Electrical Neuromodulation and Renal Denervation for Heart Failure

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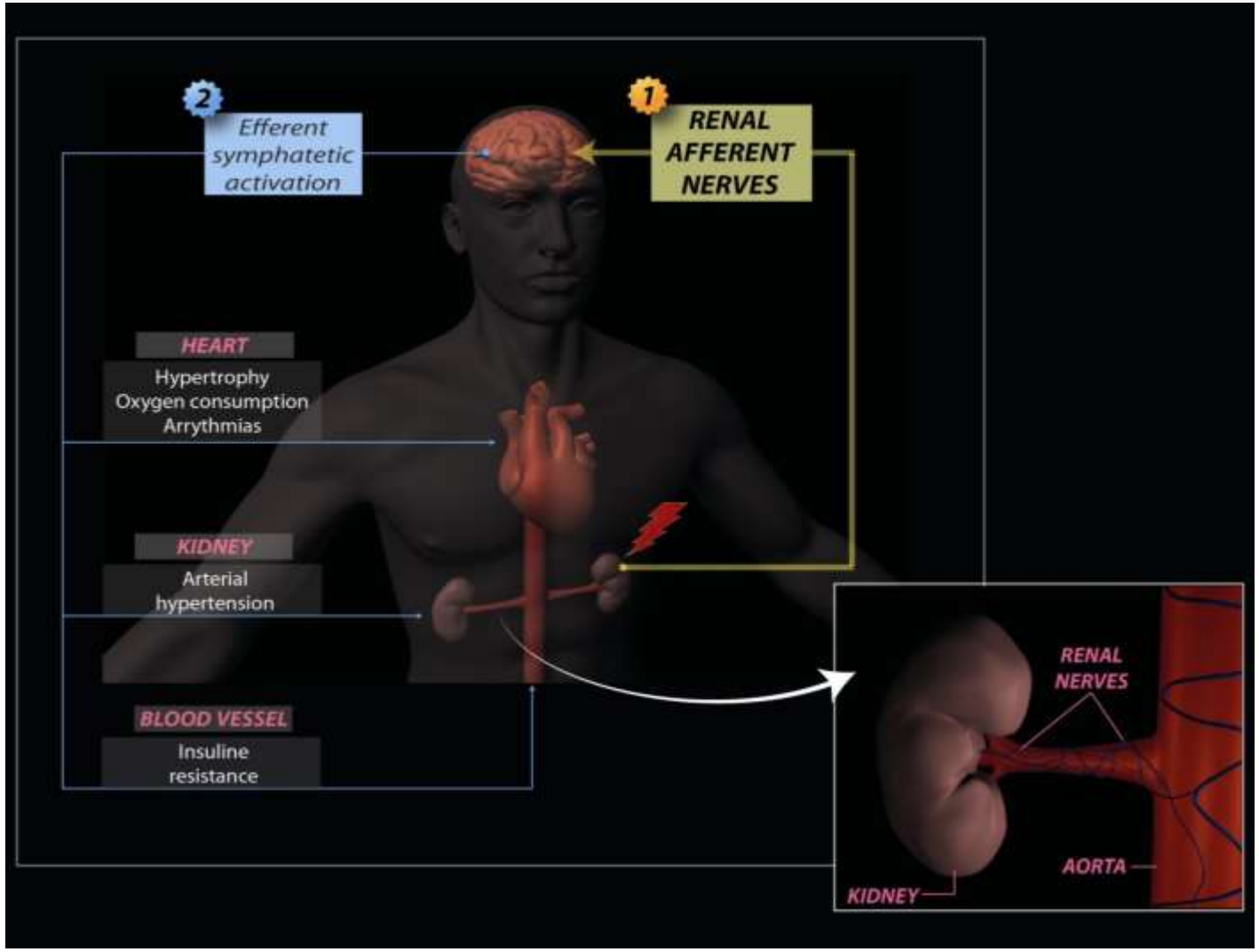
Neural modulation for AF and heart failure

- Sympathetic activation is a significant predictor of a poor prognosis
  - heart failure
  - myocardial infarction
  - chronic kidney disease
- Increase in sympathetic activity proportional to the heart failure severity
- Sympathetic drive contributes to dyspnea, Na+ retention and resistance to loop diuretics
- Increased sympathetic activity is present in obstructive sleep apnea
- HF is associated with parasympathetic withdrawal and abnormal baroreflex activity

FUNDAMENTAL LINK BETWEEN AUTONOMIC NERVE SYSTEM AND HF OUTCOMES

Paton J F et al. Hypertension 2013;61:5-13

Neural modulation for AF and heart failure



1. The autonomic nervous system plays a crucial role in the organ damage related to HF

2. Decrease in cardiac output leads to activation of the RAAS and increase in sympathetic nerve activity

4. Device based modulation of the ANS might be beneficial for HF and AF

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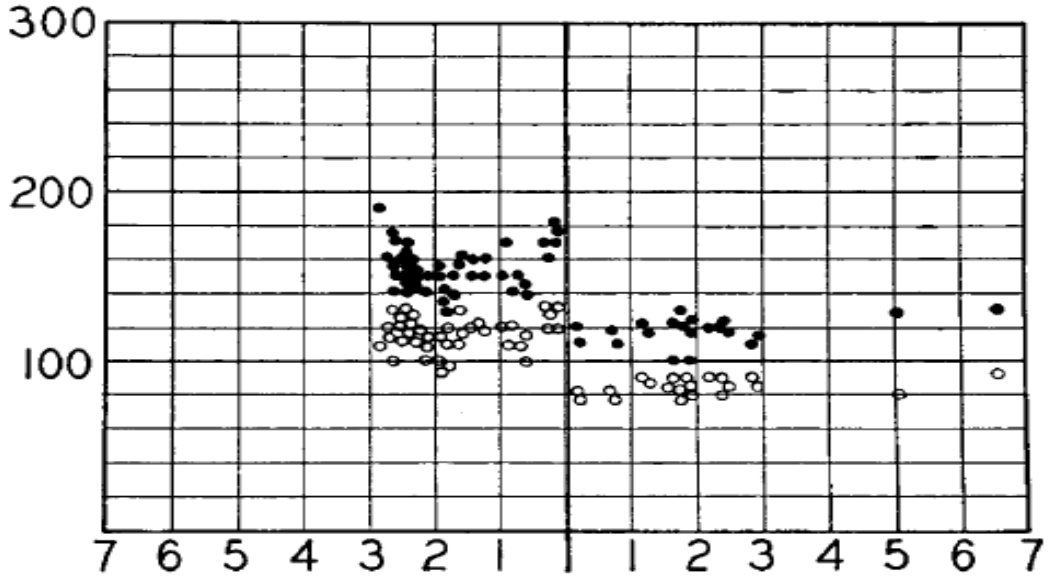
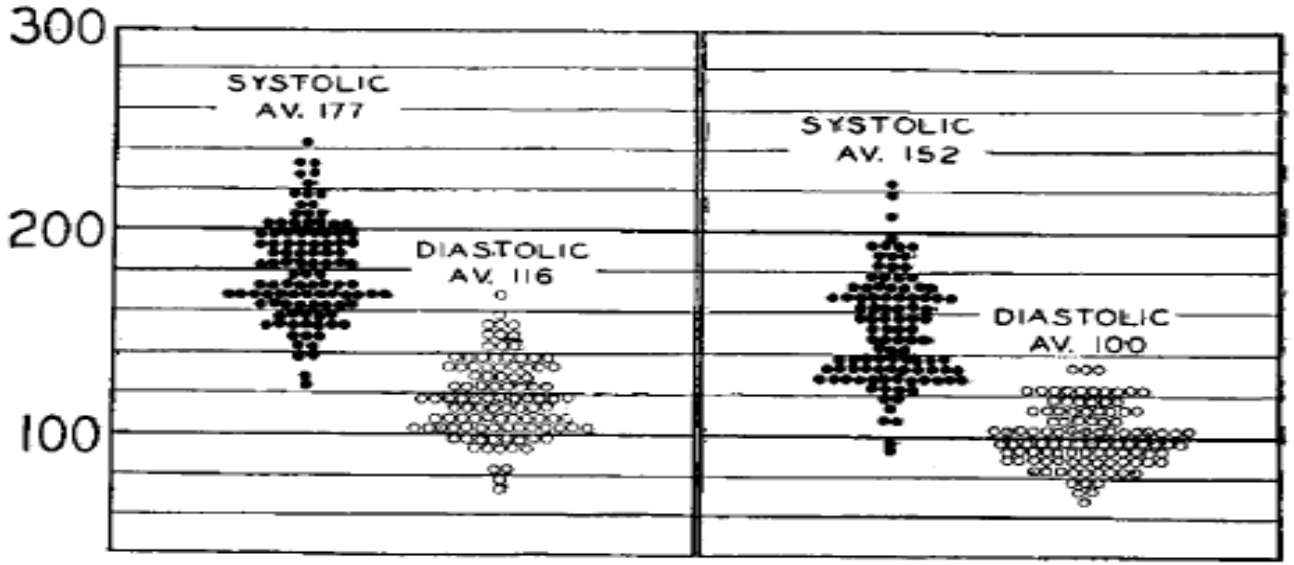
EFFECT OF SYMPATHECTOMY ON BLOOD PRESSURE IN HYPERTENSION

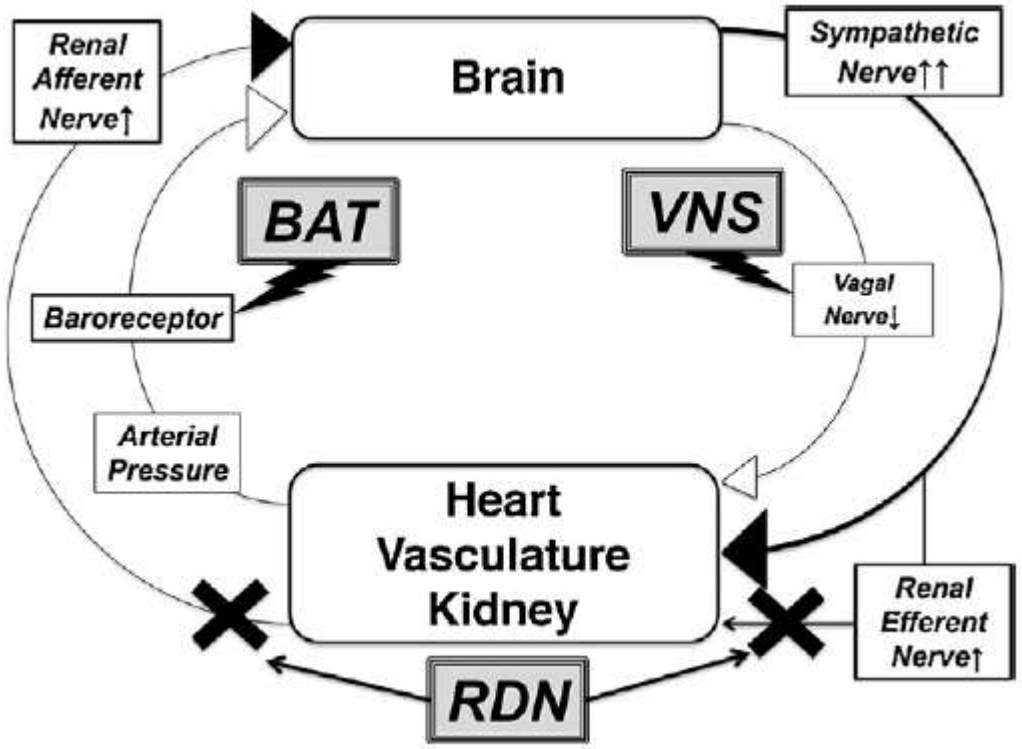
A Review of Thirteen Years' Experience at the Massachusetts General Hospital





Evelyn et al JAMA, June 18, 1949

Device therapies targeting ANS



1. Renal denervation
2. Baroreflex activation therapy (BAT)
3. Spinal cord stimulation
4. Vagus nerve stimulation (VNS)
5. Carotid body modulation
5. Left cardiac sympathetic denervation

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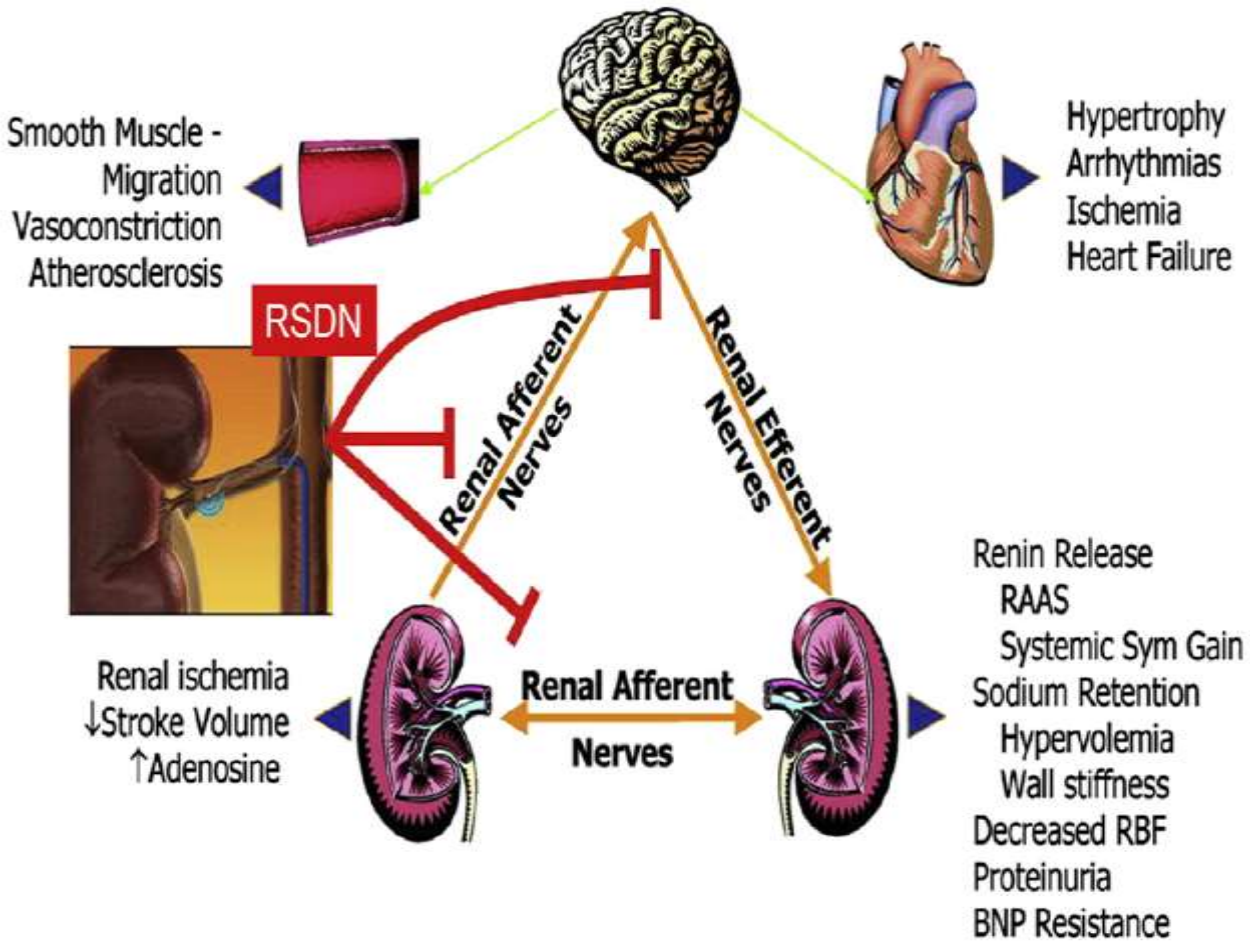
Renal denervation



PRECLINICAL:

- Rat MI model: better ventricular function, lower LVEDP, smaller LV end-diastolic and end-systolic dimensions and reduced sodium excretion
- Dog HF model: improvement in sodium excretion
- Rabbits with pacing-induced HF: normalization in the expression of angiotensin AT1 receptors.

Table 4
Clinical trials of renal sympathetic nerve denervation in heart failure

Trial	N	Criteria	Design	Endpoint[a]
REACH-Pilot	7	• Chronic HF • NYHA III–IV	Single-arm, open label	Safety study
SYMPLICITY-HF	40	• LVEF <40% • NYHA II–III • GFR 30–75	Single-arm, open label	Safety study
Renal Denervation in Patients With Chronic Heart Failure	100	• LVEF10%–40% • NYHA II–III • GFR >30	Randomized, open label, parallel	Safety, number of complications
DIASTOLE	60	• HF symptoms • LVEF ≥50% • Evidence of HFpEF • HTN • GFR >30	Randomized, open label, parallel	Change in E/E′
RDT-PEF	40	• LVEF >40% • NYHA II-III • Evidence of HFpEF	Randomized, open label, parallel	Change in symptoms and echo findings
RESPECT-HF	144	• LVEF ≥50% • NYHA II-IV • Evidence of HFpEF • Episode of ADHF	Randomized, open label, parallel	Change in LA volume index

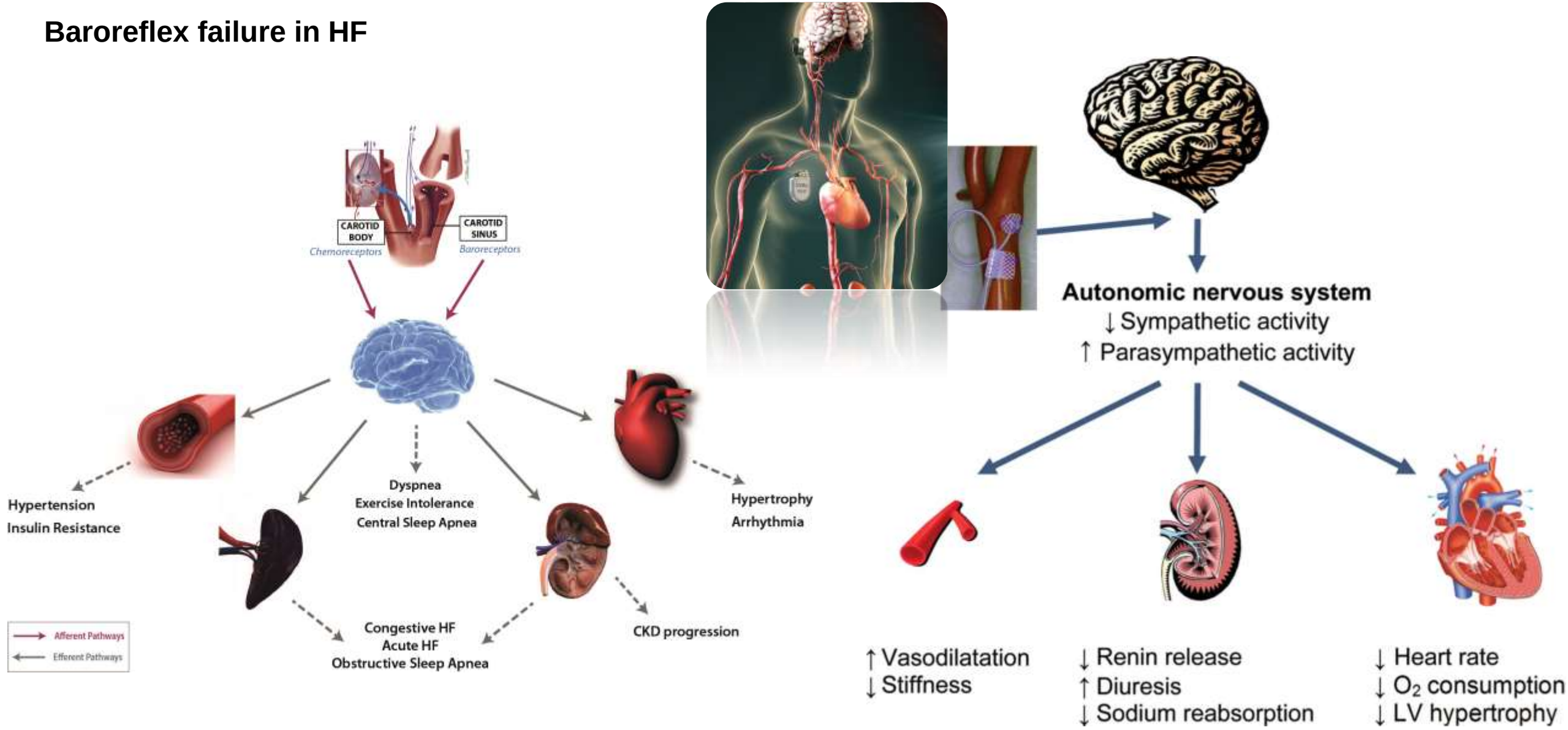
Heart Failure Clin 11 (2015) 337–348; Current Vascular Pharmacology, 2018, 16, 30-43

Renal denervation

Trial	NCT	Sponsor	n	Type of HF Population	Design of Study	Follow up (Months)	Main Findings – Efficacy	Main Findings - Safety	Current Status of Study
REACH - Pilot[67]	NCT01584700	Imperial College London	7	Chronic HF, NYHA III or IV, OMT	Open-label, non-randomized first-in-humans trial evaluation of the safety of bilateral renal denervation in patients with heart failure	6	Significant increase in 6-minute walk distance A self-reported improvement of symptoms	Non-significant trend to reduction in BP No statistically significant change in HR No deterioration of renal function	Completed
Olomouc I Pilot[68]	NCT01870310	University Hospital Olomouc	51	NYHA III, LVEF ≤ 35% on OMT	Single center, randomized (1:1) control trial, RDN + OMT vs OMT	12	(preliminary data) Significant increase in LVEF Left ventricular end-systolic and end-diastolic volume decreased NT-pro BNP significantly decreased	No significant BP decrease No change in renal function	On going
RDT-PEF[70]	NCT01840059	Royal Brompton & Harefield NHS Foundation Trust	25	NYHA ≥II, HFpEF, OMT	Single-center, randomized, open-controlled study, RDN vs OMT = 2:1	12	No statistically significant difference in VO2, BNP, E/e', left atrial volume index or left ventricular mass index Comparable change in eGFR	Plain balloon angioplasty during the RDN procedure to treat renal artery wall edema in two patients	Early Terminated

Baroreflex activation therapy (BAT)

Baroreflex failure in HF



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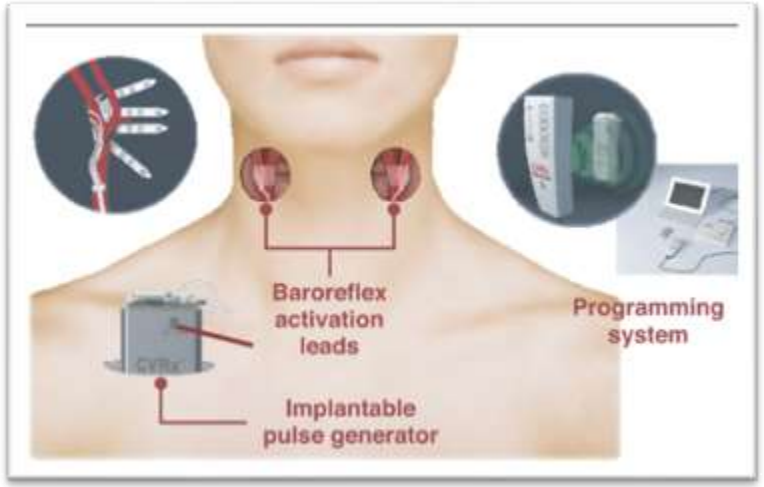
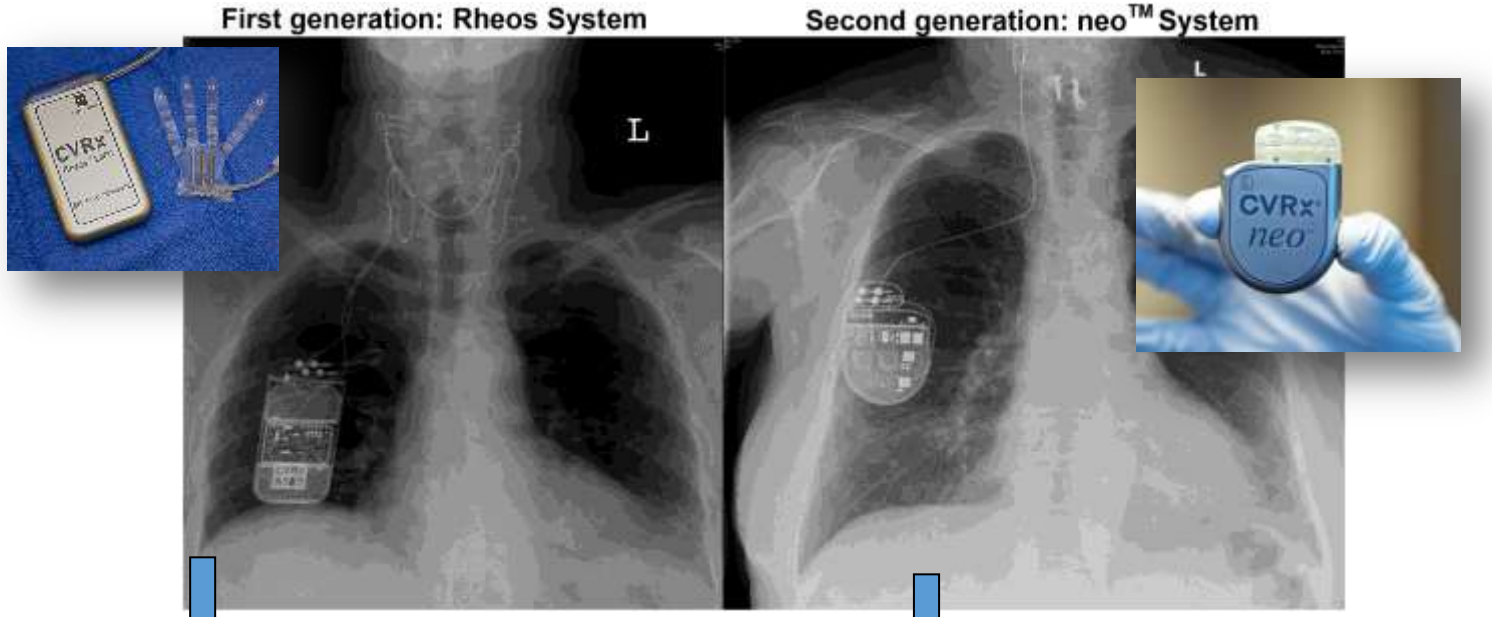
Baroreflex activation therapy (BAT)

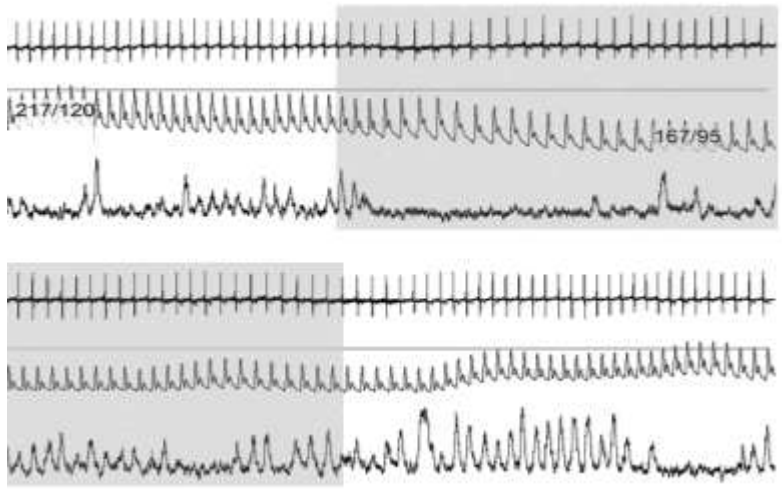
Electrical stimulation of baroreflex afferent nerves Rheos System; CVRx Inc.

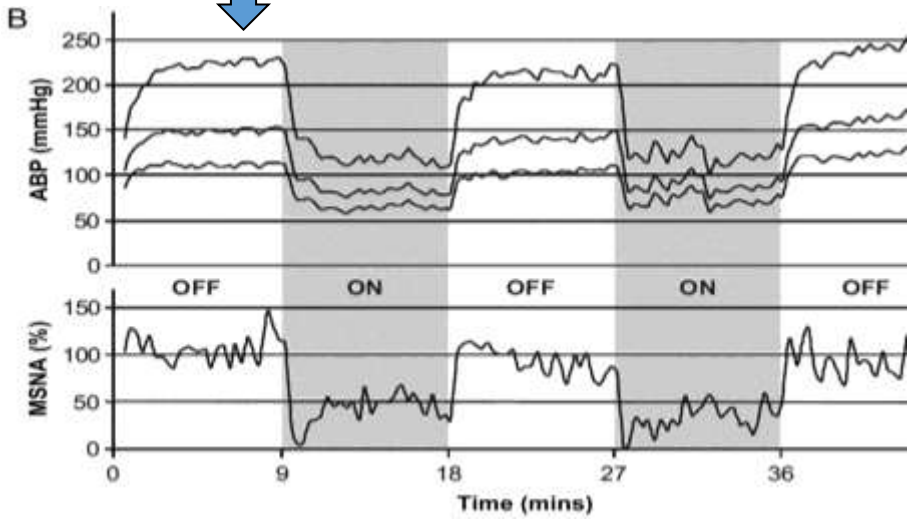




PRECLINICAL

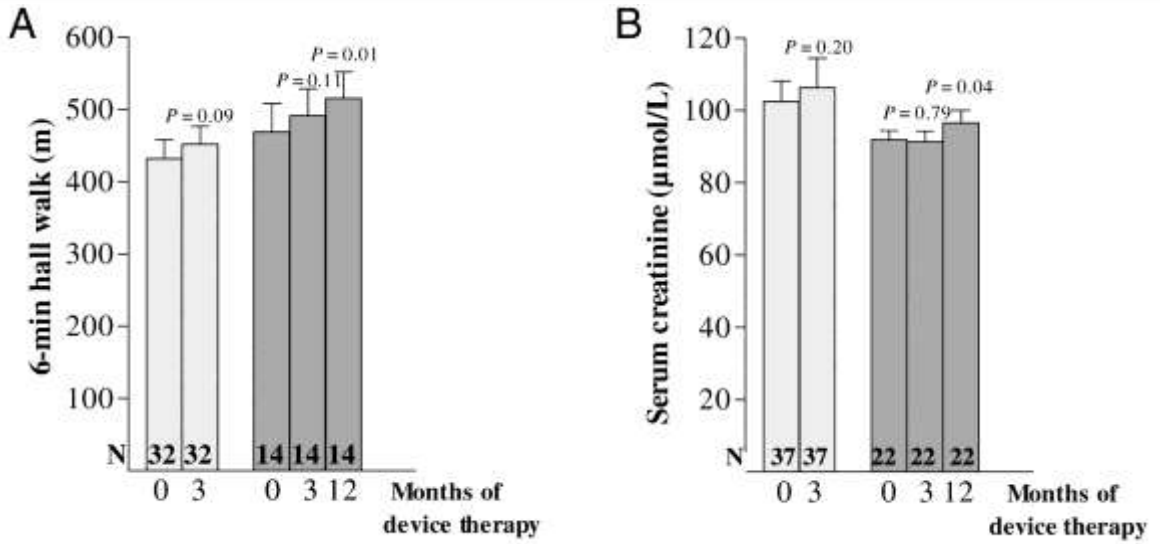
- Improved LVEF
- Reduced NE levels
- reduced LV filling pressure
- improved survival





Menne J et al. Nephrol. Dial. Transplant. 2013;28:288-295; Hypertension 2010;55:619-626.

Baroreflex activation therapy (BAT)



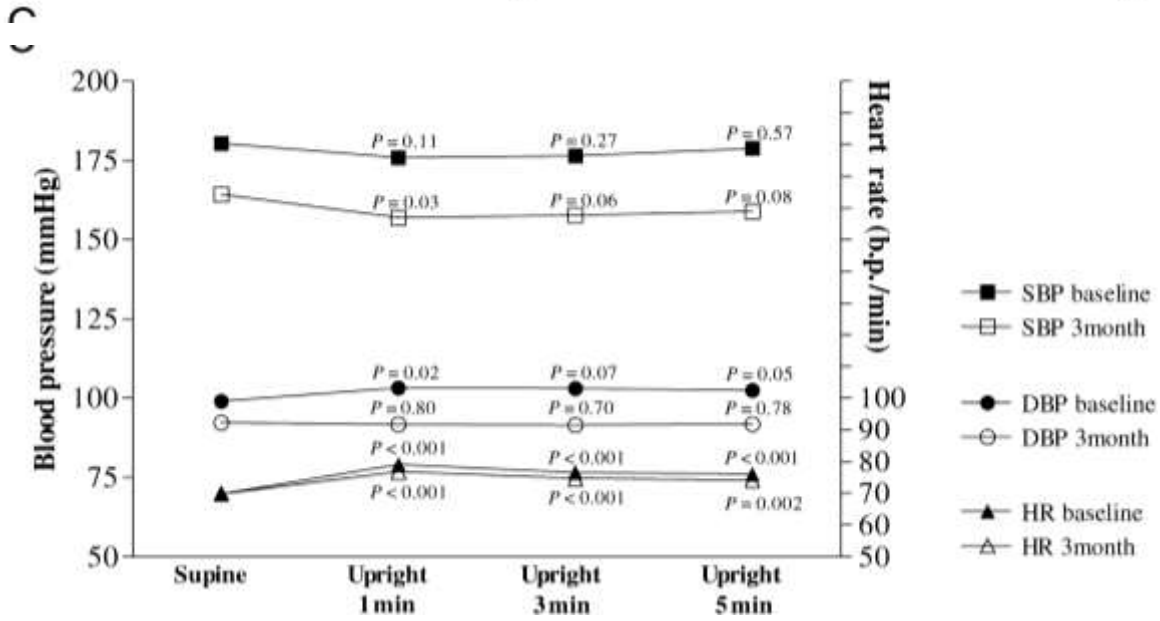


Table 1 Baseline and Change in Echocardiographic Variables in Patient Cohort

Variable	Baseline (n = 34)	Δ 3 Months (n = 34)	Δ 12 Months (n = 21)
Cardiac structure			
LAD, mm	44.8 ± 1.3	−1.2 ± 0.5*	−2.4 ± 0.8†
LADi, mm/m²	20.9 ± 0.5	−0.6 ± 0.2*	−1.2 ± 0.3†
Septal wall thickness, mm	14 (13 to 16)	−1 (−2 to 0)‡	−1 (−2 to 0)‡
LV posterior wall thickness, mm	14 (13 to 15)	−1 (−1 to 0)‡	−1 (−2 to −1)‡
Relative wall thickness	0.56 ± 0.02	−0.02 ± 0.01*	−0.05 ± 0.01‡
LVOT diameter, mm	19.6 ± 0.3	+0.5 ± 0.2†	+1.0 ± 0.3†
LVEDD, mm	50.0 ± 0.9	−0.9 ± 0.5	−1.6 ± 0.5†
LVESD, mm	31.0 ± 0.8	−1.3 ± 0.6*	−2.4 ± 1.0*
LV mass, g	302.0 ± 15.7	−39.8 ± 6.5‡	−52.8 ± 9.3‡
LV mass index, g/m²	138.9 ± 6.0	−18.0 ± 2.7‡	−24.6 ± 3.9‡
Cardiac function			
LVEF, %	65 (62 to 68)	+1 (0 to +3)†	+2 (0 to +4)*
Stroke work	199.6 ± 8.8	−29.5 ± 8.8†	−31.3 ± 10.5†
Mitral E-wave velocity, cm/s	0.78 ± 0.04	−0.01 ± 0.02	−0.06 ± 0.03
Mitral A-wave velocity, cm/s	0.84 ± 0.03	−0.03 ± 0.02	−0.11 ± 0.03†
Mitral E/A	1.02 ± 0.10	−0.01 ± 0.05	+0.07 ± 0.09
MWFS, %	13.9 ± 0.5	+1.0 ± 0.4†	+1.7 ± 0.6†
SBP, mm Hg	179.6 ± 4.3	−23.6 ± 5.4‡	−25.7 ± 5.7‡
DBP, mm Hg	104.4 ± 3.0	−11.7 ± 3.4†	−12.9 ± 4.3†
Pulse pressure, mm Hg	74.9 ± 2.7	−11.9 ± 3.1‡	−12.8 ± 2.9‡
Heart rate, beats/min	72.4 ± 1.8	−4.5 ± 1.5†	−2.7 ± 1.8
Rate pressure product, beats/min × mm Hg	13,267 ± 565	−2,197 ± 521‡	−1,994 ± 606‡

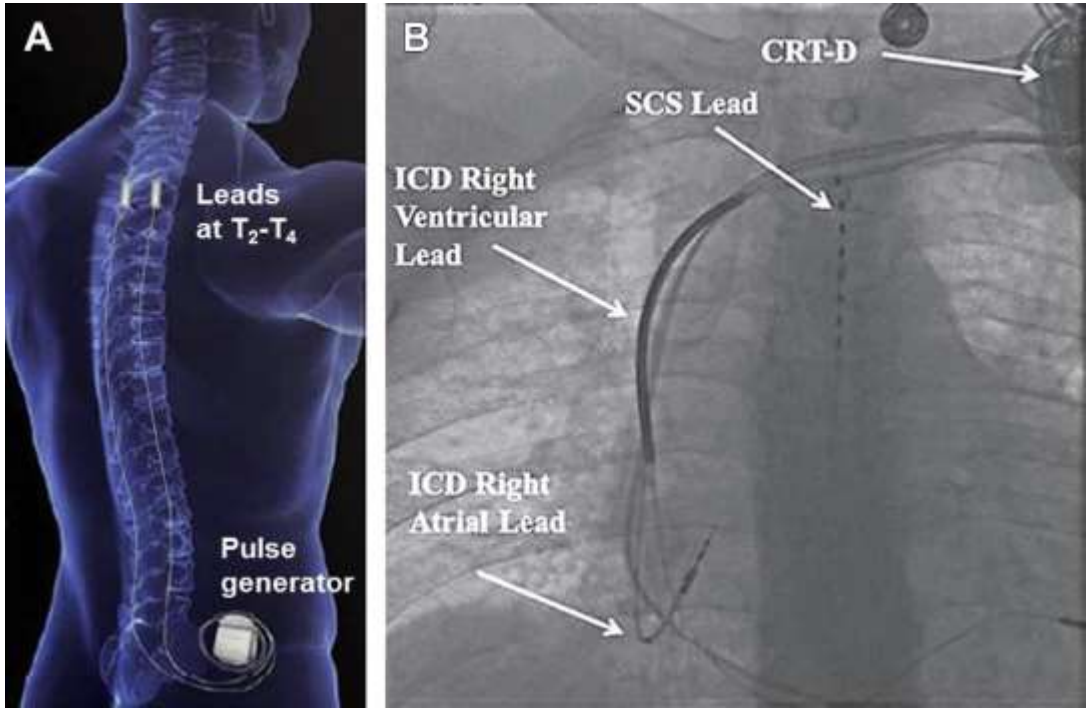
Menne J et al. Nephrol. Dial. Transplant. 2013;28:288-295; Hypertension 2010;55:619-626; Krum H et al. Eur Heart J 2011;32:537-544; J Am Coll Cardiol 2011;57:1787-1788.

Baroreflex activation therapy (BAT)

Trials	NCT	Sponsor	n	Type of HF Population	Design of Study	Follow up (Months)	Main Findings - Efficacy	Main Findings - Safety	Current Status of Study
Rheos DHF[78]	NCT00718939	CVRx, Inc.	6	NYHA III, LVEF ≥ 45%, elevated BNP or NT-Pro BNP	Prospective, randomized, double blind trial. RHEOS ON : device turn on for six months and remains on RHEOS OFF : device turned off for 6 months and then turned on	12	Significant reduction in NT-Pro BNP Significant increase in 6 minute walk test	Pending	Completed
HOPE4HF/ Barostim HF[79]	NCT01720160 NCT01471860	CVRx, Inc.	146	NYHA III, LVEF of 35%, OMT	Randomized, controlled trial. GDMT vs GDMT plus BAT (1:1)	6	Significant improvements in NYHA functional class, quality of life score, BNP and 6 minute walk distance	No difference in event free rate of all system and procedure-related major adverse neurological and cardiovascular events	Completed
XR Barostim[80]	NCT01484288	CVRx, Inc.	12	NYHA class III, LVEF ≤40%, OMT	Open-label, single arm evaluation trial	6	Significant reduction in MSNA Improvements in baroreflex-sensitivity, LVEF, NYHA, quality of life	Hospitalization and emergency department visits for worsening HF were markedly reduced	Completed

Menne J et al. Nephrol. Dial. Transplant. 2013;28:288-295; Hypertension 2010;55:619-626; Krum H et al. Eur Heart J 2011;32:537-544; J Am Coll Cardiol 2011;57:1787-1788.

Spinal cord stimulation



Trials	NCT	Sponsor	n	Type of HF Population	Design of Study	Follow up (Months)	Main Findings - Efficacy	Main Findings - Safety	Current Status of Study
Methodist SCS[97]	NCT01124136	The Methodist Hospital System	9	Symptomatic HF despite OMT, NYHA III, LVEF ≤ 30%	Prospective, randomized, double-blind, crossover pilot study SCS ACTIVE VS SCS INACTIVE for 3 months, 1 washout month and crossover to SCS ACTIVE for 3 months	7	Improvement in quality of life and NYHA in the majority of patients over the SCS-ACTIVE period No objective improvements in LVEF and NT-pro BNP	Death (1) Hospitalizations for worsening HF (3)	Completed
SCS HEART[98]	NCT01362725	St. Jude Medical	22	NYHA class III or IV, LVEF 20%–35%, LVEDD 55-80mm, implantable defibrillator, OMT	Prospective, multi-center, pilot trial 17 SCS device, 4 non-treated controls	6	Improvement in 4 of 6 efficacy parameters of the composite score Significant improvements in NYHA class, HF questionnaire, VO_2max, LVEF, and LVESV	Deaths (0) Hospitalization for worsening HF (2)	Completed
Defeat HF[99]	NCT01112579	Medtronic Cardiac Rhythm and Heart Failure	66	NYHA III, LVEF < 35%, LVEDD 55-80mm, OMT, QRS<120msec	Multicenter, Phase II, prospective, single-blind, randomized study, (3:2) randomization SCS ON vs SCS OFF At 6 months, SCS OFF crossover to SCS ON	36	No significant differences in LVESV, peak VO_2 and NT-pro BNP between groups No differences in NYHA, HF questionnaire, 6 min walk test	6 Deaths No differences in adverse events No difference in freedom from death or hospitalization for HF at 6 months	Completed[99]

PRECLINCAL

- increased the sinus cycle length and prolonged AV nodal conduction
- reduced the incidence of spontaneous VT/VF in ischemia model
- Increased vagal tone (reduction in SR, prolongation of PR interval, and lowering of BP)
- reduction in serum NE and BNP, reduction in VT/VF, improvement in LVEF and volumes in experimental MI

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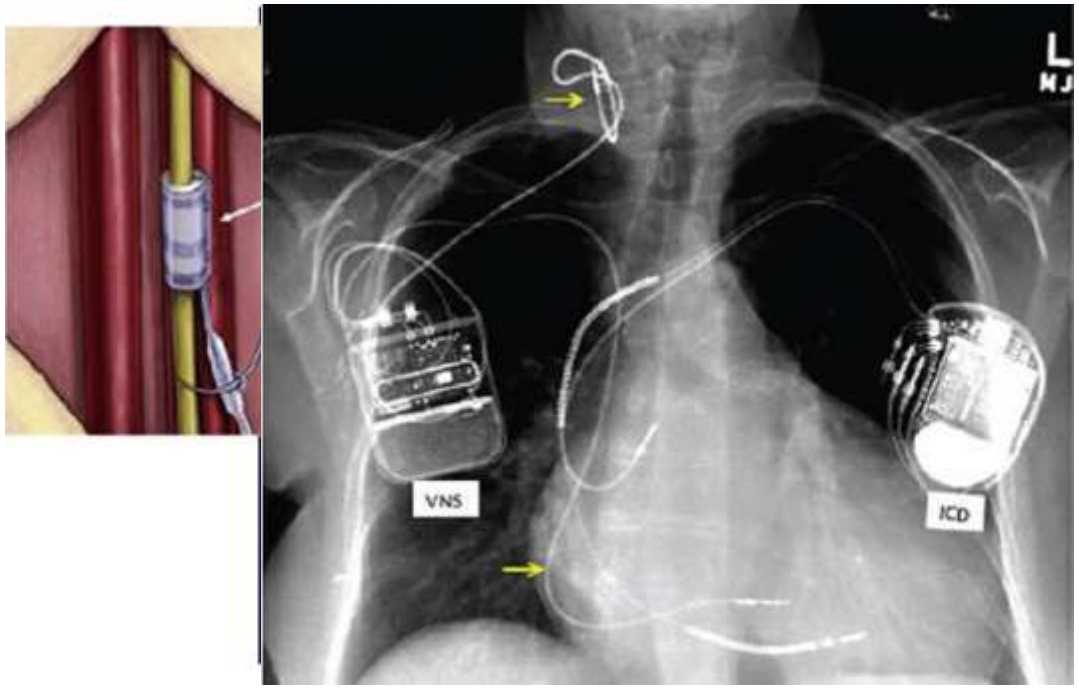
Vagus nerve stimulation



- Decreased vagal activity itself is associated with higher mortality among HF patients
- PRECLNICAL
- chronic VNS improved LV hemodynamics and survival in HF in animal models
- reduction in sympathetic activity
- Reduced inflammation
- Anti-arrythmogenic
- Protection agenist ischemia-reperfusion injury

Trials	NCT	Sponsor	n	Type of HF Population	Design of Study	Follow up (Months)	Main Findings - Efficacy	Main Findings - Safety	Current Status of Study
CF-MS-01[88]	NCT00461019	BioControl Medical	32	NYHA II-IV, LVEF < 35%	Multi-center, open-label phase II, two-staged study (8-patient feasibility phase plus 24-patient safety and tolerability phase)	6	Significant improvements in NYHA, quality of life, 6 min walk test, LVEF, and left ventricular systolic volume	3 deaths 2 device-related adverse events	Completed
ANTHEM-HF[89]	NCT01823887	Cyberonics, Inc.	60	NYHA II-III, LVEF < 40%, OMT	Multi-center, open-label, safety, tolerability and efficacy randomized (1:1) Right- vs Left-side VNS study	6	Significant improvement in LVEF, NYHA class, Significant improvements in NYHA, HF questionnaire scores, 6 min walk test	21 serious adverse events 1 death (related to the VNS system) 2 deaths (after 3 months, one sudden cardiac death, one HF medical non-compliance) Minor decrease in mean HR	Completed
NECTAR-HF[90]	NCT01385176	Boston Scientific Corporation	96	NYHA II-III, LVEF <35%, LVEDD >55mm	Multi-center, double-blind, randomized, phase II trial (2:1) randomization VNS ON vs VNS OFF (control)	6	Not statistically significant improvements in LV diameters, LV end-systolic volume, LVEF Statistically significant improvements in NYHA & HF questionnaire SF-36	3 deaths 7 infections associated to the device 19 hospitalizations	Completed
INOVATE HF[91]	NCT01303718	BioControl Medical	707	LVEF < 40%, NYHA III, OMT	Multi-center, open label, randomized, phase III trial, (3:2) randomization to VNS vs OMT	16	Not statistically significant improvements in death from any cause or first event for worsening HF Improvement in NYHA, quality of life, 6 minute walk test	62 deaths (VNS arm) 28 deaths (control arm) Rate of freedom from procedure and system-related events was 90.6%	Early Terminated

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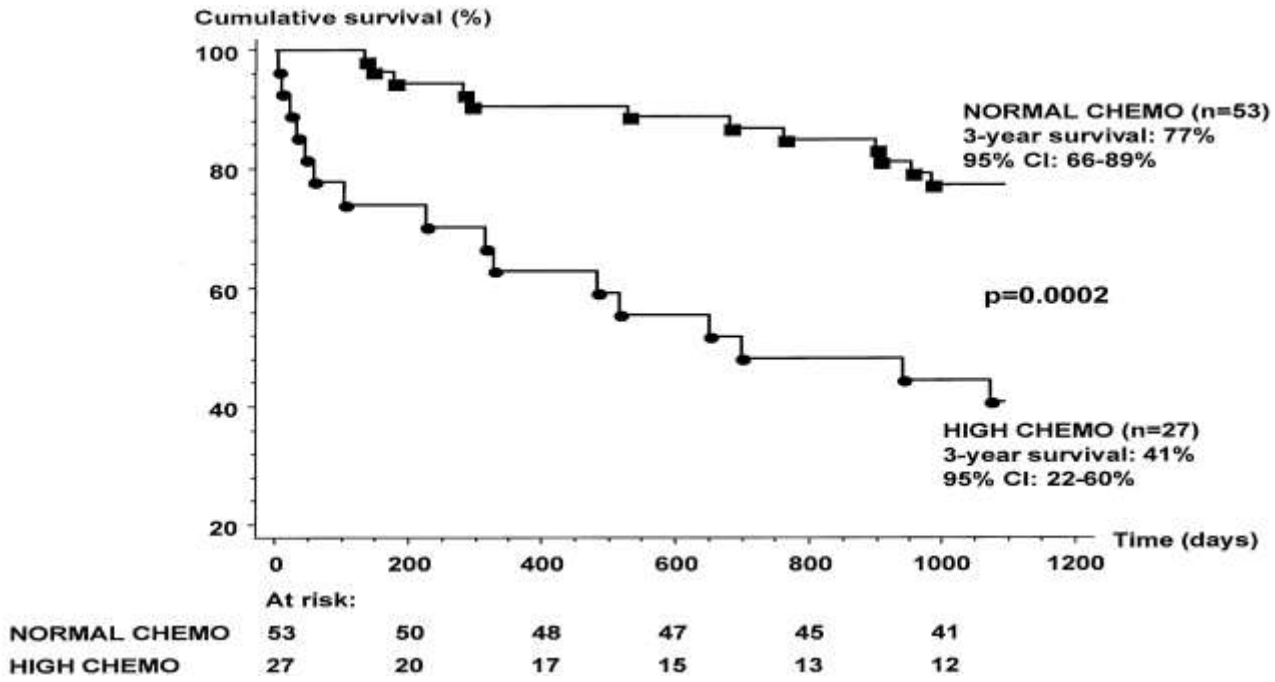
Carotid Body Modulation



Median follow up 41 months

Independent of age, peak VO2, VE/VCO2 slope and LVEF

CB is adrenergic excitatory

- Increases central sympathetic outflow
- Inhibits parasympathetic outflow
- Increases organ specific adrenergic activity
  - Increases muscle and vascular sympathetic nerve activity
  - Renal sympathetic nerve activity
  - Cardiac sympathetic nerve activity

Selective Carotid Body Modulation can reduce the pathology associated with adrenergic hyperactivity and parasympathetic suppression

Ponikowski et al. Circulation 2001;104:544-549; J Physiol. 2012. 590:4269–4277.

Unknowns

- Interaction of baroreflex activation therapy and antihypertensive medications (eg RAAS inhibitors)
- sodium retention (diuretics required for a sustained hypotensive response to baroreflex activation therapy?)
- Combination with RDN
- Desensitization of baroreceptors or cardiovascular control centres in the brain.
- stimulation mode, eg. synchro with ECG or carotid pulse contour

Conclusions

- Fundamental link between sympathetic nerve system and HF outcomes

  Sympathetic activation is a significant predictor of a poor prognosis
- Targeting of sympathetic activity may address the unmet needs
- Current therapies in evaluation in modestly sized trials powered for surrogate outcomes

  - Renal denervation
  - Baroreflex activation therapy
  - Spinal cord stimulation
  - Vagus nerve stimulation
  - Carotid body modulation
  - Left cardiac sympathetic denervation