Commentary : ***Looking beyond the atrial wall in AF-a review of 2019 and into the next decade.***

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As we enter the next decade, the 2019 publications in IJC reflect the emerging insights of imaging in the mechanistic and therapeutic arenas of AF. Advances in MR, CT and PET are providing new perspectives not only on the atrial substrate but the important influence of the autonomic nervous system and inflammation in the pathobiology of this condition which is likely to generate new therapeutic targets.

It can be surprising how simple observations in medicine can lead to new therapeutic avenues. Over the past decade, it has become clear that the volume of epicardial fat on CT is correlated with the probability of developing AF[1]. Coumel's original observations in nocturnal AF identified the importance of the autonomic nervous system[2]. This year, *Kawasaki et al* explored the relationship between epicardial fat volume and changes in sympathetic activity post-ablation using a combination of CT and PET MIBG imaging respectively[3]. The volumes of the total Epicardial Adipose Tissue (EAT) and peri-atrial EAT surrounding the left atrium were measured by CT before catheter ablation, and the periatrial to total EAT volume ratio (P/T) calculated. During the 11+/-4m follow up, AF recurrence was observed in 14/64 patients. The MIBG wash-out rate (WR) change from baseline to 3 months after ablation (dWR) and P/T were significantly greater in patients with than without AF recurrence. Patients with both greater dWR (≥6.9%) and P/T (≥17.1%) had a higher risk of AF recurrence than those with either and none of them. Periatrial EAT volume showed a significant correlation with the baseline WR. Their conclusion was elevated sympathetic tone 3 months after ablation and periatrial to total epicardial adipose tissue volume ratio might be independently associated with late AF recurrence in patients without heart failure. This is an interesting observation, although limited to a small group of non-heart failure AF cases. However, it extends other observational studies demonstrating how the inflammatory substrate of EAT promotes AF and the sympatho:vagal balance modulates arrhythmogenic foci. Indeed P/T reflects arrhythmic substrates, while delta WR is associated with arrhythmogenic triggers. The question is whether the two are linked.

The role of inflammation is highlighted further in another PET study by *Watanabe et al*. using a retrospective analysis of patients undergoing CT/PET for malignancy[4]. Among 8233 patients who underwent FDG-PET/CT as work-up for malignancies, 180 consecutive patients with AF (2.2%) were identified. For quantitative analysis, the maximum standard uptake value (SUVmax) in the left (LA) and right atrial (RA) myocardium and the target-to-background ratio (TBR) of SUVmax to blood pool activity were measured. Multivariable analysis of 11 clinical and imaging variables showed significant associations with RA SUVmax (odds ratio [OR]: 14.353, $P = 0.026$) and LA volume (OR: 1.371, $P = 0.0001$). The RA TBR was greater in cases with persistent AF than in those with paroxysmal AF ($P < 0.0001$). Pathological investigation of

4 autopsy hearts confirmed infiltration of extravascular macrophages and lymphocytes in the regions with FDG uptake. Their conclusions were that higher atrial FDG uptake was associated with AF. PET/CT could be a useful tool for detecting local inflammation in the atria with AF. This is important as it demonstrates the role of local myocarditic processes in AF and links the previous EAT imaging study to AF pathophysiology. There are parallels here between arrhythmognenic cardiomyopathies including sarcoidosis, desmosomal arrhythmogenic cardiomyopathies where inflammatory processes operate and lead to triggered and re-entrant activity. Indeed, as the study highlighted, Platonov et al. showed persistent AF patients had more extensive fibrotic replacement of atrial myocardium and more CD3- and CD45-positive leukocytes than patients with paroxysmal AF[5]. *Watanabe et al* also examined specimens of autopsy hearts obtained after the patients' PET/CT examination and found that various inflammatory cells, such as macrophages or lymphocytes, had infiltrated in areas that agreed well with the atrial regions of FDG uptake. These findings have really important implications in identifying new therapeutic targets in AF.

EAT is a highly active visceral tissue producing a host of different pro- and anti-inflammatory adipocytokines, metabolic and growth factors that can directly diffuse into the myocardium. Various lines of evidence suggest local inflammation is a key mediator in AF. This was extensively reviewed by Scott et al in IJC[6]. Importantly, EAT releases a secretome of pro-inflammatory cytokines. These agents can also exert electrophysiological effects[7,8]. Lin et al. demonstrated that epicardial, abdominal and retrosternal adipocytes all prolong the LA action potential, while epicardial adipocytes also significantly altered the resting membrane potential[8]. The late sodium current, L-type calcium channel current and transient outward current were all increased in the co-cultured cells while delayed rectifier potassium currents were smaller[8]. The authors also noted greater isoprenaline-induced delay after depolarisations in the co-cultured cells[8]. Taken together, these changes in action potential would all promote arrhythmogenicity in left atrial cardiomyocytes and illustrate the extensive direct modulatory effects of visceral fat.

In addition to this, there may be a direct link between secretome components and autonomic activity as alluded to but not specifically studied in *Kawasaki's* paper. This year, *Zhou et al* examined the regulatory role of aponectin, a secretome component, on autonomic activity looking at a model of rapid atrial pacing (RAP) induced AF. Adiponectin (APN) is a cardioprotective protein mainly secreted by adipocytes which acts as an antiatherogenic and anti-diabetic adipokine through activation of its two receptors, adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2)

In this study the question as to whether APN could regulate cardiac autonomic activity and

suppress RAP-induced AF was addressed. They studied 18 beagles were divided into the control group (saline plus sham RAP, N = 6), the RAP group (saline plus RAP, N = 6) and the APN + RAP group (APN plus RAP, N = 6). APN (10 μg, 0.1 μg/μL) or saline was microinjected into 4 major ganglionated plexi (GP) prior to RAP. Compared with the control treatment, RAP shortened effective refractory period (ERP) values at all sites and increased cumulative window of vulnerability (ΣWOV), anterior right GP (ARGP) function and neural activity, whereas APN injection reversed these changes. Mechanistically, APN ameliorated RAP-induced inflammatory response and down-regulated the expression of c-fos protein and nerve growth factor. Moreover, the APN receptors 1 and APN receptors 2 were detected both in neurons and in non-neuronal cells. APN pretreatment activated down- stream adenosine monophosphate-activated protein kinase (AMPK) signaling, inhibited nuclear factor-kappa B signaling and promoted macrophage phenotype switching from pro-inflammatory to anti-inflammatory state. Therefore, this study demonstrates that administration of APN into ganglionic plexi can suppress RAP-induced AF by regulating the cardiac autonomics. APN signaling could be a potential therapeutic target in AF.

The study provides an elegant mechanistic link between how EAT can influence autonomic activity and sheds light on utilizing secretome derived proteins as therapeutic agents to prevent or treat AF.

Beyond the role of CT and PET shedding light on the importance of inflammation in AF, a key challenge is identifying the optimal ablation targets to prevent AF and predict sites of re-entrant atrial tachycardias (AT). This was addressed by *Honarbakhsh et al* who undertook an examination of the conduction and voltage amplitude in the atria to predict sites of re-entry using basket mapping, They showed that sites of rate-dependent conduction slowing predominantly localize to scar border zone (74%) and, for the first time, define a signature of conduction restitution for prediction of localized ATs (found in 82% of cases). The exciting prospect of this method is that it could be used in sinus rhythm to predict sites where localized atrial tachycardias develop and also perhaps their relationship with AF sources. In time, this may lead to prospective targeting of these sites and reduce AT occurrence after AF ablation. The challenge is to both develop the optimal mapping and pacing protocols to efficiently map the atria and ideally relate these sites to specific imaging features e.g. fibrosis burden, wall thickness, fibre orientation along similar lines to current predictive imaging strategies in VT mapping[11]. Such an approach may enable more tailored pre-operatively planned ablation strategies in AT and AF especially if the inflammatory drivers in the process can be modified to improve outcomes.

This strategy should be coupled with earlier detection of AF using wearable technologies

which will also enable shorter detection to ablation times as highlighted by *Kawaji et al.* who enrolled 1206 consecutive patients undergoing first-time ablaton for AF[12]. The 5-year event-free rates from recurrent atrial tachyarrhythmias after the first and second ablations were significantly higher in short detection-ablation time (DAT) group (<3 y) than in long DAT group (60.2% versus 48.3%, log-rank P< 0.001; 83.2% versus 75.2%, log-rank P = 0.02, respectively), leading to reduced cardiovascular hospitalization in short DAT group. There were no significant differences between the 2 groups in the event-free rates from all-cause and cardiovascular deaths. However, heart failure hospitalization, and ischemic stroke in patients with a history of heart failure or reduced left ventricular function, the event-free rate from heart failure readmission was significantly higher in short DAT group (85.0% versus 61.0%, P = 0.004). The impact of much earlier intervention should be evaluated in future studies.

Therefore, these studies really set the scene for the next decade to better interrogate AF substrates and develop new therapeutic agents. Further research should aim to better define specific pathophysiological subgroups of AF who can be targeted for autonomic, anti-inflammatory or purely substrate focused therapeutic strategies (alone or in combination) as our armamentarium of treatment modalities expands beyond the tip of an ablation catheter.

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