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## Atrial-specific upregulation of microRNA-31 depletes dystrophin and neuronal nitric oxide synthase (nNOS), and leads to electrical remodelling in human atrial fibrillation

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**Objectives:** Atrial fibrillation (AF) is a growing public health burden and its treatment remains a challenge. AF leads to electrical remodelling of the atria, which, in turn, promotes AF maintenance and resistance to treatment. Although remodelling has long been a therapeutic target in AF, its causes remain poorly understood.

**Methods and findings :** Using atrial samples from 259 patients (51 with permanent AF) and 36 goats (24 with AF), we show that atrial-specific upregulation of microRNA-31 (miR31) in goat and human AF causes dystrophin [DYS] translational repression and accelerates mRNA degradation of neuronal nitric oxide synthase [nNOS] leading to a profound reduction in atrial DYS and nitric oxide availability. Prediction algorithms and reporter assays established DYS and nNOS as miR31 targets. In actinomycin D-treated myocytes from patients in sinus rhythm, miR31 accelerated nNOS (but not DYS) mRNA decay. Physical interaction between miR31 and DYS or nNOS within the RNA induced silencing complex [RISC] in atrial myocytes from patients with AF [hAFm] was confirmed by immunoprecipitation of Argonaut 2. MiR31 overexpression and/or disruption of nNOS signaling (with nNOS-siRNA or secondary to nNOS gene deletion) recapitulates hallmark features of AF-induced remodelling (shortening of action potential duration [APD] and loss of APD rate-dependency) and significantly increases AF inducibility in mice *in vivo*. By contrast, silencing miR-31 in hAFm restores dystrophin and nNOS and normalizes atrial electrical properties. Masking miR31 binding site on the DYS increases both DYS and nNOS protein (but not mRNA), in keeping with a stabilising effect of DYS on nNOS protein. Indeed, K48-linked polyubiquitination and proteasomal degradation of nNOS were increased in hAFm.

**Interpretation:** Atrial-specific upregulation of miR-31 in human AF is a key mechanism causing atrial dystrophin and nNOS depletion, which, in turn, contributes to the atrial phenotype begetting this arrhythmia.

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## Cardiometabolic effects of previous exercise training in a model of menopause

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Exercise training is an important non-pharmacological intervention for attenuation of metabolic and cardiovascular dysfunctions triggered by the advent of menopause. However, it is not known whether previous exercise training intervention alters the physiological and medical complications in this situation. Data from our laboratory suggest that previous aerobic exercise training induced additional benefits compared to aerobic exercise training in ovariectomized rats. Taken together, reduction in blood pressure, resting bradycardia, improved of parasympathetic modulation associated with reduced adipose tissue and improved oxidative stress profile on cardiac tissue demonstrated a positive role of this non-pharmacological approach to prevent alterations triggered by ovarian hormones deprivation.

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