The Autonomic nervous system and VT/VF

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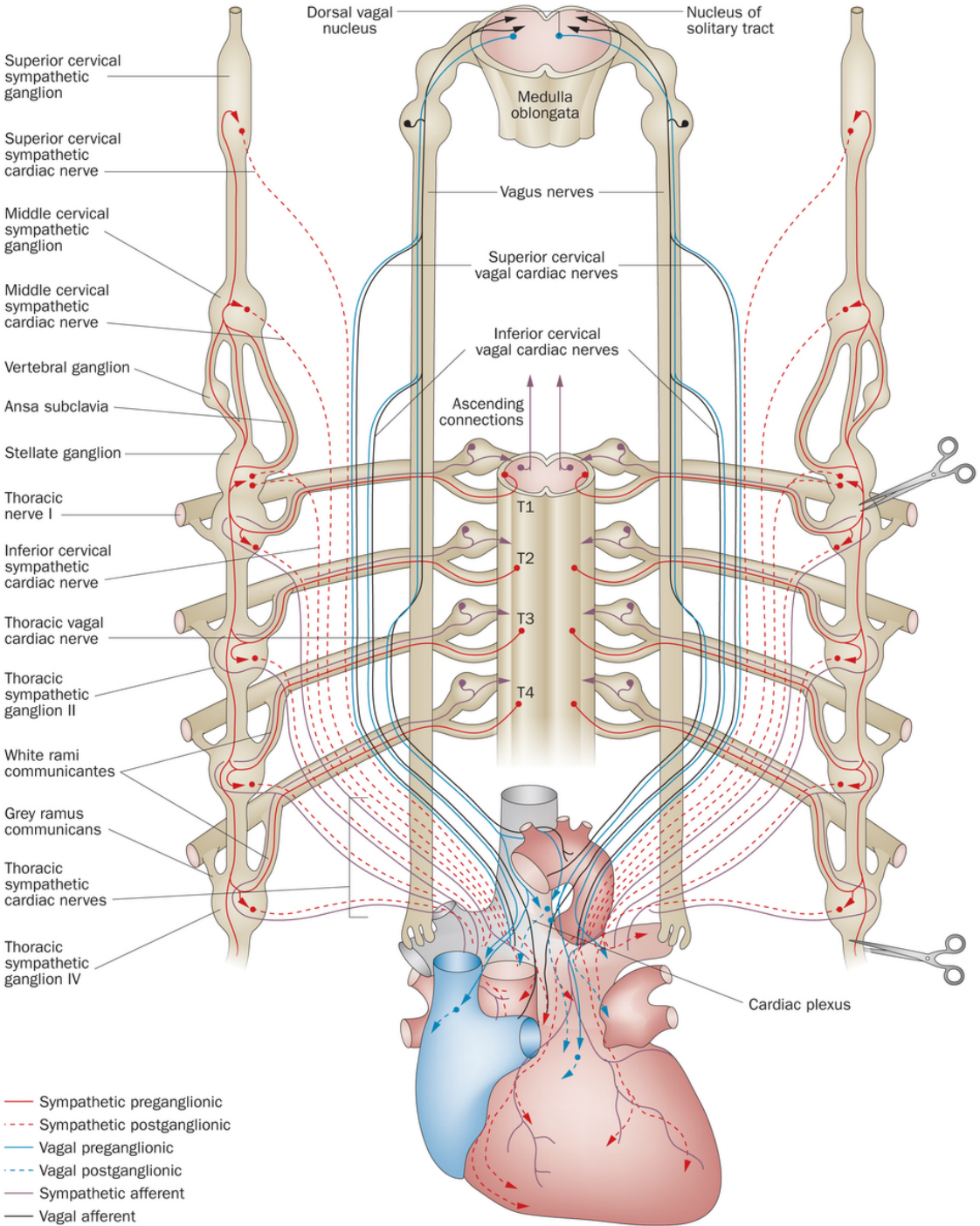
Sympathetic Denervation

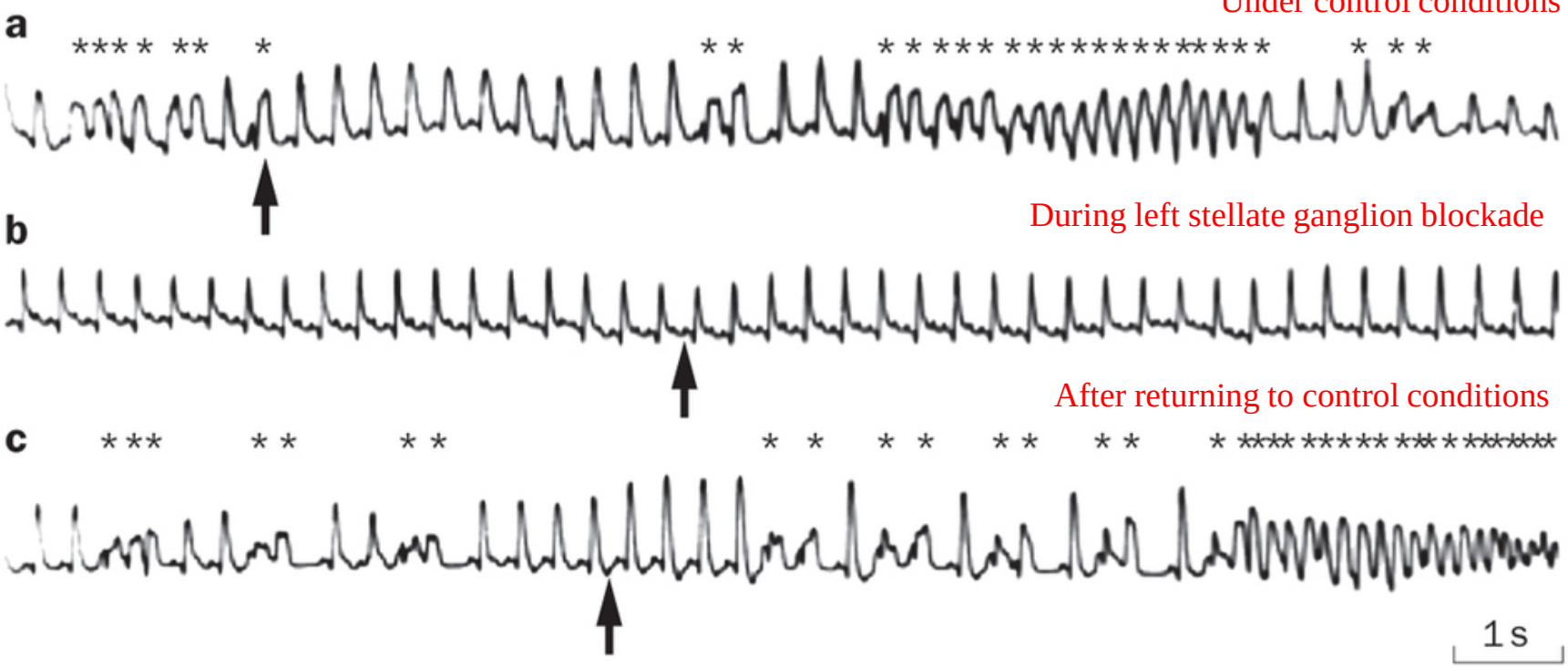
Cardiac innervation and left sympathetic cardiac denervation



Schwartz P, et al. Nature Review Cardiol 2014;11:346-353

Effects of unilateral stellate ganglion blockade on the arrhythmias associated with coronary occlusion

Peter J. Schwartz,* M.D.
H. Lowell Stone, Ph.D.
Arthur M. Brown, M.D., Ph.D.
Galveston, Texas, and Milano, Italy



Schwartz P, et al. Am Heart J 1976;92:589-599

Table II. Effects of right and left stellate ganglion blockade (RSGB, LSGB) on the occurrence of episodes of ventricular tachycardia (VT) and fibrillation (VF) associated with coronary arterial occlusion

	Episodes	*Experiments*	*Control CAO*	*RSGB CAO*	*LSGB CAO*	*Group I episodes*	*Group II episodes*	*Group III episodes*
VT	14	8	3 (21%)	11 (79%)*	0	9	0	5
VF	10	10	2 (20%)	10 (80%)†	0	4	1	5
VT + VF	24	14	5 (21%)	19 (79%)‡	0	13 (54%)	1 (4%)	10 (42%)

*p = 0.029.
†p = 0.055.
‡p = 0.003.

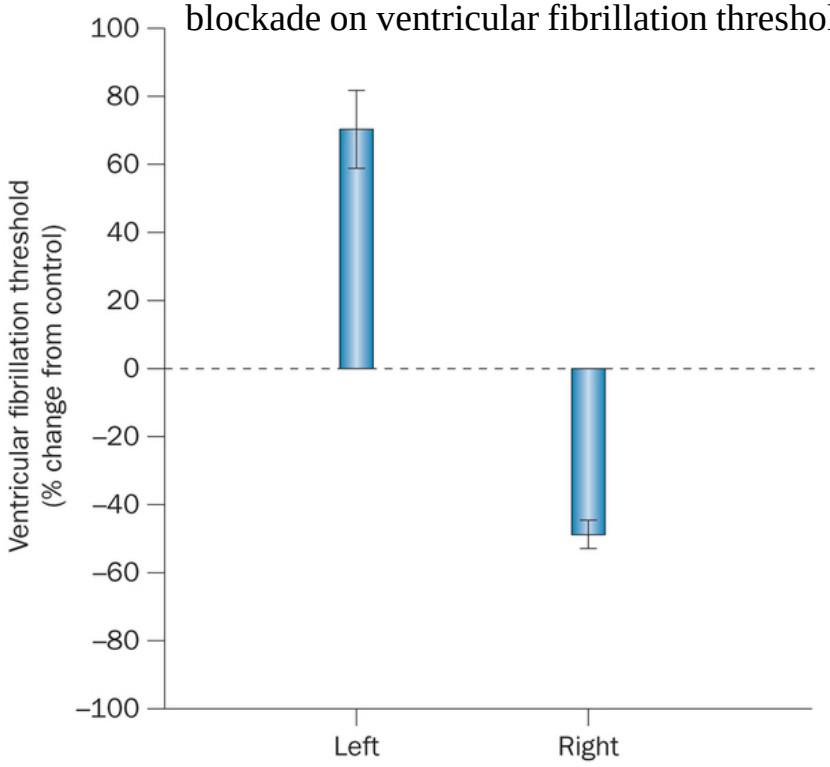
Schwartz P, et al. Am Heart J 1976;92:589-599

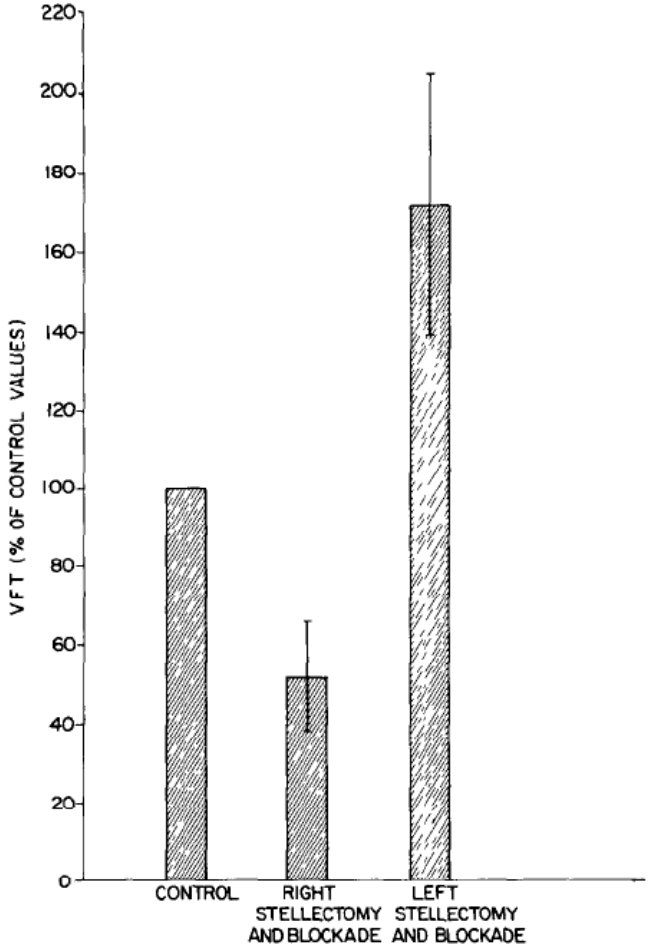
Effects of Unilateral Cardiac Sympathetic Denervation on the Ventricular Fibrillation Threshold

PETER J SCHWARTZ, MD*
NEAL G SNEBOLD, MA
ARTHUR M BROWN, MD, PhD

Galveston, Texas
Milan, Italy

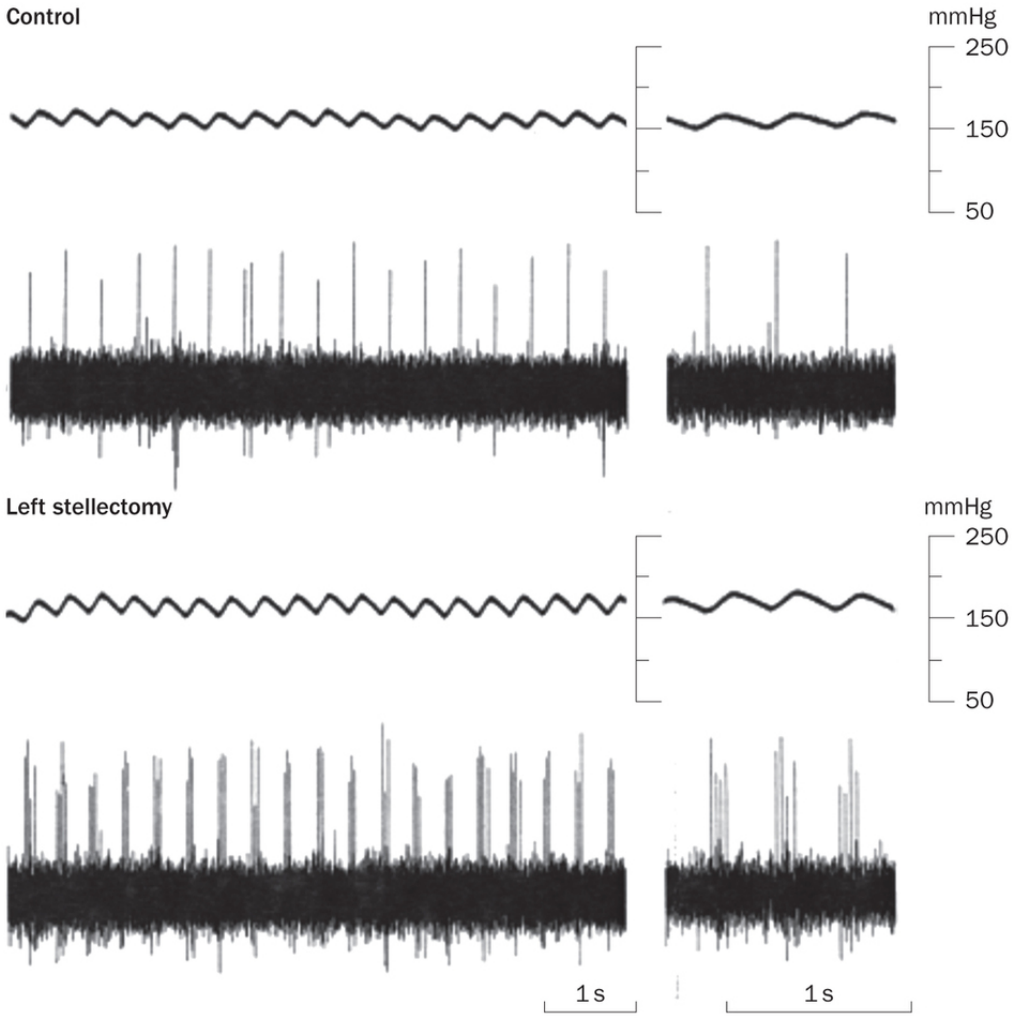
Figure 3: Effect of unilateral stellectomy and blockade on ventricular fibrillation threshold





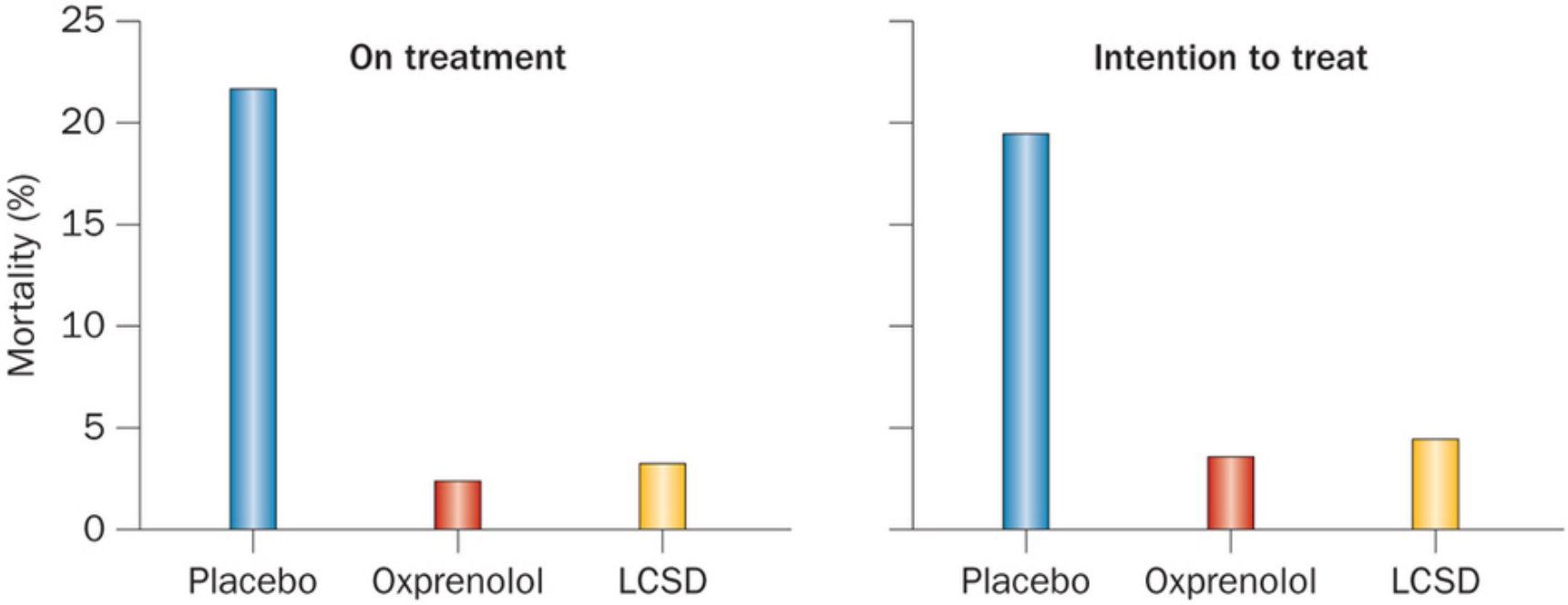
Schwartz P, et al. Am J Cardiol 1976;37:1034-1040

Left stellectomy is accompanied by a reflex increase in cardiac vagal efferent nerve activity.



Circ. Res. **69** (5), 1389–1401 (1991).

LCSD reduces the incidence of sudden cardiac death after myocardial infarction (Human).



J. Cardiovasc. Electrophysiol. **3** (1), 2–16 (1992).

Current indications for LCSD

LCSD is clearly indicated for patients with long QT syndrome or CPVT:

• when β-blockers are contraindicated, not tolerated, or a patient is not compliant

• when syncope recurs despite maximum-dose β-blockade

• when ICD shocks recur

• when a patient remains at high risk of sudden death (for example, with a corrected QT interval >600 ms, T-wave alternans, or bidirectional ventricular tachycardia during exercise), despite being asymptomatic when receiving β-blocker therapy

LCSD can be useful in patients with ischemic or dilated cardiomyopathy:

• when patients continue to have life-threatening arrhythmias that are refractory to treatment, repeated ICD shocks, or both

LCSD can be considered:

• in patients with cardiomyopathy, ischaemic heart disease, or heart failure who are at high risk of life-threatening arrhythmias

• in any patient with recurrent ventricular fibrillation, independently of the aetiology

Nerve Sprouting and Sudden Cardiac Death

Ji-Min Cao, Lan S. Chen, Bruce H. KenKnight, Toshihiko Ohara, Moon-Hyoung Lee, Jerome Tsai, William W. Lai, Hrayr S. Karagueuzian, Paul L. Wolf, Michael C. Fishbein, Peng-Sheng Chen

Abstract—The factors that contribute to the occurrence of sudden cardiac death (SCD) in patients with chronic myocardial infarction (MI) are not entirely clear. The present study tests the hypothesis that augmented sympathetic nerve regeneration (nerve sprouting) increases the probability of ventricular tachycardia (VT), ventricular fibrillation (VF), and SCD in chronic MI. In dogs with MI and complete atrioventricular (AV) block, we induced cardiac sympathetic nerve sprouting by infusing nerve growth factor (NGF) to the left stellate ganglion (experimental group, n=9). Another 6 dogs with MI and complete AV block but without NGF infusion served as controls (n=6). Immunocytochemical staining revealed a greater magnitude of sympathetic nerve sprouting in the experimental group than in the control group. After MI, all dogs showed spontaneous VT that persisted for 5.8±2.0 days (phase 1 VT). Spontaneous VT reappeared 13.1±6.0 days after surgery (phase 2 VT). The frequency of phase 2 VT was 10-fold higher in the experimental group (2.0±2.0/d) than in the control group (0.2±0.2/d, $P<0.05$). Four dogs in the experimental group but none in the control group died suddenly of spontaneous VF. We conclude that MI results in sympathetic nerve sprouting. NGF infusion to the left stellate ganglion in dogs with chronic MI and AV block augments sympathetic nerve sprouting and creates a high-yield model of spontaneous VT, VF, and SCD. The magnitude of sympathetic nerve sprouting may be an important determinant of SCD in chronic MI. **(*Circ Res.* 2000;86:816-821.)**

Neuraxial Modulation for Refractory Ventricular Arrhythmias

Value of Thoracic Epidural Anesthesia and Surgical Left Cardiac Sympathetic Denervation

Tara Bourke, MD; Marmar Vaseghi, MD; Yoav Michowitz, MD; Vineet Sankhla, MD; Mandar Shah, MD; Nalla Swapna, MD; Noel G. Boyle, MD, PhD; Aman Mahajan, MD, PhD; Calambur Narasimhan, MD, DM; Yash Lokhandwala, MD, DM; Kalyanam Shivkumar, MD, PhD

Background-
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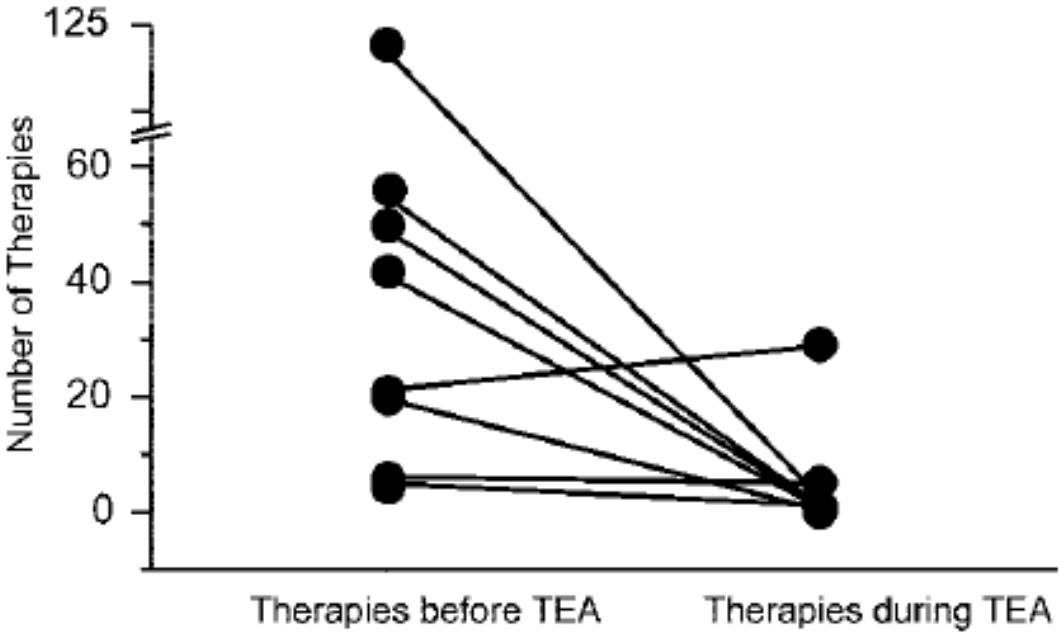


Figure 2. Effect of TEA. Line graph demonstrating number of VT therapies both before and during TEA infusion.

Safety and efficacy of renal denervation as a novel treatment of ventricular tachycardia storm in patients with cardiomyopathy

Benjamin F. Remo, MD,[*] Mark Preminger, MD,[†] Jason Bradfield, MD,[‡] Suneet Mittal, MD,[†] Noel Boyle, MD, PhD,[‡] Anuj Gupta, MD,[*] Kalyanam Shivkumar, MD PhD,[‡] Jonathan S. Steinberg, MD,[†] Timm Dickfeld, MD, PhD[*]

From the [*]Division of Cardiology, University of Maryland School of Medicine, Baltimore, Maryland, [†]The Valley Health System and Columbia University College of Physicians and Surgeons, New York, New York and Ridgewood, New Jersey, and [‡]UCLA Cardiac Arrhythmia Center, David Geffen School of Medicine at UCLA, Los Angeles, California.

BACKGROUND Modulation of the autonomic nervous system has been used to treat refractory ventricular tachycardia (VT). Renal artery denervation (RDN) is under investigation for the treatment of sympathetic-driven cardiovascular diseases.

OBJECTIVE The purpose of this study was to report the largest case series to date using RDN as adjunctive therapy for refractory VT in patients with underlying cardiomyopathy.

METHODS Four patients with cardiomyopathy (2 nonischemic, 2 ischemic) with recurrent VT despite maximized antiarrhythmic therapy and prior endocardial (n = 2) or endocardial/epicardial (n = 2) ablation underwent RDN ± repeat VT ablation. RDN was performed spirally along each main renal artery with either a nonirrigated (6 W at 50°C for 60 seconds) or an open irrigated ablation catheter (10–12 W for 30–60 seconds). Renal arteriography was performed before and after RDN.

RESULTS RDN was well tolerated acutely and demonstrated no clinically significant complications during follow-up of 8.8 ± 2.6 months (range 5.0–11.0 months). No hemodynamic deterioration or worsening of renal function was observed. The number of VT episodes was decreased from 11.0 ± 4.2 (5.0–14.0) during the month before ablation to 0.3 ± 0.1 (0.2–0.4) per month after ablation. All VT episodes occurred in the first 4 months after ablation (2.6 ± 1.5 months). The responses to RDN were similar for ischemic and nonischemic patients.

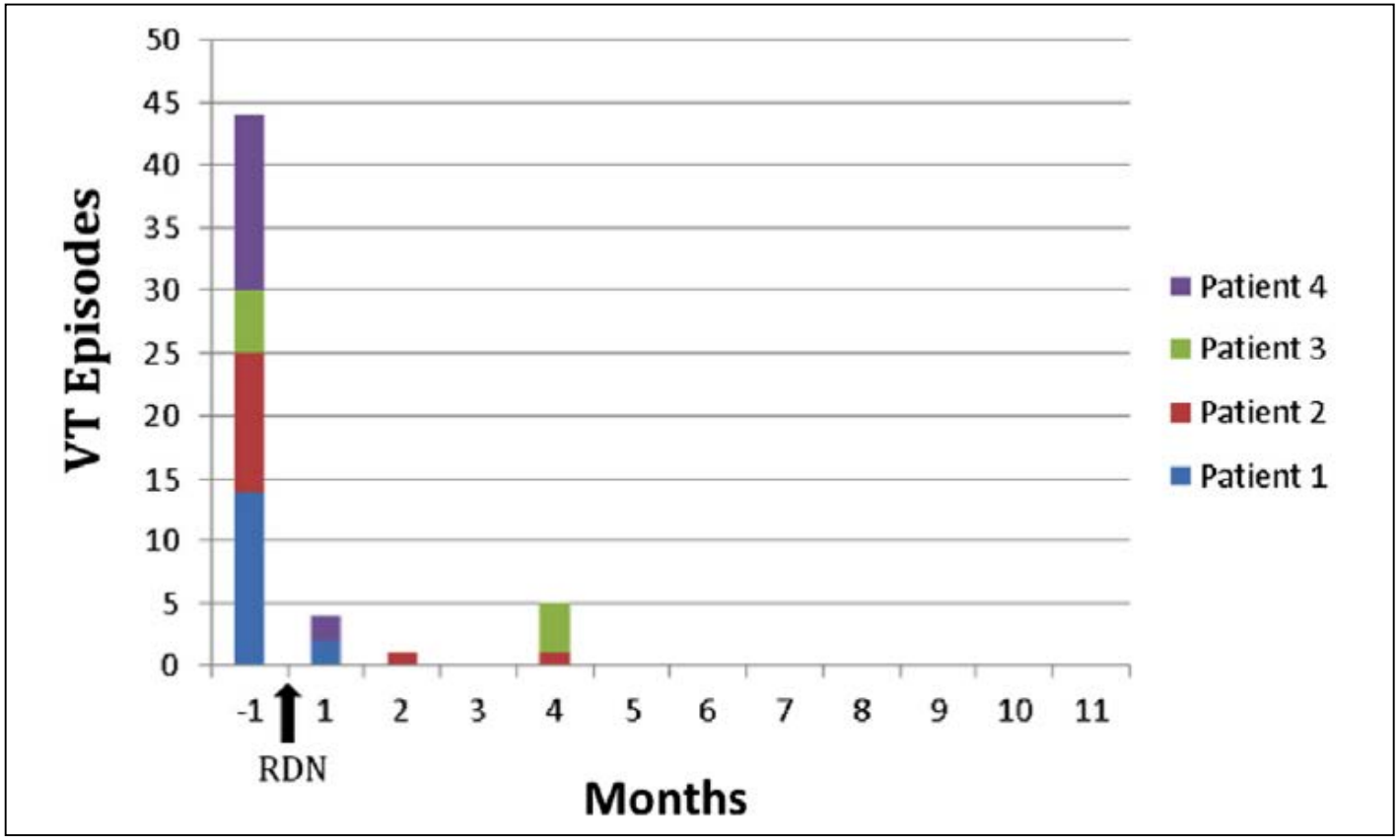
CONCLUSION This case series provides promising preliminary data on the safety and effectiveness of RDN as an adjunctive therapy in the treatment of patients with cardiomyopathy and VT resistant to standard interventions.

KEYWORDS Renal denervation; Ventricular tachycardia; Cardiomyopathy; Ventricular tachycardia storm

ABBREVIATIONS **AF** = atrial fibrillation; **ATP** = antitachycardia pacing; **BP** = blood pressure; **CL** = cycle length; **EGM** = electrogram; **FDA** = Food and Drug Administration; **HR** = heart rate; **ICD** = implantable cardioverter-defibrillator; **LAD** = left anterior descending; **LB** = left bundle; **LI** = left inferior; **LS** = left superior; **LV** = left ventricle; **LVAD** = left ventricular assist device; **LVEF** = left ventricular ejection fraction; **MRI** = magnetic resonance imaging; **PVI** = pulmonary vein isolation; **RB** = right bundle; **RDN** = renal artery denervation; **RF** = radiofrequency; **RS** = right superior; **RV** = right ventricle; **VT** = ventricular tachycardia

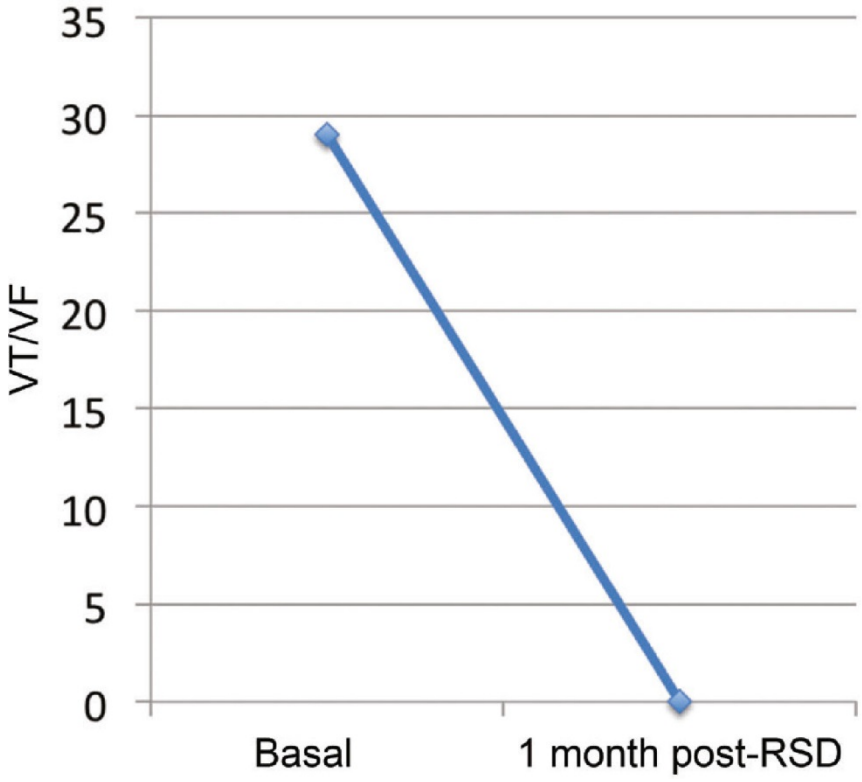
(Heart Rhythm 2014;0:0–6)

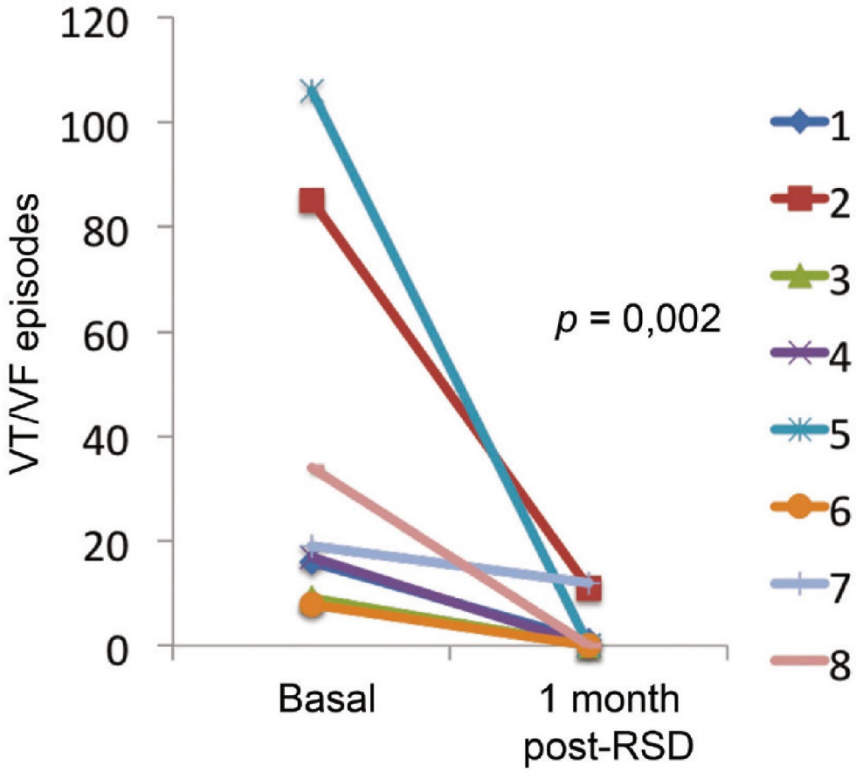
Safety and efficacy of renal denervation as a novel treatment of ventricular tachycardia storm in patients with cardiomyopathy



Remo B, et al. Heart Rhythm 2014;11:541–546

Renal sympathetic denervation in patients with ICD and electrical storm



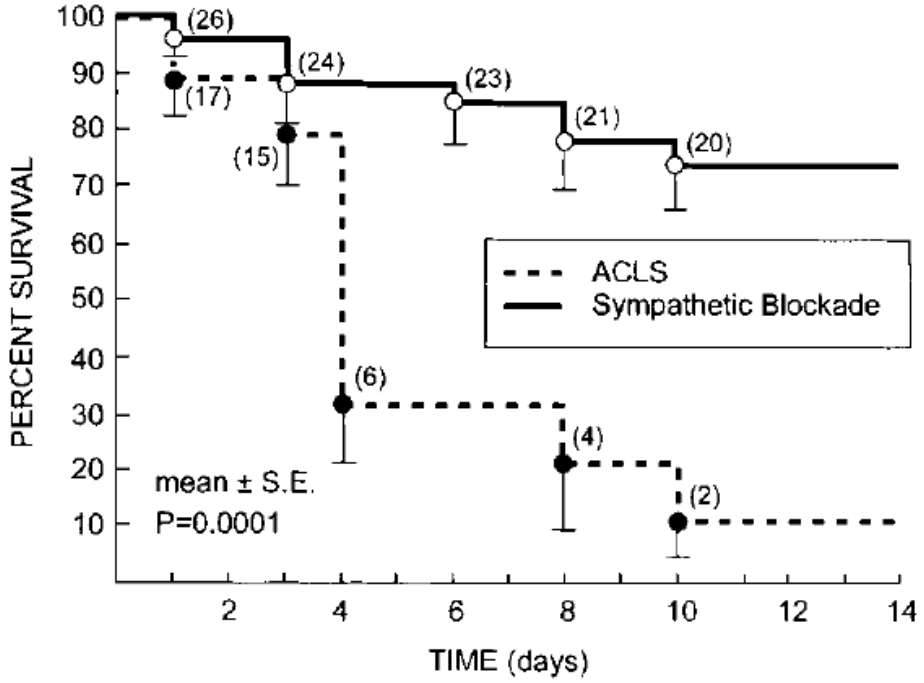


Cardiologia Invasiva 2015;2.:84-90

Beta blocker

Treating Electrical Storm

Sympathetic blockade vs. ACLS therapy



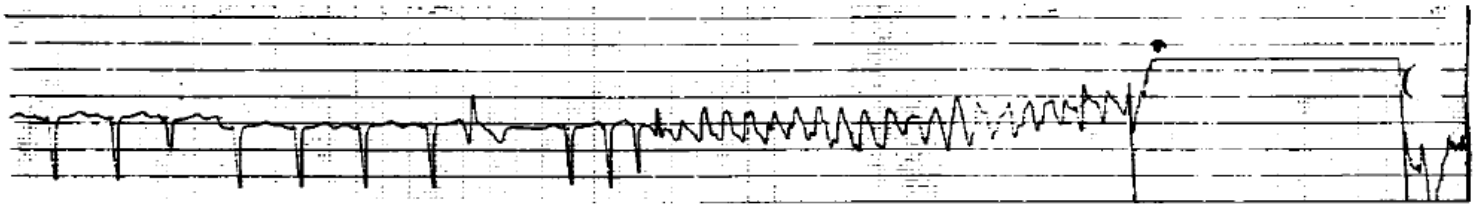
Sympathetic blockade treatment: (n=25)

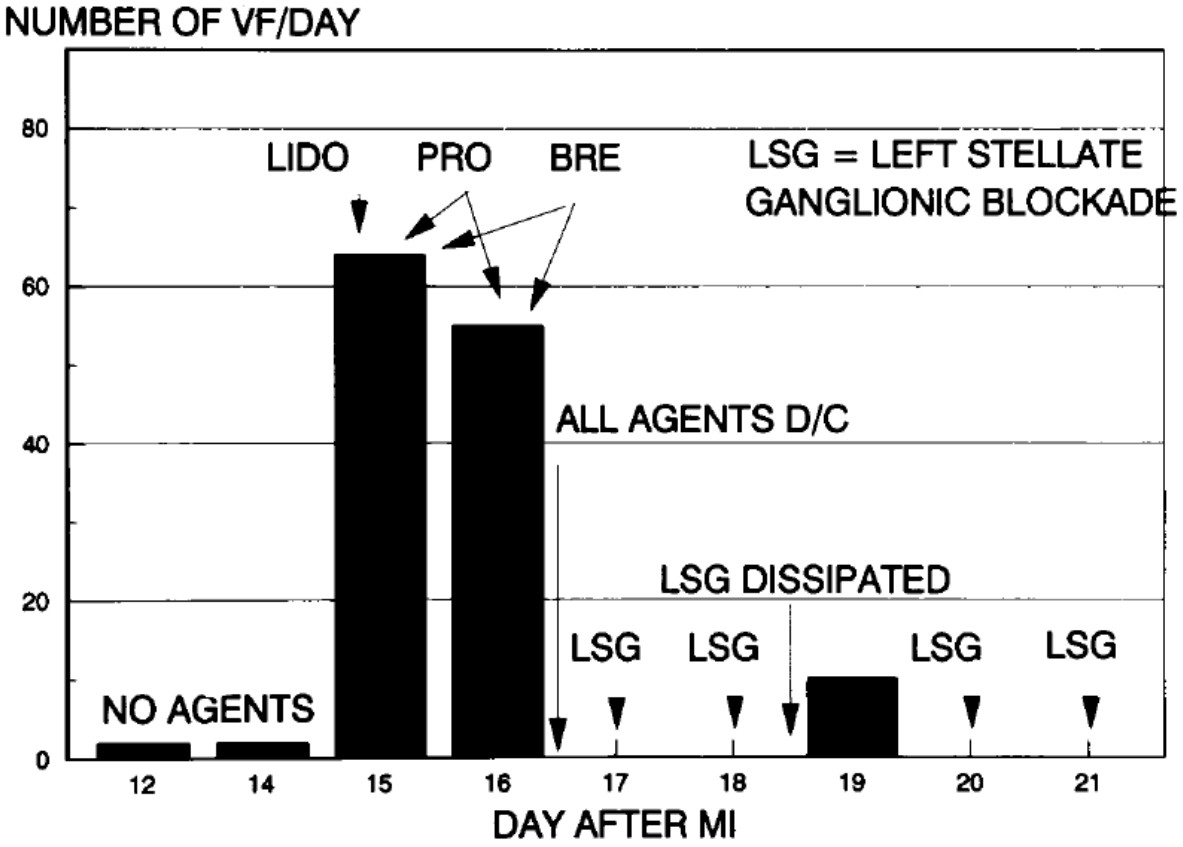
6 left stellate ganglionic blockade,

7 esmolol,

14 propranolol

Nademanee K, et al. *Circulation*. 2000;102:742-747.





Nademanee K, et al. *Circulation*. 2000;102:742-747.

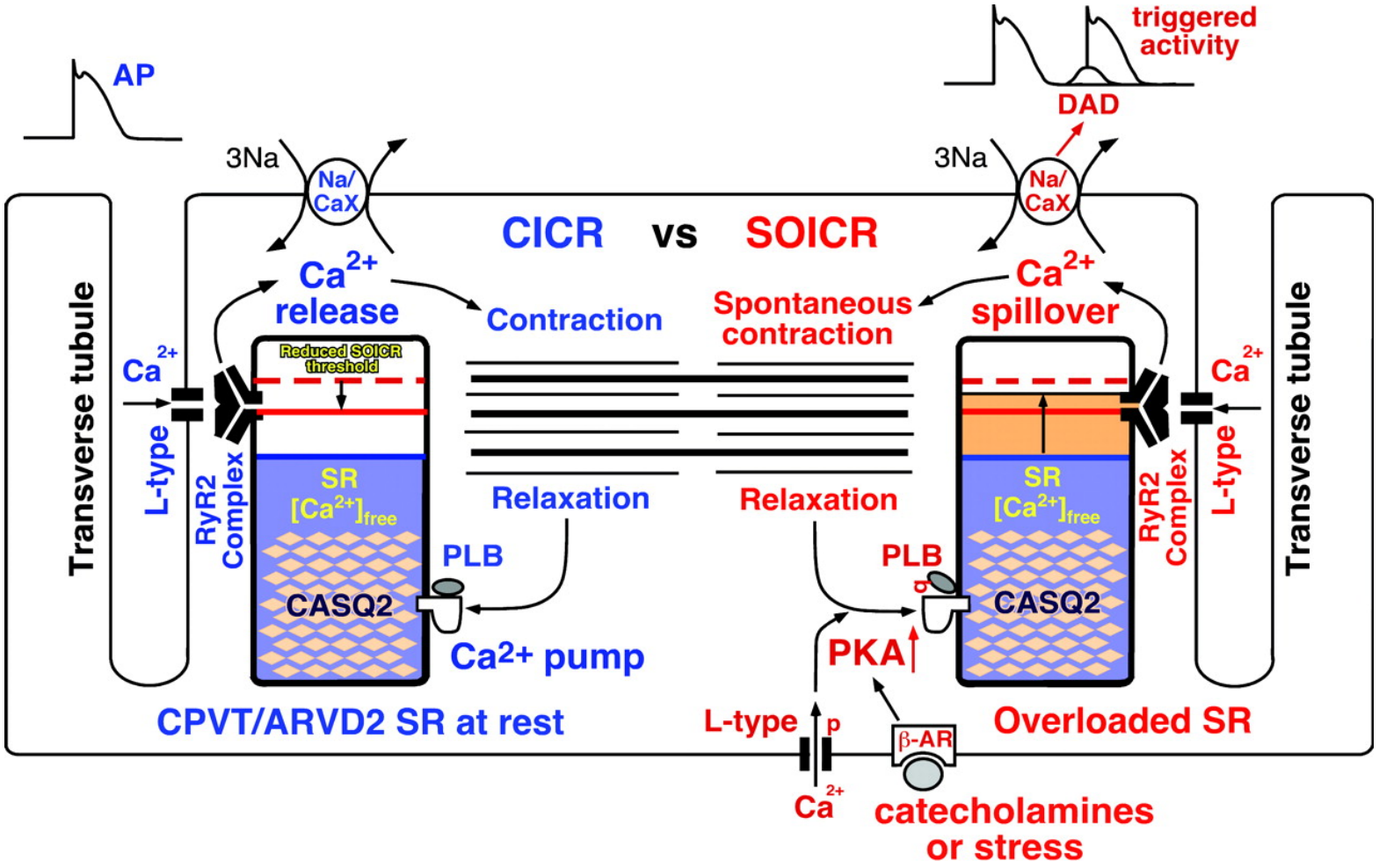
Carvedilol Reduced Arrhythmia

Outcome	Subjects With Event Carvedilol (n = 975)/ Placebo (n = 984)	Carvedilol/Placebo Hazard Ratio (95% CI)	Log-Rank p Value
Death or SV arrhythmia	133/187	0.70 (0.56, 0.88)	0.0016
Death or SV arrhythmia (excluding patients with a history of AF/AFL)	112/152	0.72 (0.57, 0.92)	0.0090
Death or AF/AFL	129/186	0.68 (0.55, 0.85)	0.0008
Death or AF/AFL (excluding patients with a history of AF/AFL)	109/151	0.71 (0.55, 0.91)	0.0057
Death or any ventricular arrhythmia	138/201	0.67 (0.54, 0.84)	0.0003
Death or any ventricular arrhythmia (excluding patients with a history of VT/VF)	137/197	0.68 (0.54, 0.84)	0.0004
Death or a malignant ventricular arrhythmia	123/173	0.70 (0.56, 0.89)	0.0028
Death or any arrhythmia	154/233	0.64 (0.52, 0.79)	<0.0001

AF/AFL = atrial fibrillation/atrial flutter; CI = confidence interval; SV = supraventricular; VT/VF = ventricular tachycardia/ventricular fibrillation.

CAPRICORN trail. J Am Coll Cardiol 2005;45:525–30

The mechanisms of Ca2-induced Ca2 release (CICR; left) and store overload–induced Ca2 release (SOICR; right)



Jiang D, et al. Circ Res 2005;97(11):1173-81.

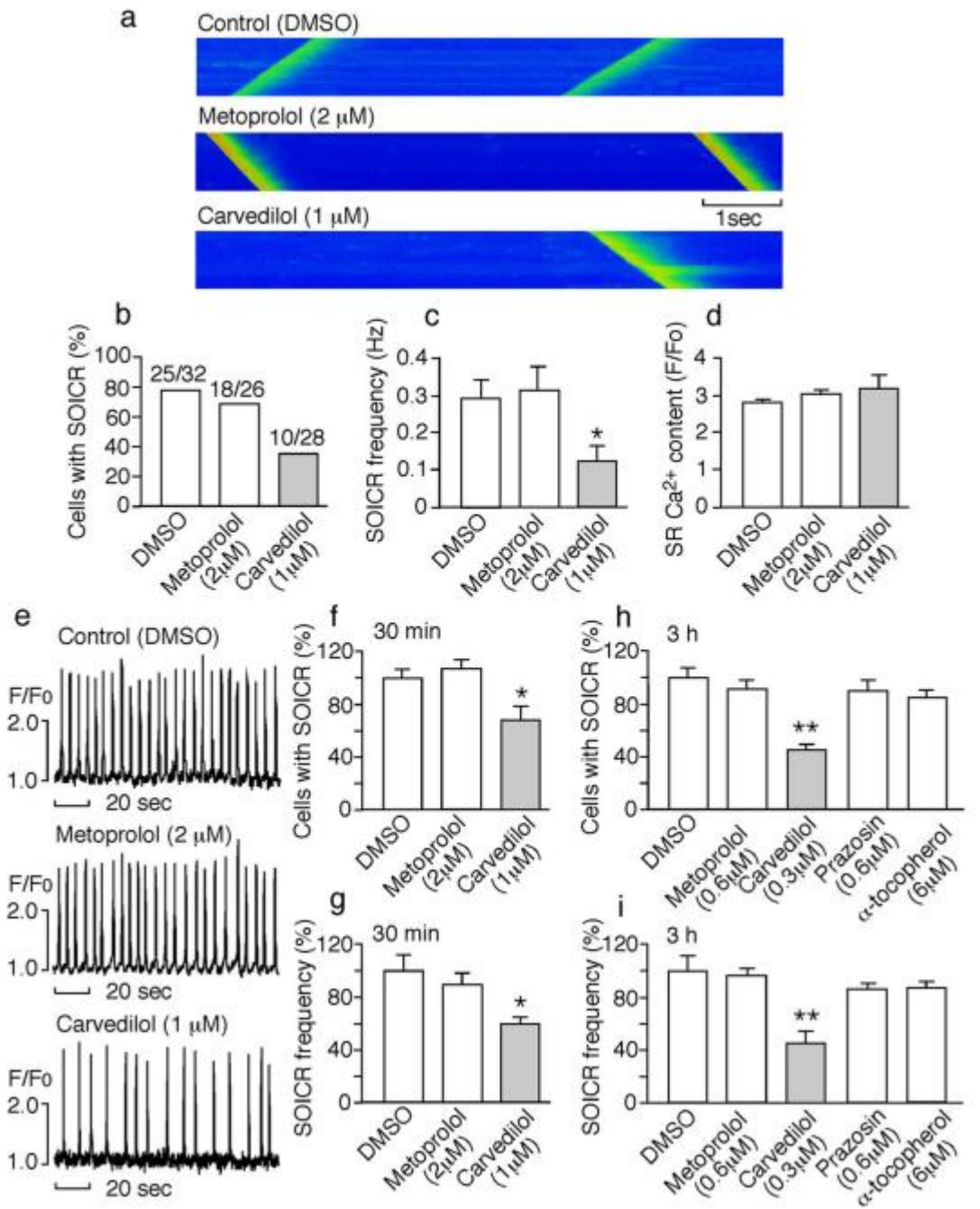
Carvedilol and its new analogs suppress arrhythmogenic store overload–induced Ca^{2+} release

Qiang Zhou[1,2,8], Jianmin Xiao[1,8], Dawei Jiang[1], Ruiwu Wang[1], Kannan Vembaiyan[3], Aixia Wang[3], Chris D Smith[3], Cuihong Xie[1,2,8], Wenqian Chen[1], Jingqun Zhang[2], Xixi Tian[1], Peter P Jones[1,8], Xiaowei Zhong[1], Ang Guo[4], Haiyan Chen[2], Lin Zhang[1], Weizhong Zhu[5], Dongmei Yang[6], Xiaodong Li[7], Ju Chen[7], Anne M Gillis[1], Henry J Duff[1], Heping Cheng[6,8], Arthur M Feldman[5], Long-Sheng Song[4], Michael Fill[2], Thomas G Back[3] & S R Wayne Chen[1,2]

Carvedilol is one of the most effective beta blockers for preventing ventricular tachyarrhythmias in heart failure, but the mechanisms underlying its favorable antiarrhythmic benefits remain unclear. Spontaneous Ca^{2+} waves, also called store overload–induced Ca^{2+} release (SOICR), evoke ventricular tachyarrhythmias in individuals with heart failure. Here we show that carvedilol is the only beta blocker tested that effectively suppresses SOICR by directly reducing the open duration of the cardiac ryanodine receptor (RyR2). This unique anti-SOICR activity of carvedilol, combined with its beta-blocking activity, probably contributes to its favorable antiarrhythmic effect. To enable optimal titration of carvedilol's actions as a beta blocker and as a suppressor of SOICR separately, we developed a new SOICR-inhibiting, minimally beta-blocking carvedilol analog, VK-II-86. VK-II-86 prevented stress-induced ventricular tachyarrhythmias in RyR2-mutant mice and did so more effectively when combined with either of the selective beta blockers metoprolol or bisoprolol. Combining SOICR inhibition with optimal beta blockade has the potential to provide antiarrhythmic therapy that can be tailored to individual patients.

Nature medicine 2011;17:1003-1009

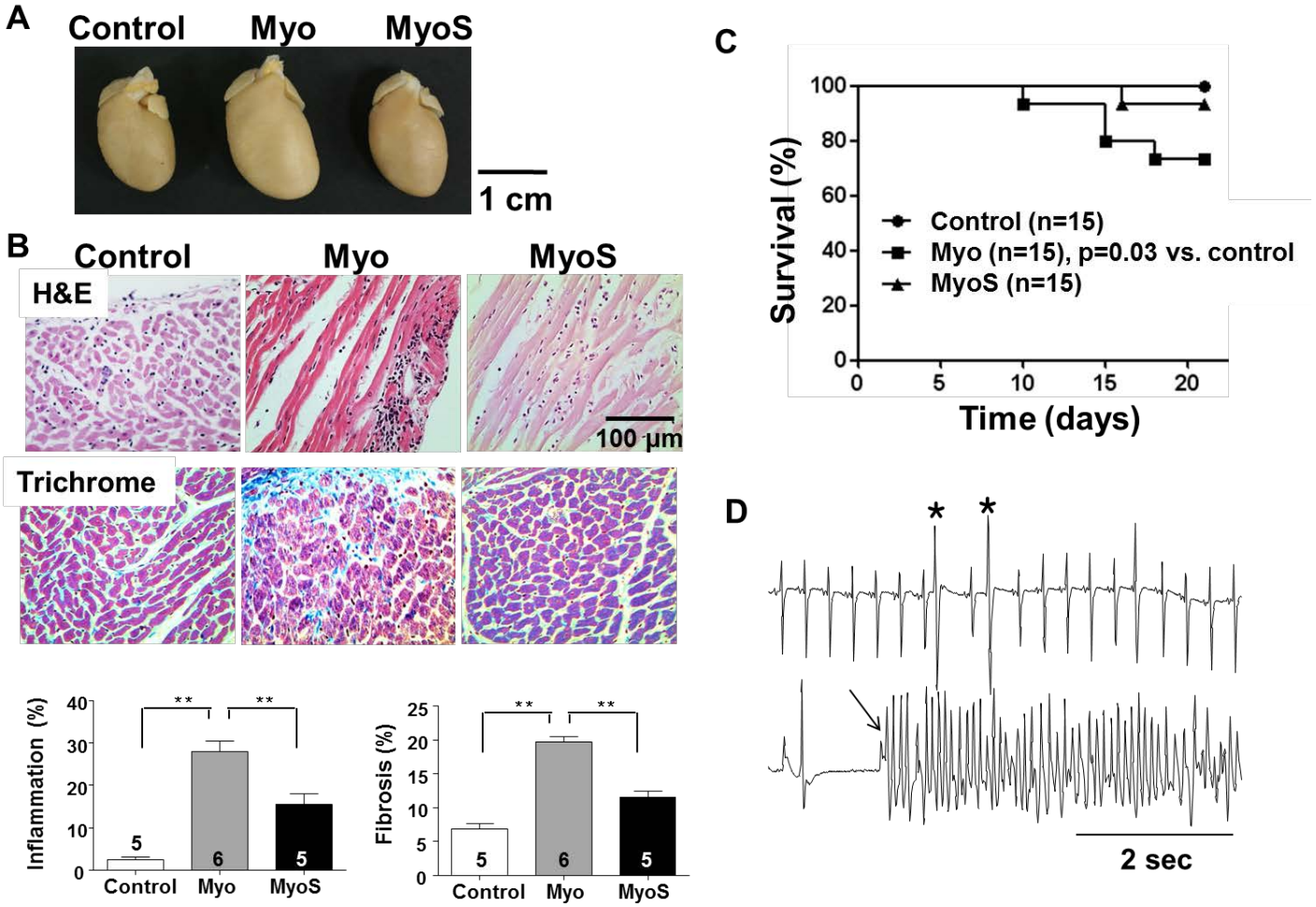
Carvedilol suppresses SOICR in mouse ventricular myocytes



Zhou et al.
Nature Medicine
2011;17:1003-1010

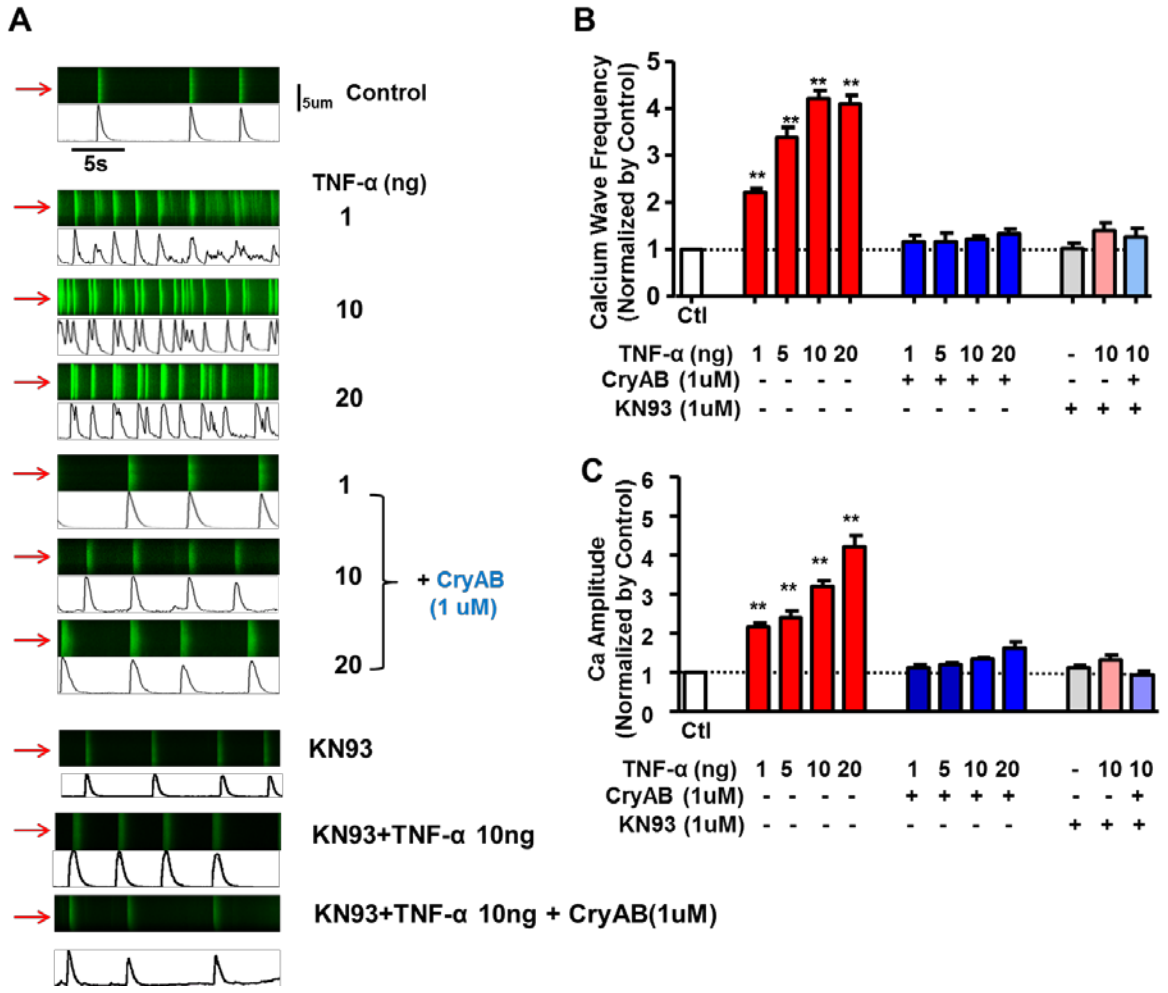
Anti-inflammatory effect

Myocarditis and arrhythmia



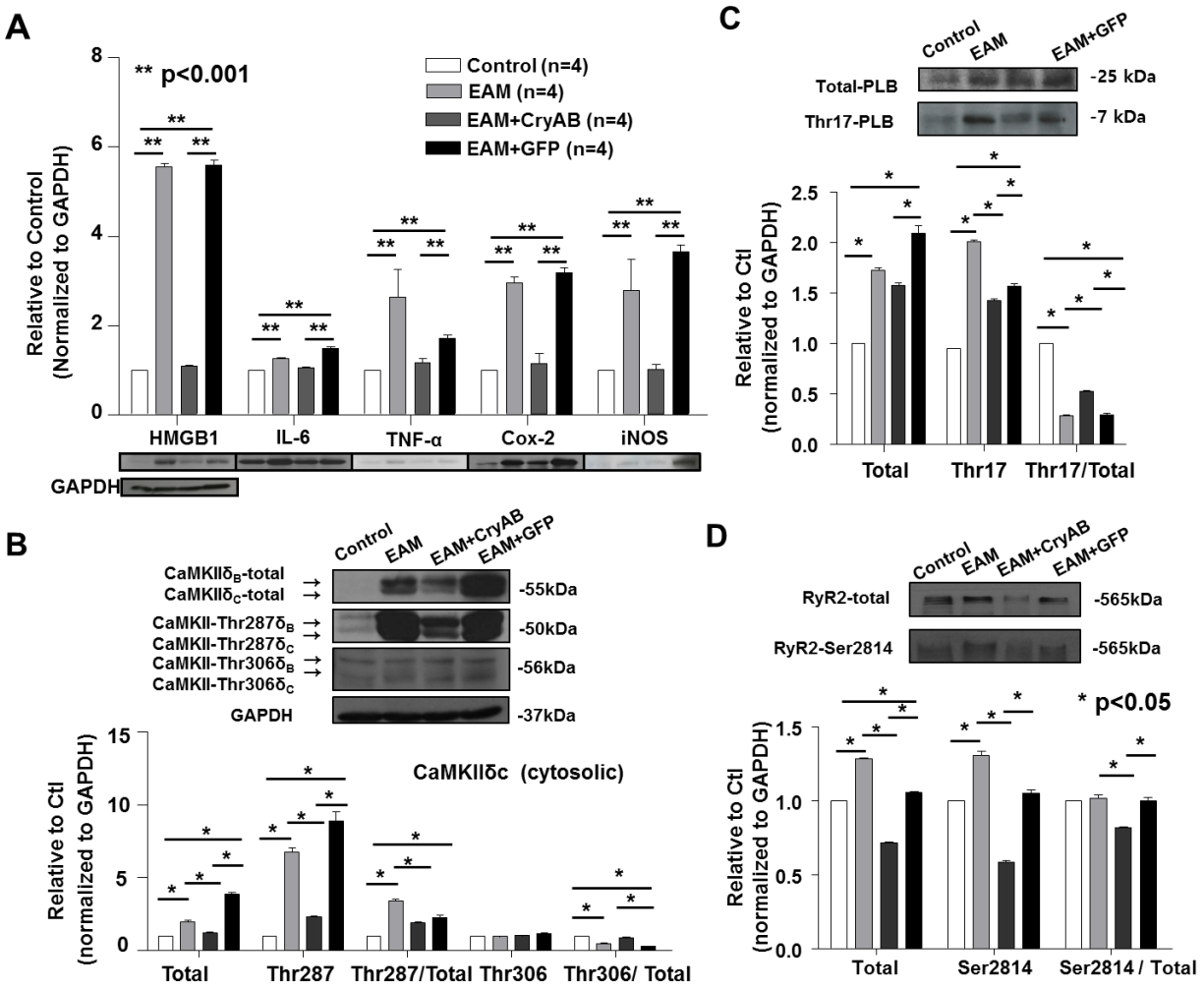
Park H, et al. Circ J. 2014;78(9):2292-301

Spontaneous Ca^{2+} release in rat neonatal myocytes treated with TNF-α



Park H, et al. Int J Cardiol. 2015;182:399-402.

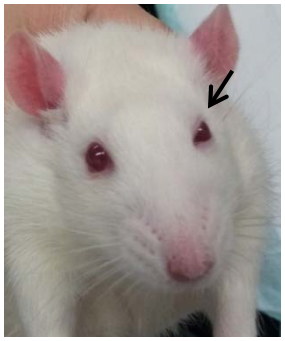
Inflammation, oxidative stress and the phosphorylation of Ca^{2+} handling protein in myocarditis



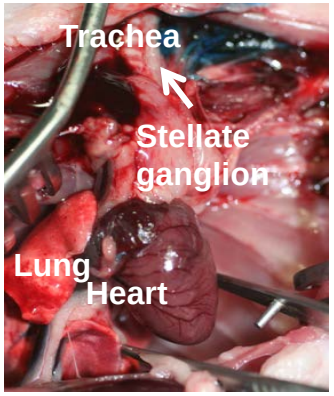
Park H, et al. Int J Cardiol. 2015;182:399-402.

Methods (Animal Model)

A



B



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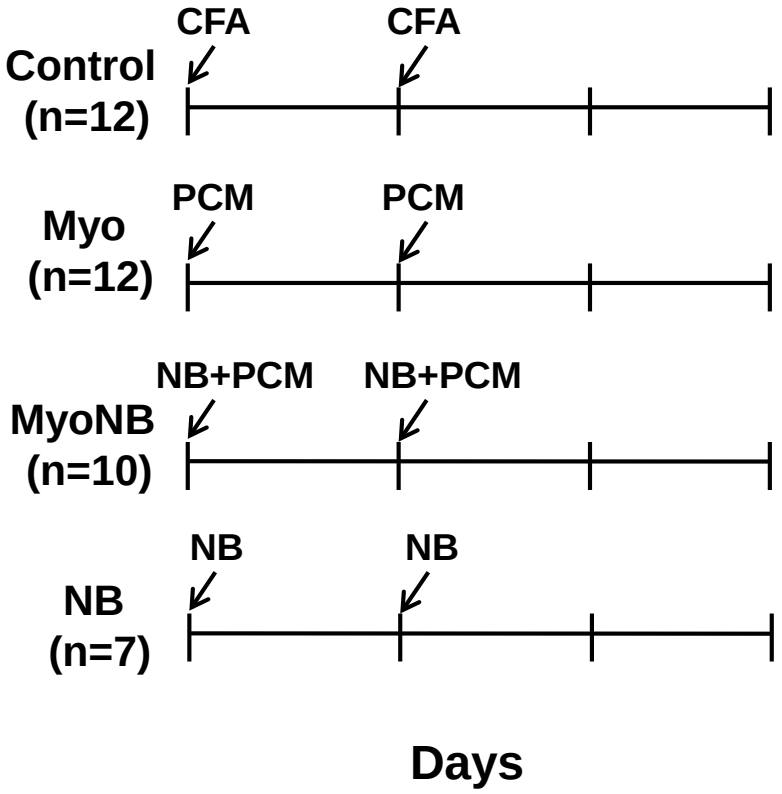
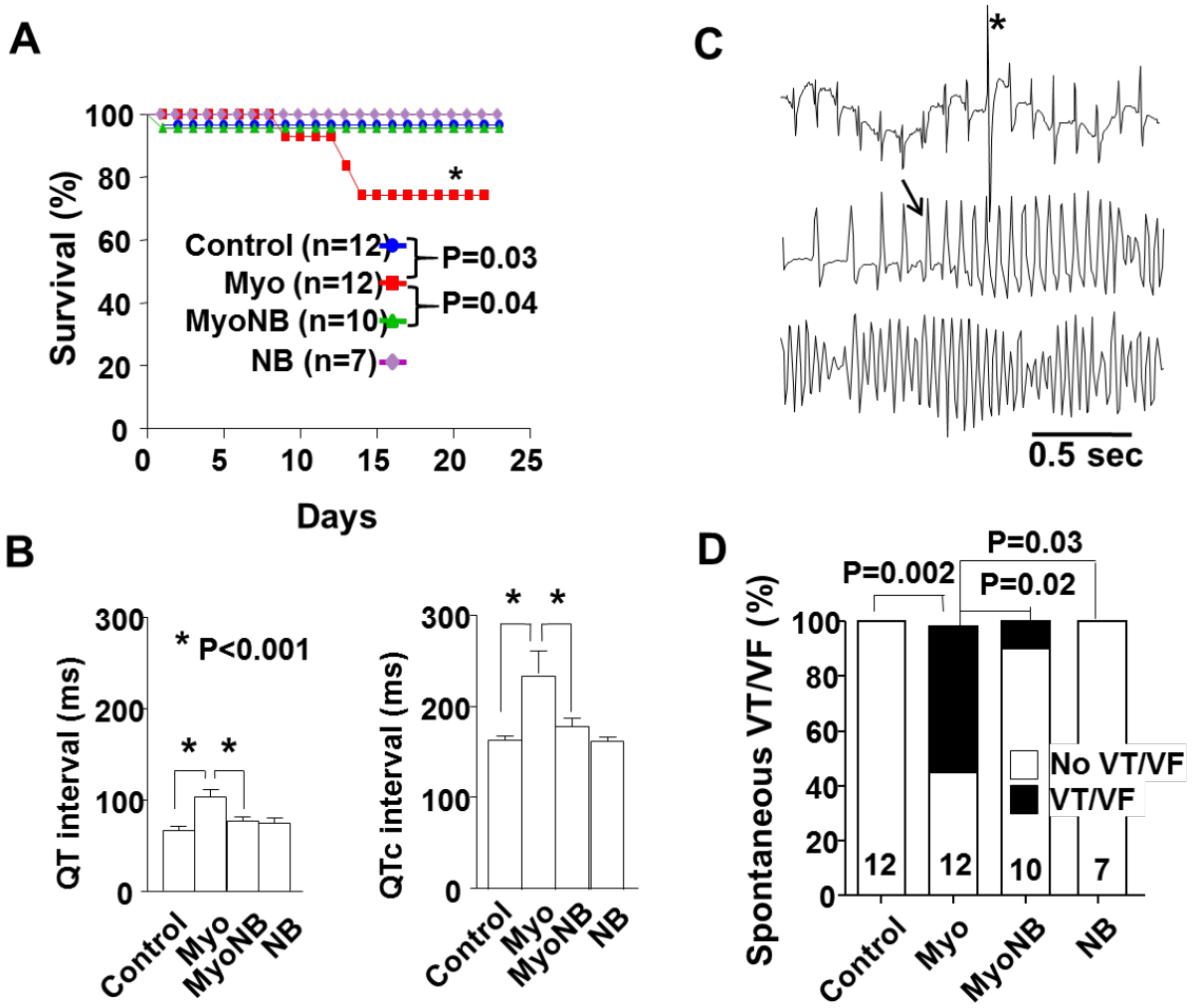
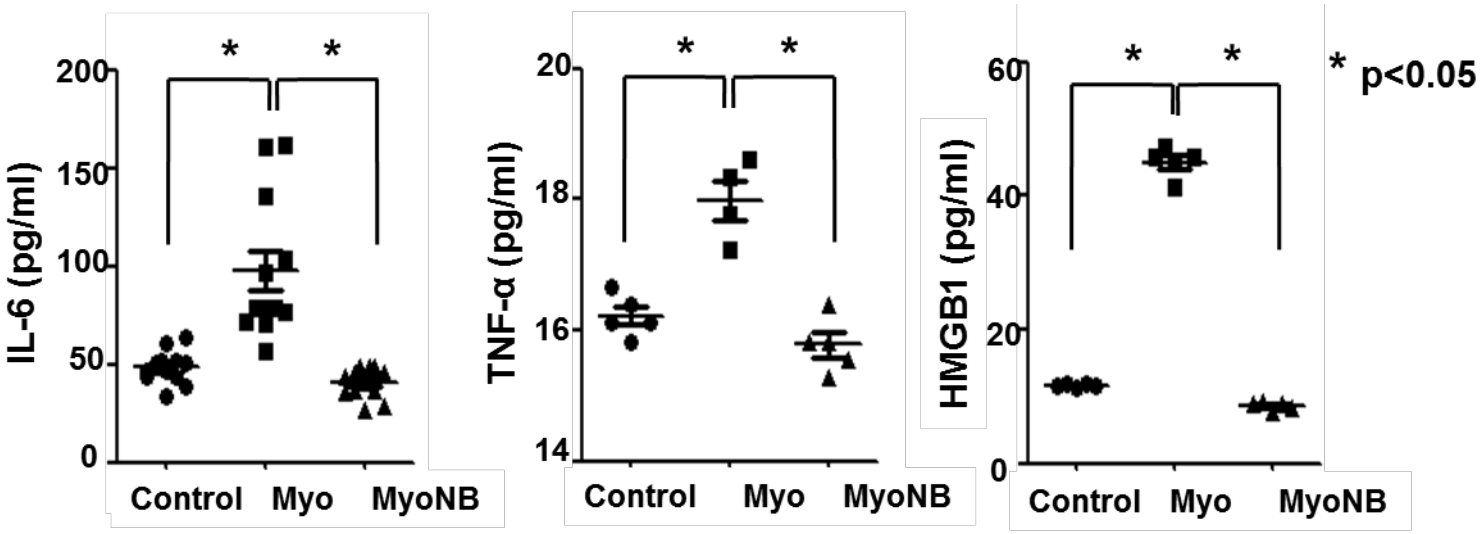


Left SGB improved survival rate and suppressed arrhythmias in EAM.

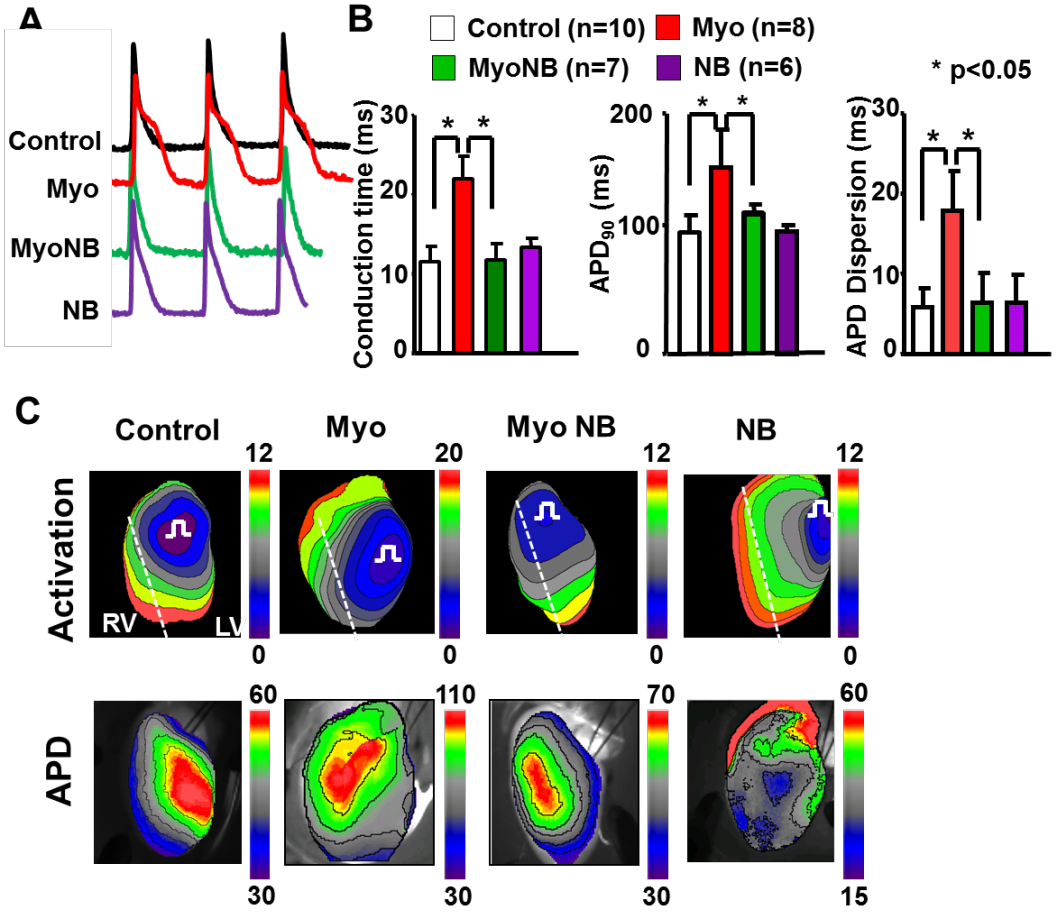


- Myo group showed lower survival rate, QT prolongation and VT episodes.
- Left SGB prevented these effects of myocarditis.

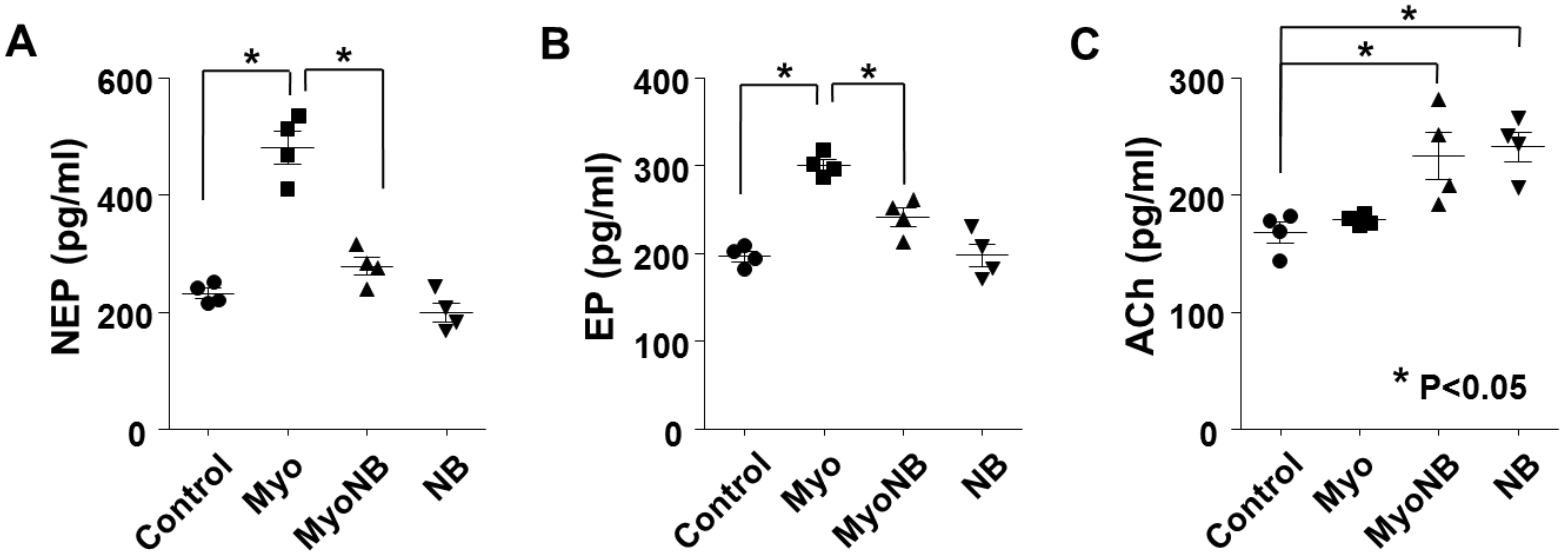
Left SGB decreased oxidative stress and inflammation in EAM



Left SGB improved conduction time and APD prolongation in EAM



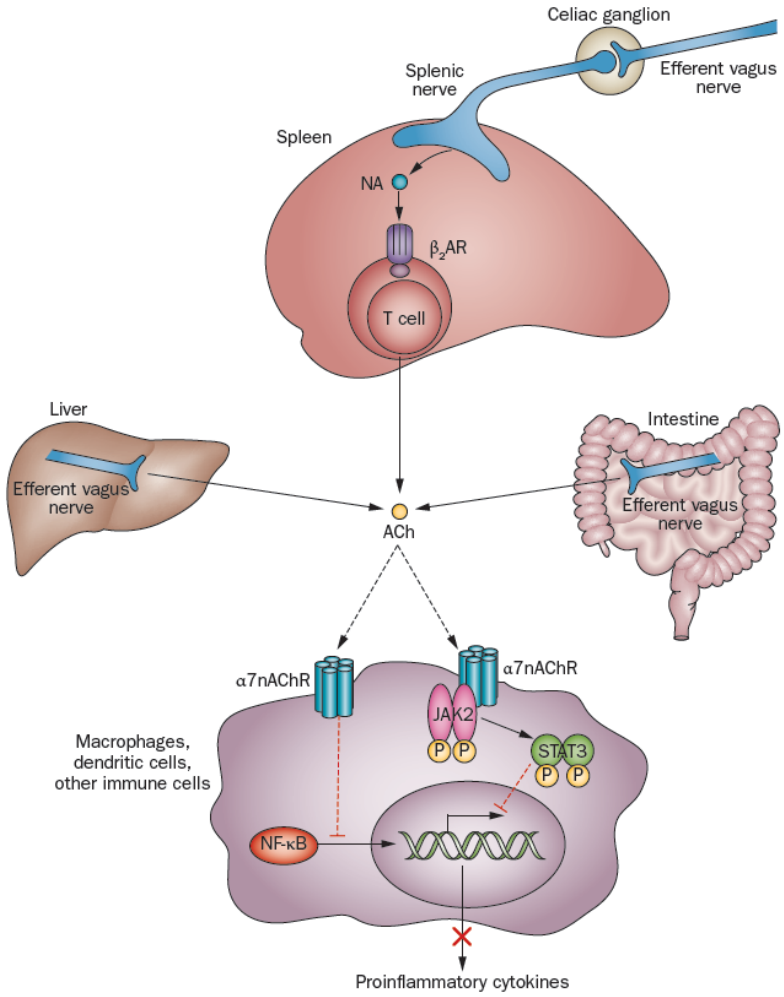
The central level of norepinephrine epinephrine, and acetylcholine



- **The left SGB significantly reduced the level of norepinephrine, epinephrine in serum as compared with the Myo group.($p<0.05$)**
- **Compared with control, the level of acetylcholine in serum increased in MyoNB group. ($p<0.05$)**

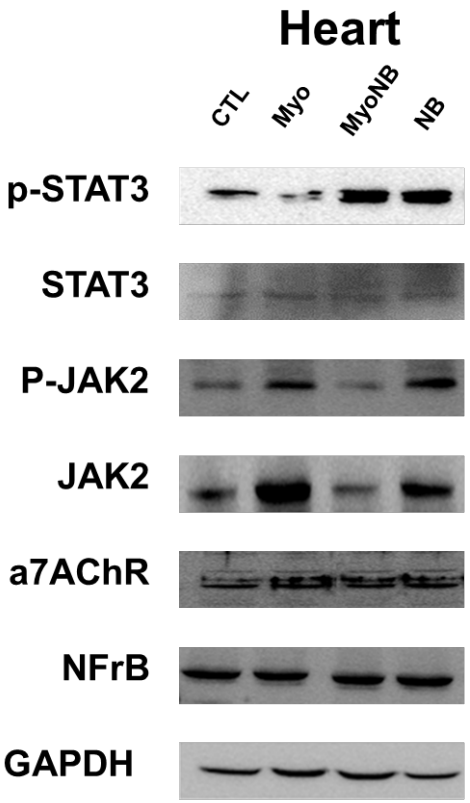
AHA 2016

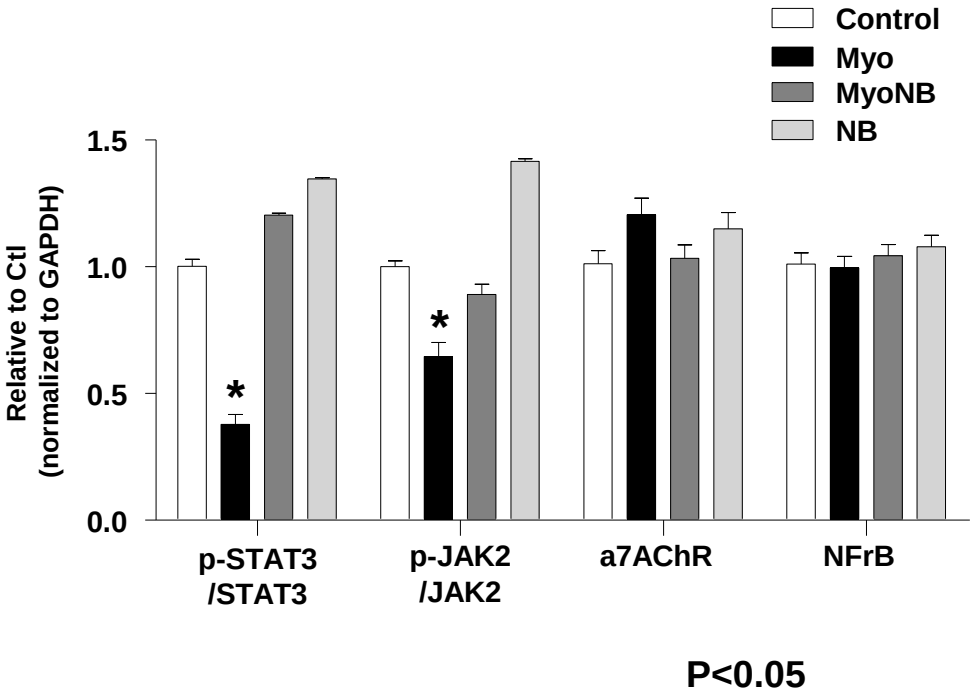
The Cholinergic Anti-Inflammatory Pathway



Nat. Rev. Endocrinol. **8, 743–754 (2012)**

Molecular mechanisms of cholinergic control of inflammation



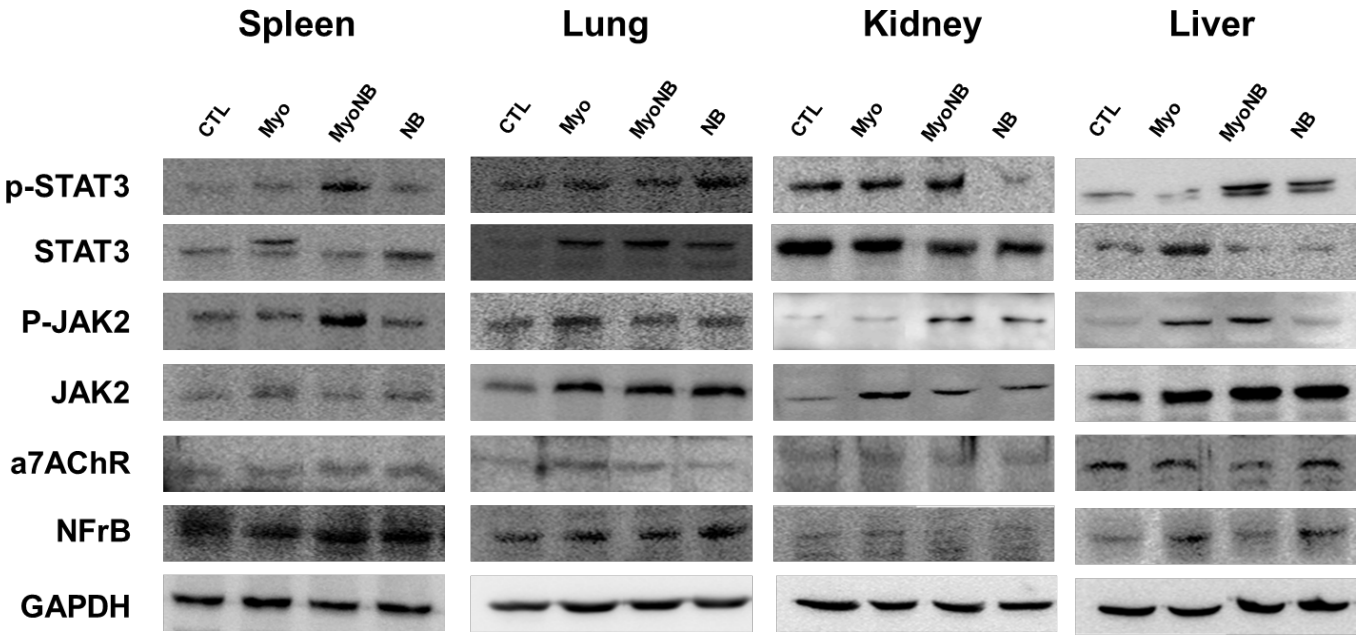


P<0.05

. The Myo group showed reduced phosphate/total STAT3 (0.5±0.1 times from control, p=0.001) and JAK2 (0.5±0.0 times from control, p=0.01). However, MyoNB showed significantly enhanced JAK2 activation (2.2±0.1 times, p=1.00) followed by STAT3 phosphorylation (2.2 ± 0.2 times, p=1.00)

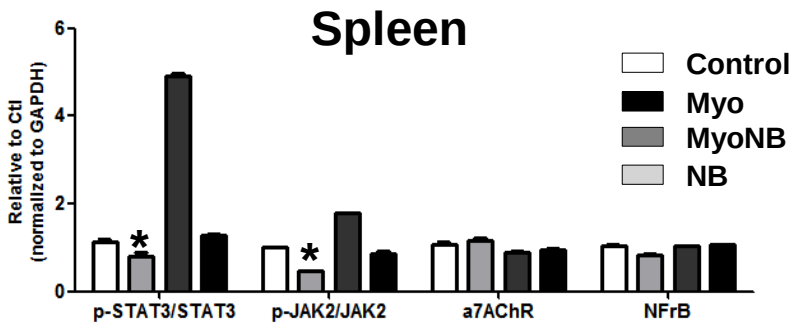
AHA 2016

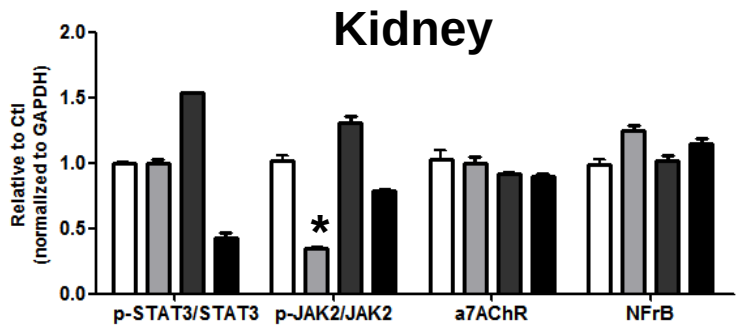
Molecular mechanisms of cholinergic control of inflammation.

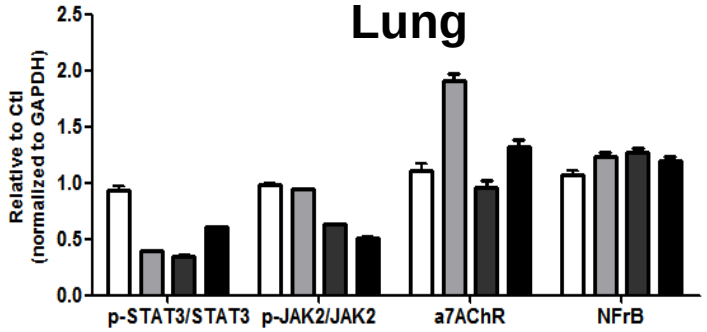


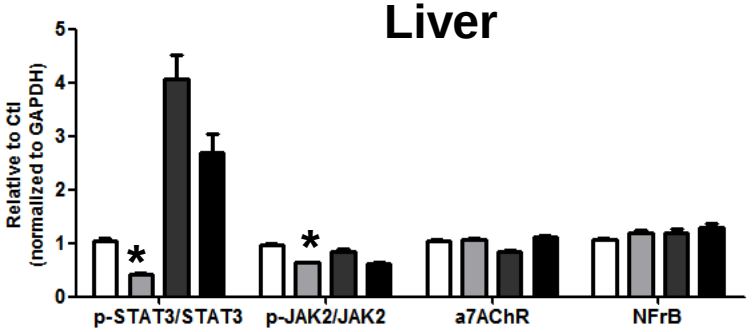
AHA 2016

Molecular mechanisms of cholinergic control of inflammation.



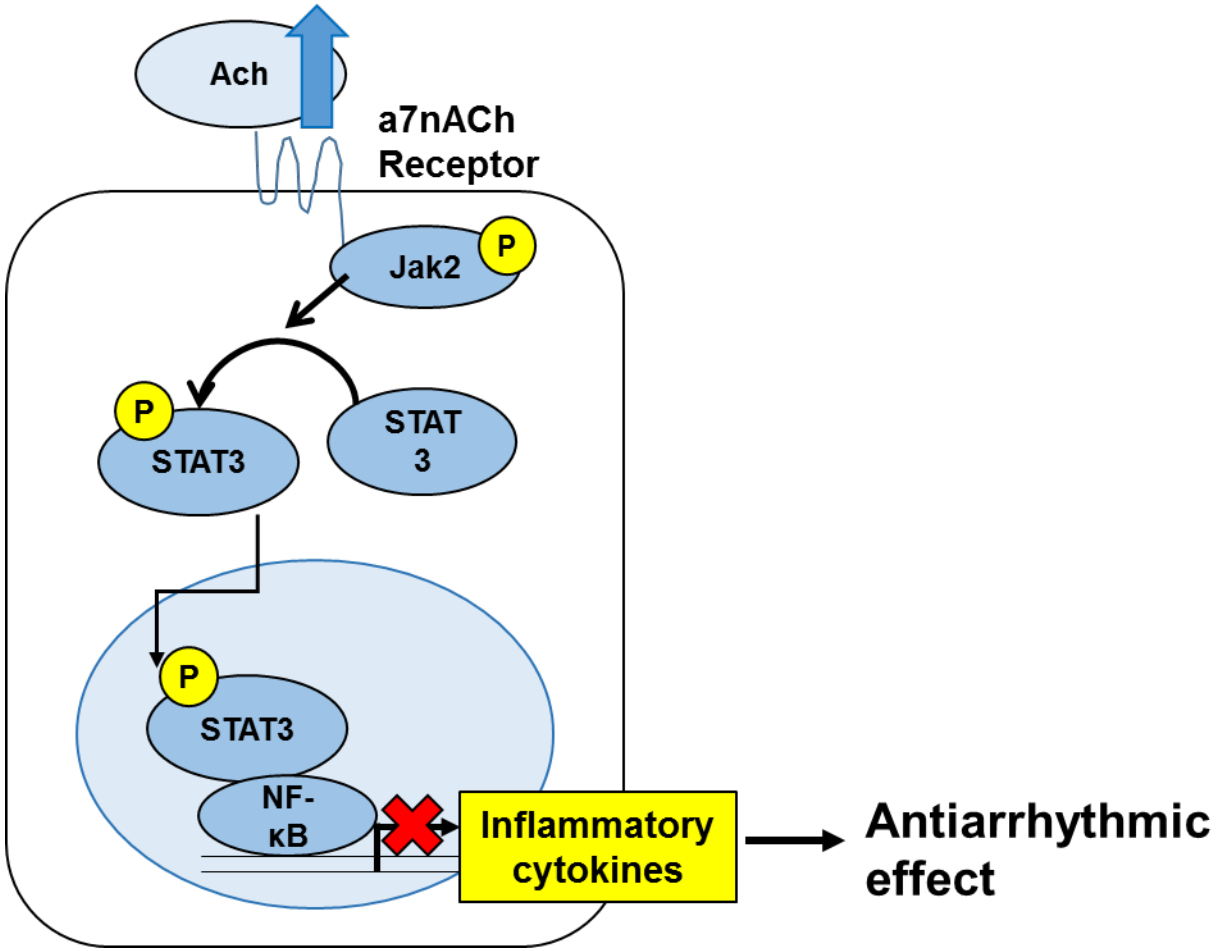






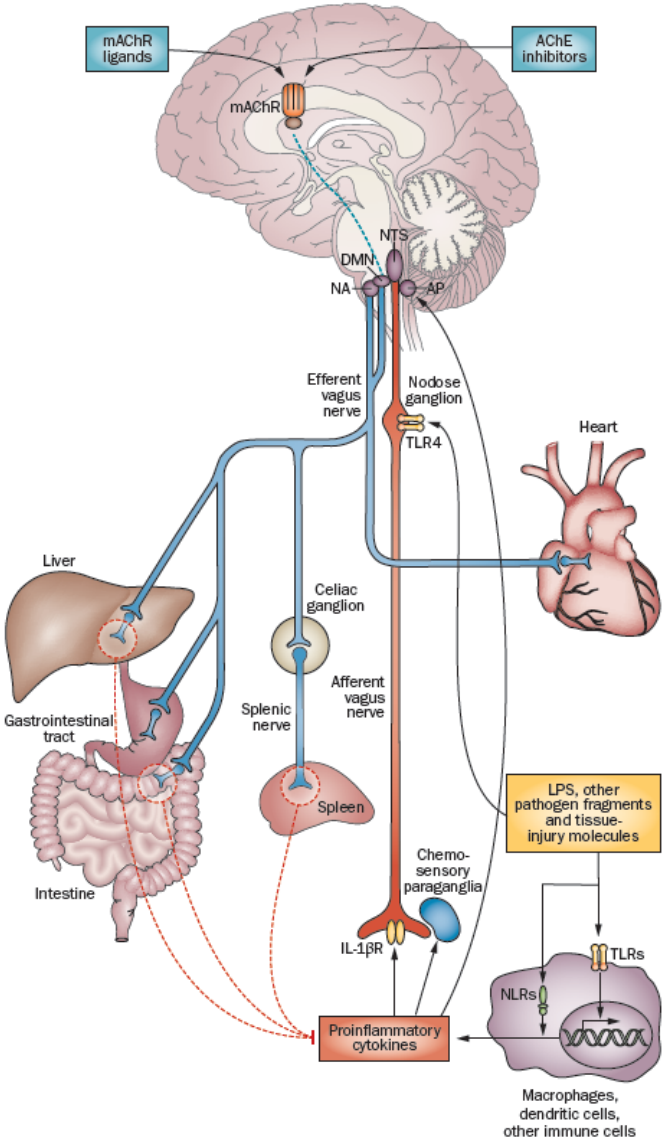
AHA 2016

Mechanism



AHA 2016

Immune-to-brain Communication



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Take-Home Message

- 부정맥은 autonomic nerve의 활성과 밀접한 관련을 가지고 있다.
- Autonomic nerve의 조절은 부정맥 치료에 중요한 modality이다.
- 자율 신경계 조절에 의한 치료 효과에 대하여는 많은 연구가 필요하다.

Thank you for your attention!