Abstract

Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with significant morbidity and mortality. In addition to mechanisms such as atrial stretch and atrial remodeling, also the activity of the autonomic nervous system has been suggested to contribute to the progression from paroxysmal to persistent AF. Catheter-based renal denervation (RDN) was introduced as a minimally invasive approach to reduce renal and whole body sympathetic activation which may result in atrial antiarrhythmic effects under some pathophysiological conditions. This review focuses on the potential effects of RDN on different arrhythmogenic mechanisms in the atrium and discusses potential anti-remodeling effects in hypertension, heart failure, and sleep apnea.

Introduction

Atrial fibrillation (AF) is prevalent in 1-2 % of the general population. The number of affected individuals is expected to double or triple within the next two to three decades due to ageing of the population. AF doubles mortality and causes marked morbidity and reduced quality of life. In addition to mechanisms such as atrial stretch and atrial remodeling, also the increased activity of the sympathetic nervous system in hypertension, heart failure, and OSA has been suggested to contribute to the development of AF. For this reason, increased activity of the sympathetic nervous system might be an interesting target for intervention to treat AF.

Modulation Of Sympathetic Nervous System By Renal Denervation

Recently, a catheter-based approach has been developed for renal sympathetic denervation (RDN). First-generation devices use radiofrequency pulses emitted from a monopolar electrode positioned under fluoroscopic guidance in each of the renal arteries. Mechanistically, it has been observed that the procedure resulted in a 47% reduction of renal norepinephrine spillover measured with the radioactive tracer 3H-norepinephrine. Additionally, firing of single sympathetic fibres, a parameter for whole body sympathetic activation, was reduced by 37%. This indicates that not just locally in the kidney, where the ablation procedure is performed, but also in the whole body, sympathetic activation can be reduced by RDN, suggesting a combined modulation of efferent and afferent signalling. RDN might therefore influence atrial electrophysiological changes as well as structural remodeling processes by modulation of autonomic nervous system.

Reduction of sympathetic activation by RDN may influence atrial electrophysiology, as well as the substrate for AF, characterized by neural, electrical and structural remodelling processes in the atrium (see figure 1).

Renal Denervation And Cardiac Electrophysiology

RDN results in a reduction in heart rate and AV-conduction velocity in pigs and in drug-resistant hypertensive humans. In chloralose/urethane anesthetized pigs, neither atrial effective refractory period (AERP) nor P-wave duration were influenced by acute RDN, thus, excluding potentially relevant changes in atrial refractoriness and atrial conduction during sinus rhythm. Additionally, sensitivity of ganglionated plexi was not altered by RDN. Norepinephrine, the neurotransmitter of the sympathetic nervous system, is released from postganglionic neurons in response to sympathetic stimuli and activates beta-receptors resulting in increased focal discharges potentially representing triggers and perpetuators of AF. Importantly, RDN not only reduces beta-receptor activation the target organs, thereby possibly reducing focal discharges, but it also reduces whole-body sympathetic activation. This may effectively inhibit systemic as well as local cardiac RAAS activation.

Renal Denervation And Neural/Autonomic Remodeling

Sympathetic hyperinnervation has been reported for atria of dogs undergoing rapid atrial pacing and increased sympathetic and vagal nerve discharges before the onset of atrial arrhythmias.
in dogs with congestive heart failure induced by rapid ventricular pacing was observed. The effect of different strategies to modulate the interaction between central sympathetic system and the heart on sympathetic hyperinnervation and atrial autonomic neural remodeling has been investigated. High thoracic epidural anesthesia reduced afferent and efferent sympathetic nerve input to the heart. In a dog model with rapid atrial pacing, high thoracic epidural anesthesia prevented sustained AF. This was associated with inhibition of atrial sympathetic nerve sprouting. Modulation of sympathetic nervous system by RDN may result in comparable prevention of atrial sympathetic nerve sprouting during AF.

Renal Denervation And Electrical Remodeling

RDN reduced duration of pacing induced AF, but, AF-induced shortening of the action potential duration was not attenuated. In humans with AF as well as in anesthetized pigs with AF induced by rapid atrial pacing, RDN reduces heart rate during AF, which might reduce clinical symptoms in patients with AF. However, shortening in atrial activation cycle length during AF was not altered by RDN. Whether RDN can influence electrical remodelling on the longer term needs to be investigated in further studies.

Renal Denervation And Structural Remodeling

Structural remodeling as a result of AF is characterized by increased atrial fibrosis formation and cardiomyocyte hypertrophy. Atrial tissue fibrosis impairs cell-to-cell electrical coupling and conduction. Long term AF leads to myocyte hypertrophy and increased endomysial fibrosis associated with dissociated conduction and electrical dissociation between the epicardial layer and the endocardial bundle network. The progressive structural remodeling of the atria is associated with increasing complexity of AF propagation as characterized by decreased width and increased number of fibrillation waves in humans and animals. Besides AF itself, other conditions like hypertension, congestive heart failure and sleep apnea can cause structural alterations in the atrium.

RDN In Hypertension And Heart Failure

The underlying pathophysiological link and the common pathway for hypertension and heart failure leading to AF is atrial pressure and/or chronic volume overload as well as ventricular diastolic dysfunction and neurohumoral activation leading to progressive atrial dilatation, prolongation of induced AF paroxysms, and local conduction delays. The effect of RDN on blood pressure is unclear. Several non-sham-controlled studies showed promising antihypertensive effects in drug resistant hypertensive patients by RDN. However, just recently, the SYMPPLICITY HTN-3 study, the first randomized, sham-controlled, blinded trial surprisingly did not show a benefit of RDN with respect to either of the efficacy end points for which the study was powered (reduction in office or ambulatory systolic blood pressure at 6 months). Some limitations like patient selection and adjustment of antihypertensive medication just before the start of the trial may explain the surprising results of SYMPPLICITY HTN-3.

In patients with drug-resistant hypertension, RDN led to a reduction of left ventricular mass. Additionally, RDN improved left ventricular ejection fraction and parameters of diastolic function (as evaluated by magnetic resonance imaging and tissue Doppler measurements) and reduced the number of patients with left atrial enlargement. Importantly, the anti-remodelling effects of RDN seem to be at least in part independent of blood pressure. In a small study in humans with drug-resistant hypertension, the atrial antiarrhythmic effects of circumferential pulmonary vein isolation (PVI) combined with RDN were investigated. At one-year follow-up, RDN improved blood pressure control and 69% of patients who received both procedures no longer had AF, compared to 29% of those in the PVI-only group.

Renal Denervation In A Pig Model For Seep Apnea

OSA is associated with increased sympathetic nervous system activation and atrial remodeling. In a pig model for OSA, shortening in atrial refractoriness acutely induced by an applied negative thoracic pressure (OSA-maneuver) was mainly mediated by combined sympathovagal activation, since it could be influenced by atropine, bilateral vagotomy and beta-receptor blockade. Compared to beta-blocker treatment, RDN resulted in an even more pronounced attenuation of shortening in atrial refractoriness during OSA-maneuvers, which might explain the superior antiarrhythmic effect of RDN compared to beta-blocker therapy in this animal model. In pigs with repetitive OSA-maneuvers over 4 hours, RDN inhibited spontaneous atrial premature beats, spontaneous AF episodes as well as AF duration. RDN attenuated postapneic blood pressure rise as well as renin angiotensin system activation, which may prevent the development of an atrial structural remodeling process in longterm OSA. The observed reduction in spontaneous atrial extrasystoles by RDN may reduce the trigger for AF in OSA. Interestingly, RDN likely exerts its antiaarrhythmic effects rather by a combined than single inhibition of either the sympathetic nervous system or the systemic RAAS, as only pharmacological blockade of both, angiotensin-receptors and β-adreno-receptors displayed effects comparable to RDN. This superiority of RDN over selective beta-receptor blockade may be explained by the fact that RDN not just...
reduces beta-receptor activation at the target organs but also, unlike beta-receptor blockade, reduces whole-body sympathetic activation and thereby reduces activation of beta-receptors as well as alpha-adrenoceptors at the target organs.

Conclusion:

RDN is a promising strategy to modulate the autonomic nervous system resulting in reduced sympathetic activity. RDN may prevent progression of AF by direct atrial electrophysiological effects as well as by anti-remodeling effects. From the pathophysiological point of view, reduction of sympathetic activition by RDN may display antiarrhythmic effects particularly in disease states with increased sympathetic drive such as hypertension, sleep apnea and heart failure. Possibly, in patients with lone atrial fibrillation without underlying heart disease, RDN may be less effective. Further clinical and basic science studies are needed to show whether sympathetic inhibition by RDN can exert antiarrhythmic effects also in a larger group of patients. Preclinical studies suggest that atrial antiarrhythmic effects are possible also independent of blood pressure.

References:


