



Advances in Cardiac Arrhythmias and Great Innovations in Cardiology, 2013, Turin

Percutaneous Renal Denervation: New treatment for resistant hypertension and more?

Dominik Linz

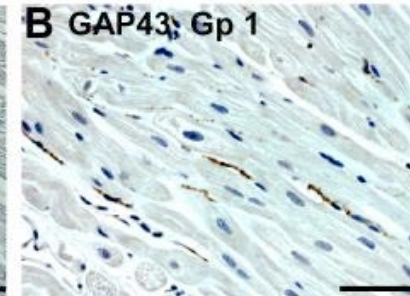
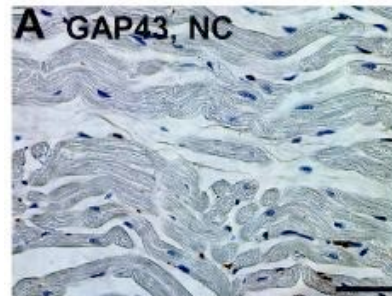
Klinik für Innere Medizin III
Kardiologie, Angiologie und Internistische Intensivmedizin
Universitätsklinikum des Saarlandes
Homburg/Saar

Neural remodelling in canines with paroxysmal atrial fibrillation

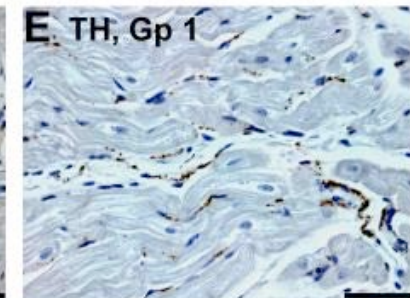
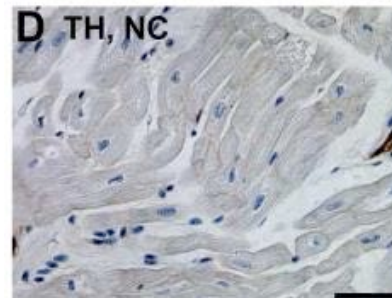
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Paroxysmal AF

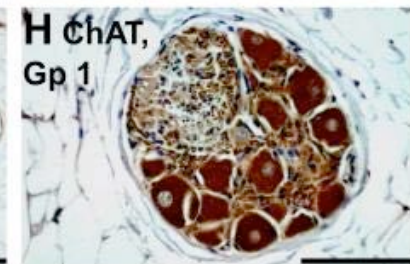
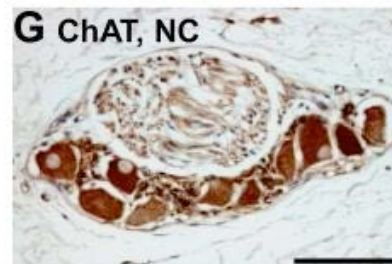
Growth-associated protein 43
(Growing nerve cones)



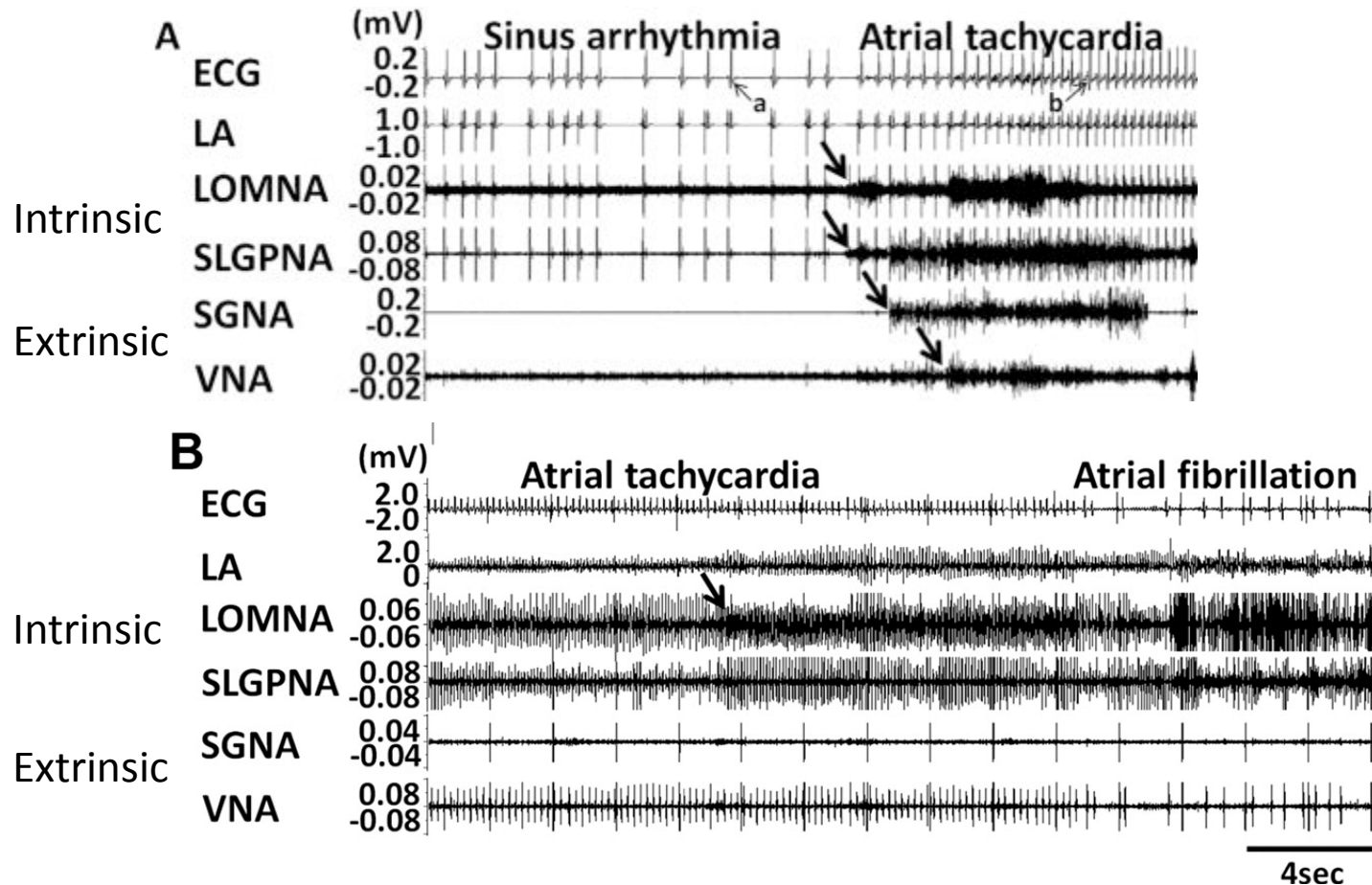
Tyrosin hydroxylase
(Sympathetic nerves)

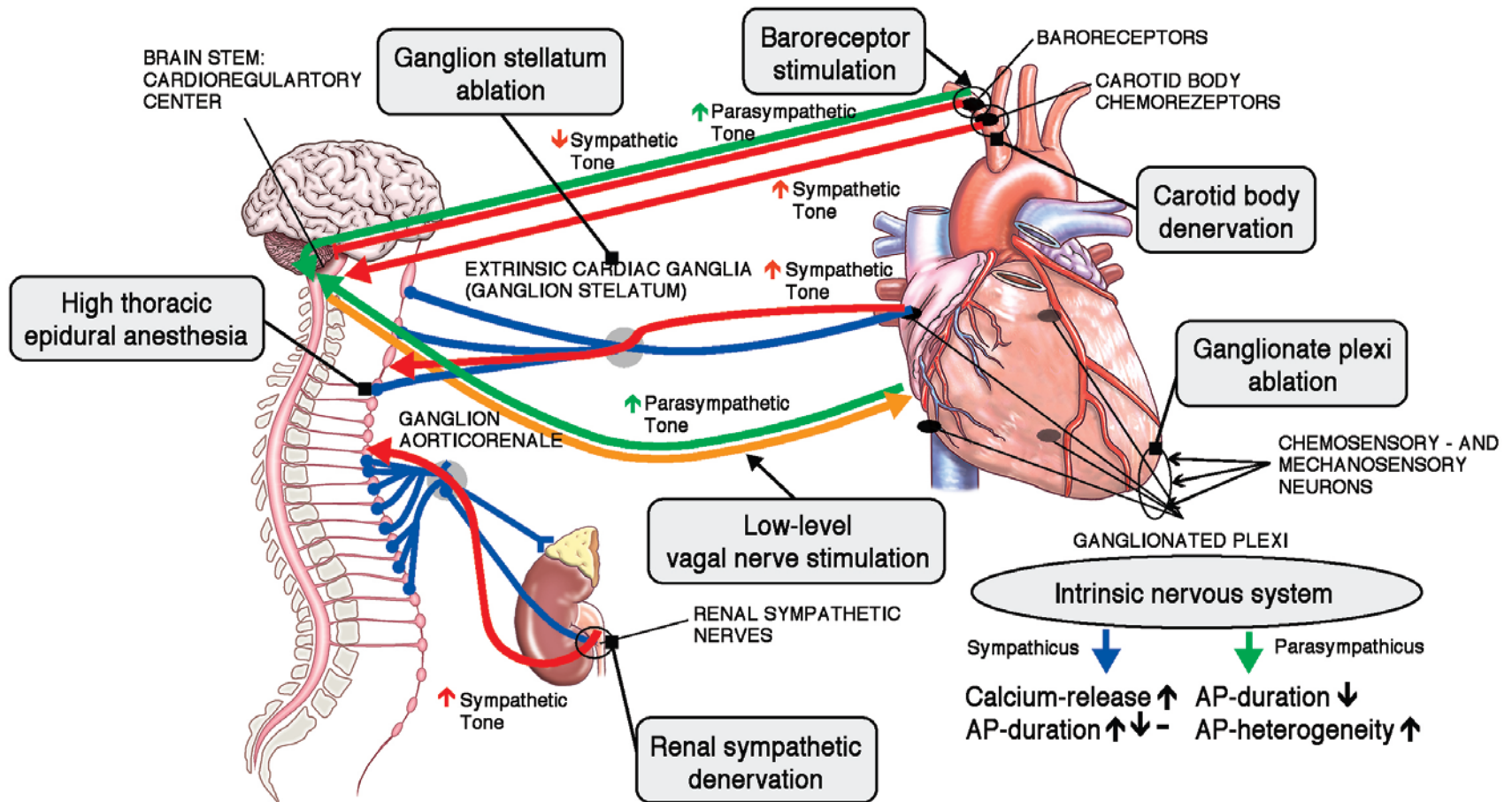


Choline acetyltransferase (ChAT)
(Cholinergic nerves)



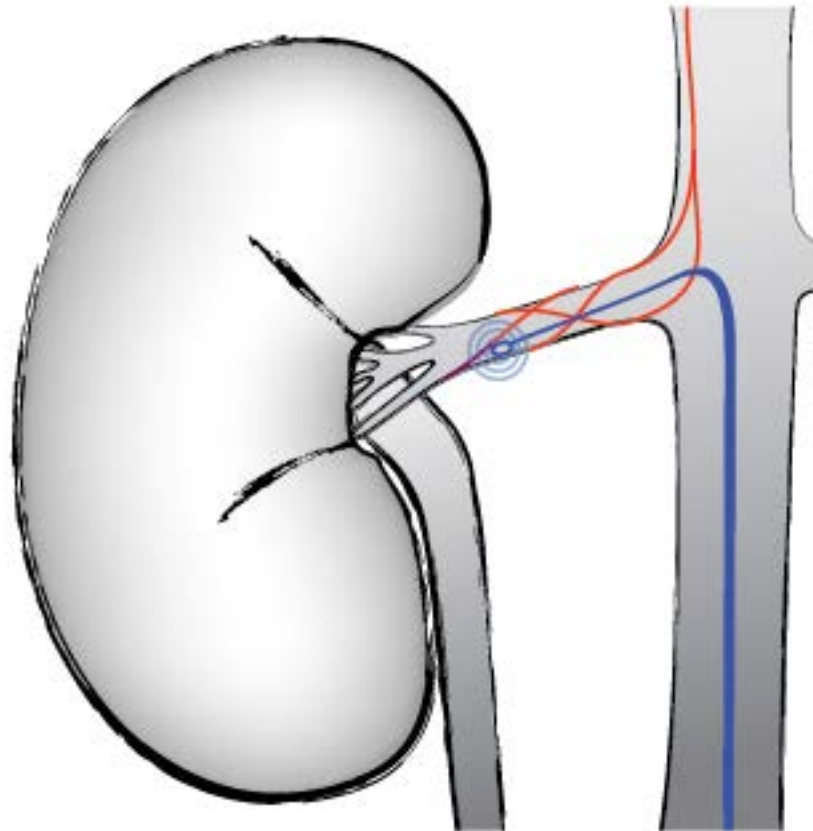
Cardiac nerve activities and conversion from PAT to PAF



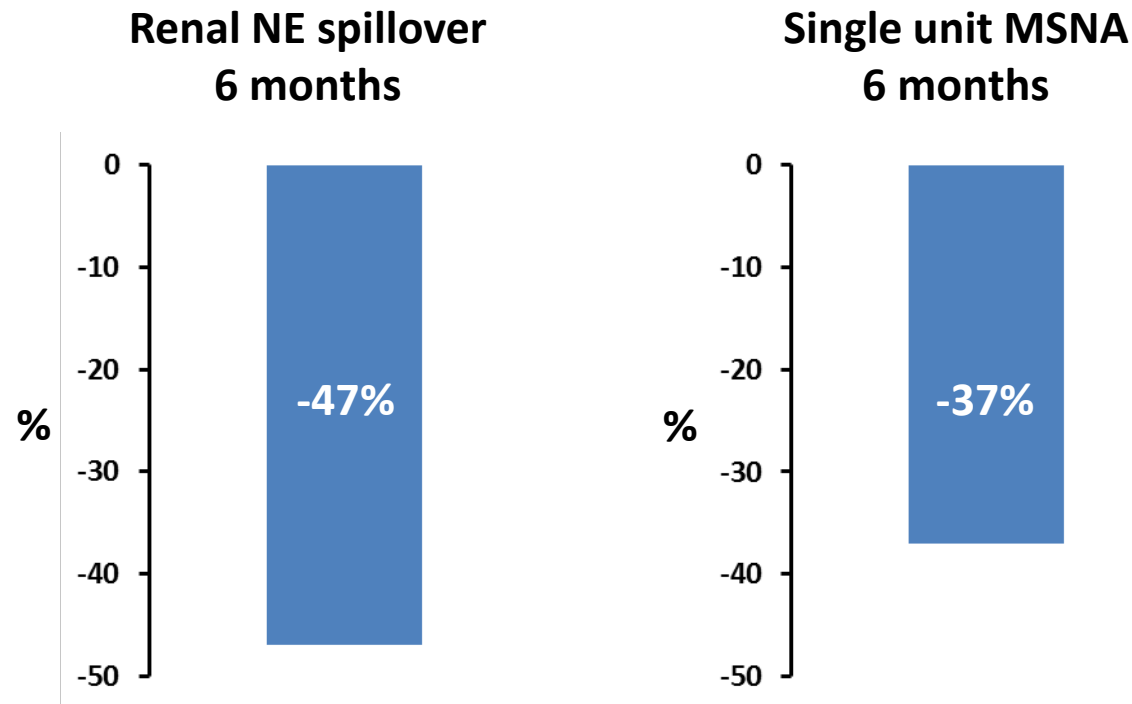


Sympathetic efferents
Sympathetic afferents
Nervus Vagus
Parasympathetic afferents

Catheter-based renal denervation (RDN)

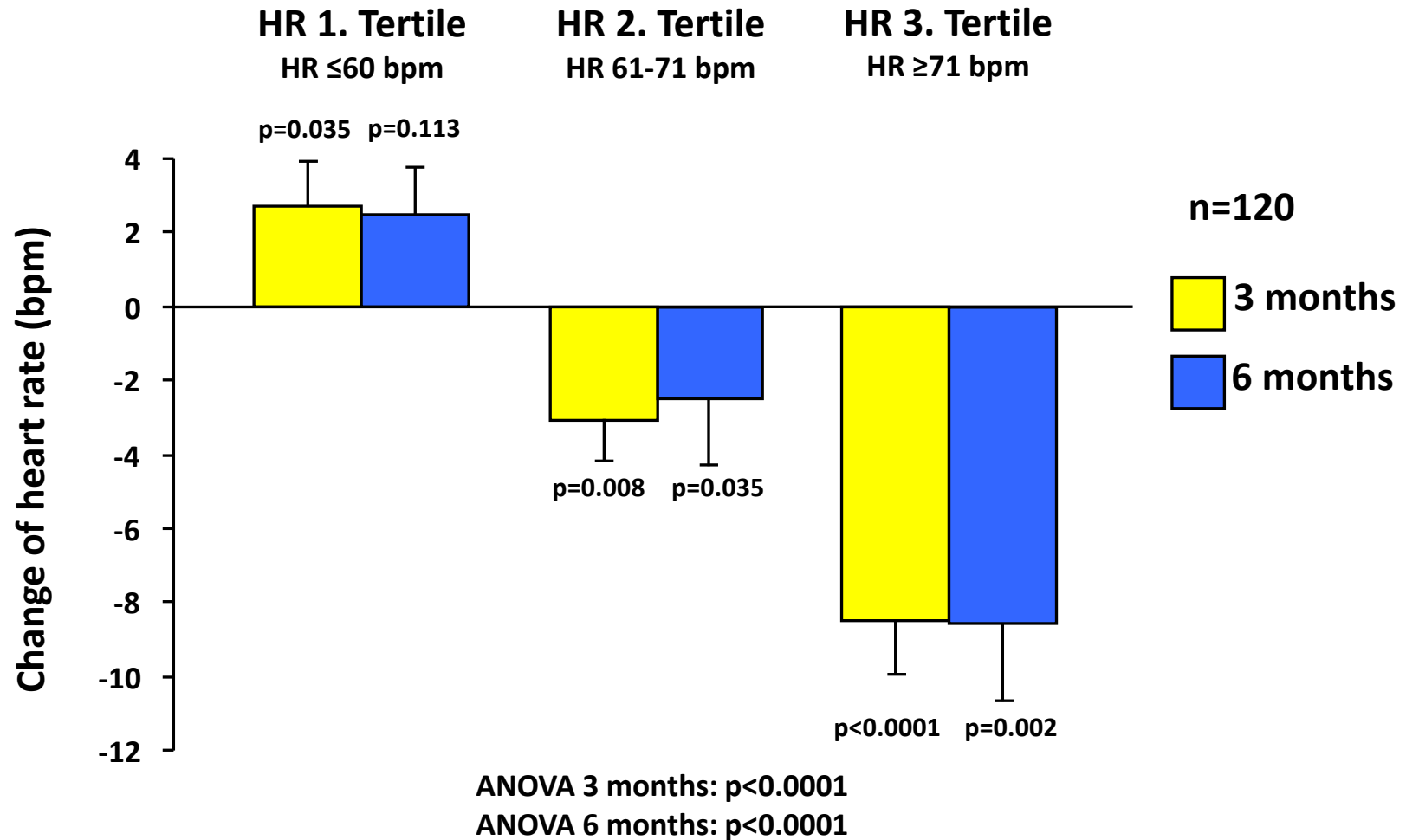


RDN reduces renal NE spillover and muscle sympathetic nerve activity

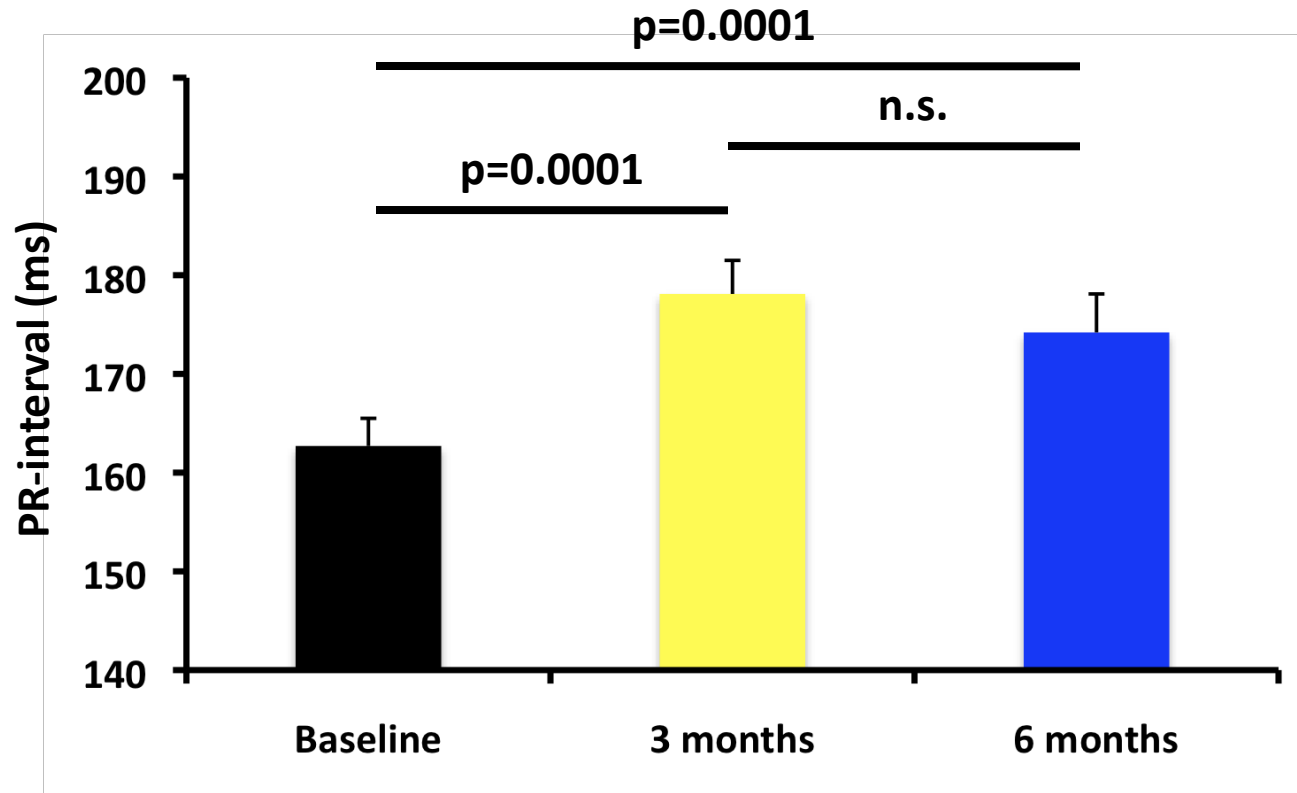


Electrophysiological and antiarrhythmic effects of RDN

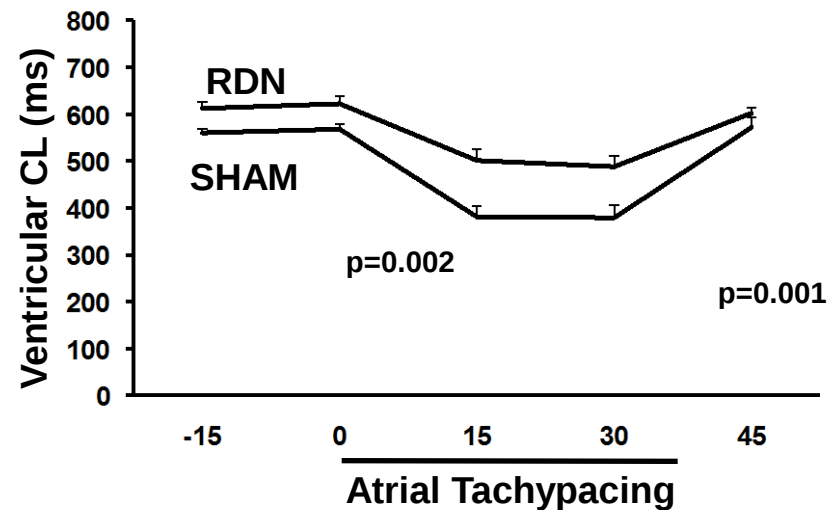
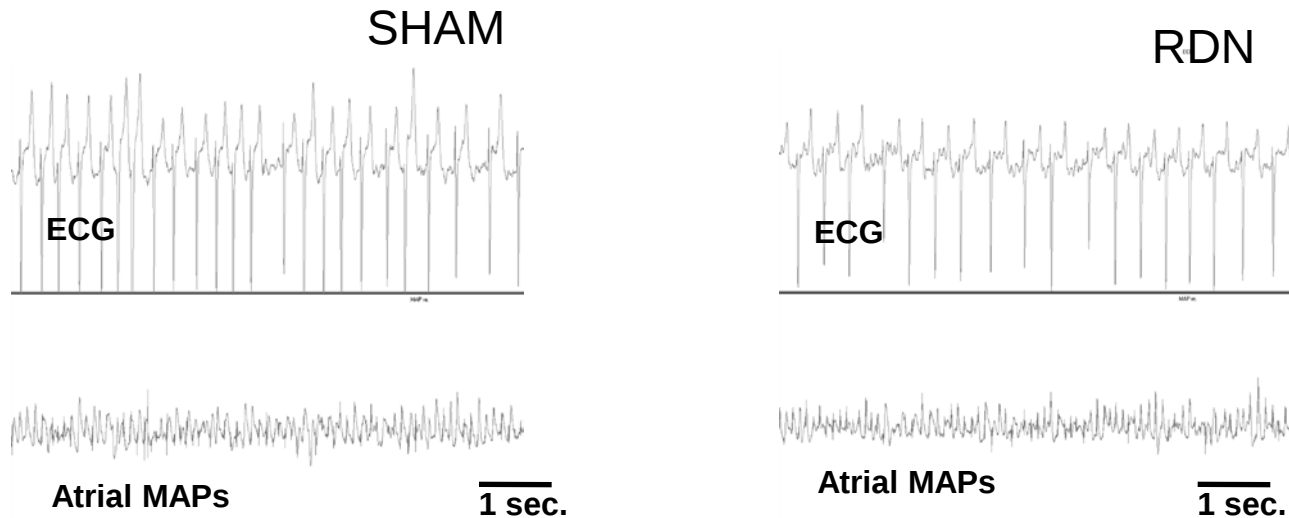
RDN reduces heart rate in hypertensive patients



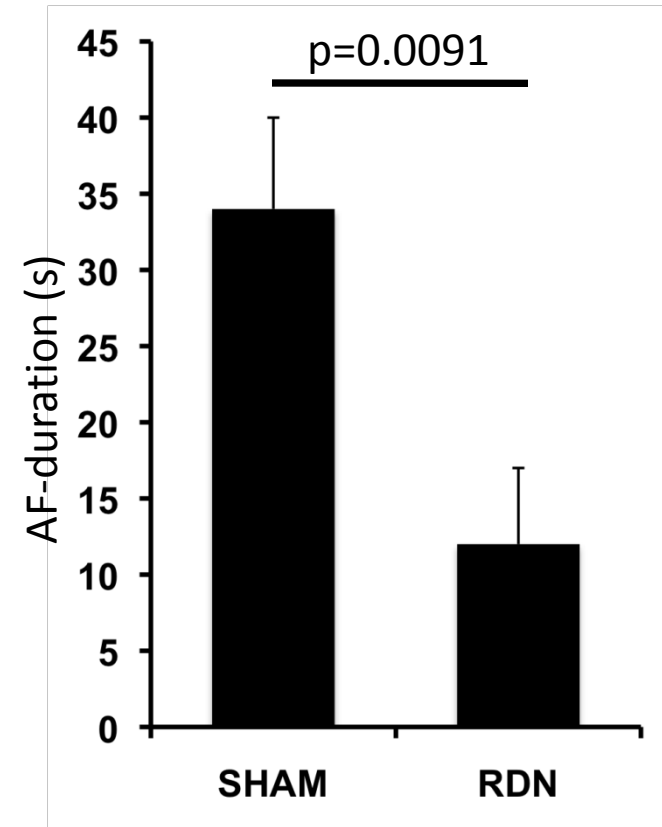
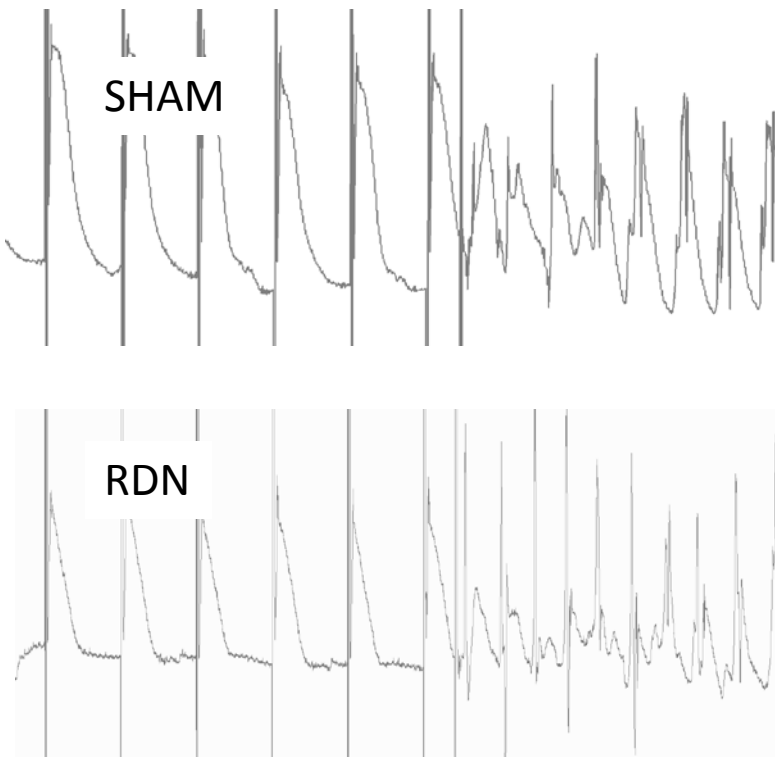
RDN reduces AV-conduction velocity in hypertensive patients



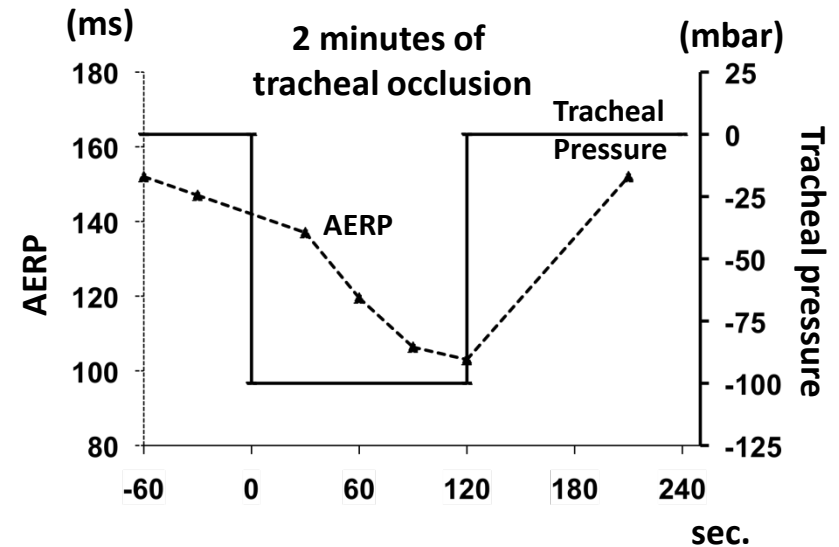
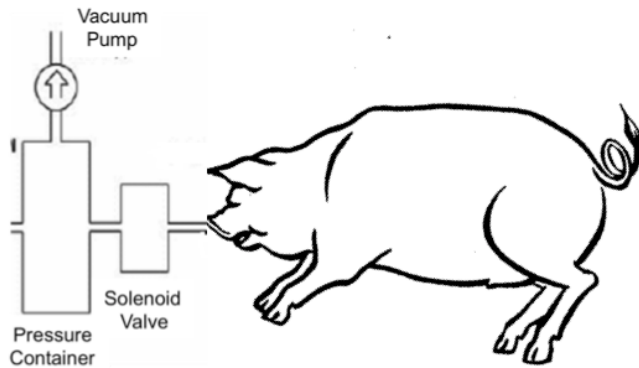
RDN provides rate control during AF in pigs



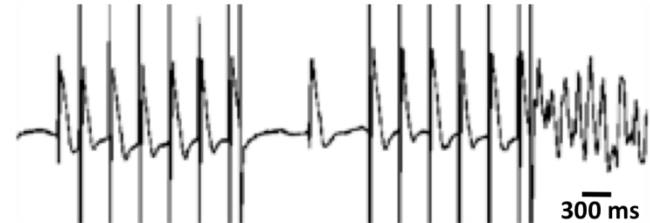
RDN reduces AF-duration



Pig model for obstructive sleep apnea



AERP-Measurement at 2 Minutes of NTP at -100mbar:



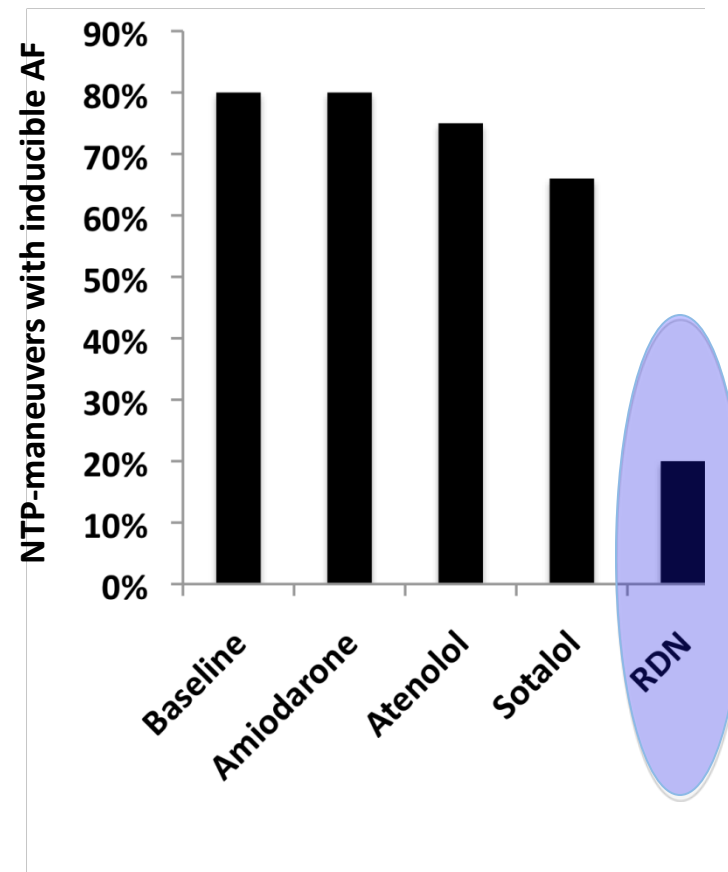
S1-S2 → AF

RDN reduces OSA-induced AF inducibility

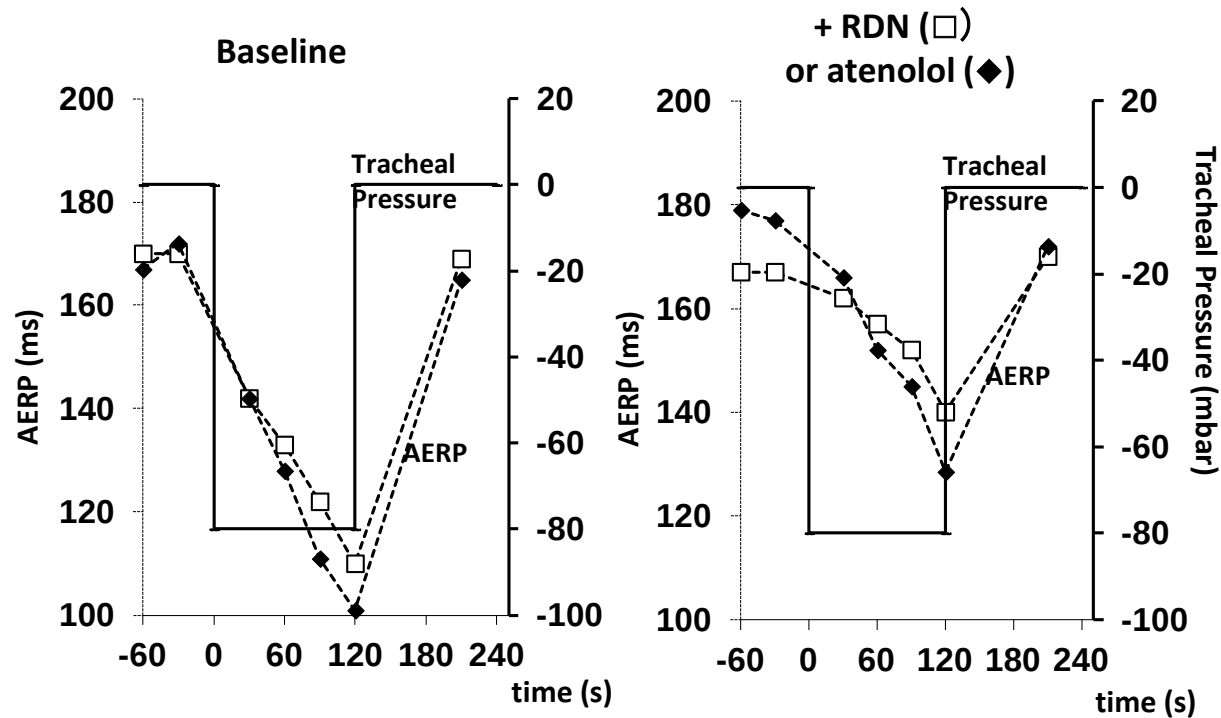


Normal breathing	0% AF
2-min of NTP at -80mbar	100% AF
2-min of NTP at -80mbar after Atenolol	75% AF (n.s.)
2-min of NTP at -80mbar after RDN	20% AF (p=0.0001)

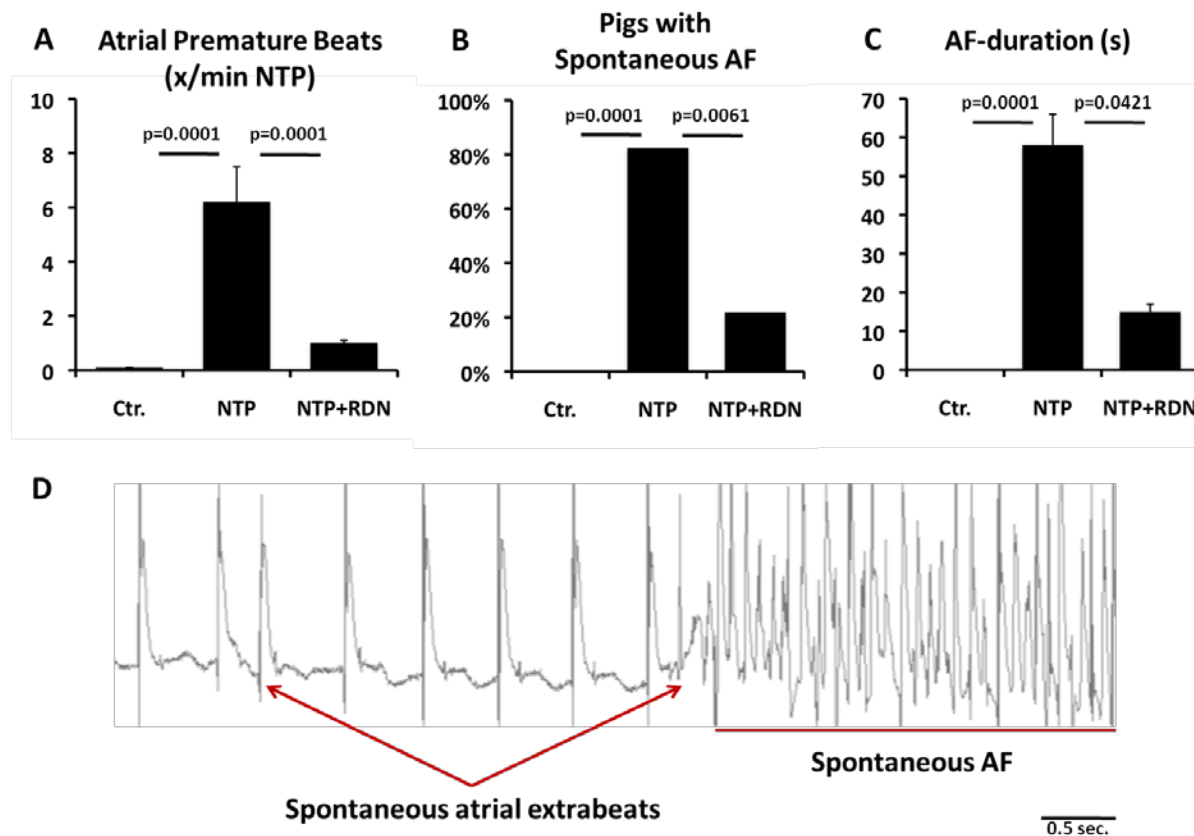
Amiodarone and Sotalol fail to inhibit AF in a pig model for OSA



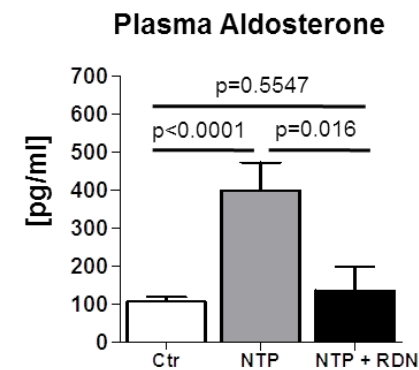
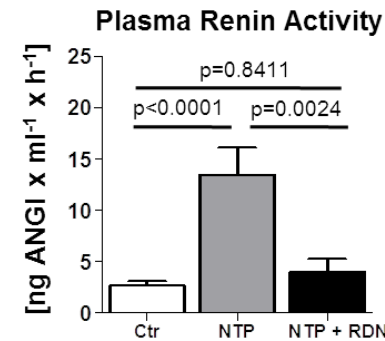
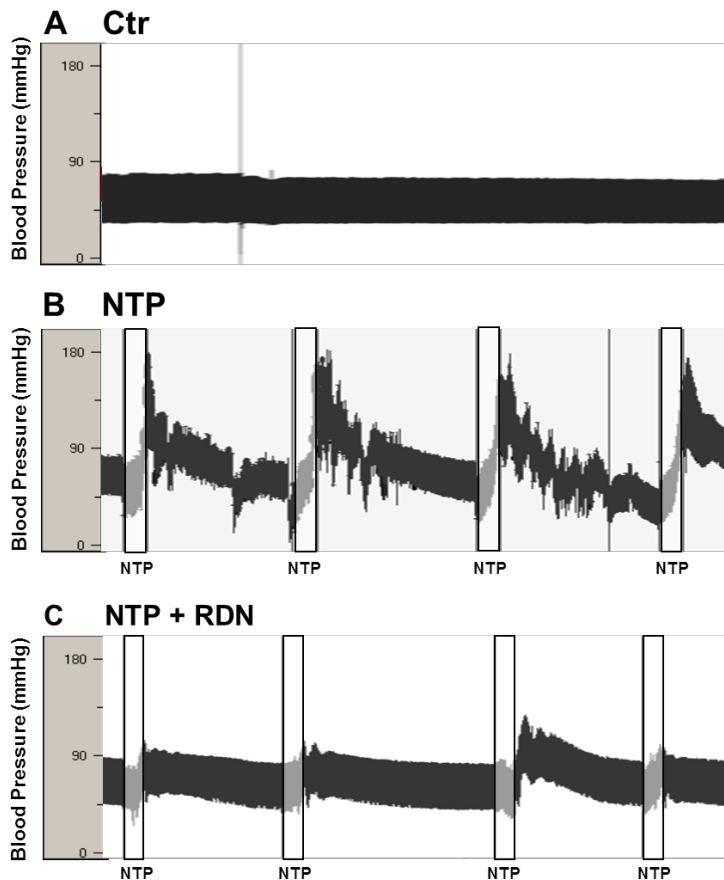
RDN reduces OSA-induced AERP-shortening



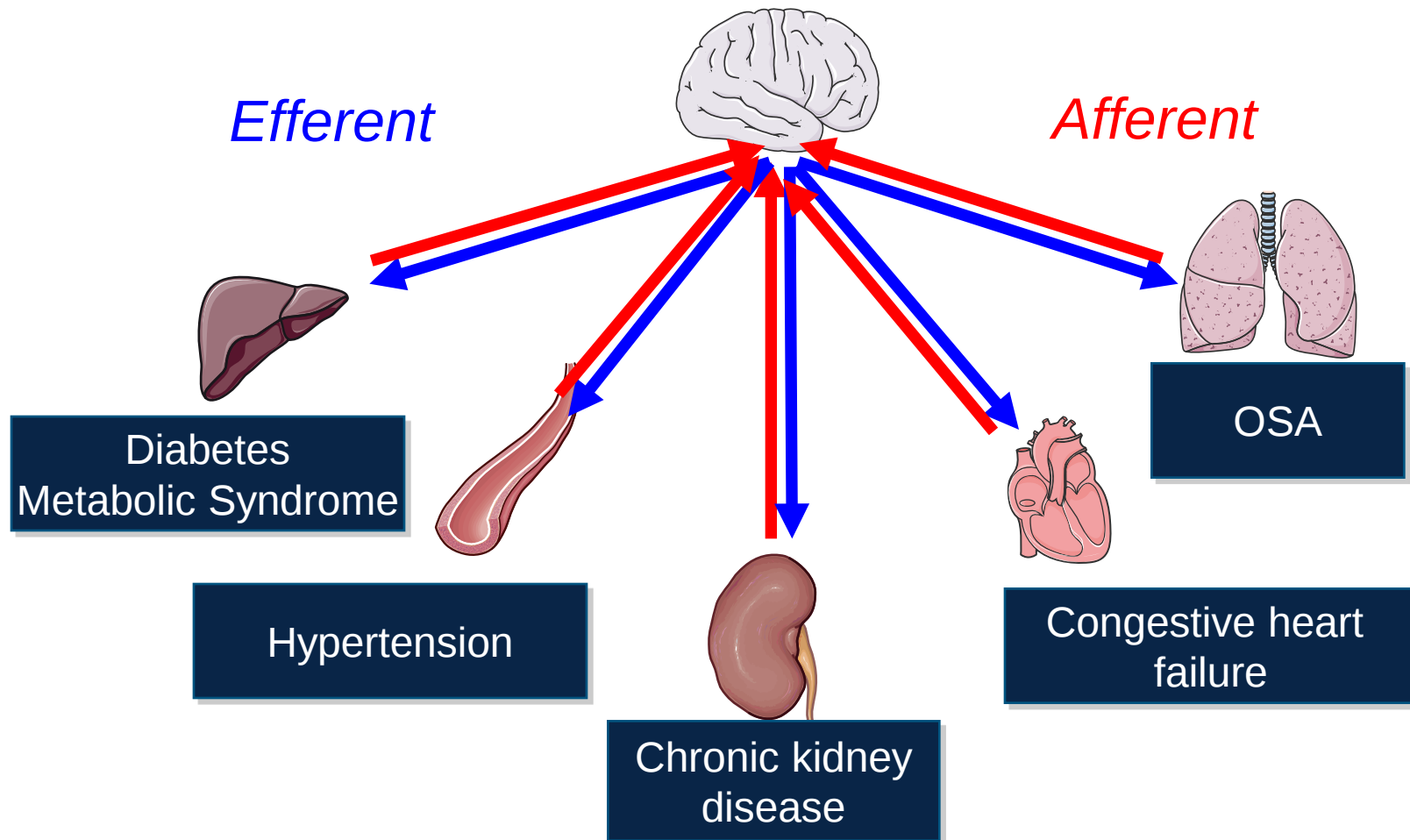
RDN inhibits spontaneous atrial fibrillation during repetitive obstructive respiratory events



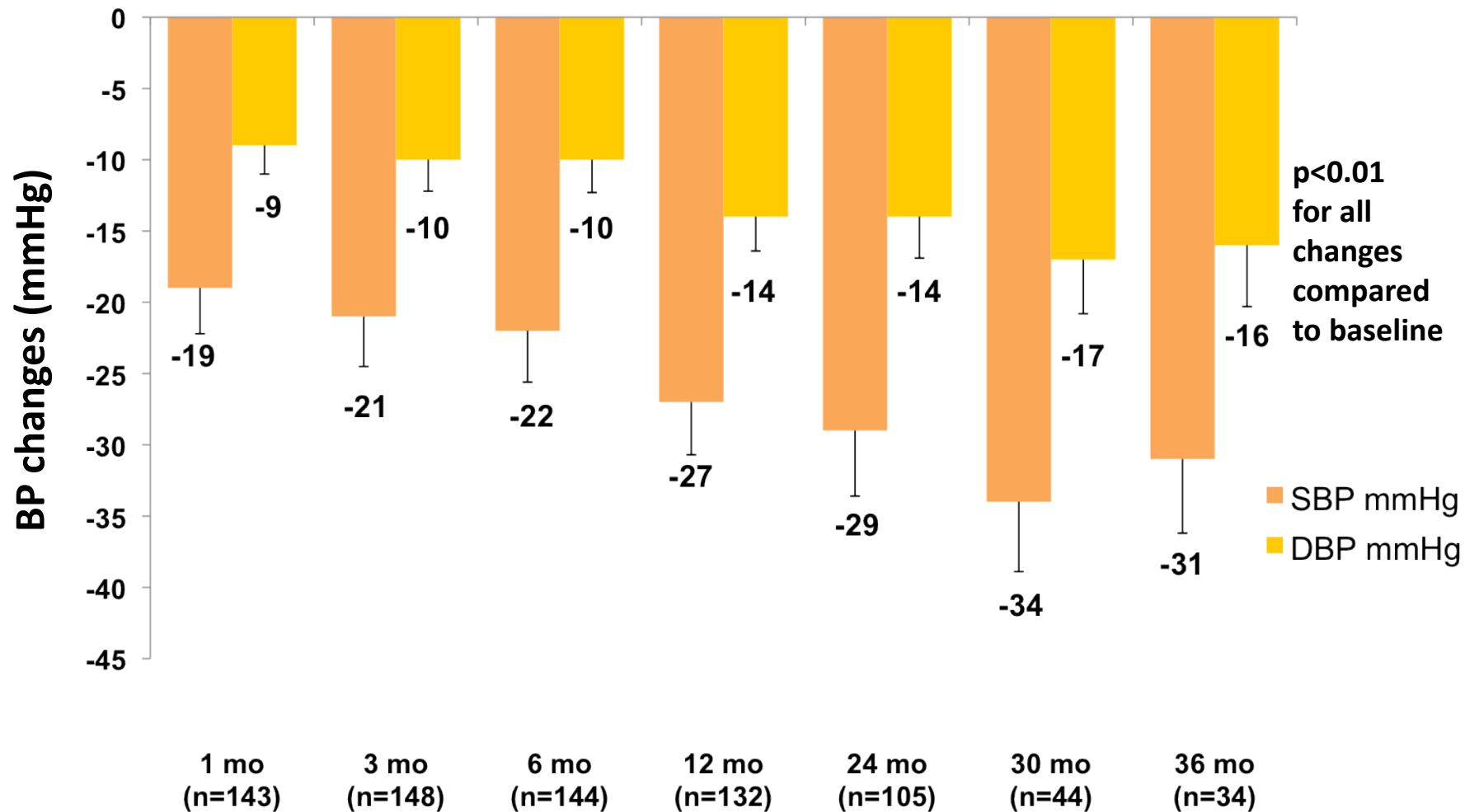
RDN inhibits post-apneic blood pressure rises and OSA-induced RAAS activation



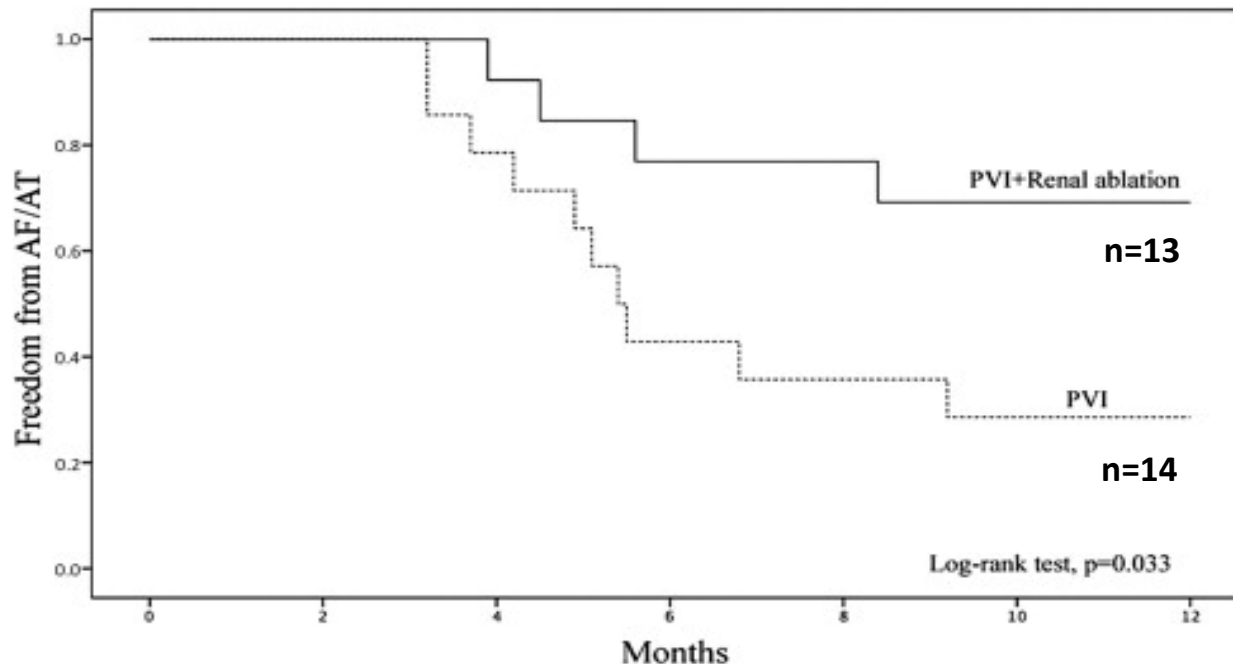
Potential targets for renal sympathetic denervation



Blood pressure reduction sustains over 3 years

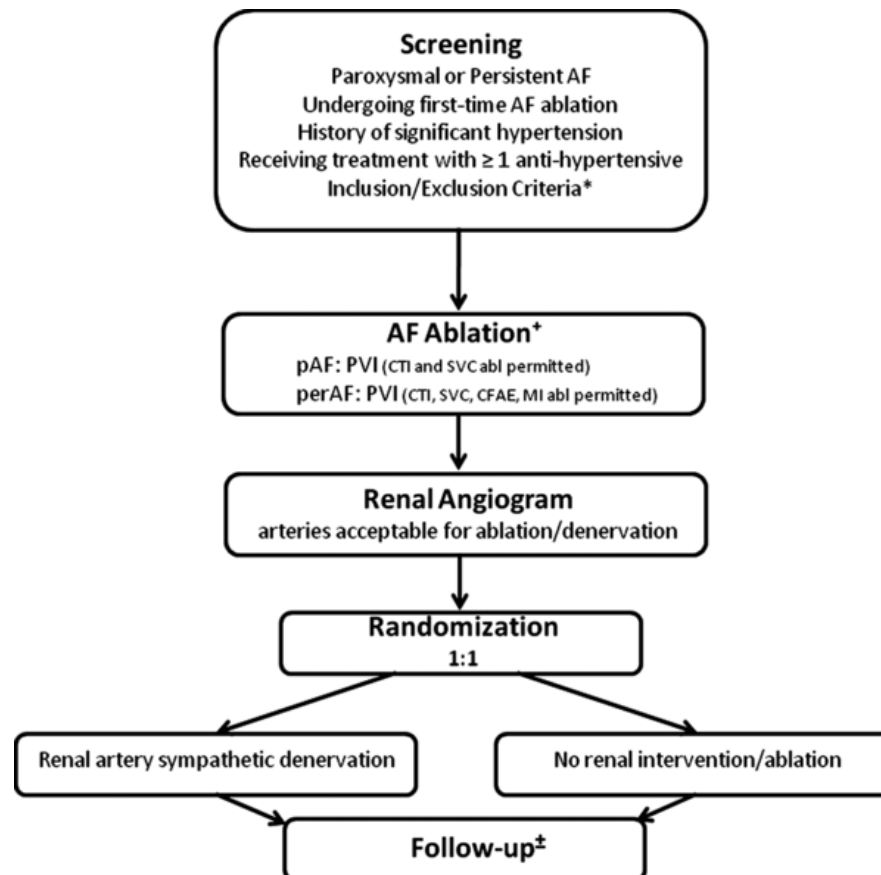


PVI with versus without concomitant RDN in patients with refractory symptomatic AF

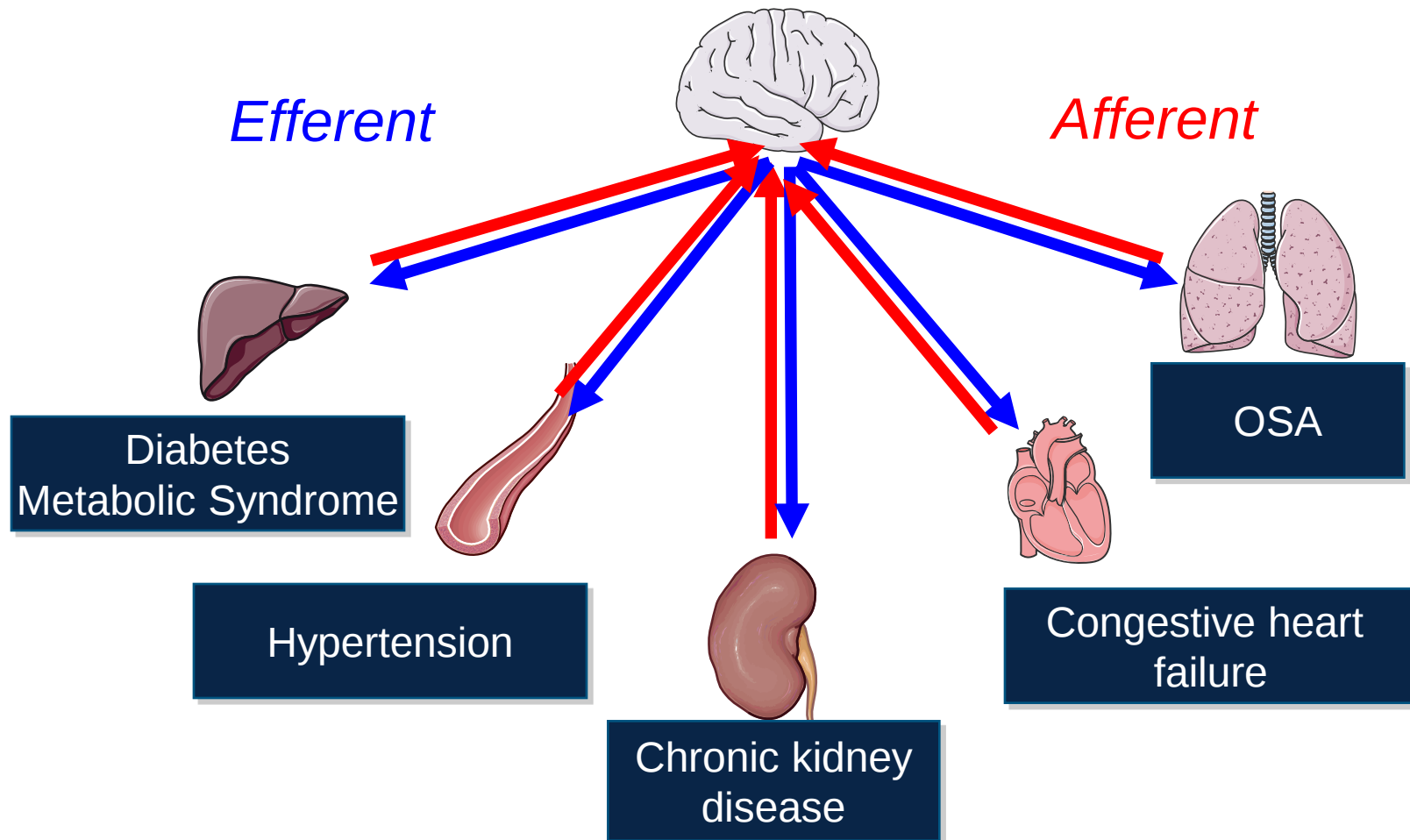


Study patients:
Paroxysmal or persistent AF
Refractory to ≥ 2 AADs
(not Amiodarone)
Drug-resistant hypertension

Adjunctive renal sympathetic denervation to modify hypertension as upstream therapy in the treatment of AF (H-FIB) Study

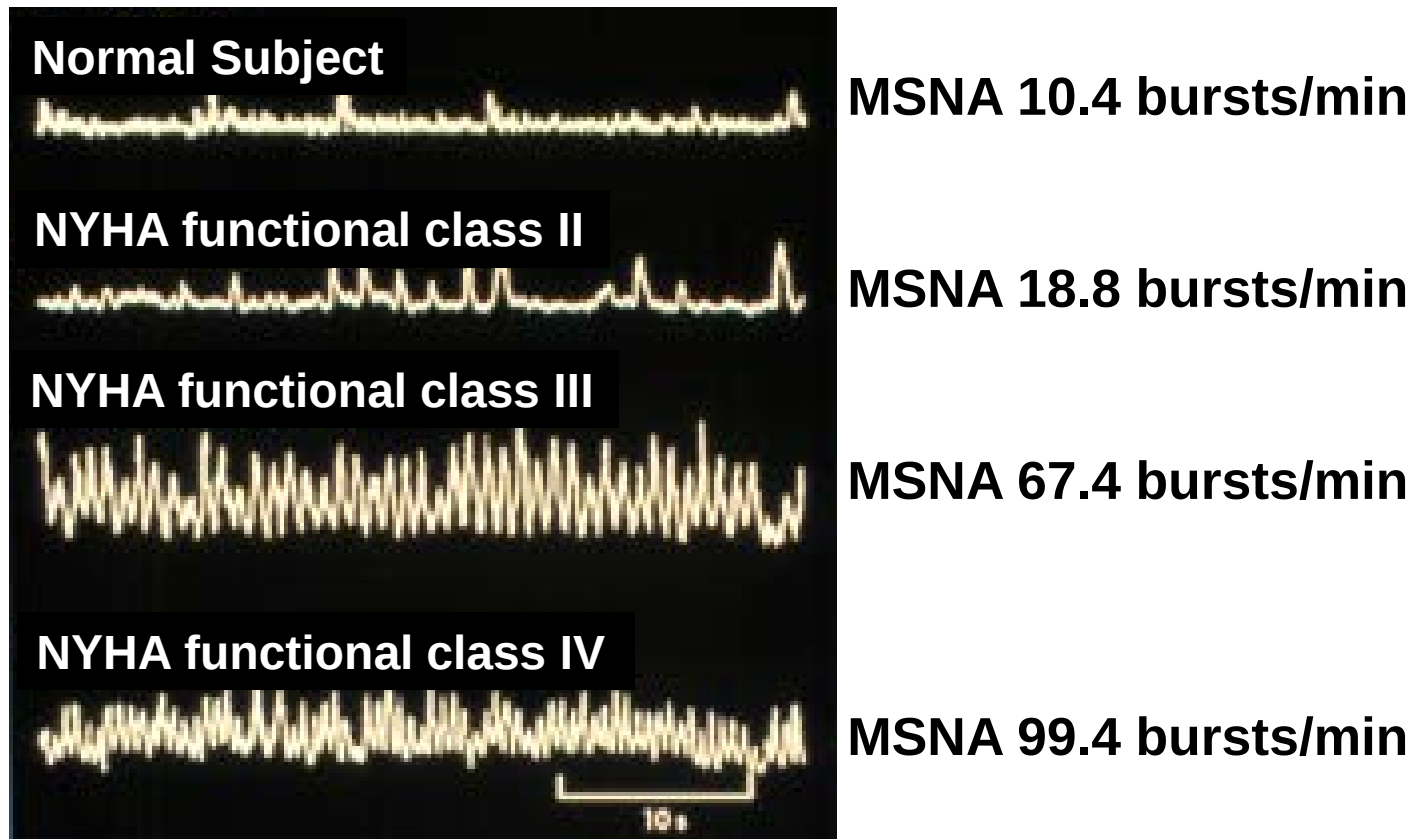


Potential targets for renal sympathetic denervation

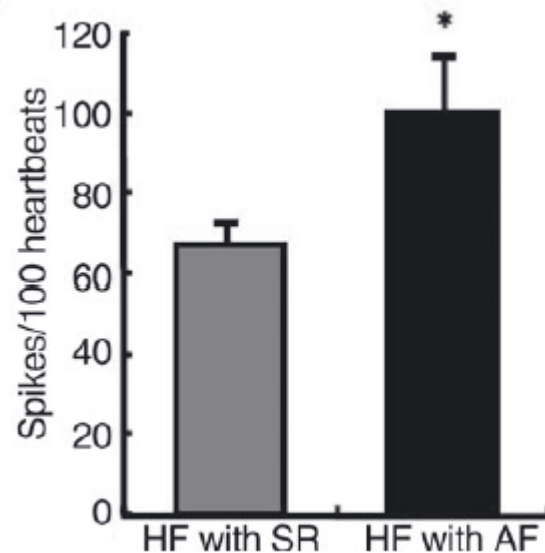
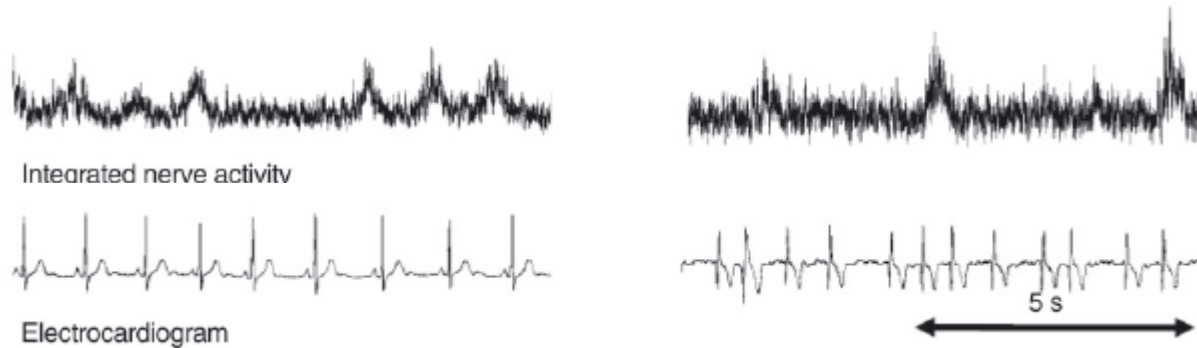


Sympathetic activity correlates to NYHA class

- CHF is characterized by increased SNS activity
 - proportional to severity of CHF

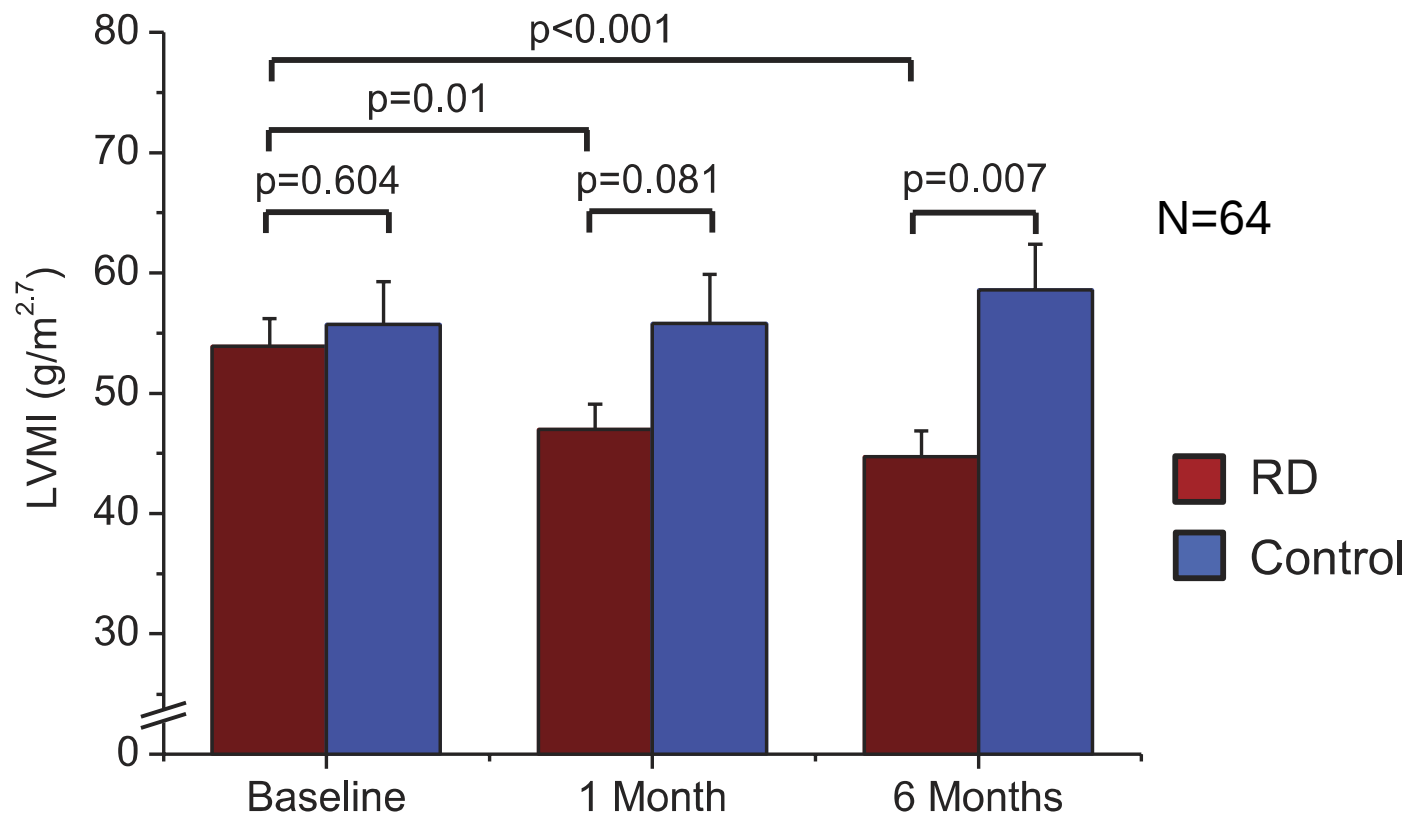


Higher sympathetic activity in patients with CHF+AF compared to CHF+SR



N=21

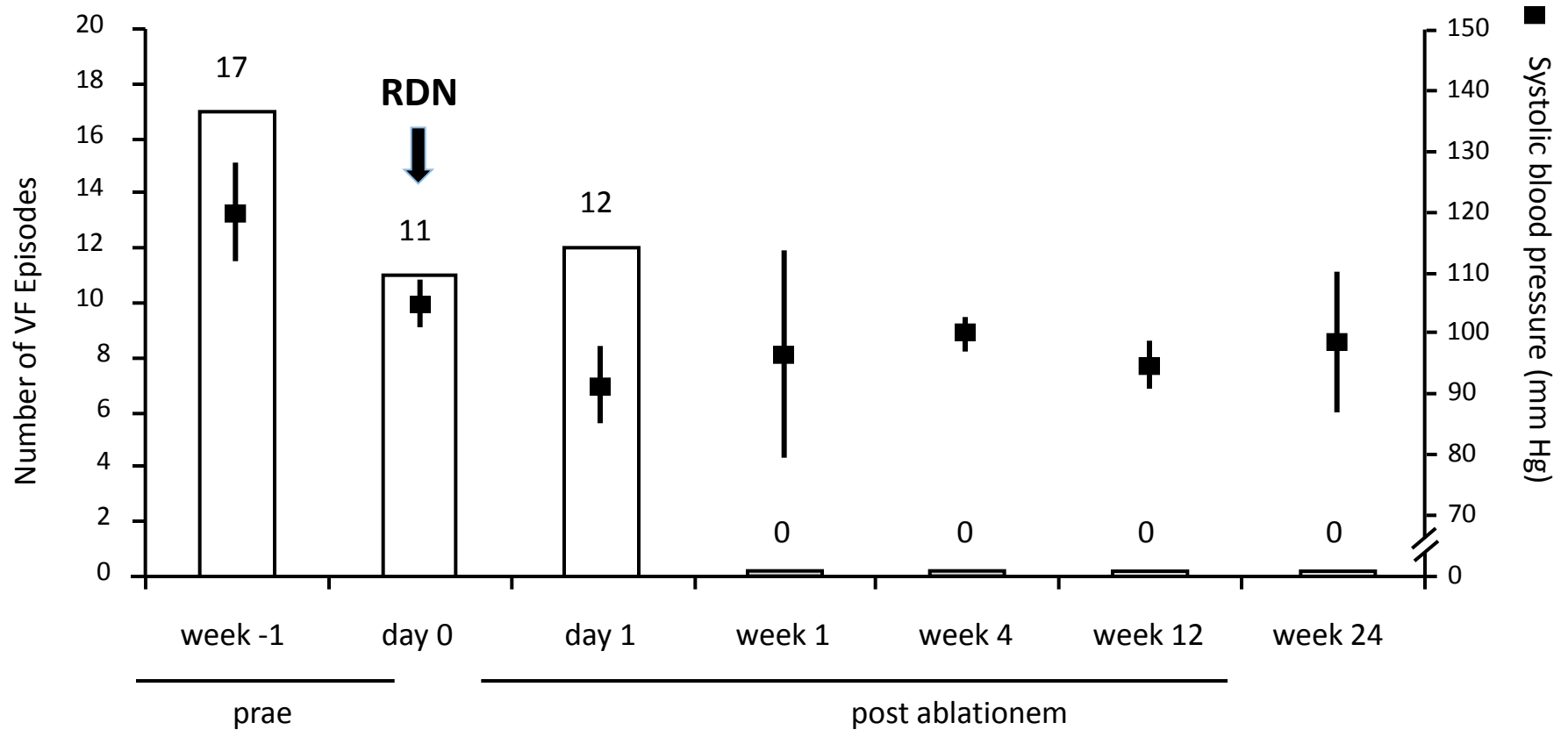
RDN reduces left ventricular hypertrophy



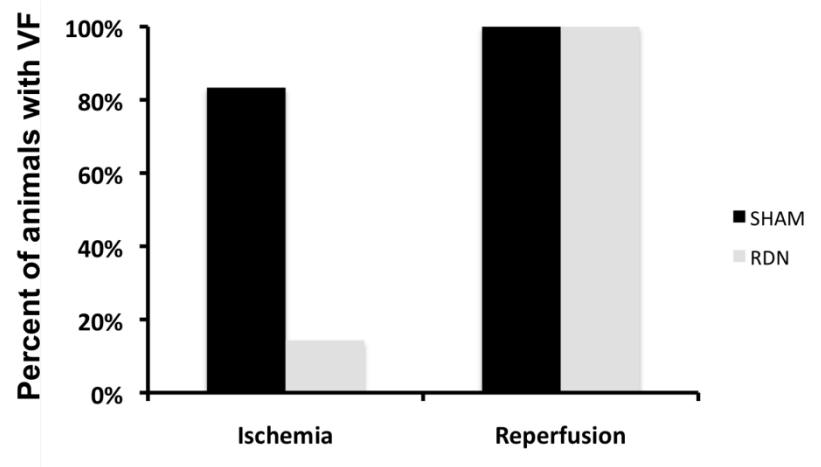
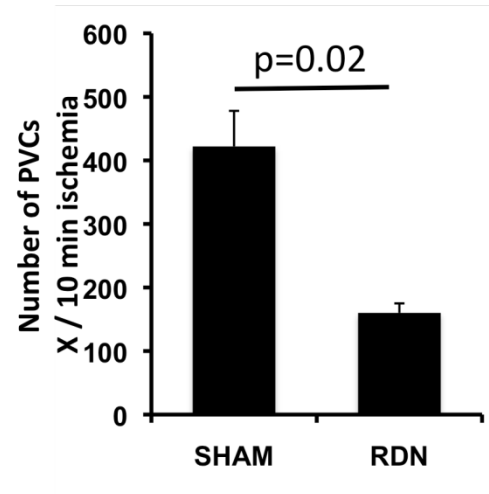
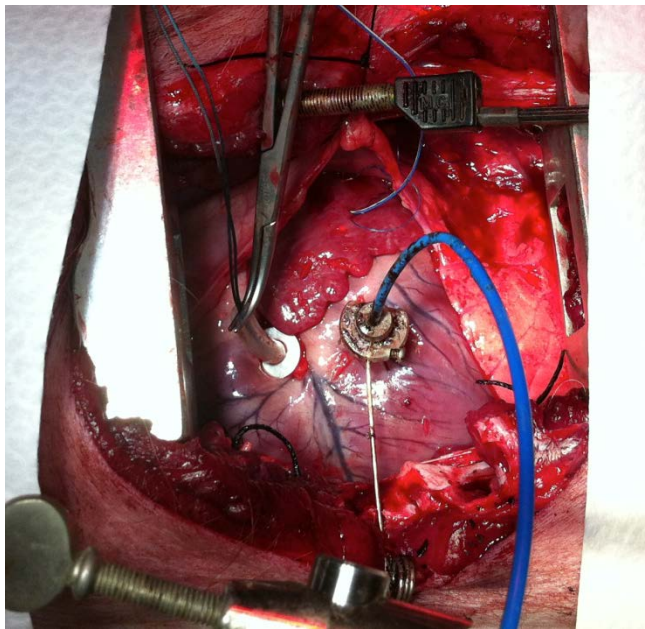


RDN improves left ventricular diastolic function

RDN for Treatment of Electrical Storm



Renal Denervation Suppresses Ventricular Arrhythmias in a Pig Model for Acute Ventricular Ischemia / Reperfusion.

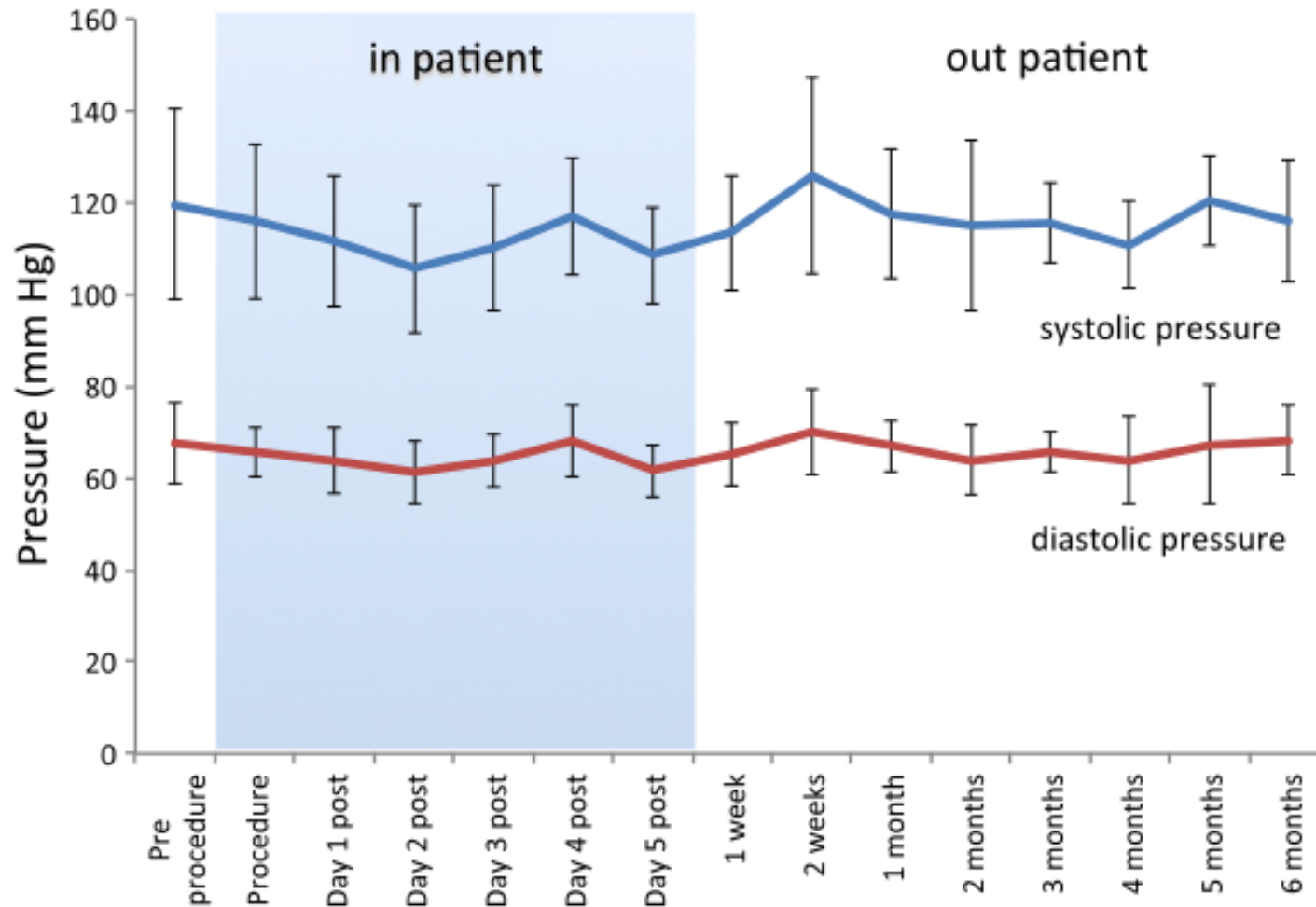


First-in-man safety evaluation of renal denervation for chronic systolic heart failure: Primary outcome from REACH-Pilot study

Justin E. Davies ^{a,*}, Charlotte H. Manisty ^a, Ricardo Petraco ^a, Anthony J. Barron ^a, Beth Unsworth ^a,
Jamil Mayet ^a, Mohamad Hamady ^a, Alun D. Hughes ^a, Peter S. Sever ^a, Paul A. Sobotka ^b, Darrel P. Francis ^a

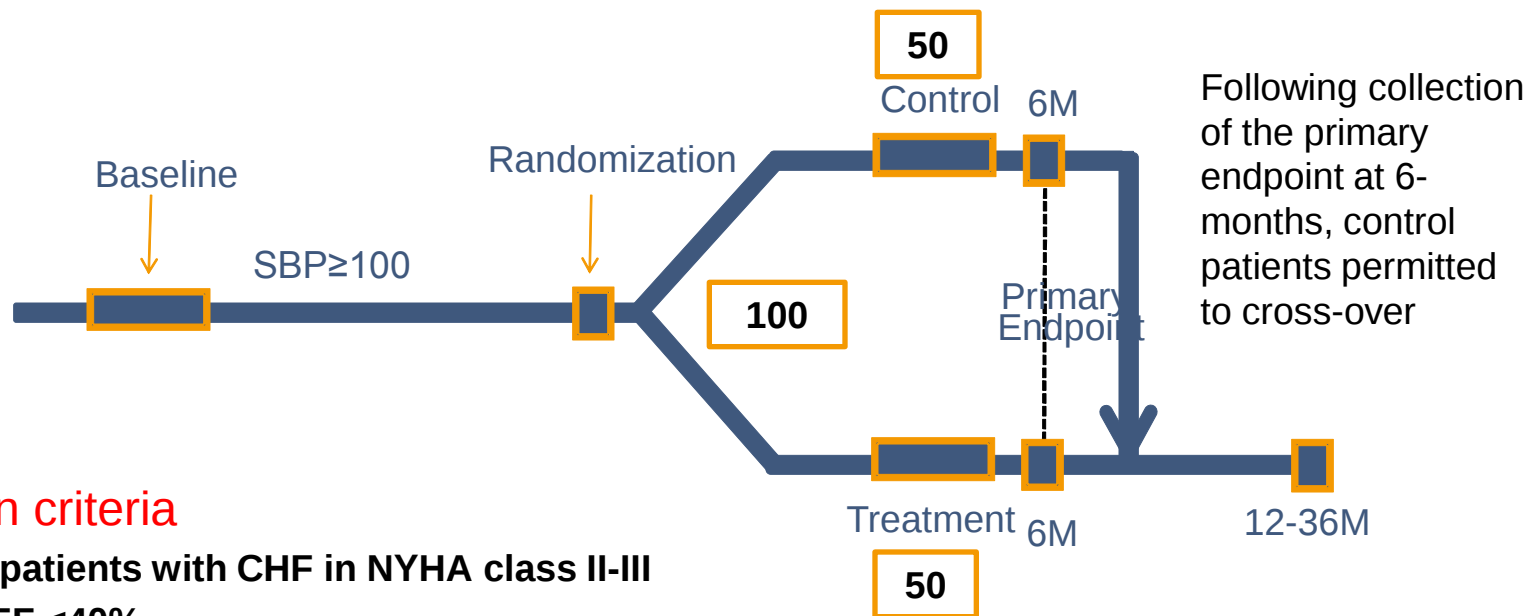
- 7 patients (mean age 69 years)
- chronic systolic heart failure
- mean BP 112/65 mmHg
- maximal tolerated heart failure therapy
- Follow-up for 6 months

No changes in BP after RDN



REnAI DenervAtion in PatienTs with chronic heart failure – The RE-ADAPT-CHF study

- International, multicentre, randomized trial



Inclusion criteria

- 100 patients with CHF in NYHA class II-III
- LV-EF <40%
- eGFR >30 ml/min/1.73m²
- Optimal and stable medical therapy

Conclusions

- AF is characterized by increased sympathetic activity and neural remodeling
- Sympathetic modulation by RDN can reduce sympathetic activity and positively influence other organ systems
- RDN may display atrial antiarrhythmic effects by direct electrophysiological effects as well as by antiremodeling effects (upstream therapy)
- First studies show antiarrhythmic effects also in the ventricle in CHF
- Randomized studies are currently conducted and necessary to assess the effect of RDN on arrhythmias and CHF

Thank you!

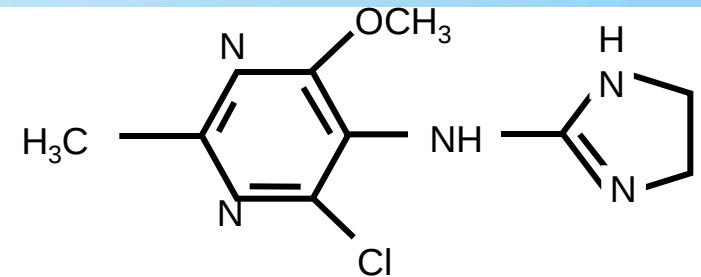
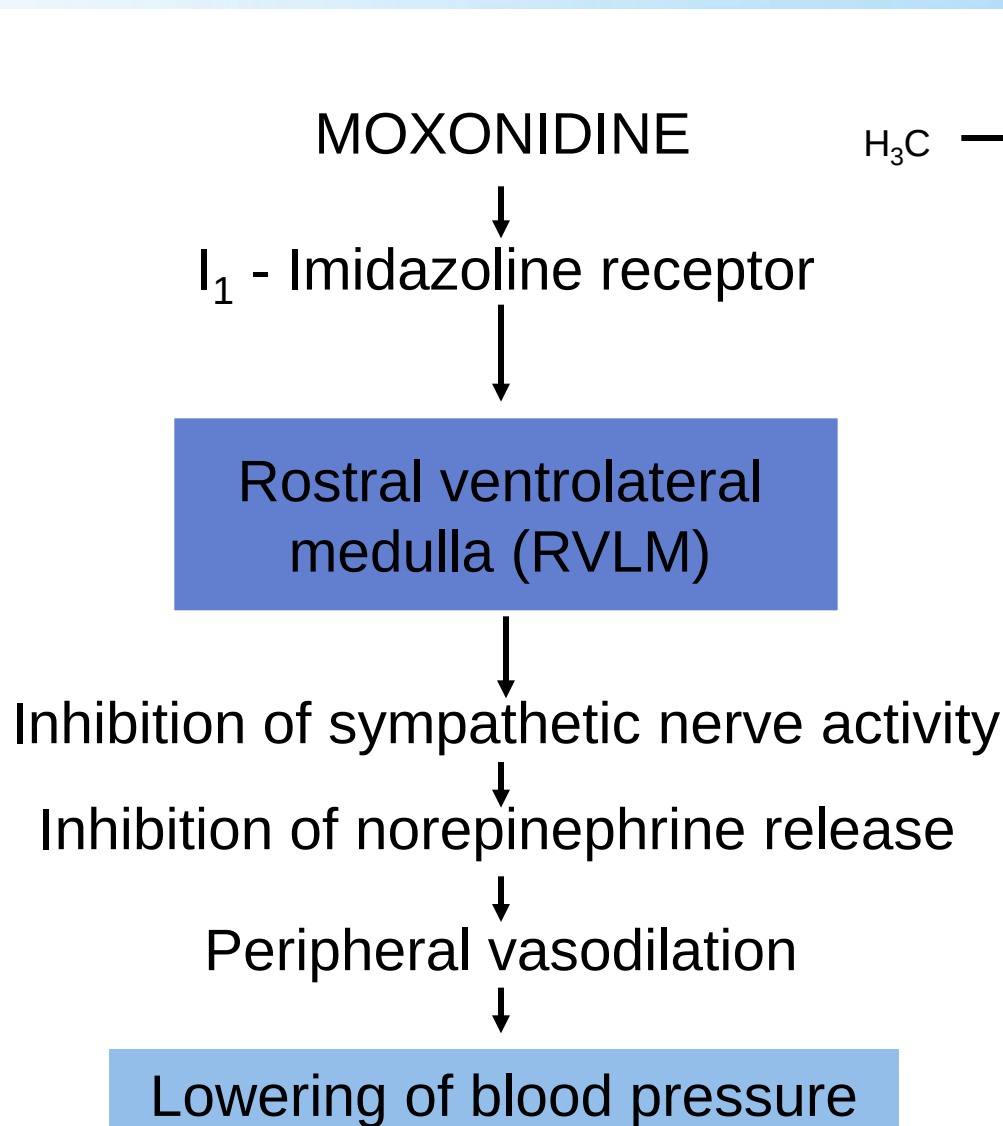


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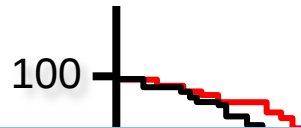
Adverse mortality effect of central sympathetic inhibition with sustained-release moxonidine in patients with heart failure (MOXCON)

Jay N. Cohn^{a,*}, Marc A. Pfeffer^b, Jean Rouleau^c, Norman Sharpe^d, Karl Swedberg^e, Matthias Straub^f, Curtis Wiltse^g, Theresa J. Wright, for the MOXCON Investigators^g

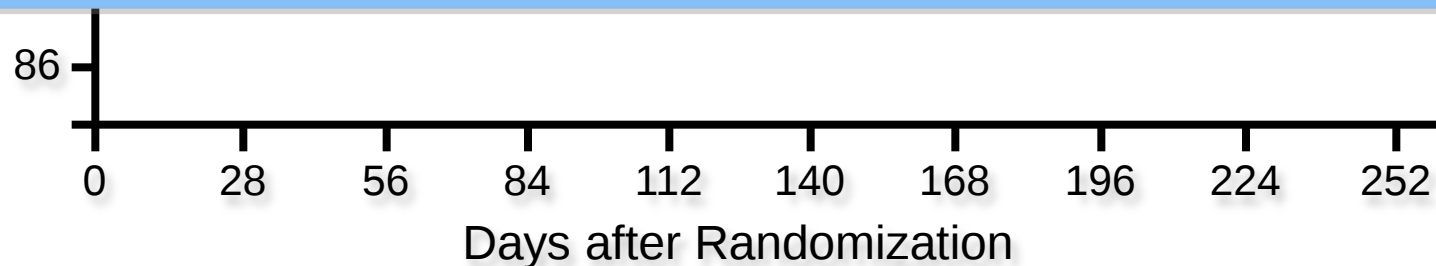
Primary endpoint

- reduction in all-cause mortality compared to placebo
- 4500 patients with CHF in NYHA functional class II-IV
- Maximally tolerated dose of moxonidine:
 - 0.25 to 1.5 mg twice daily
- exclusion criterion: use of a b-blocker within one month prior to randomization

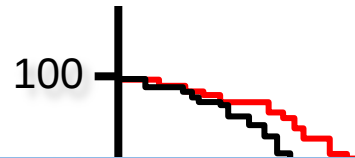
Moxonidine in heart failure increased mortality



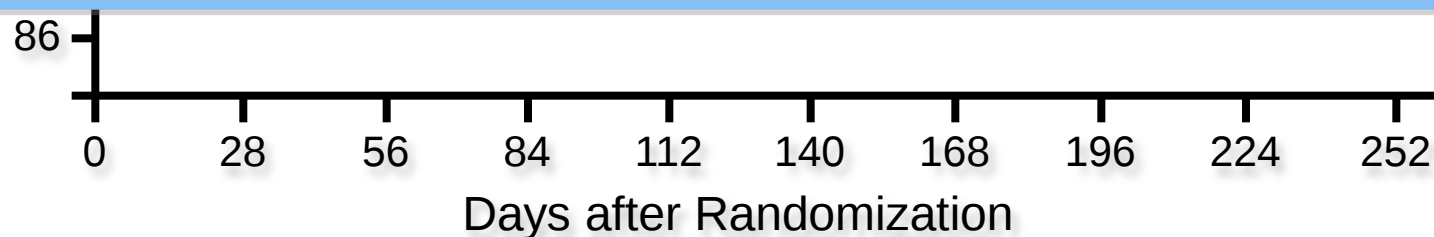
- Trial was stopped prematurely in 1999 by DMSB
- 82 total deaths amongst the first 2000 patients enrolled
 - 53 in moxonidine group vs. 29 in placebo ($p=0.012$)



Moxonidine in heart failure increased mortality

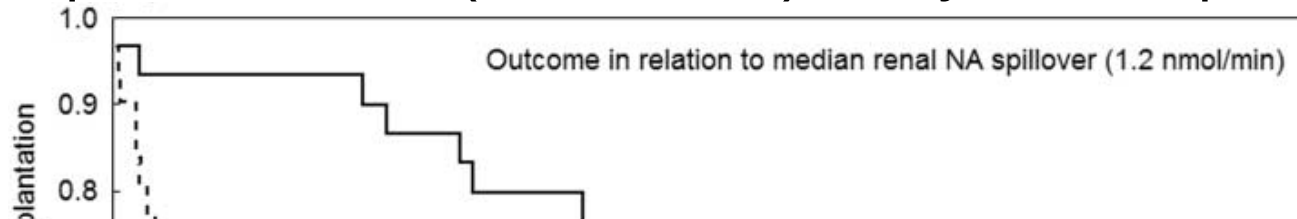


- Rapid up-titration to 1.5 mg BID
- More adverse events in moxonidine group
- 983 compared to 89 in the placebo group
 - Severe bradycardia 41 vs 4, $p < 0.001$
- Compliance to other drug treatment?



High renal NE spillover is related to poor outcome

- N=61 patients, CHF (LV-EF 26%), 5.5 y follow-up

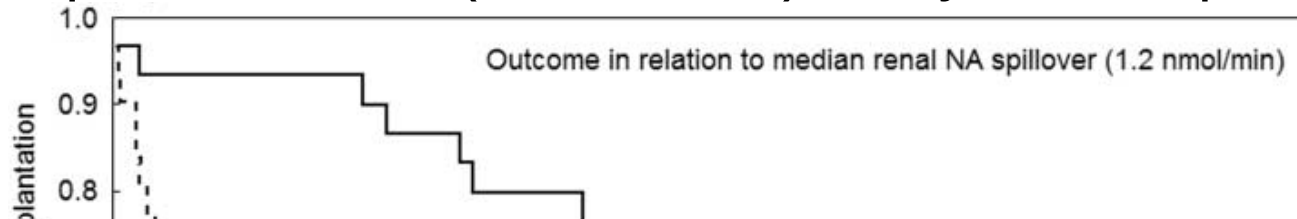


Predictor	HR	95%-CI	p
Renal NE spillover	3.5	1.6-7.4	0.001
Total body NE spillover	1.8	0.9-3.6	0.1
Cardiac NE spillover	4.8	0.7-32.6	0.1



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- N=61 patients, CHF (LV-EF 26%), 5.5 y follow-up



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