International Journal of Cardiology 287 (2019) 174–180

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Clinical importance of atrial cardiomyopathy

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ARTICLE INFO

Article history:
Received 3 July 2018
Received in revised form 29 October 2018
Accepted 27 November 2018
Available online 28 November 2018

Keywords:
Fibrillation
Anticoagulation
Thrombogenesis
Therapy
Stroke

ABSTRACT

Atrial fibrillation (AF) is the most common cause of thromboembolic complications. The risk of suffering a thromboembolic complication correlates with the CHA2DS2-VASc score identifying patients at increased risk. It is based on patient age, prior thromboembolic events, and clinical comorbidities, but not based on pathophysiological changes in different types of atrial cardiomyopathy (ACM) as classified in the expert consensus on ACM published in 2016. The impact of different types of ACM has also been acknowledged in the expert consensus statement on catheter ablation of atrial fibrillation. The aim of this review is to review data on clinical importance of ACMs.

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1. Definition and classification of atrial cardiomyopathy

An atrial cardiomyopathy (ACM) is defined as "any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically-relevant manifestations." [1]

Diseases like arterial hypertension, heart failure, diabetes and myocarditis or aging are known to induce or contribute to an atrial cardiomyopathy. The induced changes are not specific. The extent of pathological alterations varies over time causing intraindividual and interindividual differences. A recent consensus document proposed a working histological/pathophysiological classification scheme for atrial cardiomyopathies using the acronym EHRAS (for **E**HRA/**HR**S/**A**PHRS/**S**OLAECE), defining 4 classes [1]:

Class I: principal cardiomyocyte changes;
Class II: principally fibrotic changes;
Class III: combined cardiomyocyte-pathology/fibrosis;
Class IV: primarily non-collagen infiltration (with or without cardiomyocyte changes) [1].

This simple classification helps to convey the primary underlying pathology in various clinical conditions. This classification is purely descriptive and in contrast to other classifications there is no progression in severity from EHRAS Class I to EHRAS IV. The classification may be useful to describe pathological changes in biopsies and to correlate pathologies with results obtained from imaging technologies. It has to be stated, however, that the proposed classification scheme is arbitrary and individual patients may also fulfill overlapping criteria. Furthermore, as the proposed scheme is rather new, clinical studies on the positive utility of the proposed classification are lacking to date.

While Class I is often seen in lone atrial fibrillation (AF) patients, genetic diseases and diabetes mellitus, Class II is more often observed in aging and cigarette smoking. Chronic heart failure patients are prone to a Class III pattern, while Class IV is often found in isolated atrial amyloidosis, granulomatosis, and diseases that are accompanied by inflammatory infiltrates or glycosphingolipid deposits [1].

In addition to histological changes in the tissue, ACM effect the atrial endocardium as well. Therefore, ACM may contribute to atrial thrombogenesis and stroke. At the level of atrial tissue, increased cytosolic calcium via activation of calcium-dependent proteases and phosphatases leads to the destruction of contractile filaments, to an impaired function of mitochondria, and hypertrophy of atrial myocytes as demonstrated in fibrillation human atria [2,3]. Besides calcium overload, AF causes increased generation of reactive oxygen species (ROS). Effects of oxidative stress on atrial myocardium have been shown in vitro and in vivo [4–8]. In sum, these processes cause increased synthesis of prothrombotic tissue factors at the endocardium of the left atrium (endothelial alteration) such as plasminogen activator inhibitor (PAI) 1, von Willebrand factor (vWF), adhesion molecules (ICAM, VCAM, selectins) and changes in TNF receptor superfamily

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https://doi.org/10.1016/j.ijcard.2018.11.121
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members like CD40/CD154 that control interaction between platelets, leukocytes and endothelial cells, as shown in a rabbit animal model by Kamyama et al., but also in various human experimental studies [9–12].

2. Relation between atrial fibrillation and atrial cardiomyopathy

All recently defined forms of ACM have in common that they are accompanied by electrical and structural remodeling as well as alteration in electromechanical coupling. These changes most often lead to the development of atrial fibrillation (AF).

Much is known on the impact of AF on quality of life, morbidity, and mortality due to increased risk for thromboembolism, aggravation of heart failure, or peripheral organ dysfunction [13–19].

In AF the major disease progression agent from paroxysmal to persistent/long persistent to permanent AF is usually the arrhythmia itself. However, in guidelines and consensus statements the presence of different forms of ACM is now widely acknowledged as a precursor and/or driver that leads to initiation or progression of AF as a disease [1,13].

This is in line with hypotheses of concerning the mechanisms that lead to the development of AF outlined in the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation by.

Calkins et al. [2] (Fig. 1). Besides focal triggers that are often located within the pulmonary veins (PV), multiple wavelets, single reentrant circuits with fibrillatory conduction, and functional reentry resulting from rotors or spiral waves may play a role on initiation and perpetuation of AF. Also, AF maintenance results from dissociation between epicardial and endocardial layers, with mutual interaction producing multiplying activity that maintains the arrhythmia [2]. These mechanisms have in common that they depend on electrical and structural atrial changes that can be observed in ACMs [2].

Yet, the exact impact of ACMs on AF disease management and progression are still under debate [20] due to the fact that for most forms clinical trials that evaluate differences in outcome or treatment options are lacking.

3. Clinical importance of atrial cardiomyopathies

As early as in 1997, Frustaci et al. uniformly found profound histopathological changes in patients with lone AF (AF without underlying cause, i.e. valvular heart disease or heart failure) that included inflammation and patchy fibrosis [21], but it took until now to categorize these changes in the 2016 comprehensive expert consensus mentioned in the first chapter.

Interestingly, another two years later, a medline search on "Atrial Cardiomyopathy" merits only 57 scientific article hits. Some of these articles are experimental or animal studies, others are reviews. Only a minority of these articles evaluate clinical effects of ACM in studies conducted in humans. Before evaluating these data that show evidence for clinical importance of ACM, the correlation between histopathological patterns seen in the different EHRAS Classes with clinical disease shall be discussed. Despite an overlap of different Classes of ACM in individual patients, there are disease entities that induce a gross pattern EHRAS Class of ACM. Thus, for example obese or diabetic patients are more prone to develop Type IV-f ACM (fatty infiltration) while in elderly patients or patients with chronic heart failure an EHRAS Class II or III (fibrotic or mixed cardiomyocyte/fibrotic) pattern is seen. While in EHRAS Class I ACM the alterations in atrial function are dependent on cardiomyocyte dysfunction alone, EHRAS Class II–IV ACM show different macroscopic tissue alterations. These can be observed via histopathological examination or by imaging technologies like gadolinium enhanced cardiovascular magnet resonance imaging (MRI).

When looking at the term ACM, one has to divide the clinical disease entities that have impact on the individual AF patient: On the one hand the thromboembolic risk, on the other hand morbidity factors that can be contributed to the rhythm disturbance per se. This is important, as it has to be acknowledged that ACM in itself may increase thromboembolic risk without AF [1,22,23]. This stunning result was also observed in the "Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial" (ASSERT), where thromboembolic events and AF had no temporal correlation and in fact thromboembolic events frequently preceded first documented AF [24].

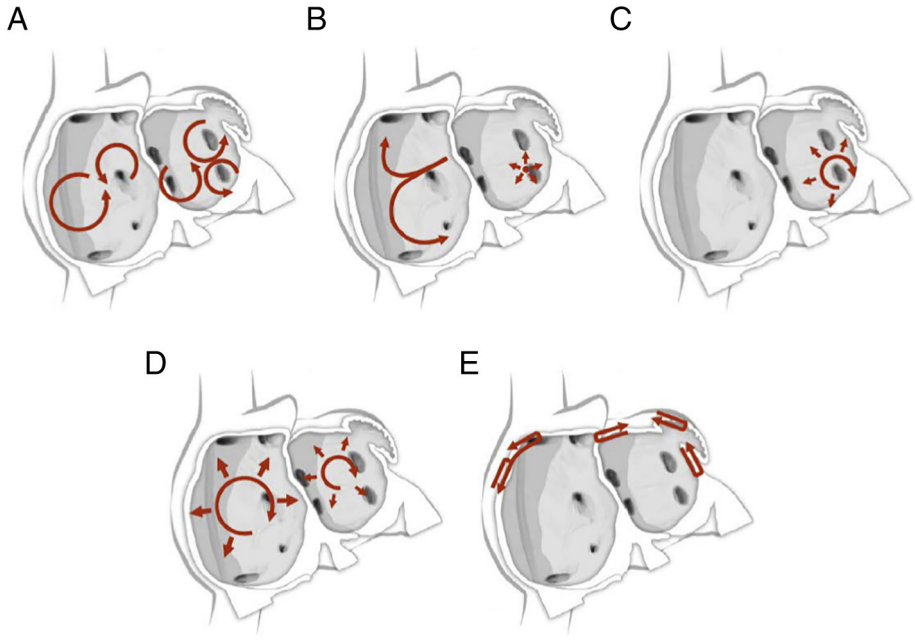

Fig. 1. Schematic drawing depicting various hypotheses and proposals concerning the mechanisms of atrial fibrillation, adopted from [2]. A: Multiple wavelets hypothesis. B: Rapidly discharging automatic foci. C: Single reentrant circuit with fibrillatory conduction. D: Functional reentry resulting from rotors or spiral waves. E: AF maintenance resulting from dissociation between epicardial and endocardial layers, with mutual interaction producing multiplying activity maintaining the arrhythmia.

Concerning rhythm alterations we know that AF is a progressive disease and AF burden correlates with disease duration, atrial enlargement and the consecutive atrial histopathological changes accompanied by ACM. This again has impact on the disease management, be it medical therapy or catheter ablation based approaches [25].

3.1. Cardiomyocyte related atrial cardiomyopathy (EHRAS Class I)

Although the EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies links cardiomyocyte related atrial cardiomyopathy to muscular dystrophies, obstructive sleep apnea, AF-induced remodeling, high blood pressure, diabetes mellitus, valvular heart disease or drug induced changes [1,26], a medline search on various search terms on this specific form of ACM does not yield >20 hits. Most data come from rodent knock out experimental models like in the cardiac-specific liver kinase B1 knockout mouse AF model reported by Ozcan et al. [27] or the heritable ACM myosin light chain 4 dysfunction rat model investigated by Peng et al. [28]. Hucker et al. gave an overview on genetics involved in cellular ACM in 2016 [29]. Since then, however, to our knowledge, no more data on genomics and/or proteomics have been published. Thus, it can be stated, that our understanding of pure EHRAS Class I ACM is still basic and far from comprehensive.

3.2. Fibrotic atrial cardiomyopathy (EHRAS Class II)

MRI quantification of fibrotic alterations in human atria are more and more entering clinical use for evaluation the optimal ablational approach in interventional treatment of AF [30–34]. For disease severity, the Utah-Score has been proposed [34]. It shows the percentage of fibrotic atrial and pulmonary vein tissue that is visualized by late gadolinium enhanced CMR:

Utah I: ≤5% area of late enhancement
Utah II: >5–20% area of late enhancement
Utah III: >20–35% area of late enhancement
Utah IV: >35% area of late enhancement.

Fig. 2 shows late gadolinium enhancement MRI images of the different Utah Classes I–IV as published by Vergara et al. [34].

In another study, Akoum et al. analyzed Utah Scores in 144 patients that underwent pulmonary vein isolation (PVI) and septal and posterior wall debulking. Three months later LA and pulmonary vein antral scarring were analyzed by CMR. AF Recurrence was predicted by circumferential PV scarring in Utah stage 2 and by overall LA wall scarring in Utah stage 3. No recurrence predictors were identified in Utah stage 4. This emphasizes the importance of ACM-assessment to develop optimal treatment strategies for AF. There is, however, disagreement in the published literature regarding the reproducibility, accuracy, precision, and reliability of MRI measured atrial fibrosis. Therefore comparison with other methods may yield better results.

Another semiquantitative method of fibrotic tissue evaluation is echocardiography based 3D speckle tracking [35]. Due to the feasibility of this in vivo visualization and quantification of EHRAS Classes II and III changes, more studies on clinical impact, prognosis and management strategies are underway.

In a subset of ACM patients, the rule of Wijfels that "AF begets AF" [36] may not always hold true. In some cases ACM may lead to first onset persistent AF with poor prognosis concerning rhythm control especially in young obese hypertensive male patients [37]. Stiles et al.

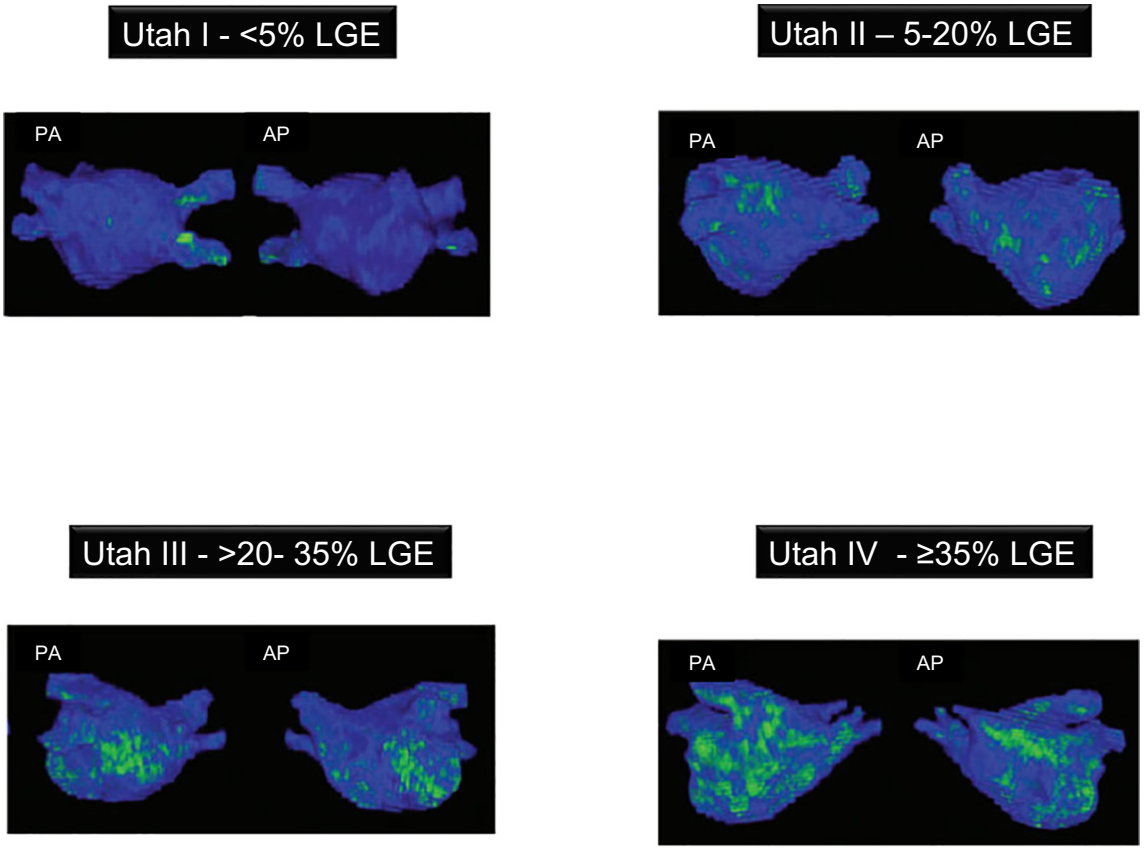

Fig. 2. University of Utah late gadolinium enhanced (LGE) based magnet resonance imaging (MRI) staging system for the amount of left atrial fibrosis. Adopted from [34].

come to the same conclusion, as in paroxysmal lone AF "sinus rhythm does not beget sinus rhythm" [38]. They demonstrated that in this study patients with paroxysmal AF, remote from arrhythmia, had bi-atrial abnormalities. These consisted of larger atrial volumes, longer ERP, longer conduction time along linear catheters, longer bi-atrial activation time, slower conduction velocity, greater proportion of fractionated electrograms, longer corrected sinus node recovery time, and lower voltage [38].

Another study by Ju et al. identified idiopathic isolated fibrotic ACM as a source for scar-related atrial tachycardia in 26 patients (mean age 46 ± 13 years) with 52 non-surgical scar-related atrial tachycardias (AT) [39]. Catheter ablation was acutely successful for all patients, and pacemaker implantation was performed in seven patients who presented with sinus node dysfunction or atrial standstill after termination of the AT. In three patients with multiple AT recurrences, the diseased areas of the right atrium were resected and dechannelled via mini-invasive surgical interventions. Histological examinations revealed profound fibrosis without amyloidosis or adipose deposition. Viral and familial investigations yielded negative results. Fibrosis progression over a median of 45 (5–109) months of follow-up manifested as atrial arrhythmia recurrence in seven patients and atrial lead non-capture due to newly developed atrial standstill in two patients. Interestingly, two of these rather young AT-patients (7%) suffered four stroke events before receiving anticoagulation treatment [39]. Also, Daccarett et al. identified fibrotic ACM as an independent risk factor for stroke [40]. This emphasizes the clinical importance of identifying these ACM only patients and warrants further studies that evaluate stroke risk in this special non-AF patient population.

3.3. Fatty atrial cardiomyopathy (EHRAS CLASS IVf)

Epicardial adipose tissue (EAT) is metabolically active and a source for adipokines, and inflammatory cytokines. It can also be a surrogate parameter for coronary artery disease as shown in a clinical study by Meenakshi et al. [41]. It is of mesothelial origin and hence shares its vascular supply from coronary arteries with the myocardium. EAT thus influences the myocardium via paracrine and vasocrine effects. It has been shown that human ventricular epicardial adipose tissue strongly correlates with coronary artery disease progression [42,43]. Venteclef et al. found adipo-fibrokine Activin A of human EAT but not subcutaneous adipose tissue to induce fibrosis in rat organo-cocultures, an effect that could be reversed by an Activin A antibody [44].Hatem and Sanders state that Activin A is produced in abundance in heart failure and diabetic patients [45]. Also, Packer recently discussed EAT as a transducer of the adverse effect of systemic inflammation and metabolic disorders on the human heart [46]. He linked this form of ACM to the

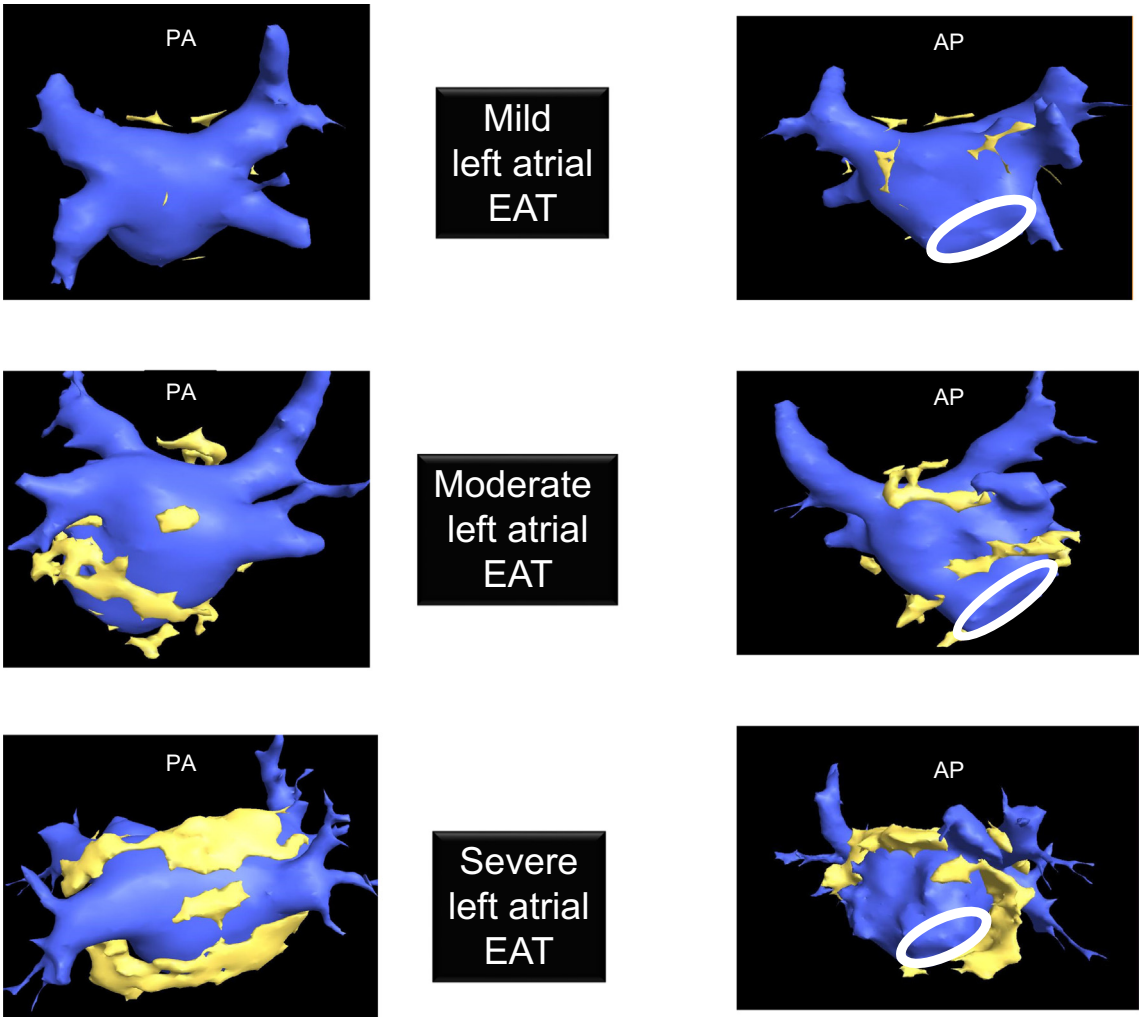

Fig. 3. Depiction of 3D reconstruction of the left atrium (blue, mitral valve localization marced with white circle) and adjacent epicardial adipose tissue (EAT) marked in yellow. Antero-posterior (AP) and postero-anterior (PA) view for three patients with mild (upper panel), moderate (middle panel) and severe (lower panel) EAT. For details see text.

development of heart failure with preserved ejection fraction (HFpEF), a disease state that to date despite large prevalence and significant morbidity has few treatment options. The authors therefore postulates atrial and ventricular EAT to be a possible source for new biomarkers and an important treatment target for this patient population.

In comparison to MRI based quantification of atrial fibrosis and in contrast to CT based ventricular epicardial adipose tissue (EAT) imaging, visualization of atrial epicardial or intramyocardial adipose tissue is not used very often. Mahajan et al. conducted a feasibility study with 10 merino cross sheep that showed accurate and reproducible MRI based assessment of atrial fibrofatty pericardial tissue [47]. Pericardial tissue was defined as the sum of EAT (between myocardium and visceral pericardium) and paracardiac adipose tissue adherent and external to the parietal pericardium. However, there is few data on imaging of atrial EAT in humans. We have therefore visualized EAT by multisliced (360 slices) CT scans that were then processed using the Philips EP Navigator software that allows for automated 3D organ reconstruction. This technique is described in detail elsewhere [48]. In short the automated reconstruction can be preprocedurally cross-checked and modified/corrected by the investigator. It allows for 3D visualization of all heart chambers, the trachea, the coronary sinus, and the aorta. These organs then can be used as a coloured 3D overlay picture to conventional X-ray, for example during an electrophysiology study. We have visualized human atrial EAT by marking areas of negative Hounsfield units (below −30 HU). Fig. 3 depicts posterior-anterior (pa) and anterior-posterior (ap) view of three patients with mild, moderate or severe EAT burden (yellow) circumferential to the left atrium (blue; localization of the mitral valve depicted with a white circle). Accumulating data suggest that quantification of EAT and fibrotic remodeling of adipose tissue may be a future cornerstone for a specifically tailored therapy strategy. Haemers et al. performed detailed histological analyses of atrial samples collected from patients with AF and from a sheep AF model [49]. They found that AF disease progression is associated with fibrosis of fatty subepicardial infiltrates and is accompanied by inflammatory processes. They hypothesized that these subepicardial infiltrates contribute to conduction heterogeneity and thus foster AF.

Wong et al. have summed up current evidence and clinical implications of the positive correlation between epicardial fat and AF [50]. To them, however, therapy-wise this field is still in its infancy concerning unraveling of genetics and pathways that may be targets for future therapy. Furthermore, data on the influence of EAT on clinical outcome parameters such as morbidity, AF burden/progression, or AF ablation success are currently lacking.

4. Upstream therapy for atrial cardiomyopathy

Angiotensin Converting Enzyme (ACE)-inhibitor therapy or ARBs might reduce stroke risk in AF patients. Several studies have evaluated upstream therapy for hampering initiation of atrial remodeling that leads to ACM and AF. Besides life style modification/weight loss, substances included were statins, mineralocorticoid receptor blockers, Angiotensin Receptor Blockers (ARB), ACE-inhibitors and omega-3 polyunsaturated fatty acids [51,52].

Middeldorp et al. recently presented results of the "PREVEntion and regReSsive Effect of weight-loss and risk factor modification on Atrial Fibrillation": the REVERSE-AF study [53]. They could show that weight loss was progressively associated with a significant reduction in AF burden, underlining the importance of metabolic effects on ACM.

However, most randomized trials on upstream medical therapy, like in the study by Suleiman et al. on the effect of statin therapy on AF recurrence after pulmonary vein ablation therapy, have failed to show beneficial effects of these substances [54]. In the "Angiotensin II-antagonist in paroxysmal atrial fibrillation (ANTIPAF) study" one year of 40 mg of Olmesartan once daily did also not reduce the number of AF episodes in patients with documented paroxysmal AF [55].

Although there have been no randomized controlled studies (RCTs) in the primary prevention setting, in retrospective metaanalyses of upstream therapies Savelieva et al. found a sustained reduction in new-onset AF with ACE-inhibitors and ARBs in patients with significant underlying heart disease (e.g. left ventricular dysfunction and hypertrophy), and in the incidence of AF after cardiac surgery in patients treated with statins [56,57]. However, the recently published

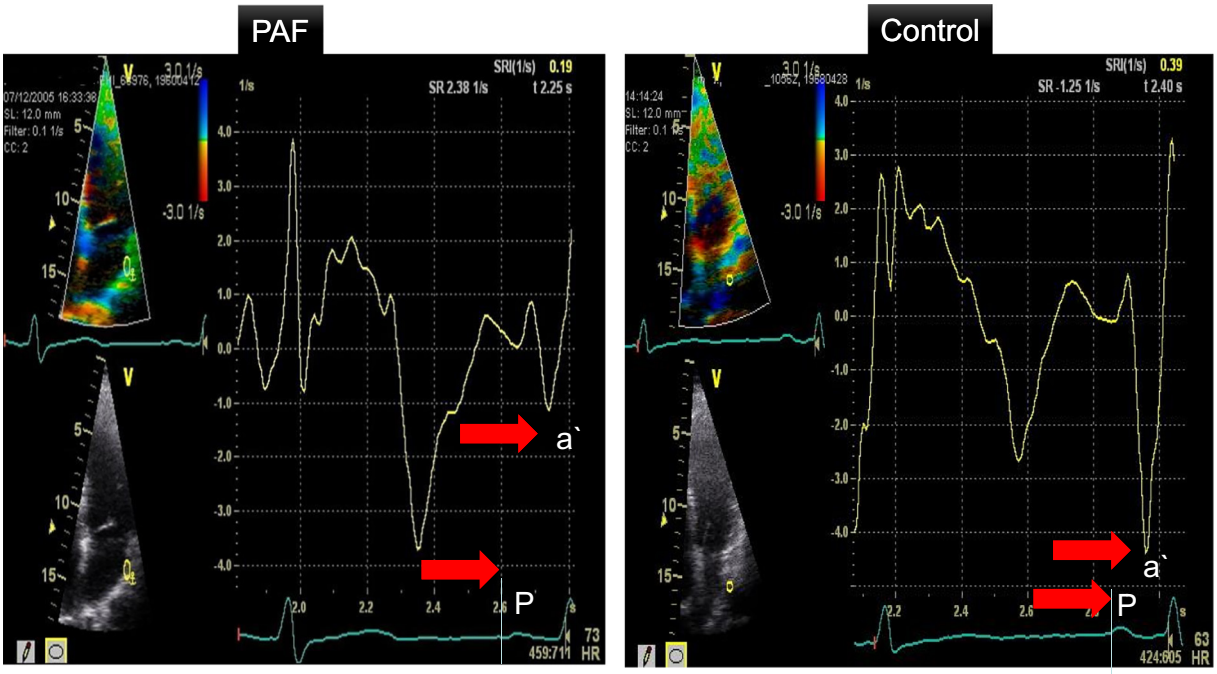

Fig. 4. Recording of strain rate at the lateral left atrial wall in patients with paroxysmal AF (PAF) and in a control patient with sinus rhythm. Differences in strain rates are clearly visible (marked with an arrow; a′). The surface P-wave is also marked. Time between P-wave onset and a′ was used to calculate the electromechanical time index in each patient. Adopted from [59].

RACE-3 trial showed positive effects of upstream therapy in patients with heart failure and AF if ACE-inhibitors were combined with statins and spironolactone [58].

Hypertensive patients and those with congestive heart failure appear to benefit most. Inhibition of angiotensin II and consecutive oxidative stress might directly protect atrial myocytes and their contractile performance.

In line with these result, our working group recently published data that evaluated atrial mechanical function in patients with paroxysmal AF using tissue Doppler analysis (TDA) during sinus rhythm [59]. Velocity (V), strain (S) and strain rate were measured in the medial segment of each wall of the left atrium (anterior, posterior, inferior und lateral wall) and in the mitral valve annulus. Tissue Doppler imaging results suggest that ACE-Inhibitor and Angiotensin II inhibitor therapy (AT2-Anta) increase contractile performance of the atria in patients with paroxysmal AF. Therapy with AT-2 Anta, was associated with an increased velocity of the left inferior wall and the systolic strain rate of the left lateral wall (Fig. 4). Importantly, a hint for the presence of ACM might be diagnosed using the surface P-wave duration since the P wave is prolonged in patients prone to AF. Lehtonen et al. could show that this parameter was associated with modifiable risk factors and correlated with the development of AF [60]. They concluded that P-wave duration may "represent intermediate steps of ACM on a pathway leading to AF". These data are in line with the metaanalysis conducted by He et al. that could demonstrate a positive correlation between p-wave indices like p-wave duration, p-wave terminal force in V1 and p-wave area for incident ischemic stroke risk [61]. Further prospective longitudinal studies need to be conducted, however, to evaluate the prognostic significance of various echocardiographic indices in correlation with medical intervention strategies in the future.

5. Conclusion

ACM is a disease progression driver with a specific attributable stroke risk independent from AF. The rather newly defined EHRAS Classes for ACM show differences in the histopathological substrate that to date do rarely influence our treatment management, be it oral anticoagulation for stroke prevention or specific medical or interventional ablation approaches to treat AF. However, the studies presented in this review show accumulating data that disease progression and treatment success is correlated with different severity stages (UTAH Score) and ACM types (EHRAS Classes). Yet, it has to be mentioned that clinical data on ACMs are scarce, and for some ACMs like EHRAS Class IVi (inflammatory cell driven) or IVa (amyloid accumulation) they are even more lacking than for fibrotic or fatty ACM. However, the authors believe that the histopathological changes in ACM influence disease progression, prognosis and treatment strategies – especially concerning individually tailored medical and ablational approaches for substrate modification in diseased atria. Further randomized prospective trials are warranted to increase our knowledge about this tailored therapy that take into consideration the underlying pathology that lead to AF. It encompasses optimal oral anticoagulation treatment, interventional ablational approaches based on type and severity of ACM, and medical upstream/downstream therapies that may even include genetically based approaches in the future.

Acknowledgment

This work was funded by research grants from the "Josef-Freitag-Stiftung" and "Deutsche Herzstiftung e.V."

Conflict of interest

M.H.: Speaker fees from Astra Zeneca, Boehringer Ingelheim, Bayer Health Care, BMS/Pfizer, Daiichi-Sankyo.

A.G.: Speaker fees from Astra Zeneca, Berlin Chemie, Boehringer Ingelheim, Bayer Health Care, BMS/Pfizer, Daiichi-Sankyo. A.B. None.

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