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Can Metformin Prevent Atrial Arrhythmogenic Remodelling?

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Background

Structural, electrical and metabolic remodelling of the atria facilitates the initiation and perpetuation of atrial fibrillation (AF). Targeting the atrial myopathy that serves as a substrate for AF could help prevent disease progression and reduce therapeutic resistance (**Figure 1**).

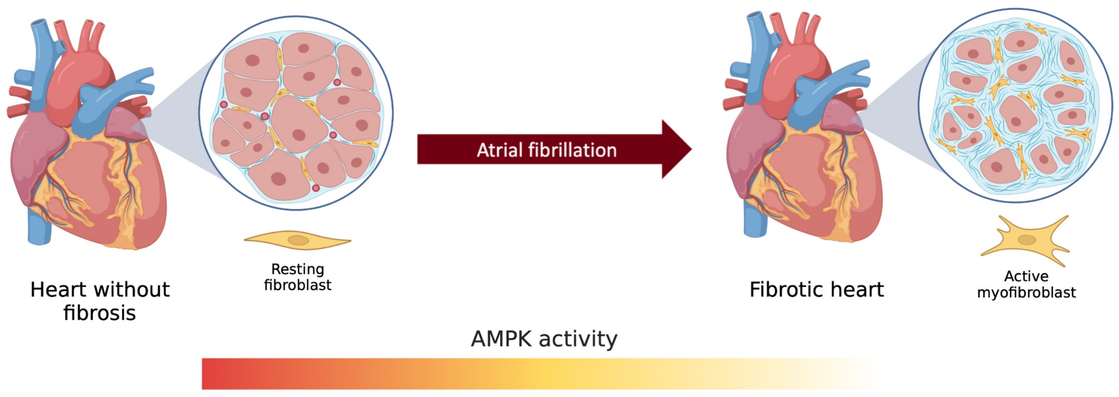

Figure 1 Atrial fibrillation (AF) leads to atrial fibroblast activation and fibrosis, which disrupts electrical wave propagation. Chronic AF is associated with low atrial activity of AMP-activated protein kinase (AMPK) - an important regulator of cardiac metabolism. The antidiabetic drug metformin activates AMPK and may prevent dysregulation of electrical excitability and atrial fibrillation.

Aim

To evaluate the effect of metformin on atrial arrhythmogenic remodelling. We hypothesised that metformin reduces AF-induced electrical remodelling.

Methods

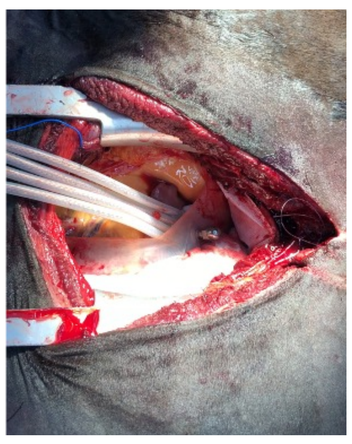

Figure 2 Atrial multi-electrode contact mapping

Horses receiving either metformin (n = 7) or placebo (n = 7) had AF induced by right atrial tachypacing. Right and left atrial effective refractory periods (aERPs) were recorded by extra stimulus (S2) epicardial pacing (**Figure 2**) at pacing cycle lengths 1000ms and 500ms.

Right atrial ERPs

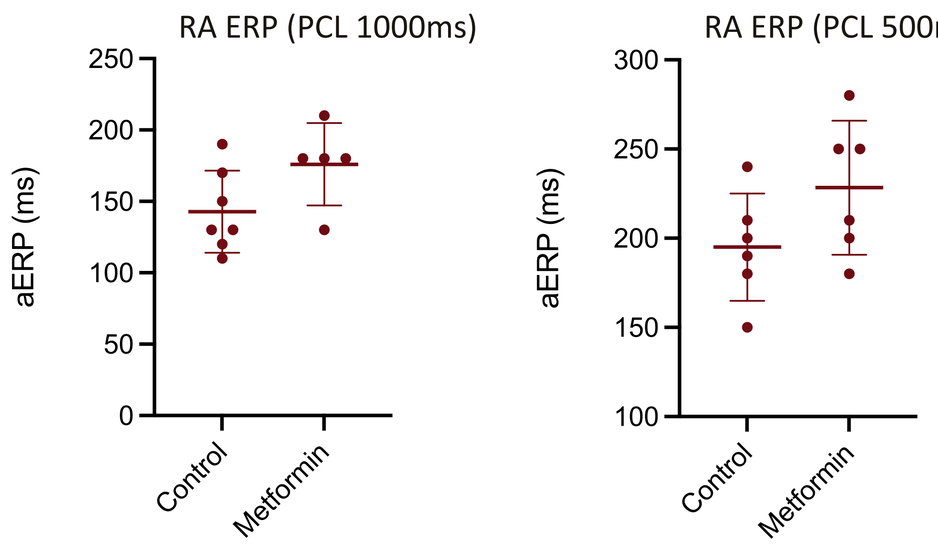

Figure 3 Preliminary data suggest that metformin treated horses (n = 6) have longer right atrial effective refractory periods (aERPs) after 4 months of atrial fibrillation compared to controls (n = 7). Mean right atrial (RA) ERPs at pacing cycle length (PCL) 1000ms were 176 and 142ms, respectively (p = 0.07) and mean RA ERPs at PCL 500ms were 228 and 195ms (p = 0.12).

Interregional RA ERP dispersion

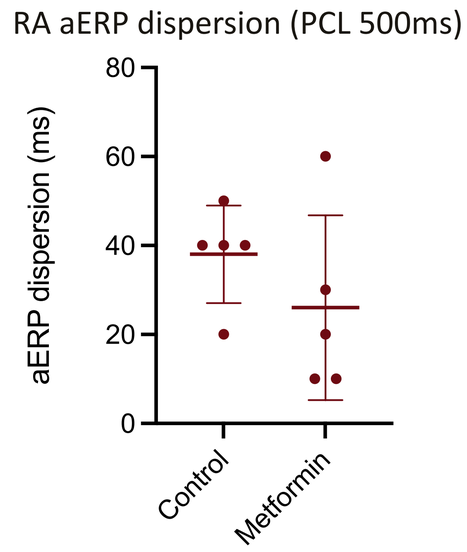

Figure 4 In this preliminary data, metformin treated horses (n = 5) tend to have less dispersion of right atrial effective refractory periods (aERPs) after 4 months of atrial fibrillation compared to controls (n = 5). The mean interregional right atrial ERP dispersion at pacing cycle length (PCL) 500ms were were 38 and 26 ms, respectively (p = 0.28).

Transvenous biopsy collection

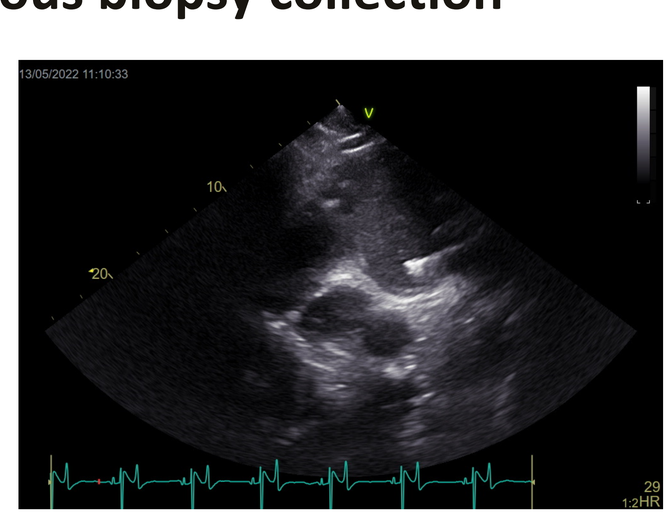

Figure 4 Endomyocardial bioptome in the right atrium of an awake sedated horse for transvenous biopsy collection (left) guided by ultrasound (right)

Structural remodelling

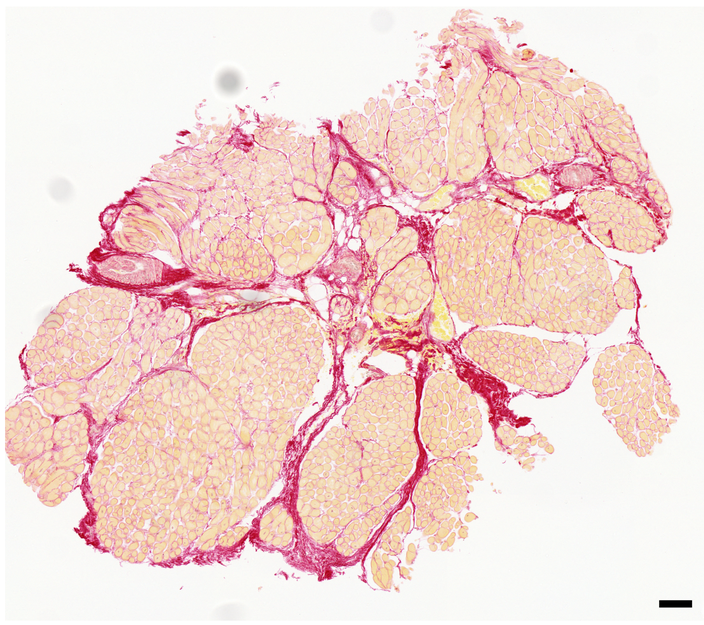

Figure 5 Histological section of right atrial transvenous biopsies stained with Picro-Sirius Red demonstrating interstitial fibrosis (red) after 4 months of atrial fibrillation. Future work will determine whether metformin alleviates interstitial fibrosis during chronic AF. Scale = 100µm.

Conclusion

Metformin may attenuate AF-induced electrical remodelling. Future work will evaluate its effect on structural and metabolic remodelling.

Wish to know more?

Scan the QR code for a virtual tour through our experimental protocol

Ethics approval and funding

The study is approved by The Danish Animal Experiments Inspectorate (license number 2020-15-0201-00425) and is performed in accordance with the European Commission Directive 86/ 609/EEC.
This work is supported by a research grant from the Danish Cardiovascular Academy (PhD2021001-DCA) and the independent Research Fund Denmark (1032-00053B).

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