in patients over the age of 80 years to the younger cohort [461,463].

7.8. Hypertension

Hypertension is another well-recognised risk factor for development of atrial fibrillation. Mapping studies have demonstrated the presence of a more advanced atrial substrate in hypertensive patients compared with controls [177,464]. Hypertension has been shown to be a risk factor for recurrence of AF after AF ablation in numerous studies on univariate analysis, but it is less clear whether this is independent of factors such as atrial size. Recent preliminary studies have suggested that aggressive treatment of hypertension improves post-ablation outcomes [200,464,465].

7.9. Heart failure and atrial fibrillation ablation

Contractile dysfunction has similarly been associated with advanced atrial remodelling and predisposition to atrial fibrillation both in basic and in clinical studies [113,433]. Numerous studies have evaluated the efficacy of catheter ablation of both paroxysmal and persistent atrial fibrillation with significant impairment of systolic function [437,466–473]. The weight of evidence is that sinus rhythm can be successfully achieved in 50–80% of patients although repeat procedures are common and follow-up periods are usually not more than 12 months. Successful ablation has been associated with significant improvements in ejection fraction and reduction in atrial size in the majority of studies [470,474].

7.10. Metabolic syndrome and obesity

A number of studies have evaluated the impact of the metabolic syndrome on catheter ablation outcomes in atrial fibrillation patients [475–480]. Although the data are mixed, the weight of studies and a systematic review [477] suggest a higher risk of AF recurrence. In the ARREST AF study, patients with BMI over 27 undergoing AF ablation had a much lower risk of recurrence if weight loss was achieved and maintained [200]. Observational studies have demonstrated a significantly lower risk of recurrent AF in patients with treated compared with untreated OSA [481].

7.11. Impact of diabetes on ablation outcomes

Several studies have documented an increased recurrence rate of atrial fibrillation after an ablation procedure in patients with diabetes mellitus [204,475,482]. An abnormal atrial substrate and non-PV triggers have been shown to underlie this worse outcome.

7.12. Role of myocarditis

Markers of inflammation such as CRP and IL-6 have been linked to risk of AF [267,483–485]. Recently, giant-cell myocarditis involving only the atria has been shown to result in atrial fibrillation with enlarged atria [149]. Patients with apparently lone atrial fibrillation frequently demonstrate histological findings consistent with an atrial myocarditis [486]; and those with past myocarditis may have atrial electrical scar, conduction abnormalities, or atrial standstill [146,487–489]. Baseline CRP levels have been associated with the risk of recurrent AF after catheter ablation [278]. Recently, colchicine has been used to prevent atrial

fibrillation recurrence after PV isolation [490]. It is also possible that AF in itself can result in inflammation and the development of an ‘atrial myocarditis’ [491].

7.13. Impact of atrial fibrillation duration on atrial myopathy and atrial fibrillation ablation outcomes

Longitudinal studies in AF patients have demonstrated clinical progression of AF over time in a significant proportion with risk strongly associated with drivers such as increasing age, structural heart disease, and hypertension [492]. Chronic AF results in structural change with a recent study showing that in proportion to AF burden, atrial remodelling may progress significantly even over a time period as short as 1 year.

Numerous studies have demonstrated that atrial size and occasionally mechanical function may improve following ablation [493], but at least one invasive study showed no improvement in atrial electrophysiology 6 months after successful ablation [219]. Overwhelmingly, studies evaluating long-term outcomes after ablation of persistent atrial fibrillation have demonstrated lower rates of procedural reversion to sinus rhythm and higher late recurrence rates reflecting more advanced atrial substrate.

7.14. Impact of ongoing atrial fibrillation on electrical and structural remodelling

It is now well known that in the presence of an appropriate heterogeneous AF substrate, a focal trigger can result in sustained high-frequency re-entrant AF drivers, named rotors. The waves that emerge from these rotors undergo spatially distributed fragmentation and so give rise to fibrillatory conduction. When high-frequency atrial activation is maintained for at least 24 h, ion-channel remodelling changes the electrophysiologic substrate, promoting perpetuation of re-entry and increasing the activity of triggers, further contributing to AF permanence [494]. Atrial fibrillation itself leads to remodelling, causing electrophysiological (electrical), contractile, and structural changes [495,496]. Although AF can typically be reversed in its early stages, it becomes more difficult to eliminate over time due to such remodelling [238,497]. Dominant-frequency analysis points to an evolution of mechanisms in AF patients, with PV sources becoming less predominant as AF becomes more persistent and atrial remodelling progresses [498]. The data suggest that in patients with long-standing persistent AF, atrial remodelling augments the number of AF drivers and shifts their location away from the PV/ostial region.

7.15. Impact of catheter ablation on atrial pathology

Several studies have examined LA size before and after catheter ablation and have demonstrated a 10–20% decrease in the dimensions of the LA after catheter ablation of AF [499,500]. Although the precise mechanism of this decrease in size is not known, it appears consistent with reverse remodelling. It has been suggested that earlier aggressive intervention to maintain sinus rhythm, including AF ablation if needed, may aid to prevent ‘chronicization’ of AF and improve long-term outcomes [501]. A large-scale multicentre trial is presently testing this idea [502].

The true impact of atrial cardiomyopathies on the success of catheter ablation has not been elucidated. Nevertheless, it is very likely that atrial pathology affects energy delivery to tissue and specific forms of cardiomyopathy may differentially affect ablation procedures. However, the true impact and interaction of various energy sources with different atrial pathologies need to be studied.

8. Conclusion

Atrial cardiomyopathies as defined in this consensus paper have a significant impact on atrial function and arrhythmogenesis. The EHRAS classification (EHRAS Class I–IV) is a first attempt to characterize atrial pathologies into discrete cohorts. Because disease-related histological changes in atrial tissue are often poorly characterised, not necessarily specific and vary considerably over time their classification is challenging. Further studies are needed to implement and validate the EHRAS classification and to assess its value in guiding clinical understanding and management of AF. Nevertheless, a more precise, defined classification of atrial pathologies may contribute to establishing an individualised approach to AF therapy, which might improve therapeutic outcomes.

Supplementary material

Supplementary material is available at Europace online.

Conflict of interest

A detailed list of disclosures of financial relations is provided as Supplementary material online.

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