Fat infiltration in the infarcted heart as a paradigm for ventricular arrhythmias

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ABSTRACT

Recent research has revealed that infiltrating Adipose Tissue (inFAT) co localizes with scar in infarcted hearts and may be a factor in Ventricular Arrhythmias (VAs), a potentially fatal cardiac rhythm problem. The impact of inFAT on VA hasn't been well demonstrated, though. With the help of a combined prospective clinical and mechanistic computational study, we examined the function of inFAT versus scar in VA. We show that inFAT, rather than scar, are a primary driver of arrhythmogenic propensity and are frequently present in crucial areas of the VA circuit by using individualised computational heart models and comparing the outcomes of simulations of VA dynamics with measured electrophysiological abnormalities during the clinical procedure. We came to the conclusion that inFAT, not scar is primarily responsible for conduction slowing in crucial sites within the VA circuitry, thereby mechanistically promoting VA. Our findings challenge preconceived notions and pave the way for previously unconsidered anti-arrhythmic approaches by implicating inFAT as a key player in infarct related VA.

Keywords: Electrophysiological; Arrhythmogenic; Pro-arrhythmic; Anti-arrhythmic; Clinical procedure

INTRODUCTION

A significant global leading cause of death is sudden cardiac death. The risk of sudden cardiac death is significantly increased by life threatening VAs, particularly in patients with a history of myocardial infarction. VA prevalence and recurrence rates continue to be unacceptable high despite improvements in anti-arrhythmic medications and catheter ablation treatments, in part because the underlying substrate is still not well understood. Comprehensive characterization of this substrate might enhance currently used and provide information for new treatment approaches to lessen VA burden. Traditional dogma has long held that the arrhythmia substrate is comprised of disease induced heterogeneous scarring and fibrosis infiltration in ventricles with ischemia (infarction) or non-ischemic cardiomyopathies. Scar and fibrosis encourage uni directional obstruction and slowing of electrical wave conduction, which supports the development of arrhythmias. The identification of VA ablation targets on Late Gadolinium Enhanced-Cardiac Magnetic Resonance Imaging (LGE-MRI) has been used in numerous clinical investigations. However, despite their great efforts, VA recurrence rates have not significantly decreased, indicating that scar characterisation may not be enough to detect and treat VA [1].

LITERATURE REVIEW

Heart histology examinations frequently show that inFAT penetrates the myocardium and co-localizes with fibrosis. However, it continues to be a poorly understood feature of post-infarct remodelling, and its clinical significance is unclear. Recent research from our team and others points to a connection between inFAT and arrhythmia. Clinically, Contrast Enhanced-Computed Tomography (CE-CT) can detect inFAT. The precise function of inFAT in VA predisposition is unclear, nevertheless, because it coexists with fibrosis. No study has yet evaluated the arrhythmogenic potential of post-infarct inFAT against scar in patients with ischemic cardiomyopathy or offered insight into the possibility that scar and inFAT might work in concert to increase the likelihood of VA. Here, we present a combined prospective clinical personalized mechanistic computational investigation to characterise the function of inFAT versus scar in post-infarct VAs in detail. In this two center study, post-infarct patients were enlisted who were receiving VA ablation, and for the first time, CE-CTs and LGE-MRIs were collected concurrently from these patients. This allowed for the simultaneous visualisation of inFAT and scar distributions. A customised computational approach was used to determine the mechanistic roles of inFAT versus scar in arrhythmogenesis because imaging and intraprocedural Electro Anatomic Mapping (EAM) alone cannot tell which type of remodeling inFAT or scar is responsible for the aberrant electrical behaviour in the ventricles [2].

Novel hybrid CT-MRI 3D heart models were created for this purpose from each patient's imaging scans. Our findings refute long-held beliefs about infarct related VA and implicate inFAT as a key factor in post-infarct arrhythmias, paving the way for fresh approaches to efficiently lessen a patient's arrhythmic burden [3,4].

DISCUSSION

We clarify the significance of inFAT versus scar in infarct related VT probability in this first combined multi center prospective clinical and tailored computational analysis. We found that inFAT exhibits more pro-arrhythmic electrical anomalies than scar through imaging and intraprocedural EAM data. We show that inFAT, not scar is the main driver of substrate arrhythmogenic propensity using personalised heart models. InFAT is frequently present along with scar in the VT isthmus, which is the ideal target for ablation therapy. Last but not least, we determine that inFAT, and not scar, is the main source of arrhythmogenic conduction slowing that is present at important areas of the VT circuitry utilising a combined analysis of both the clinical EAM and mechanistic simulation data. Our findings challenge accepted notions concerning infarct related arrhythmias and identify inFAT as a significant contributor to VT, providing a novel avenue for the development of possible anti-arrhythmic treatments [5].

Our study questions accepted theories about VT caused by infarcts. Long thought to be the main contributor to pro arrhythmic structural changes in the substrate for VT, infarct scars distribution. According to classical teaching, the chronic infarct's heterogeneous scarring and electrical alterations gradually turn into the substrate required for VT. Not all areas of the scar are necessarily arrhythmogenic, and not every patient with a post-infarct will get VT. Approximately three years after an infarction, when the

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majority of VTs first appear, inFAT also exists in the post-infarct substrate and begins to manifest. In agreement, inFAT appears to be more prevalent in VT patients. For a number of reasons, inFAT is not a helpless spectator. First, independent of other crucial clinical parameters, inFAT predicts arrhythmic load. It has been demonstrated that inFAT is a reliable predictor of a composite outcome, which includes death, ventricular arrhythmias, and VT recurrence. In the present work, we showed that higher inFAT levels predicted enhanced VT burden in hybrid CT-MRI models, although an increase in scar volume did not predict raised VT burden. Second, inFAT is frequently found at areas that are important for VT. In our study, we first showed that regions of inFAT were associated with greater conduction slowing, even in the absence of scar. Furthermore, we showed that regions with inFAT have an increased sensitivity to VT because the majority of important VT isthmuses in both hybrid CT-MRI and LGE based cardiac models were found there. This result is in line with earlier research that showed crucial VT locations were frequently close to inFAT. Thus, inFAT contributes significantly to infarct-related VT rather than acting as a passive spectator.

Our research also identifies the mechanism by which inFAT encourages re-entrant VTs. Adipose tissue in the heart can have pro-inflammatory and paracrine effects that impede conduction and cause aberrant repolarization. Myocardial tissue near inFAT specifically in the ventricles has reduced conduction speed and aberrant electrograms. The fact that inFAT consistently displays smaller voltage amplitudes and higher conduction slowing than scar suggests that inFAT is more likely to be pro-arrhythmic than scar. Furthermore, we found that larger amounts of inFAT, but not scar, were significantly associated with larger volumes of clinically defined conduction abnormalities within heart model VT circuits [6]. Particularly at the VT entry and common pathway, which are important locations for ablation, these conduction anomalies overlapped with inFAT. Conduction slowing at these particular parts of the circuit is known to be crucial for maintaining re-entrant VT. As a result, inFAT mechanistically encourages re-entrant VT by slowing conduction in the circuit's essential parts. Three main mechanisms structural modifications to the cardiac architecture, paracrine effects, and adipocyte myocyte electrical coupling could cause inFAT to impede conduction. Since adipocytes are not excitable, just their presence will cause a change in the usual structure of the myocardium. The changed myocardial structure will delay conduction and interfere with normal electrical propagation. Another potential mechanism of conduction slowing is the paracrine actions of adipokines released by inFAT. On the secretome profile of inFAT, however, there is currently no information. It is well known that Epicardial Adipose Tissue (EAT), a type of tissue different from inFAT, is metabolically active and secretes a number of adipokines.

It has been demonstrated that these adipokines affect myocyte electrophysiology and delay conduction in atrial tissues. EAT and inFAT are distinct organisms, however there might be some overlap in the adipokines that both tissue types secrete. The connection between EAT and inFAT in the post-infarcted ventricles has to be studied. Thirdly, electrotonic interaction between adipocytes and myocytes has been theorised to affect myocyte excitability by modifying sodium channel inactivation and raising the chance of spontaneous depolarizations. Adipocyte myocyte heterocellular coupling in intact hearts hasn't been demonstrated, though. As a result, we would speculate that there are two main processes by which inFAT slows conduction. Our findings could lead to a number of improvements in clinical management, in our opinion. From a procedural standpoint, non-invasive detection of inFAT on imaging may assist in reducing treatment times and enhancing ablation effectiveness. Because not all areas with electrical anomalies revealed on EAM are necessarily arrhythmogenic, intraprocedural EAM of the post-infarct substrate is a labor intensive approach that occasionally fails to highlight the important VT sites 26. But according to our research, areas with inFAT are probably also home to important VT sites. Therefore, rather than mapping the entire infarct with inFAT, time and effort might be spent on these specific arrhythmogenic regions. Furthermore, understanding the distribution of inFAT would influence how ablations are administered. More severe ablation tactics, such as more lesions given or a more sophisticated ablation technique, should be used in these locations if crucial VT sites are discovered deep within the inFAT distribution. From a non-procedural standpoint, we picture novel tactics that put an emphasis on reducing the degree of inFAT in post-infarct VT patients. Medical therapy can help reduce cardiac adiposity and may complement existing standard of care VT treatments for VT. For instance, pharmacological agents like Sodium Glucose Co-Transporter 2 (SGLT 2) inhibitors have been shown in randomised controlled trials to decrease arrhythmic events and can decrease the amount of cardiac adiposity. Reducing inFAT would take away the substrate needed to support VTs, which would logically lead to a reduction in the burden of arrhythmia.

CONCLUSION

In conclusion, we offer the first combined prospective clinical and computational investigation that compares inFAT to scar in infarct related VT, to the best of our knowledge. We show that inFAT, as opposed to scar, is a key factor in determining the burden of arrhythmias and mechanistically encourages VT. These findings challenge accepted theories about infarct related VT pathogenesis and identify inFAT as a novel, significant player. We anticipate that this new information will spur the development of novel, patient specific therapeutic approaches that target inFAT to more effectively address the burden of VT caused by infarcts.

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