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Ritorno al futuro
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PALAZZO DEI CONGRESSI

AUTONOMIC DYSFUNCTION AND HEART FAILURE IN THE ELDERLY

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Autonomic dysfunction

Autonomic dysfunction or dysautonomia is a dysregulation of the autonomic nervous system (ANS), which is responsible for the control of all innervated organs and tissues.

Wehrwein EA et al. Compr Physiol. 2016

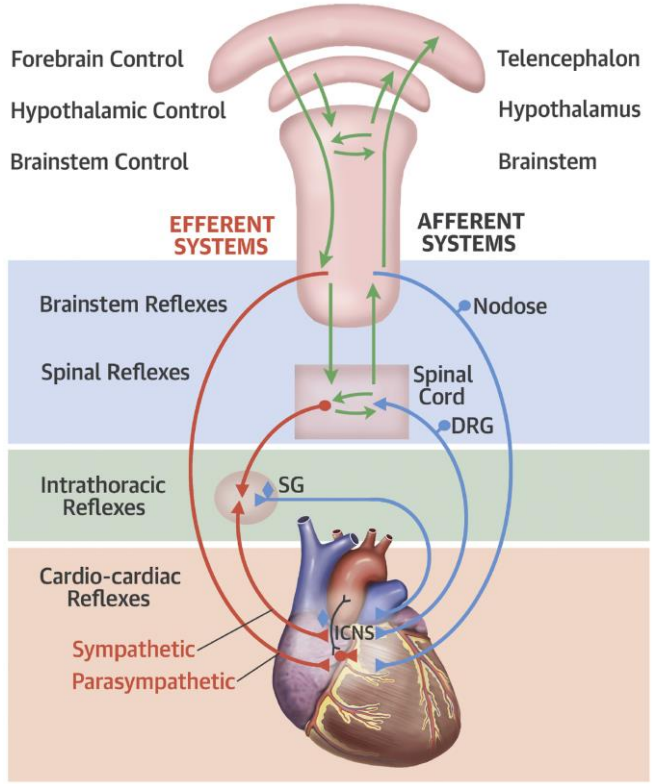
ANS maintains homeostasis by regulating physiologic functions such as respiratory rate, pupillary response, bowel motility, urination, heart rate and blood pressure

Thornton and Mitchell. J Fam Pract. 2017
Klein CM et al. Semin Neurol. 2008

Autonomic Neural Control of the Heart

Autonomic control of the heart is achieved by afferent neural impulses that are transmitted from the heart to the intrinsic neurons of the heart, to extracardiac intrathoracic ganglia (e.g., stellate ganglion), to the spinal cord, and to the brain stem. These afferent neural signals are processed by various parts of the nervous system to regulate the cardiomotor neural output to the heart via the sympathetic and parasympathetic nerves.

This neuroaxis is organized as multiple levels of integrative centers. At the level of the heart, the intrinsic cardiac nervous system (ICNS) is a distributed network system located in the cardiac ganglia that are ganglionated plexi (GPs) that exist in the fat pads around the heart. These connect with the intrathoracic extracardiac ganglia (the sympathetic paravertebral ganglia), the extrathoracic cardiac ganglia (the nodose, dorsal root ganglia), and the central nervous system. At each level, the system has the ability to modulate cardiac activity with short and long efferent feedback loops.



DRG: dorsal root ganglion; ICNS: intrinsic nervous system; SG: stellate ganglion.

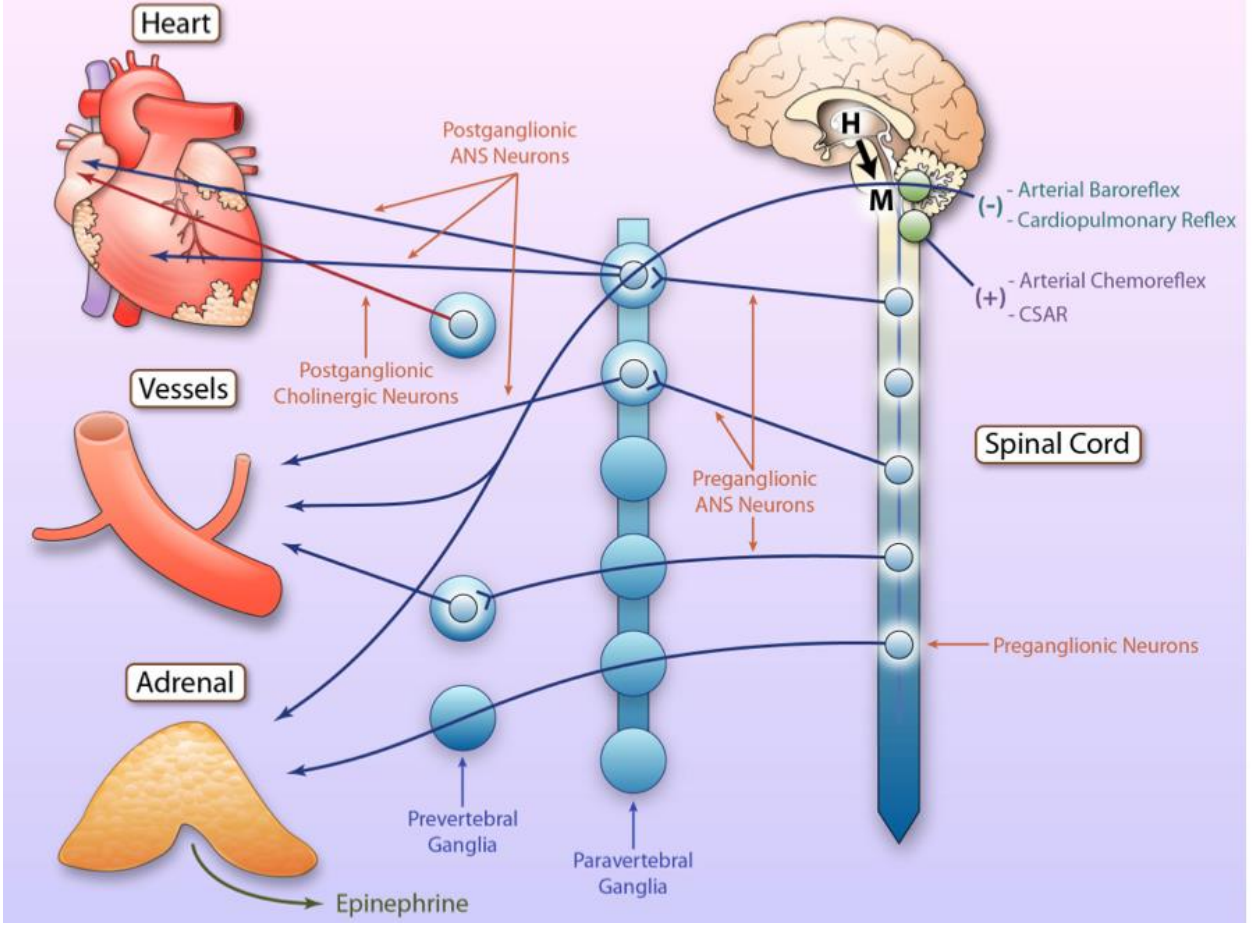
Goldberger JJ et al. J Am Coll Cardiol 2019

Sympathetic Nervous System

ANS dysfunction may result from primary disorders of the autonomic nerves (diabetes mellitus or various syndromes of primary autonomic failure) or secondarily in response to cardiac (or other systemic) disease.

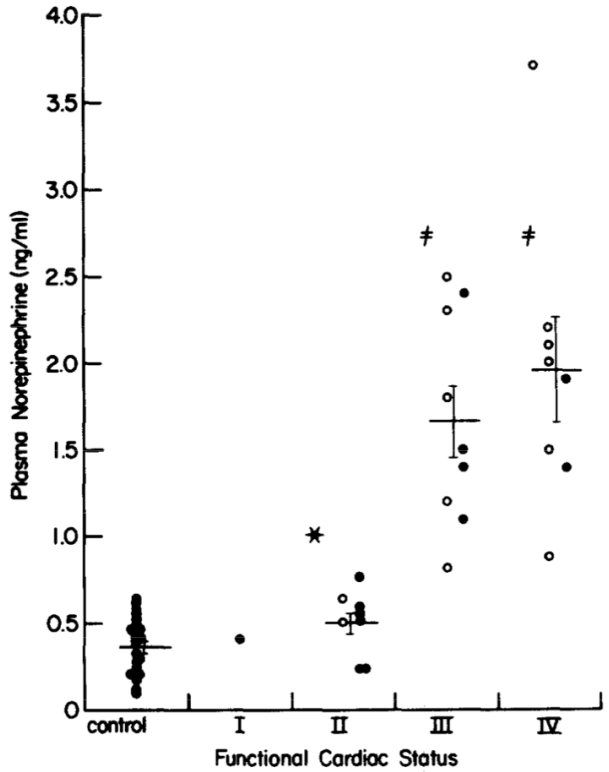
Cardiac disease may promote both anatomic (primary) and functional (secondary) changes in cardiac autonomic function.

These changes may, in turn, contribute to the progression of disease and/or be involved in arrhythmogenesis.



Lymperopoulos A, Rengo G, Koch WJ. Circ Res 2013

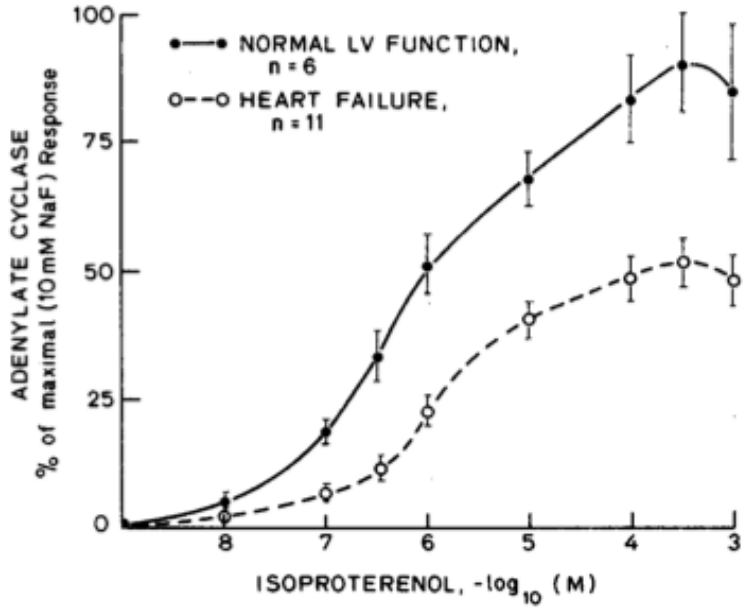
Plasma Norepinephrine in congestive heart failure



Thomas JA et al Am J Cardiol 1978

Decreased catecholamine sensitivity and β-AR density in failing human hearts

	METHOD A *			METHOD B †		
	fmol/mg membrane protein	*fmol/g wet weight*	*fmol/mg myosin*	*fmol/mg membrane protein*	*fmol/g wet weight*	*fmol/mg myosin*
I: normal left ventricular function (6)	34.6±2.8	373.8±62.1	19.0±3.67	52.5±7.5	2523.6±341.2	123.2±13.6
II: heart failure (8)	17.0±2.3	186.2±29.2	8.30±2.08	24.8±4.2	1254.6±289.2	54.9±11.8
P value	0.0003	0.012	0.029	0.008	0.017	0.0048



Reduced number of β-AR
Downregulation

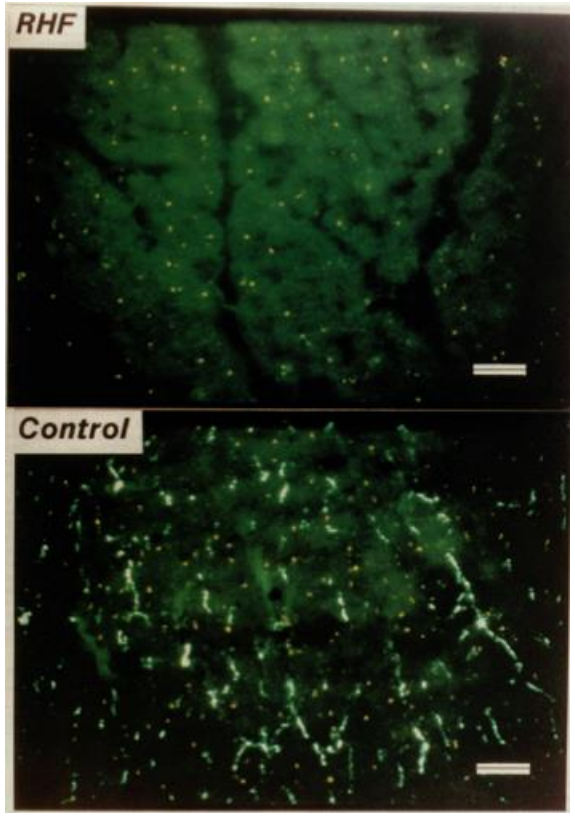
Reduced β-AR function
Desensitization

The NEW ENGLAND JOURNAL of MEDICINE

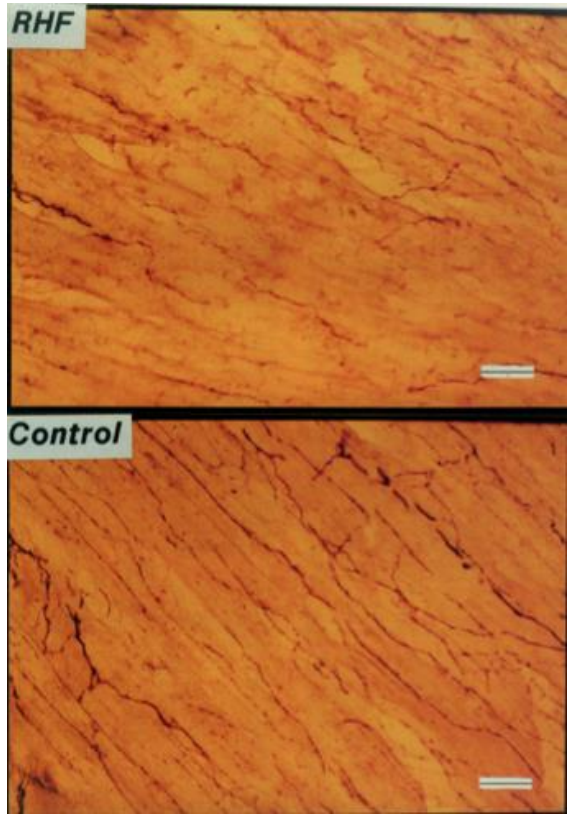
Bristow MR et al N Engl J Med 1982

Cardiac Noradrenergic Nerve Terminal Abnormalities in Heart Failure

Cardiac SPG-induced histofluorescence microphotographs demonstrating catecholaminergic profiles (bluish green) in HF and control



Right ventricular tyrosine hydroxylase immunoreactive nerve profiles (brown) in HF and control

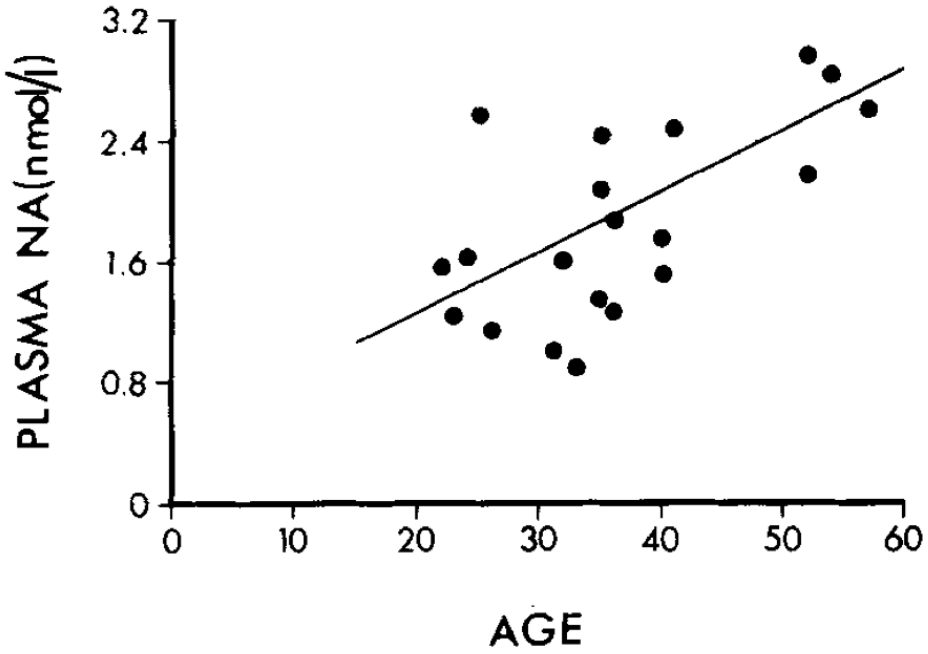


Himura Y et al Circulation 1993

Plasma Norepinephrine in elderly subjects

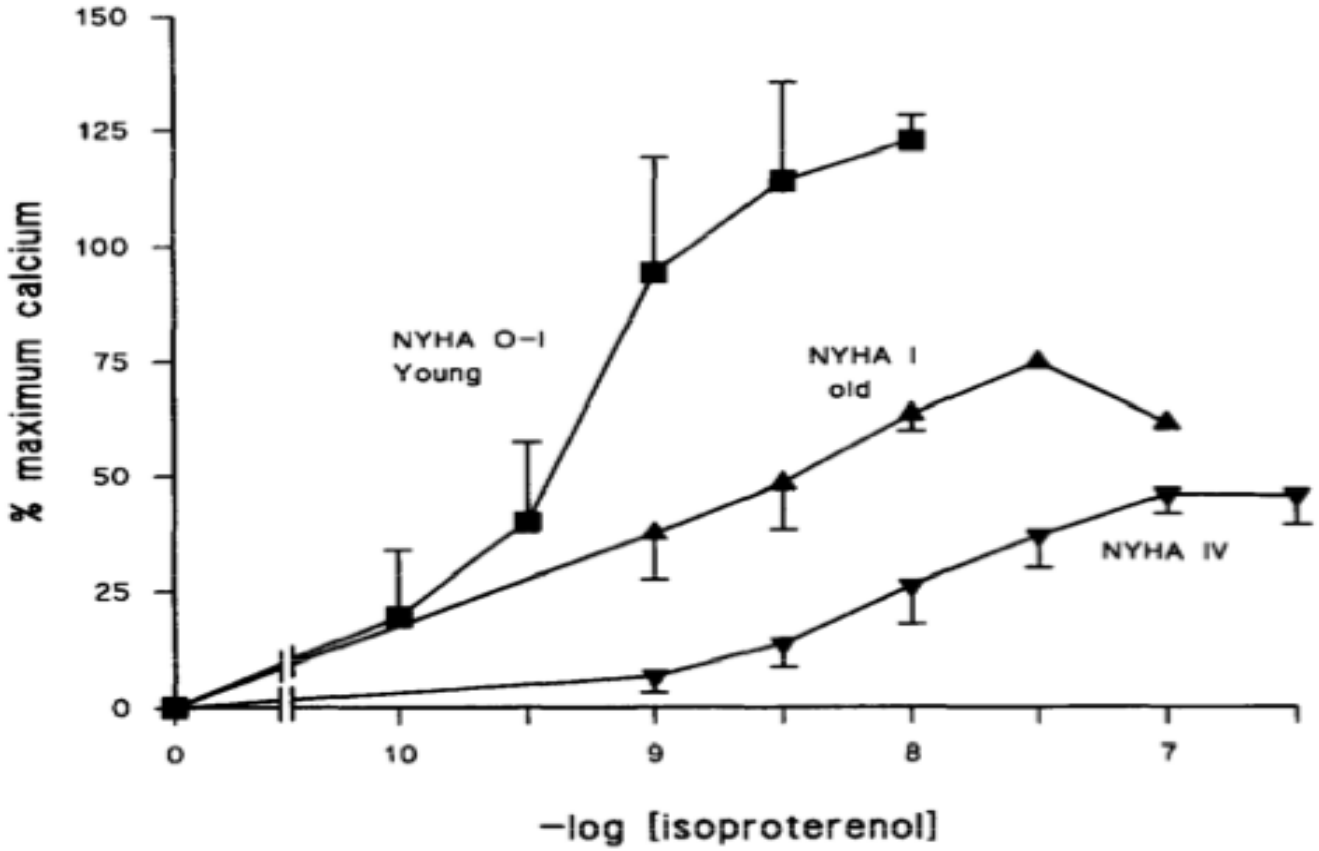
Much of the current knowledge about age-related changes in SNS is derived from studies of circulating catecholamine levels, norepinephrine kinetics and microneurographic recordings from sympathetic nerves of skeletal muscle. Evidence suggests that basal plasma noradrenaline levels increase with age

Shimazu T et al. Niho Rinsho 2005



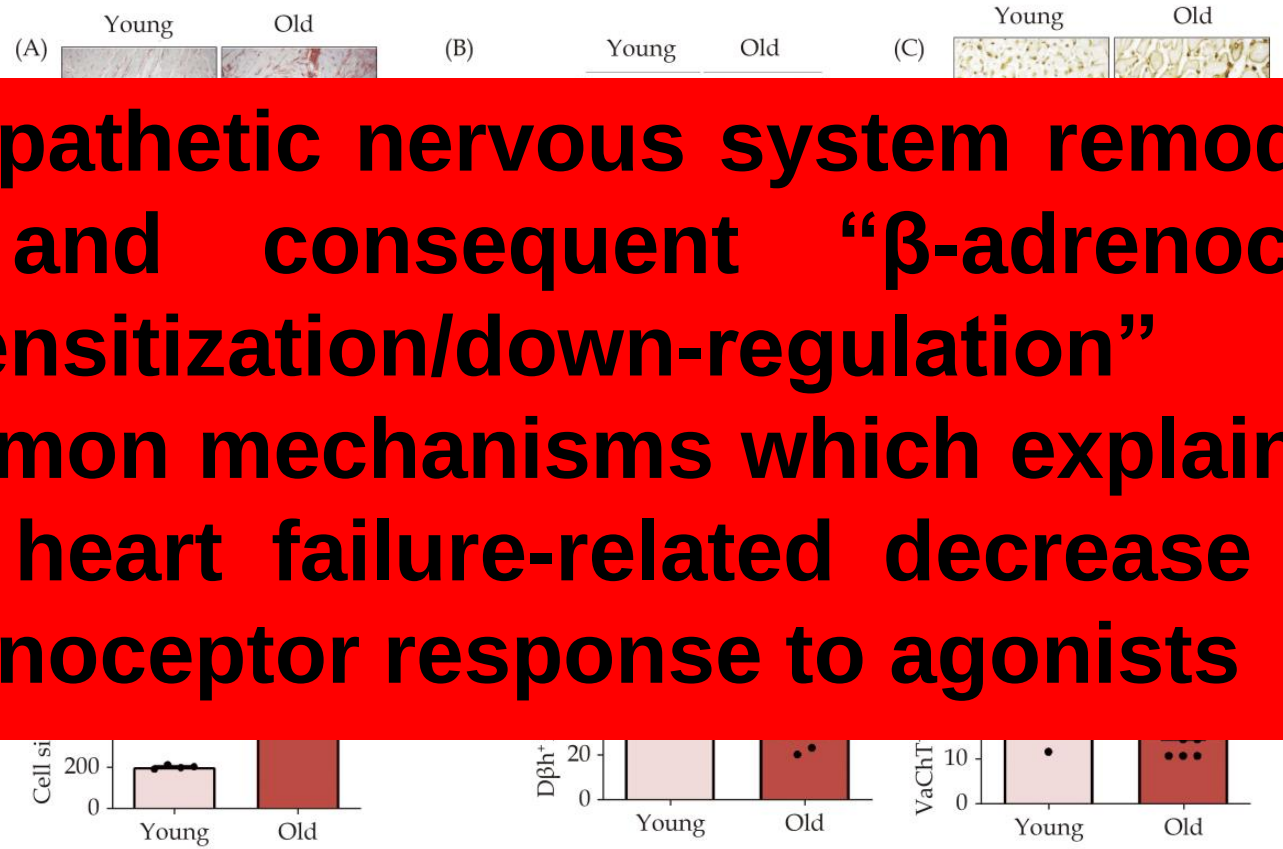
Wallin BG et al Acta Physiol Scand 1981

β-AR function changes with age of subjects in myocytes from non-failing human ventricle



Davies CH & Ferrara N et al Cardiovasc Res 1995

Impact of aging on cardiac fibrosis, hypertrophy, vascularization, and ANS



Sympathetic nervous system remodeling de and consequent "β-adrenoceptor desensitization/down-regulation" are common mechanisms which explain age- and heart failure-related decrease in β-adrenoceptor response to agonists

Elia A. et al J Geriatr Cardiol. 2021

Orthostatic Hypotension

- Prevalence of Orthostatic Hypotension is 9-30% in community dwelling adults aged above 65 years, is >50% in nursing home residents and it is higher in frail subjects.

- Orthostatic hypotension increases the risk of syncope and falls, leading to hospitalization and functional impairment, CVD and all-cause mortality.

- Orthostatic Hypotension may be asymptomatic

Measure BP 1 min and 3 min after standing from a seated position in all patients at the first measurement to exclude orthostatic hypotension. Lying and standing BP measurements should also be considered in subsequent visits in older people, people with diabetes, and people with other conditions in which orthostatic hypotension may frequently occur.

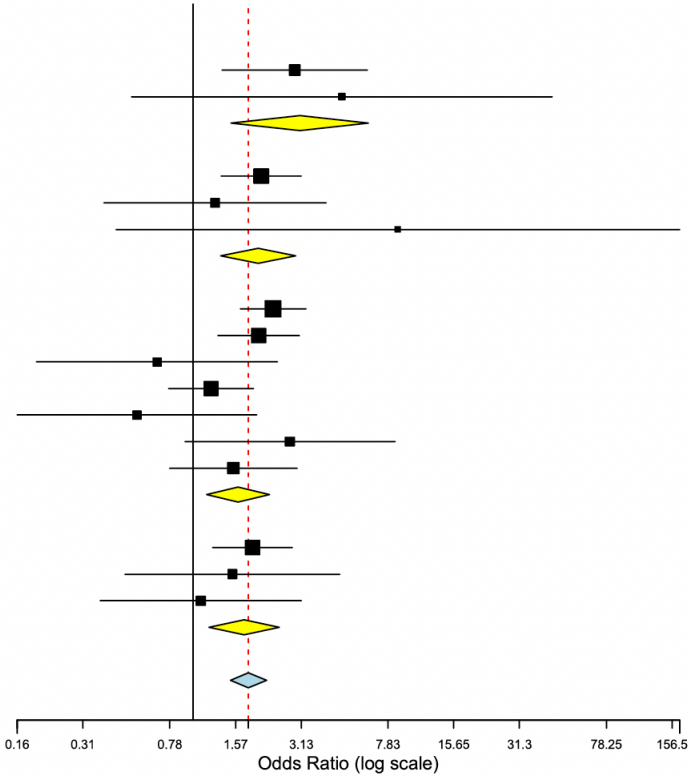
Williams B et al. Eur Heart J 2018

- Medication review to identify drugs related to OH
- Antihypertensives almost always should be stopped (or not started). When absolutely needed, administration should be at night.
- Education
- Fluids and salt
- Exercise

Benetos A et al. Circ Res 2019

Frail older adults are more likely to have autonomic dysfunction

Studies	OR (95% CI)	OH	No OH
Romero-Ortuno R. et al, 2011 (IOH) (n = 442)	2.924 (1.360, 6.289)	12/85	19/357
Shaw B. et al, 2019 (IOH) (n = 55)	4.800 (0.522, 44.146)	5/6	25/49
Subgroup IOH (I^2=0 % , P=0.679)	**3.083 (1.495, 6.357)**	**17/91**	**44/406**
Kocyigit S. et al, 2019 (OH1) (n = 496)	2.054 (1.343, 3.141)	59/113	133/383
Okyar Bas A. et al, 2022 (OH1) (n = 102)	1.262 (0.392, 4.065)	6/13	36/89
Shaw B. et al, 2019 (ROH) (n = 55)	8.660 (0.443, 169.128)	4/4	26/51
Subgroup ROH (I^2=0 % , P=0.462)	**1.993 (1.341, 2.960)**	**69/130**	**195/523**
Chen L. et al, 2019 (OH3) (n = 693)	2.325 (1.645, 3.287)	93/181	160/512
Kocyigit S. et al, 2019 (OH3) (n = 496)	1.995 (1.296, 3.071)	56/108	136/388
Okyar Bas A. et al, 2022 (OH3) (n = 102)	0.684 (0.192, 2.439)	4/12	38/90
Rockwood M. et al, 2012 (OH3) (n = 1347)	1.210 (0.774, 1.890)	31/389	64/958
Romero-Ortuno R. et al, 2011 (COH) (n = 442)	0.553 (0.157, 1.956)	28/416	3/26
Shaw B. et al, 2019 (COH) (n = 55)	2.779 (0.918, 8.415)	17/25	13/30
Wojszel Z. et al, 2019 (OH3) (n = 353)	1.528 (0.779, 2.995)	14/57	52/296
Subgroup COH (I^2=48.69 % , P=0.069)	**1.607 (1.152, 2.241)**	**243/1188**	**466/2300**
Kocyigit S. et al, 2019 (OH5) (n = 496)	1.876 (1.230, 2.860)	58/115	134/381
Okyar Bas A. et al, 2022 (OH5) (n = 102)	1.514 (0.489, 4.694)	7/14	35/88
Shaw B. et al, 2019 (DOH) (n = 55)	1.083 (0.375, 3.133)	15/27	15/28
Subgroup DOH (I^2=0 % , P=0.626)	**1.715 (1.184, 2.483)**	**80/156**	**184/497**
Overall (I^2=16.75 % , P=0.266)	**1.797 (1.485, 2.173)**	**409/1565**	**889/3726**



Debain A. et al Ageing Res Rev 2023

Physiological ageing → **SNS Hyperactivity** ← **Heart Failure**

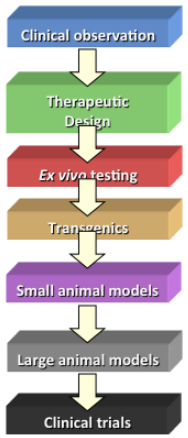
Aiming at preservation of cardiac output

Long term-sustained

β-blockers

Myocardial oxigen consumption *(J Mol Cell Cardiol 1985);*
Cardiac interstitial fibrosis *(Eur J Pharmacol 2004);*
Myocyte apoptosis *(Cardiovasc Res 2004);*
Adverse remodeling *(Am J Physiol Heart Circ Physiol 2007);*
Reduction of the inotropic reserve *(NEJM 1982);*
Myocardial ROS production *(J Cell Mol Med 2007);*
Risk of arrythmias *(NEJM 1991);*
Renin-angiotensin-aldosterone system *(Am J Physiol 1992);*
Renal and peripheral vascular resistance *(JACC 2009);*

Effective Model of Translational Research



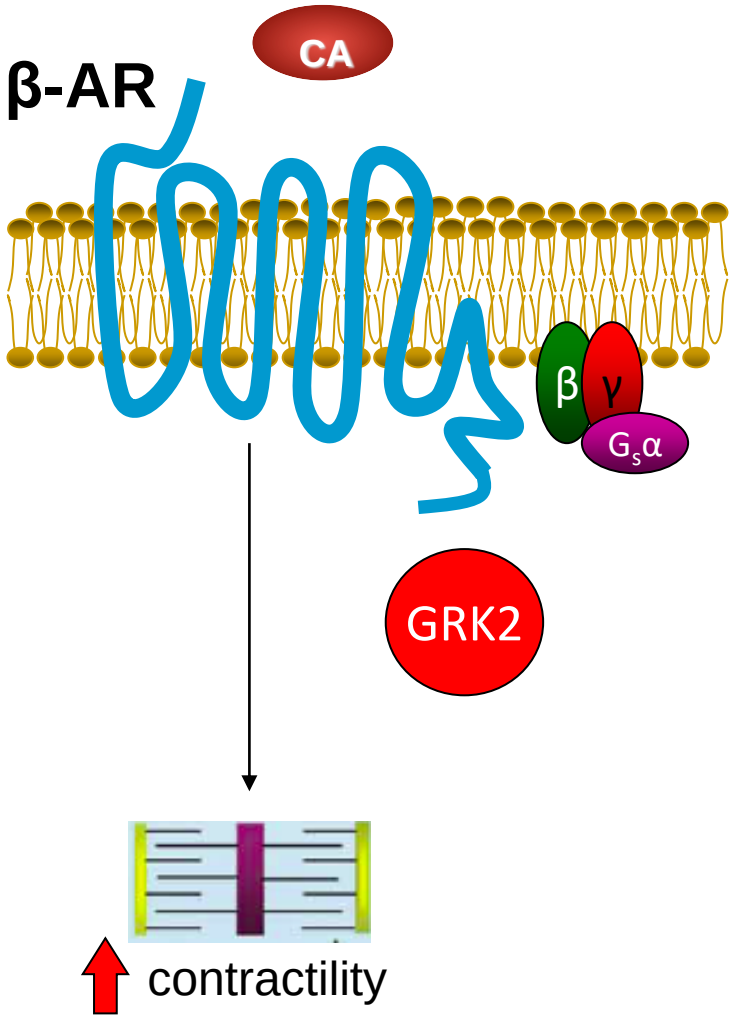
Circulation 1993

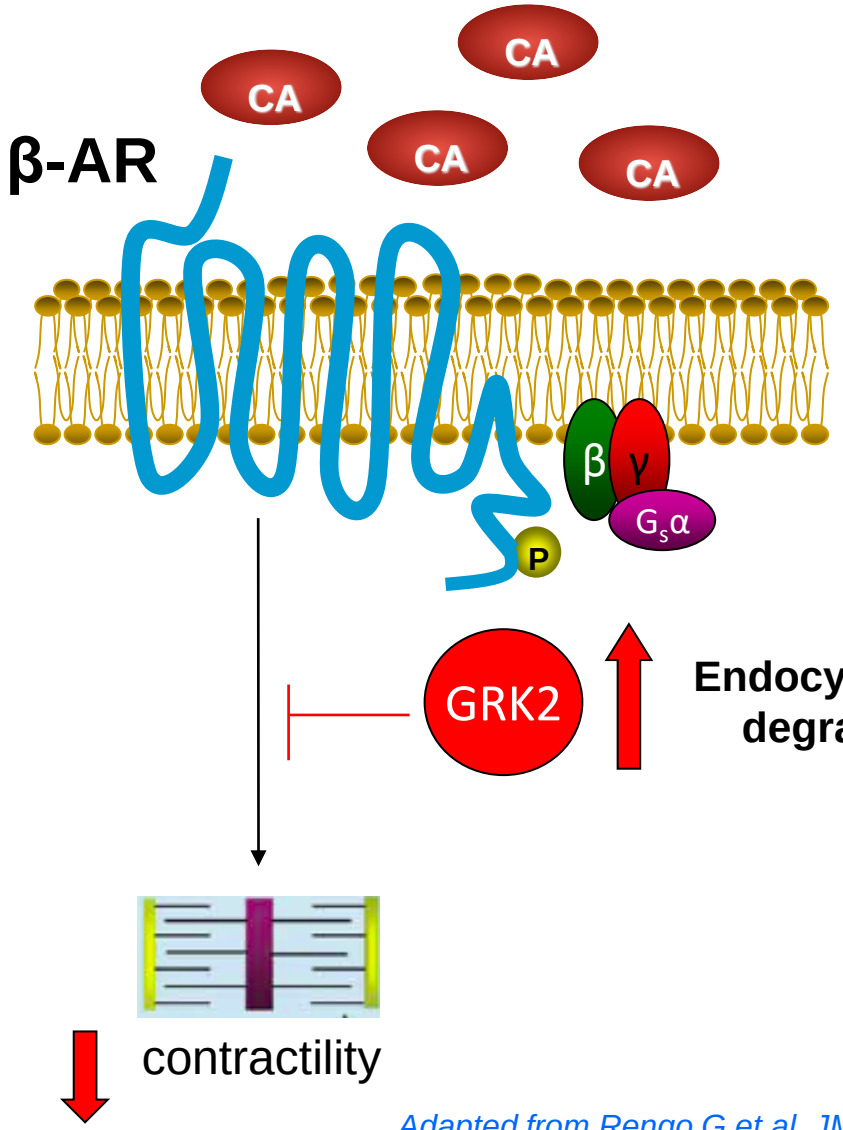
Circulation 2004

Science 1995, PNAS 1998, 2001, JACC 2002, Circ. Res 2008

Circulation 2000, 2001, 2009

Eur Heart J. 2012





Adapted from Rengo G et al. JMCC 2010

Methods to assess cardiac autonomic function

Method	Advantages	Limitations
Plasma/urinary catecholamines	• Easily measurable;	• High variability; • Overestimation due to reduced renal clearance in HF; • Systemic NE does not reflect organ-specific concentrations.
Norepinephrine Cardiac/Renal spillover	• Information on organ-specific sympathetic activity; • Indipendent from HF severity;	• Invasive tecniques; • Available in specialized centres.
Heart rate variability **Heart rate recovery** **Heart rate turbolence**	• Easily and non-invasively performable;	• HRV reflects sinoatrial response to sympathetic/vagal stimulation; • No individual HR spectral component is specific for sympathetic cardiac modulation.
Baroreflex sensitivity **Autonomic Reflex testing (Ewing's maneuvers)**	• Sinus node response to baroreceptor activation; •Sinus node response to breathing maneuvers, Valsalva, tilt, handgrip • Non invasive;	• Lack of accuracy in testing and time consuming
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European Heart Journal (2001) **22**, 1136–1143
doi:10.1053/euhj.2000.2407, available online at http://www.idealibrary.com on IDEAL®

Effect of cardiac sympathetic nervous activity on mode of death in congestive heart failure

H. P. Brunner-La Rocca, M. D. Esler, G. L. Jennings and D. M. Kaye

Alfred and Baker Medical Unit, Baker Medical Research Institute, Alfred Hospital, Melbourne, Australia

Vol. 311 No. 13 PLASMA NOREPINEPHRINE — COHN ET AL. 819

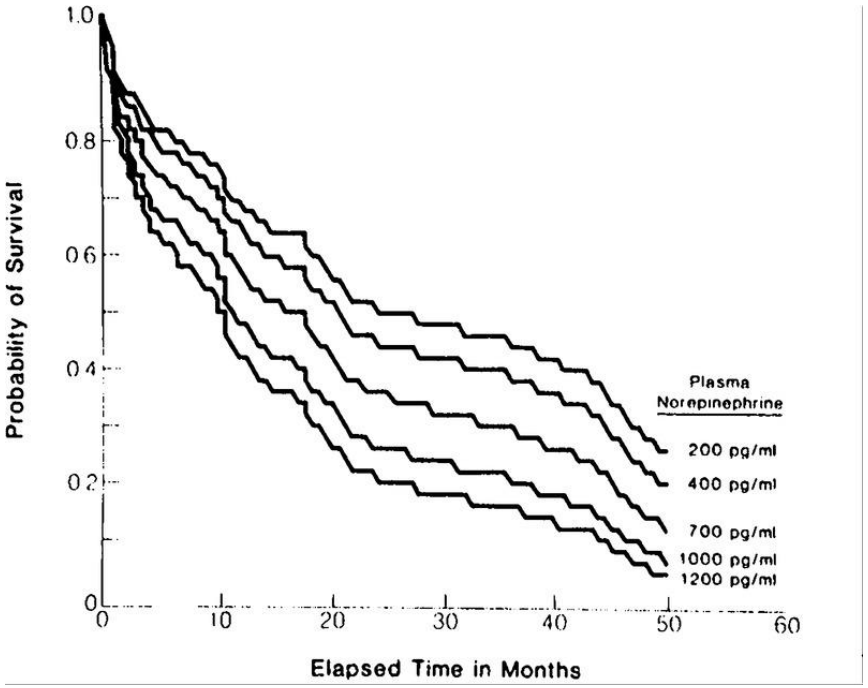
PLASMA NOREPINEPHRINE AS A GUIDE TO PROGNOSIS IN PATIENTS WITH CHRONIC CONGESTIVE HEART FAILURE

JAY N. COHN, M.D., T. BARRY LEVINE, M.D., MARIA TERESA OLIVARI, M.D., VICTORIA GARBERG, R.N., DENNIS LURA, B.S., GARY S. FRANCIS, M.D., ADA B. SIMON, PH.D., AND THOMAS RECTOR, PH.D.

JACC Vol. 26, No. 5
November 1, 1995:1257–63 1257

Adverse Consequences of High Sympathetic Nervous Activity in the Failing Human Heart

DAVID M. KAYE, MBBS, PHD, FRACP,* JEFFREY LEFKOVITS, MBBS, FRACP,
GARRY L. JENNINGS, MDBS, FRACP, PETER BERGIN, MBBS, FRACP,
ARCHER BROUGHTON, MBBS, PHD, FRACP, MURRAY D. ESLER, MBBS, PHD, FRACP



Cohn JN et al. New N Engl J Med 1984

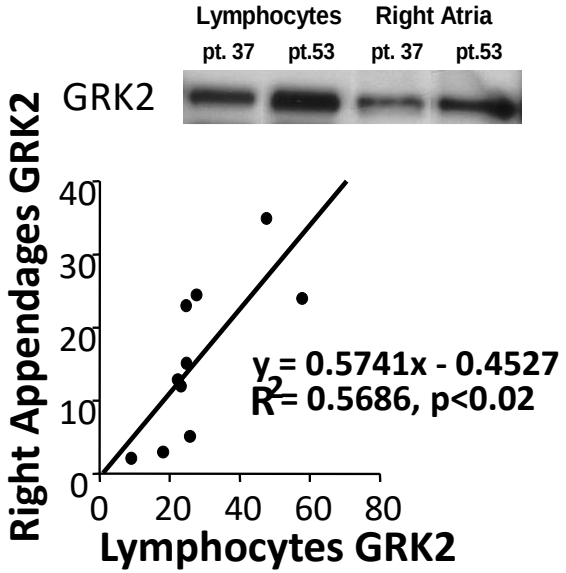
Novel markers looking at SNS hyperactivity and Outcome in HF

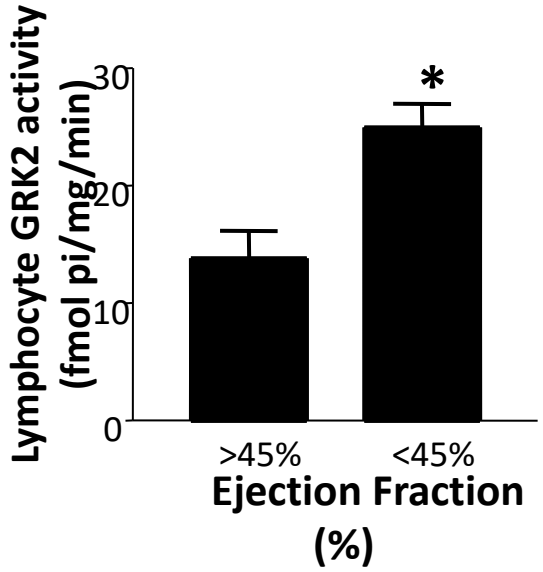
SNS hyperactivity correlates with cardiac levels of GRK2 expression/activity that induces βAR dysfunction

GRK2 the HbA1c of Heart Failure dependent SNS hyperactivity

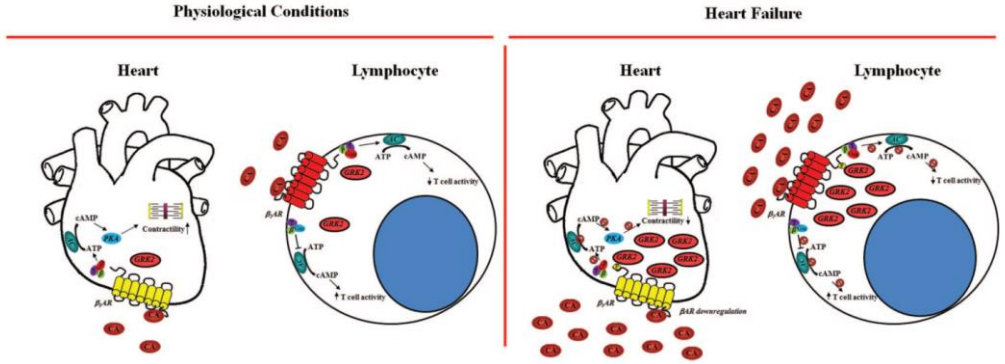
gives important information on SNS hyperactivitation and on the level of SNS-dependent cardiac βAR dysfunction

Elevated myocardial and lymphocyte GRK2 expression and activity in human HF





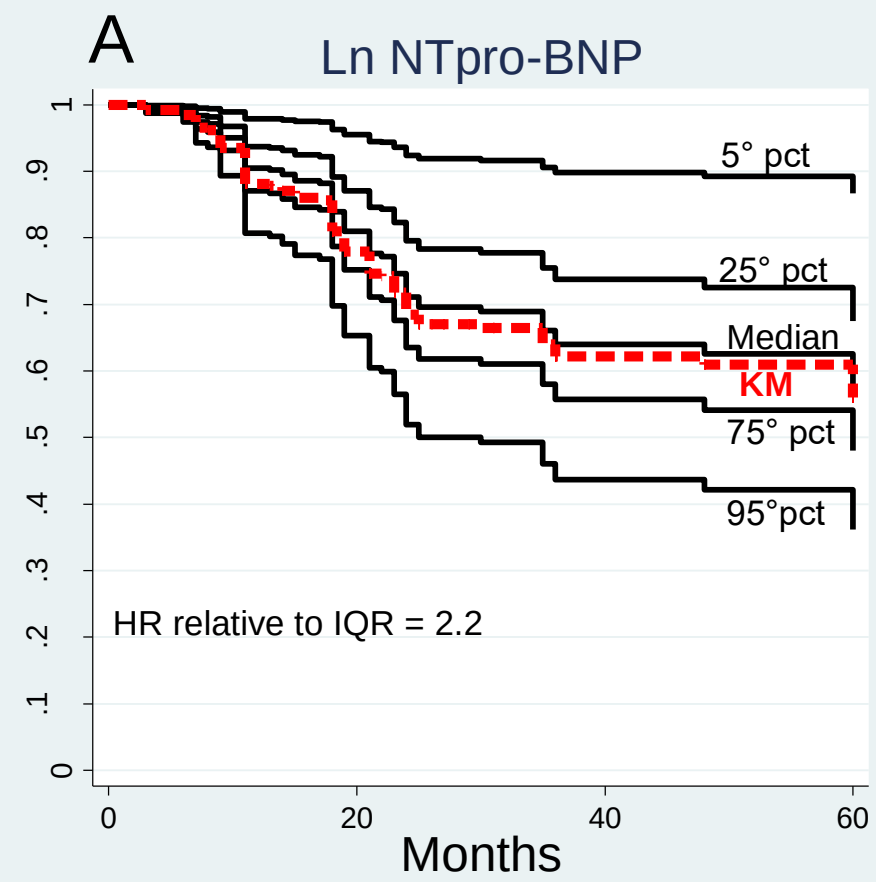
Iaccarino G et al. Eur Heart J 2005

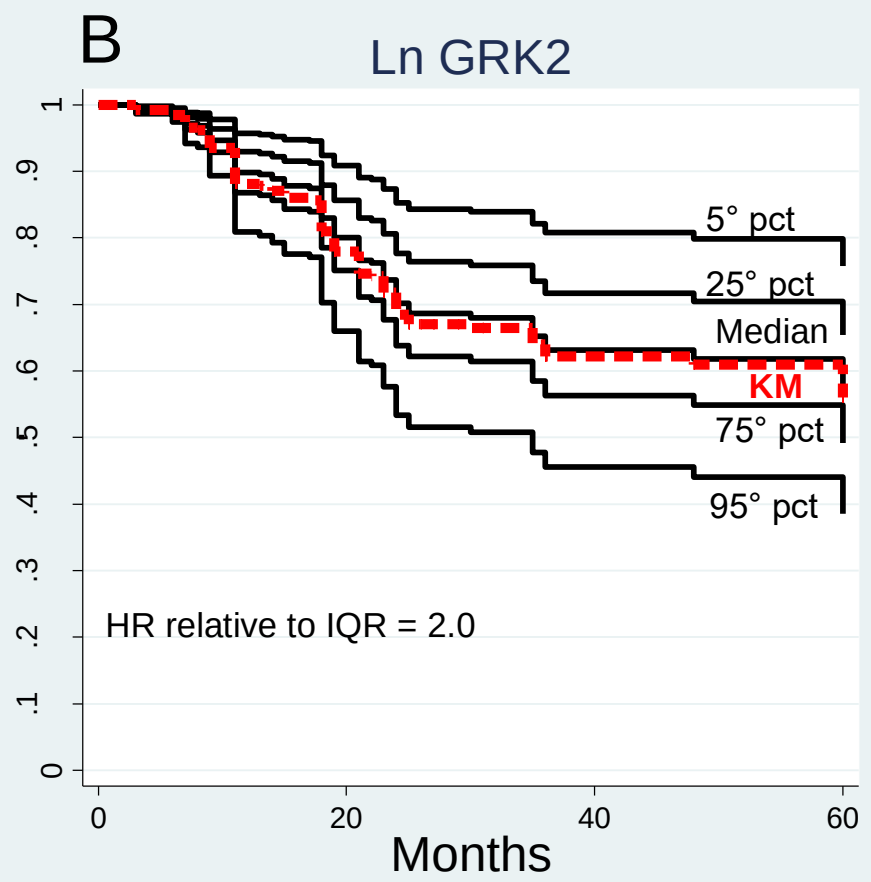


Rengo G et al. Circulation HF 2013

Lymphocyte GRK2 protein levels independently predict prognosis in patients with HF

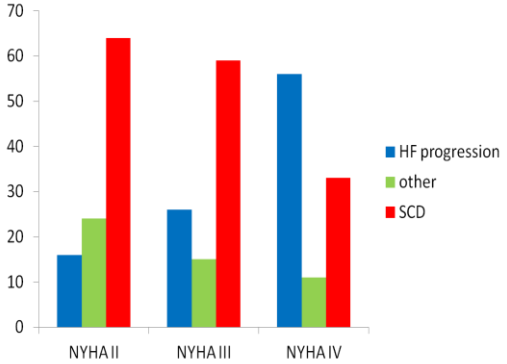
257 HF patients with LVEF 31.4±8.5%. At the time of enrollment, plasma NE, serum NT-proBNP, and lymphocyte GRK2 levels, as well as clinical and instrumental variables were measured. Over a mean follow-up period of 37.5±20.2 months (range, 3–60 months), age, left ventricular ejection fraction, NYHA class, NT-proBNP, and lymphocyte GRK2 protein levels were independent predictors of CV mortality in HF patients. GRK2 levels showed an additional prognostic and clinical value over demographic and clinical variables.



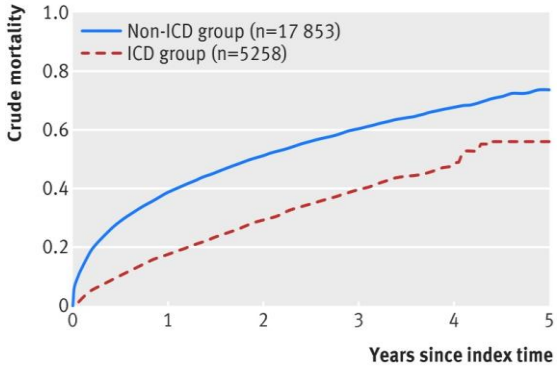


Rengo G et al. Circ Res 2016

Autonomic Nervous System Dysfunction and Arrhythmias



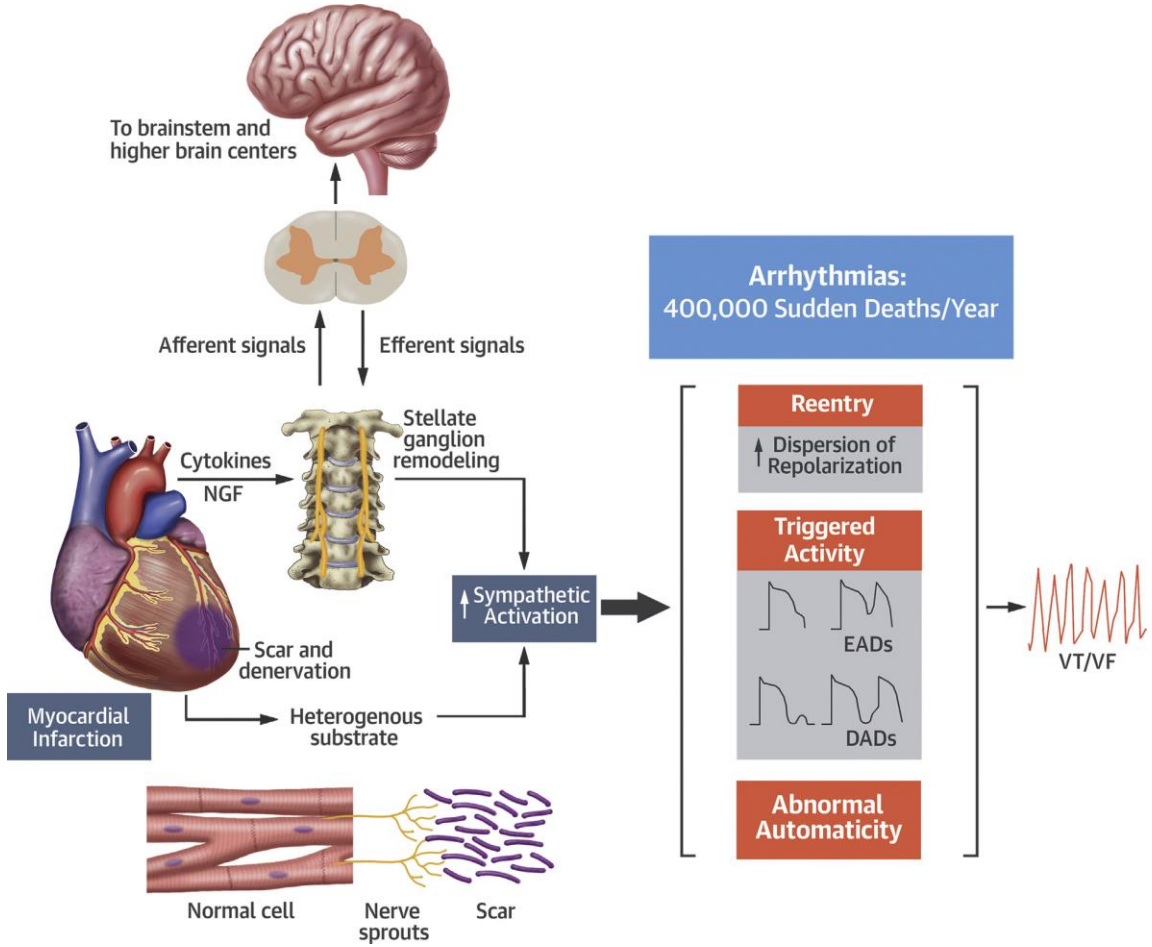
Real world effectiveness of ICD in HF



Chih-Ying Chen et al BMJ 2015

Recommendations	Class[a]	Level[b]
Primary prevention		
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II–III) of an ischaemic aetiology (unless they have had a MI in the prior 40 days—see below), and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status.[161,165]	I	A

McDonagh TA. et al Eur Heart J 2021



Goldberger JJ et al. J Am Coll Cardiol 2019

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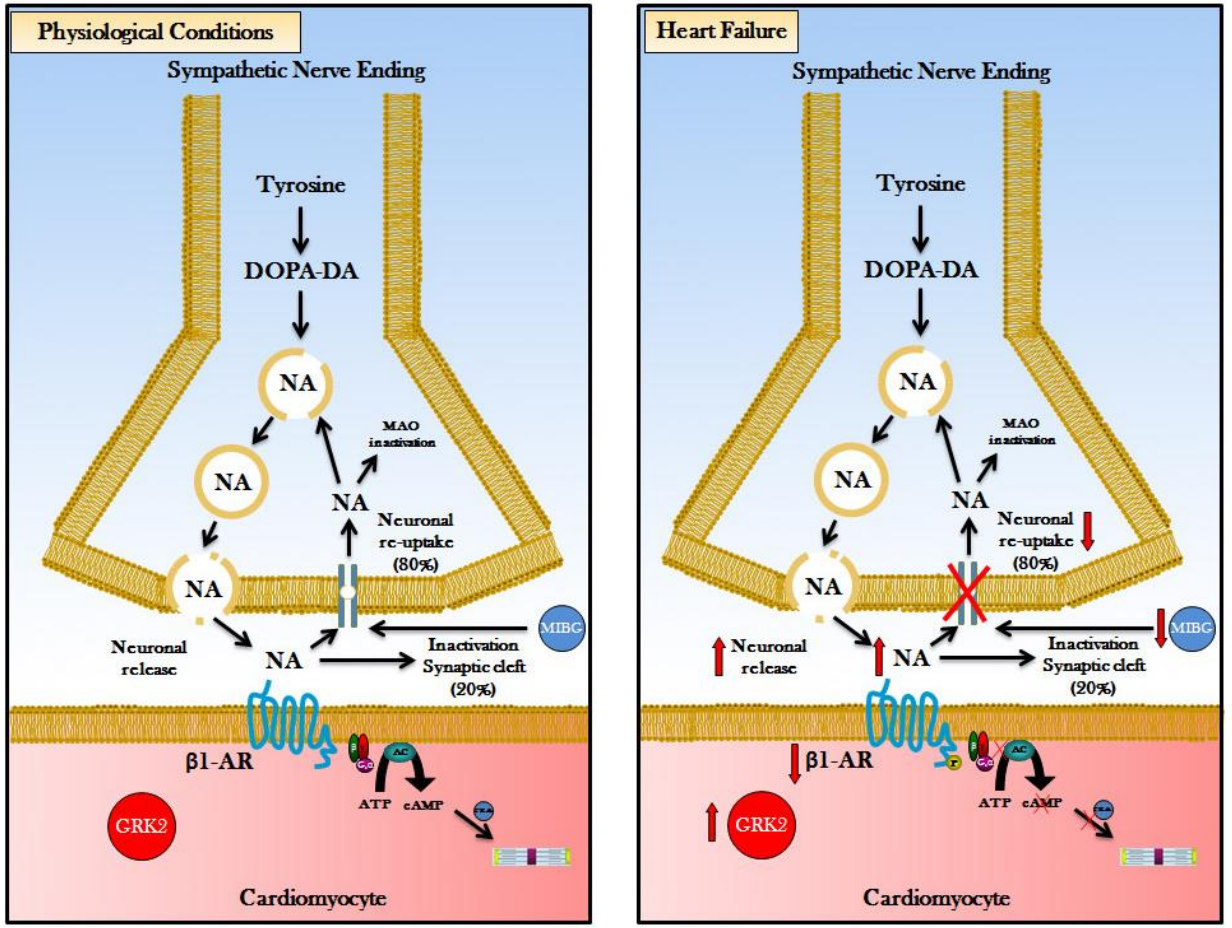
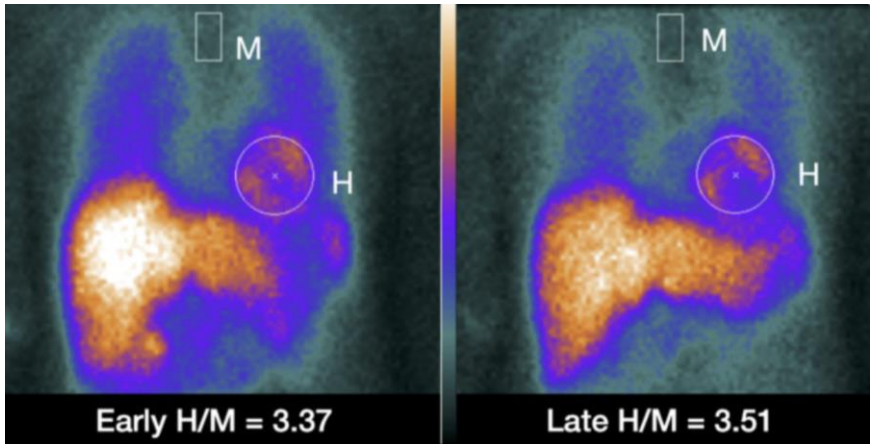
Cardiac Sympathetic imaging (^{123}I-MIBG)	• Information on cardiac-specific sympathetic dysregulation; • Non invasive;	• Expensive technique; • Patients exposition to radionuclides.

Adrenergic hyperactivity, NET Down-Regulation, and Compromised *β-adrenergic receptor signaling in Heart Failure*



Adapted from de Lucia et al. Front Physiol 2013

Cardiac ^{123}I-mIBG imaging in heart failure



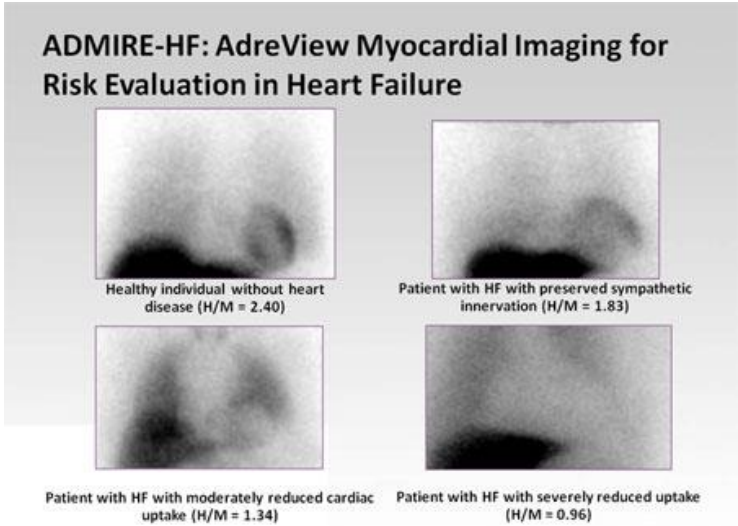
(A) $$WO = \frac{\text{Early H/M - Late H/M}}{\text{Early H/M}} \times 100\ (\%)$$

(B) $$WO = \frac{\text{Early H - Late H x DCF}}{\text{Early H}} \times 100\ (\%)$$

(C) $$WO = \frac{\text{(Early H - Early M) - (Late H - Late M) x DCF}}{\text{Early H - Early M}} \times 100\ (\%)$$

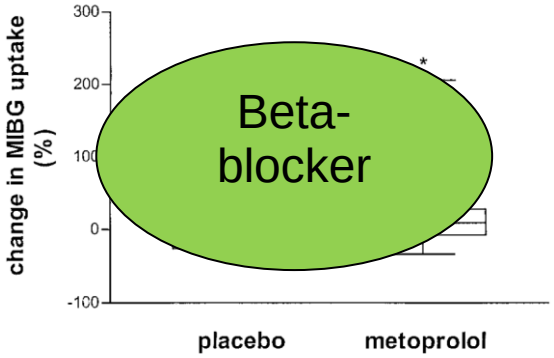
Click on image to zoom

Verschure DO et al. Pharmaceuticals 2022



Haider N et al. JACC Cariovasc Imaging 2010

Effects of disease-modifying HF therapies on cardiac sympathetic innervation



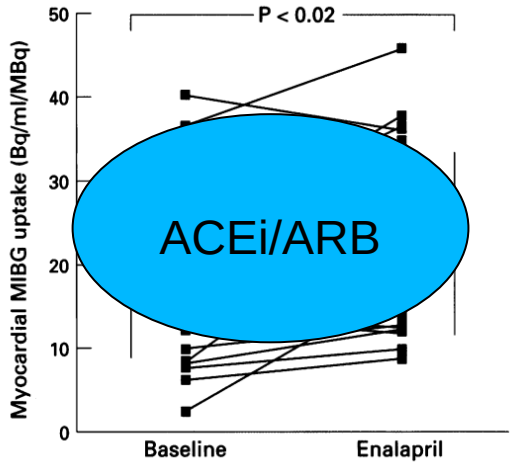
de Milliano PAR et al. Am Heart J 2002

Patient No.	TDS Baseline	TDS 6 Months	H/M Ratio Baseline	H/M Ratio 6 Months
Spironolactone group				
Mean ± SD				1.86 ± 0.27*‡
Control group				
Mean ± SD				1.63 ± 0.15

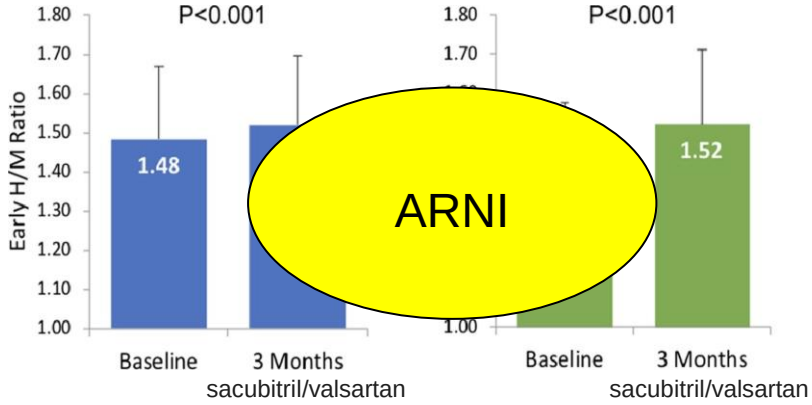
MRA

*p < 0.0001 vs. baseline. †p < 0.01 vs. control group. ‡p < 0.05 vs. control group. §p < 0.000
H/M = heart/mediastinum count; TDS = total defect score; WR = washout rate.

Kasama S et al. J Am Coll Cardiol 2003



Somsen GA et al. Heart 1996



Sayer G et al. J Cardiac Fail 2018

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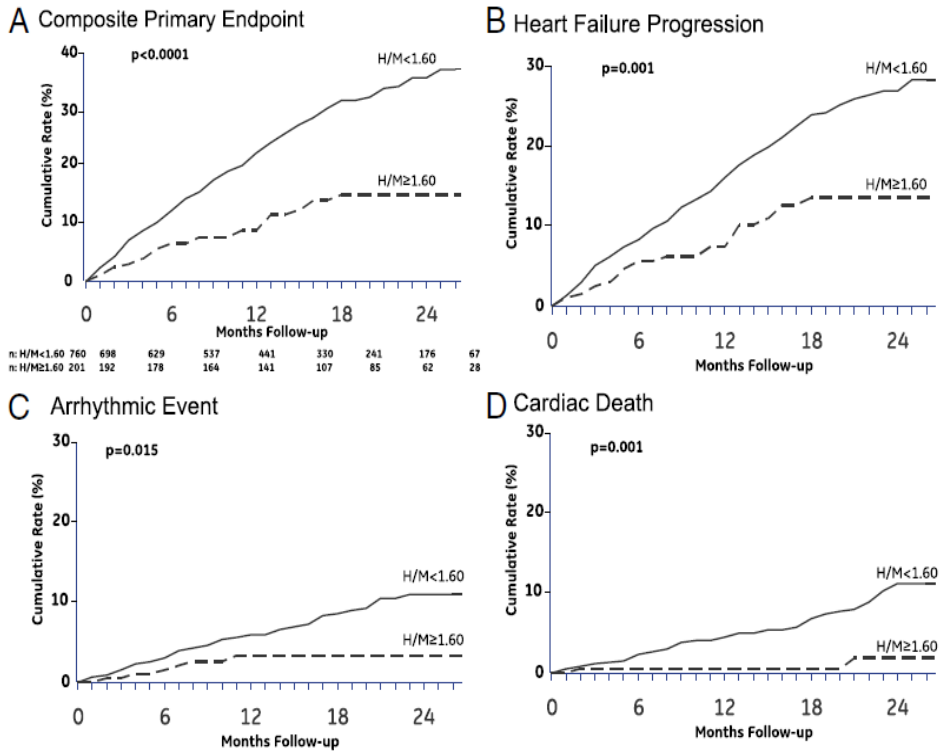
doi:10.1016/j.jacc.2010.01.014

Myocardial Iodine-123 *Meta*-Iodobenzylguanidine Imaging and Cardiac Events in Heart Failure

Results of the Prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) Study



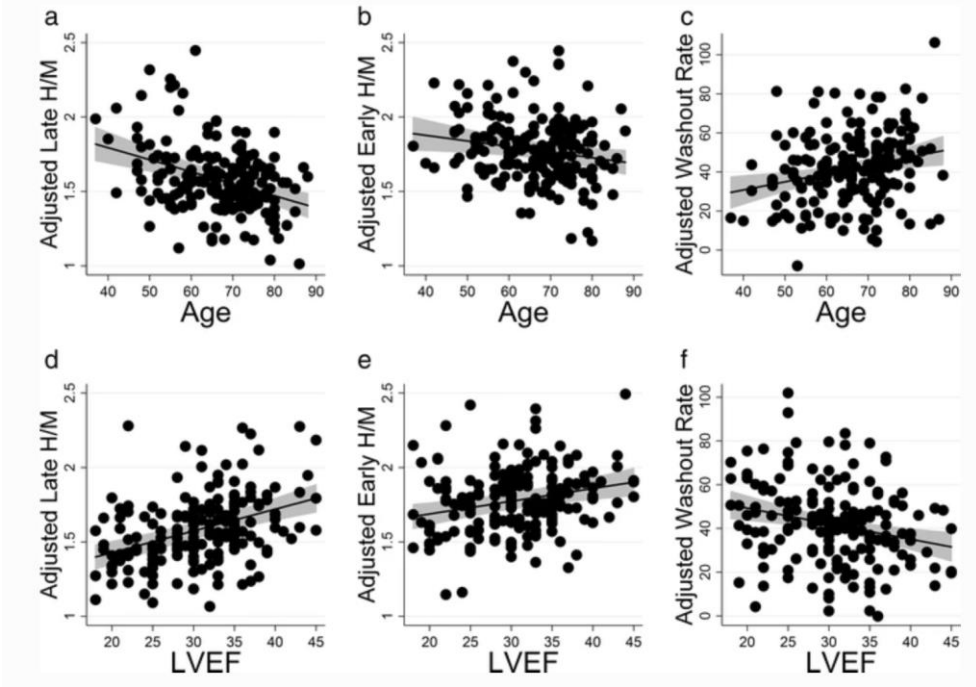
Independent age-related effect on cardiac SNS innervation assessed by 123I-mIBG imaging in HF

^{123}I-mIBG imaging has been successfully used to assess cardiac SNS activity in HF patients and to predict prognosis.

SNS hyperactivity characterizes also physiological ageing, and there is conflicting evidence on cardiac 123I-mIBG uptake in healthy elderly subjects compared to adults.

180 HF patients (age= 66.1±10.5 yrs, LVEF= 30.6±6.3%) undergoing cardiac 123I-mIBG imaging.

In elderly patients, both early and late H/M ratios were significantly lower compared to younger patients ($p < 0.05$). By multivariate analysis, H/M ratios (both early and late) and washout rate were significantly correlated with LVEF and age.



Rengo G et al. Eur J Nucl Med Mol Imaging. 2016

Impact of the number of comorbidities on cardiac sympathetic derangement in HF patients

HF is frequently associated with comorbidities, which have been individually associated with reduced cardiac adrenergic innervation and higher risk of major arrhythmic events. However, very comorbid HF patients are less likely to experience fatal arrhythmias.

We assessed the impact of 7 comorbidities/conditions (smoking, COPD, DM, PAD, AF, IHD, CKD) on cardiac adrenergic innervation, through ^{123}I-mIBG imaging, in a population of patients with systolic HF.

Multiple regression analysis revealed that the number of comorbidities was not associated with MIBG parameters of cardiac denervation. These results are consistent with the observation that very comorbid HF patients suffer lower risk of sudden cardiac death.

Regression analysis for ^{123}I-mIBG cardiac scintigraphy parameters

	Late H/M R^{2a}: 0.235			Early H/M R^{2a}: 0.125			Washout Rate R^{2a}: 0.047		
Variables	***B***	***SE***	***Sig.***	***B***	***SE***	***Sig.***	***B***	***SE***	***Sig.***
Gender	-0.054	0.037	0.147	-0.026	0.038	0.496	1.970	3.265	0.547
Age	-0.006	0.001	≤ 0.0001	-0.003	0.001	0.013	0.244	0.117	0.038
BMI	-0.013	0.003	≤ 0.0001	-0.016	0.003	≤ 0.0001	-0.188	0.281	0.505
LVEF	0.013	0.002	≤ 0.0001	0.008	0.002	≤ 0.0001	-0.602	0.173	≤ 0.001
Comorbidities*	-0.010	0.011	0.373	0.004	0.011	0.691	-0.317	0.973	0.745

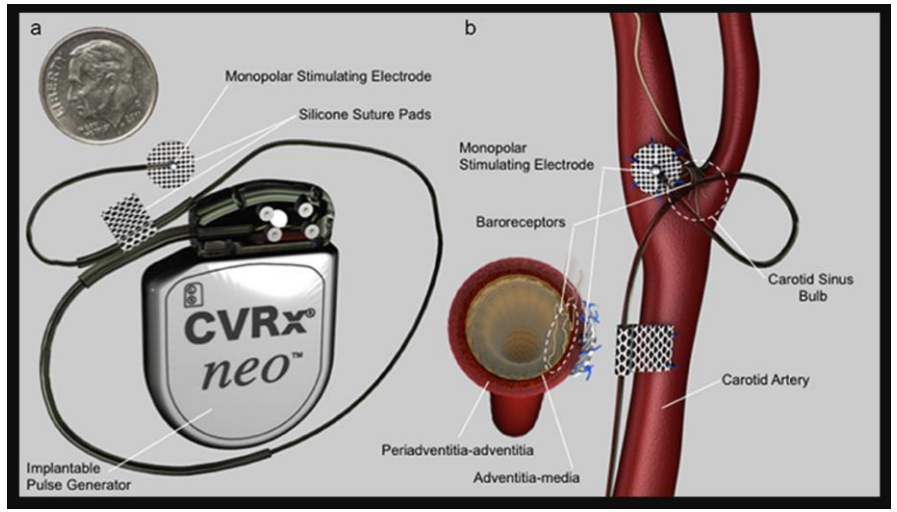
Bencivenga L et al. Eur J Internal Med 2021

Autonomic nervous system modulation as a treatment for HF

Vagal Nerve Stimulation (VNS)

Spinal Cord Stimulation (SCS)

Baroreceptor Activation Therapy (BAT)



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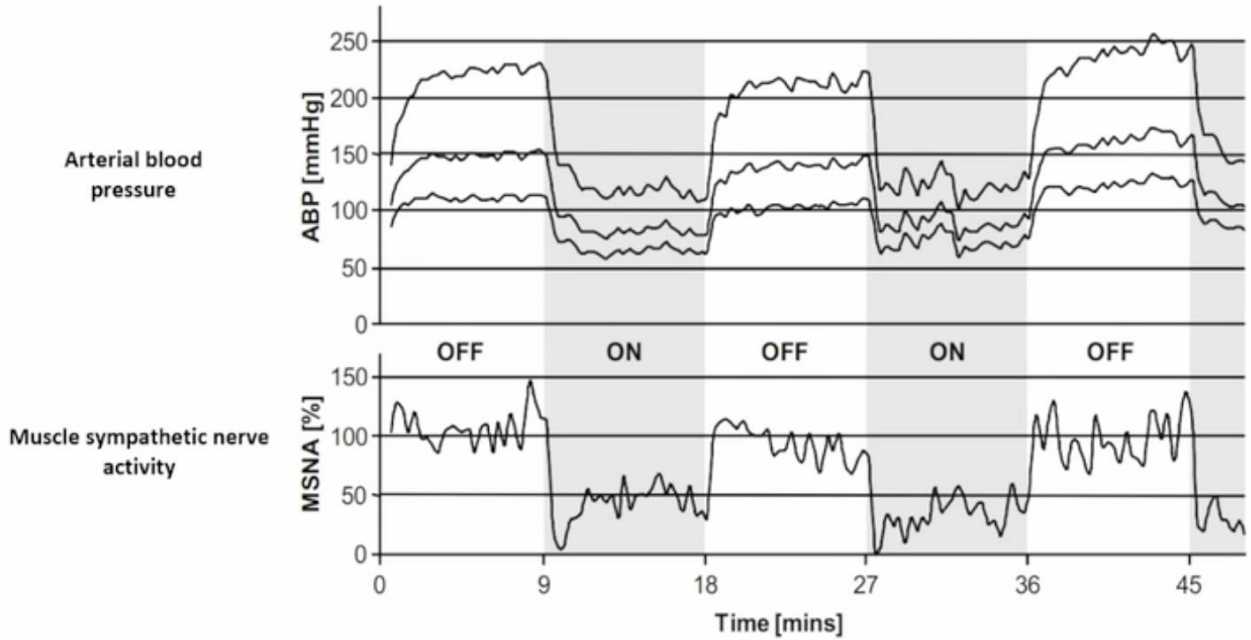

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Baroreflex regulation in HF

Heart Failure

Baroreflex Regulation

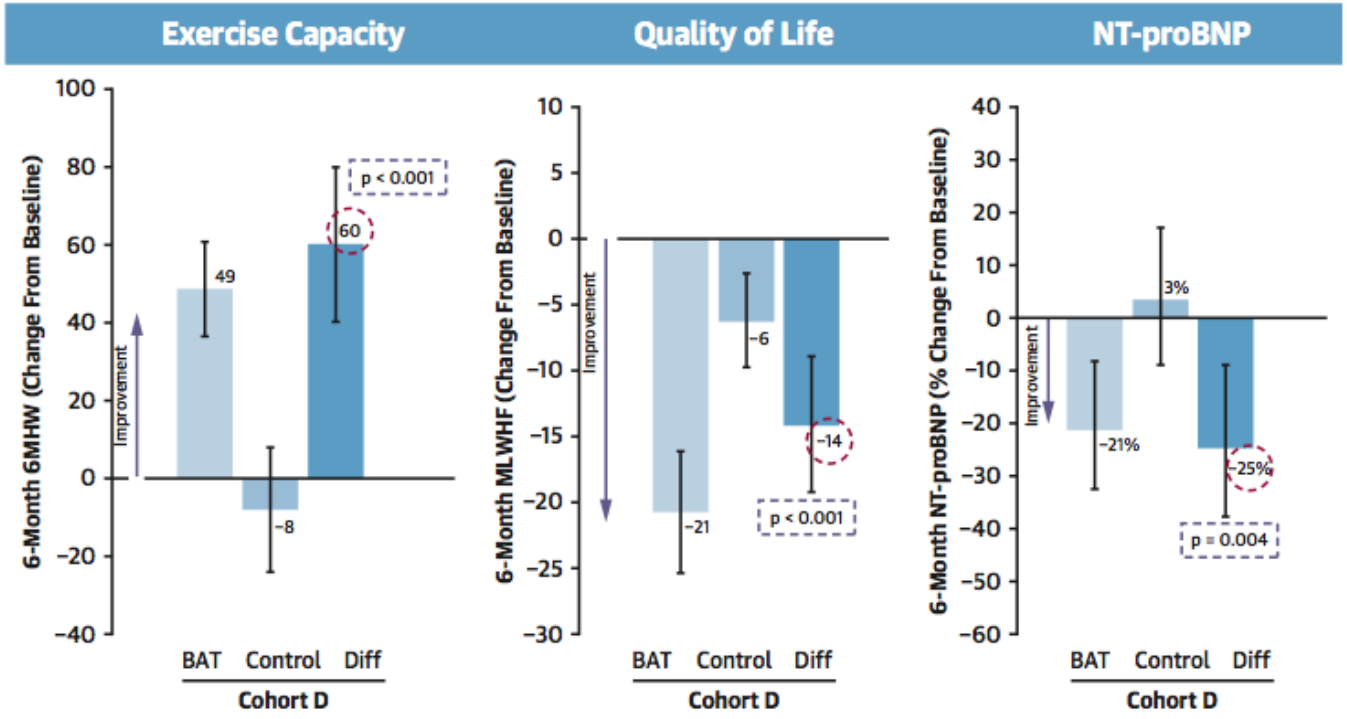
Physiologic effects	Sympathetic Tone NE levels Angiotensin II Filling pressure NTproBNP levels Parasypathetic tone
Clinical effects	HF symptoms QoL Exercise capacity Morbidity and Mortality

The BeAT (Baroreflex activation therapy) trial in patients with HFrEF

Multicenter, prospective, randomized, controlled trial; subjects were randomized 1:1 to receive either BAT plus optimal medical management (BAT group) or optimal medical management alone (control group).

4 patient cohorts were created from 408 randomized patients with HFrEF using the following enrolment criteria: current NYHA functional class II or III; EF<35%; stable medical management for >4 weeks; and no indication for CRT implantation.

BAT was safe and resulted in a significant improvement in QoL, exercise capacity, and NT-proBNP.
The safety endpoint included the major adverse neurological or cardiovascular system or procedure-related event rate.



Zile MR et al. J Am Coll Cardiol 2020

Take home message

• Physiological aging and heart failure are characterized by altered autonomic function;

• Due to ANS complexity, the development of a simple method to assess autonomic dysfunction is particularly challenging;

• However, interrogation of ANS function in heart failure (e.g., cardiac MIBG imaging) gives relevant prognostic information on arrhythmic risk and mortality;

• Beta-adrenergic blockers are the most established autonomic intervention associated with improved outcomes. Other interventions (e.g., baroreflex activation therapy) have shown promise for the management of HF patients.