# Is Renal Denervation Antiarrhythmic?

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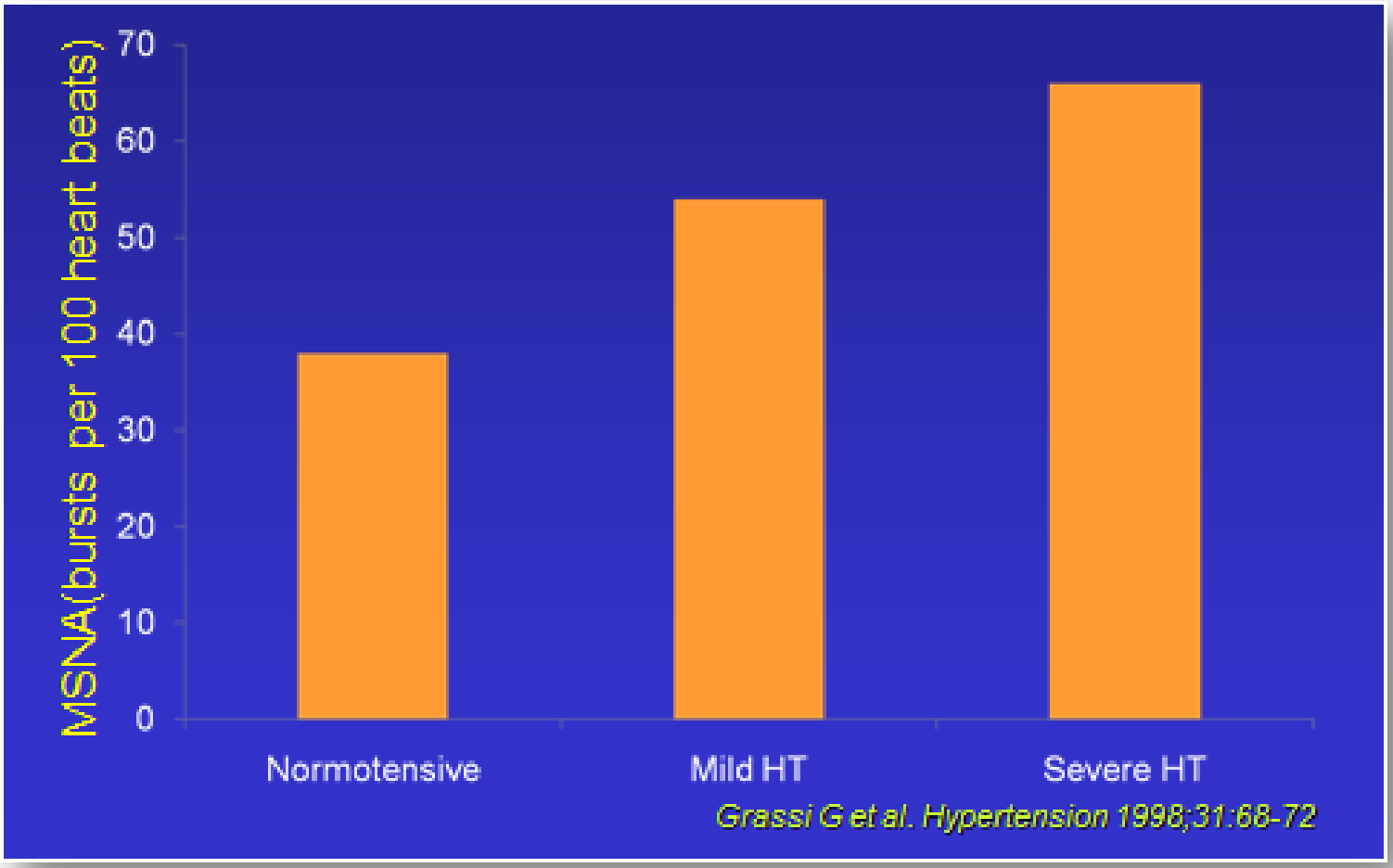
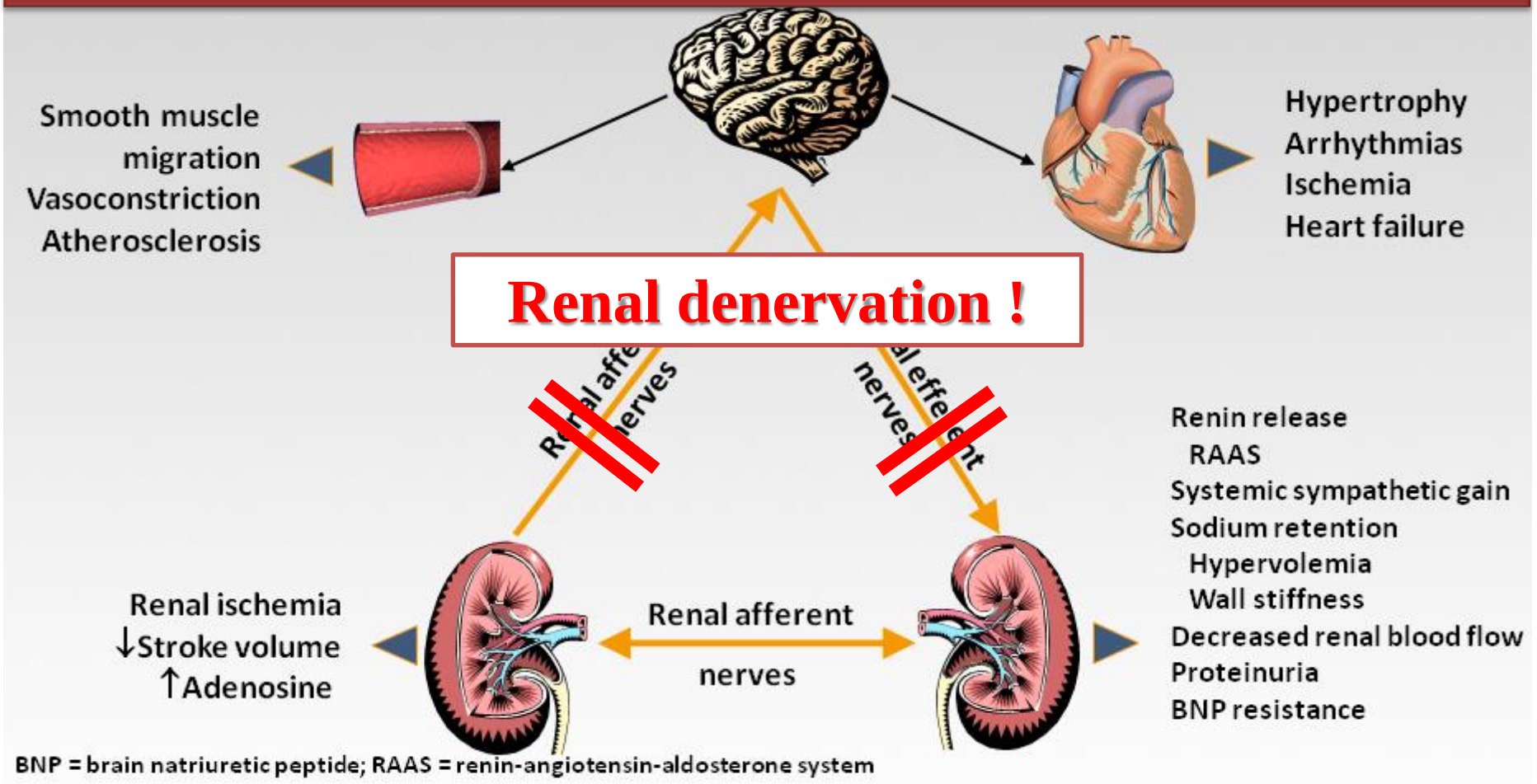
**Yonsei University College of Medicine**

# Relationship between *Sympathetic activity* and *Severity of hypertension*



# Renal Denervation in resistant HTN

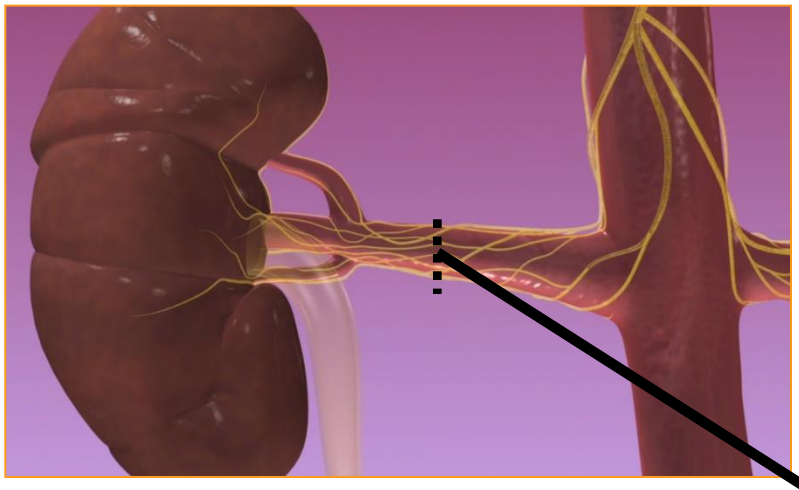
"Sympathetic deactivation by RDN" could be significantly related with
- → *marked decrease of BP ↓↓*
- → *improvement of associated worse milieu*

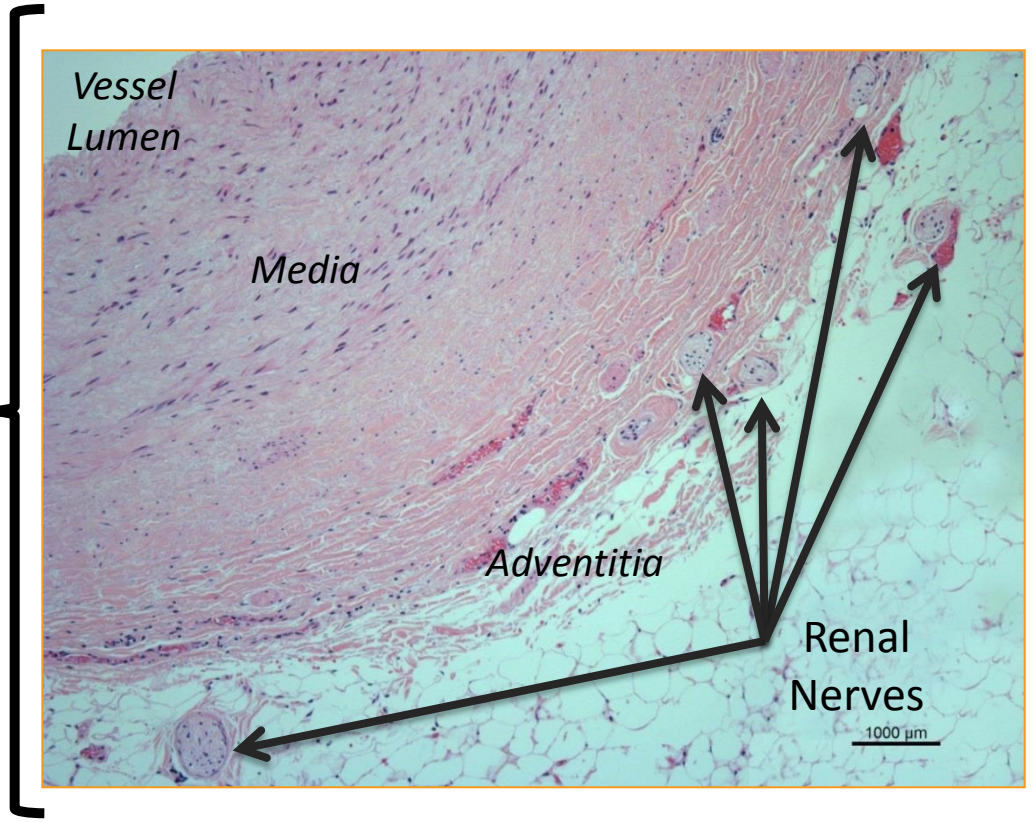





*Krum H, et al. Circulation 2011;123:209-215*

# Renal Anatomy allowing Catheter-Based Approach

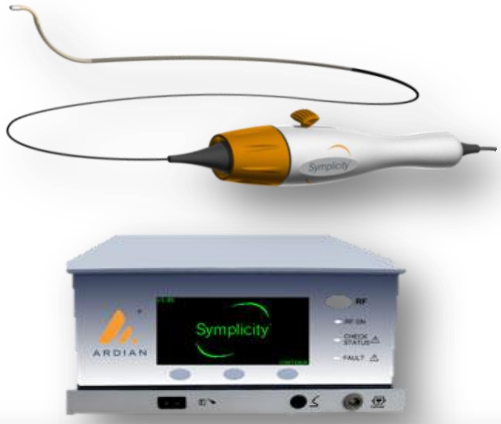


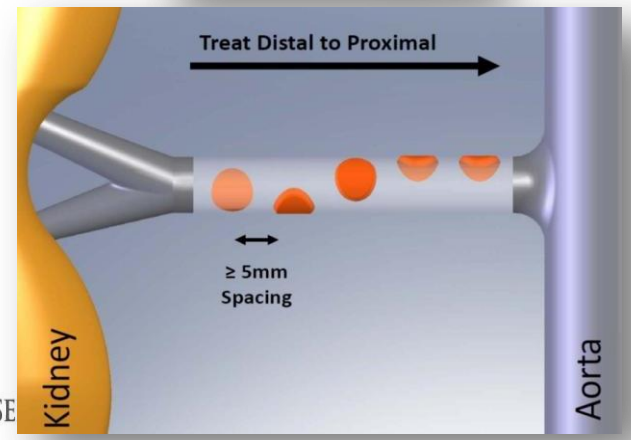


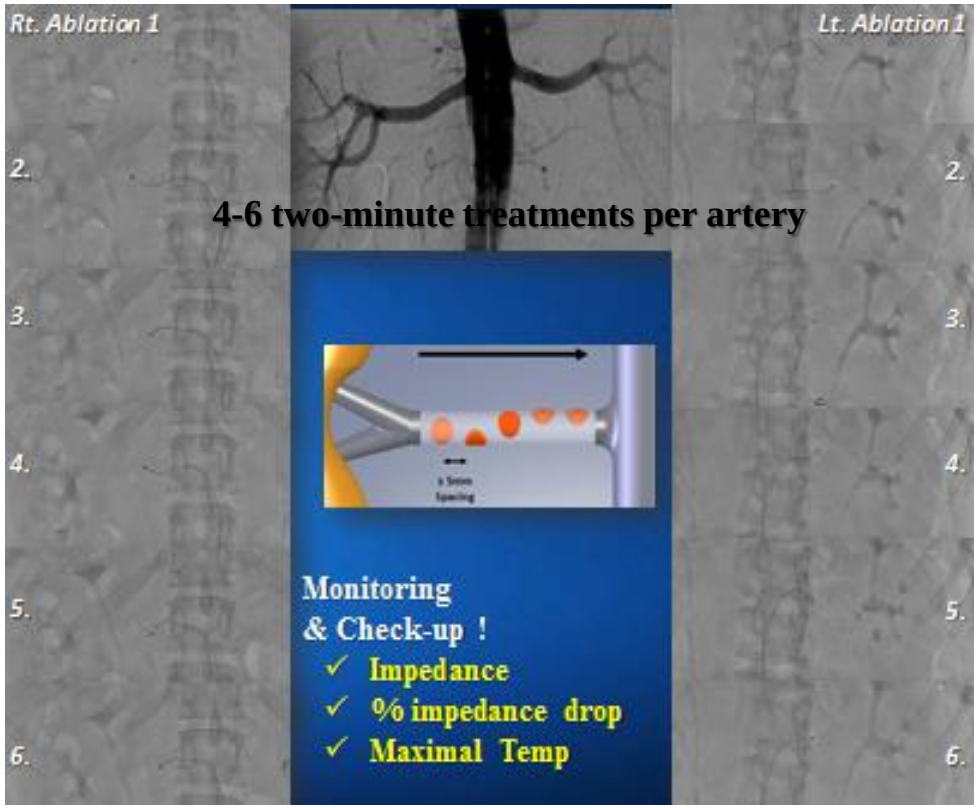

**Arise from T10-L2**
**Primarily lie within the adventitia**
**The only location that renal efferent & afferent nerves travel together**

# Catheter-based renal denervation for resistant hypertension

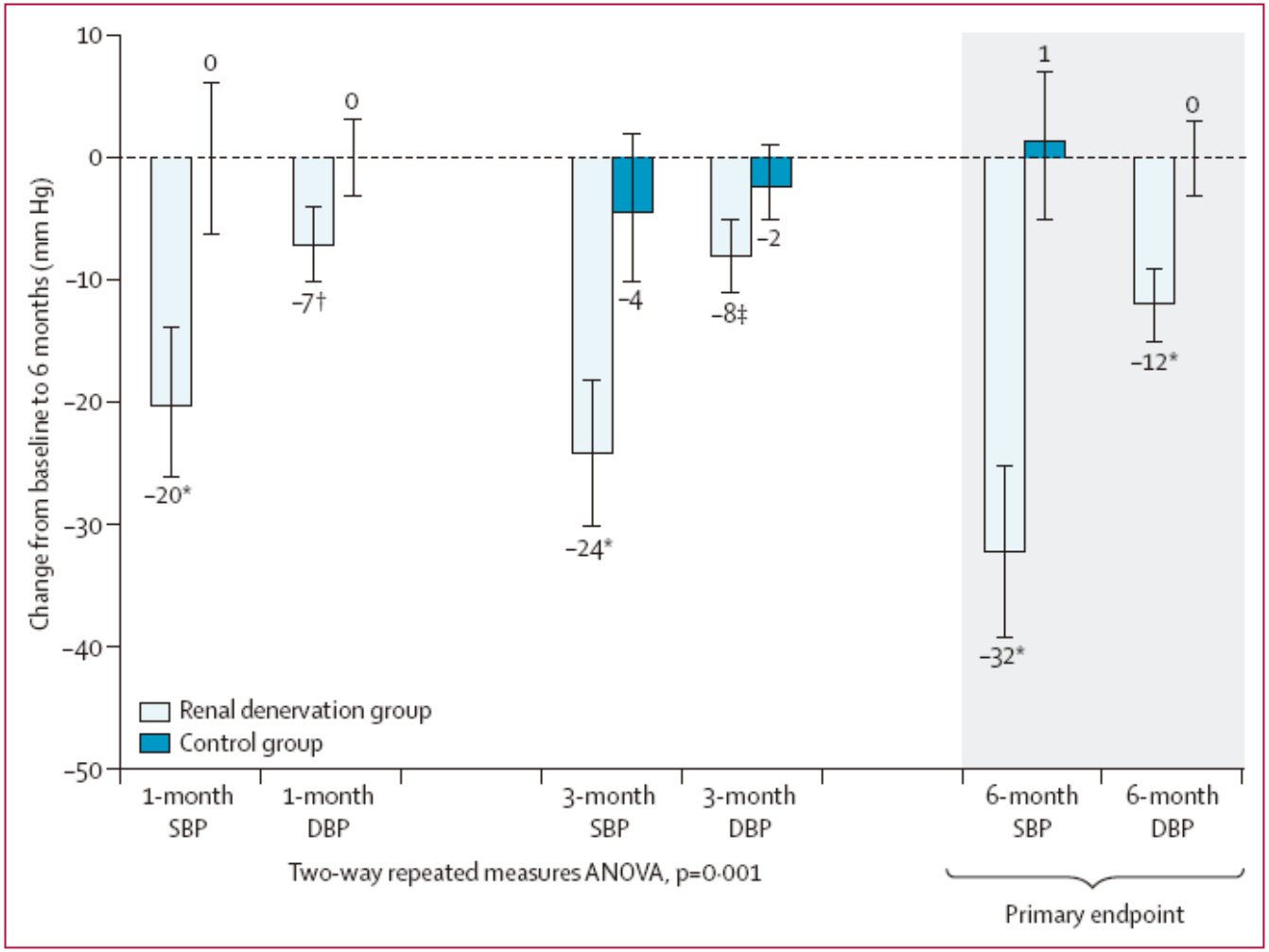
# Symplicity® Catheter System™; 1st proven RDN catheter through clinical trials



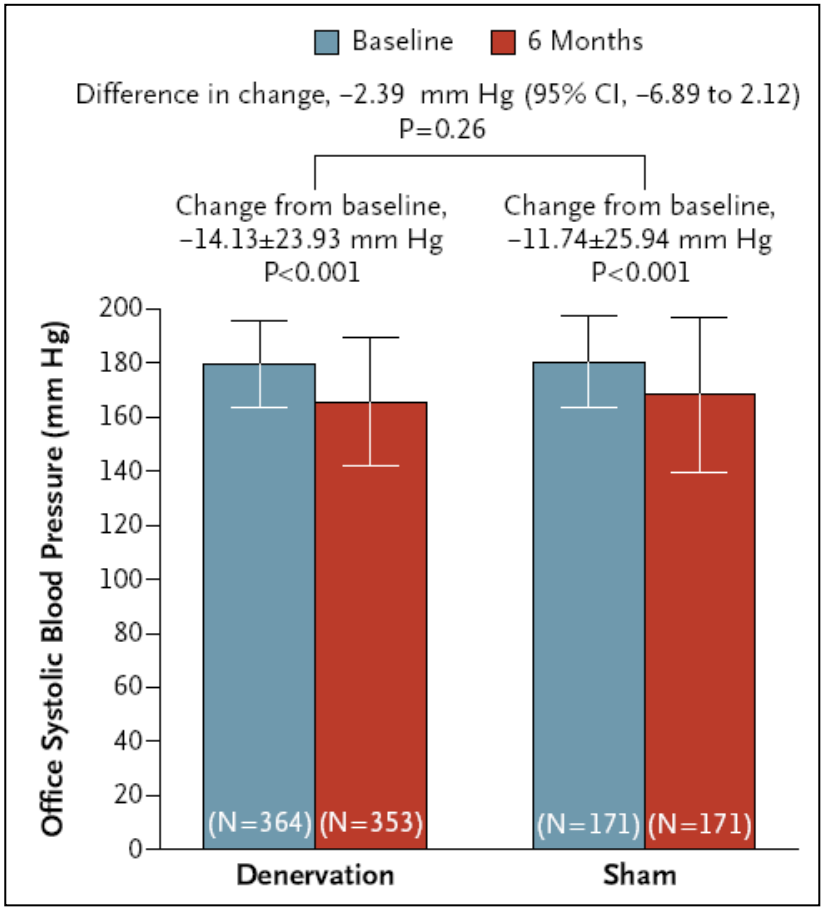
# Paired changes in office-based measurements of systolic and diastolic blood pressures

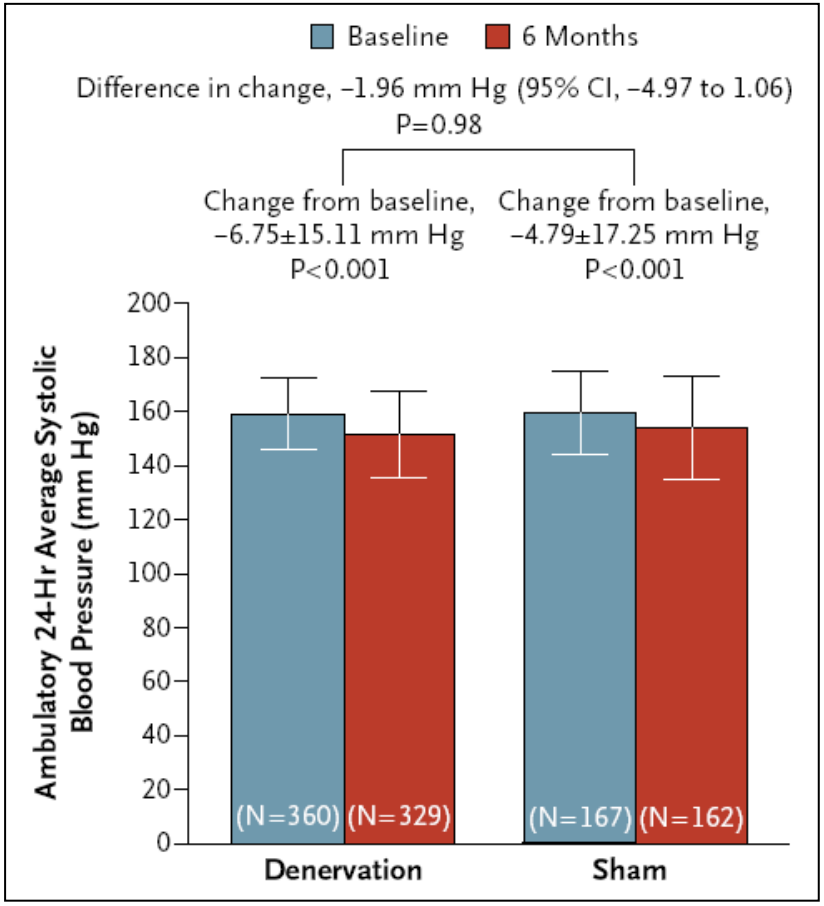





**The Symplicity HTN-2 Trial. Lancet 2010; 376: 1903–09**

# A Controlled Trial of Renal Denervation for Resistant Hypertension



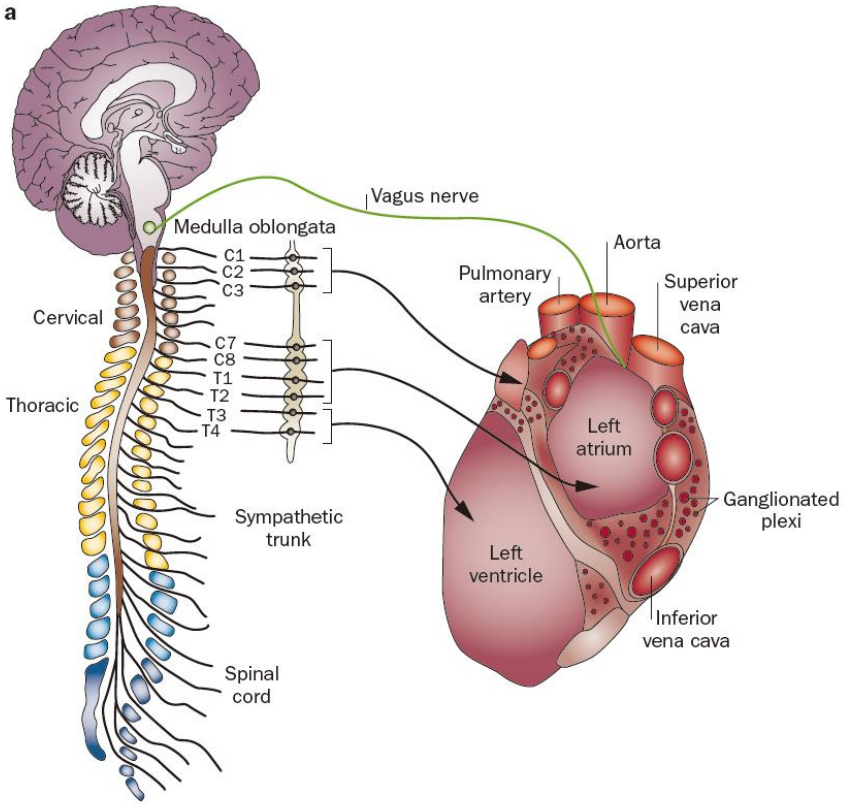



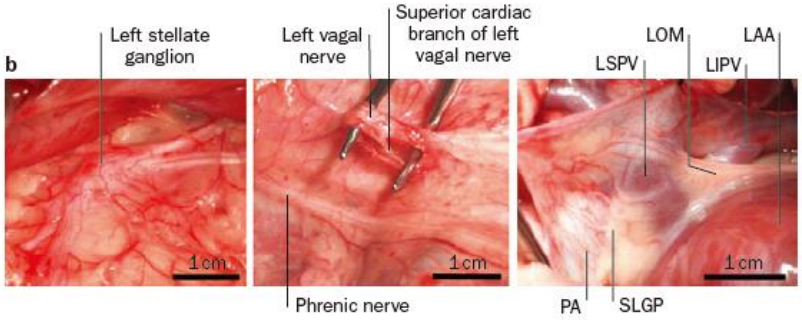


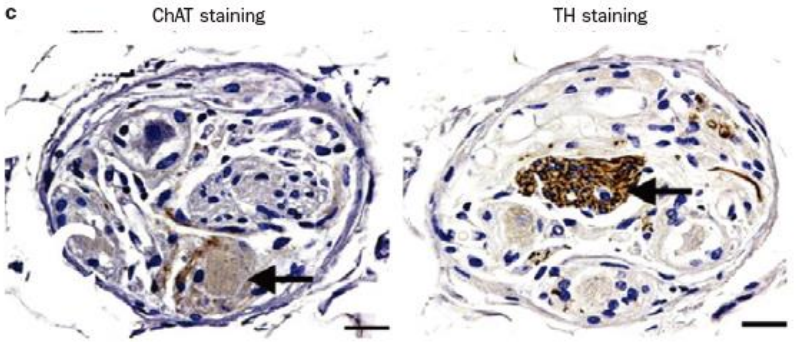

SYMPLICITY HTN-3, N Engl J Med 2014;370:1393-401

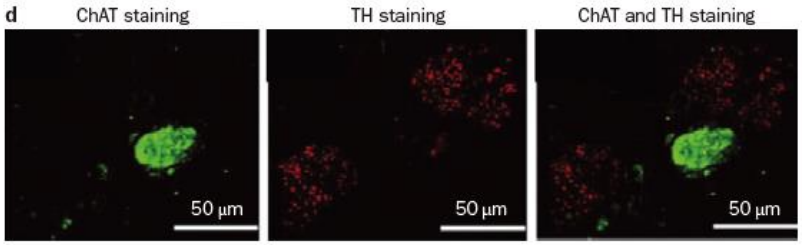
# Atrial fibrillation & Renal denervation

# Autonomic innervation of the heart



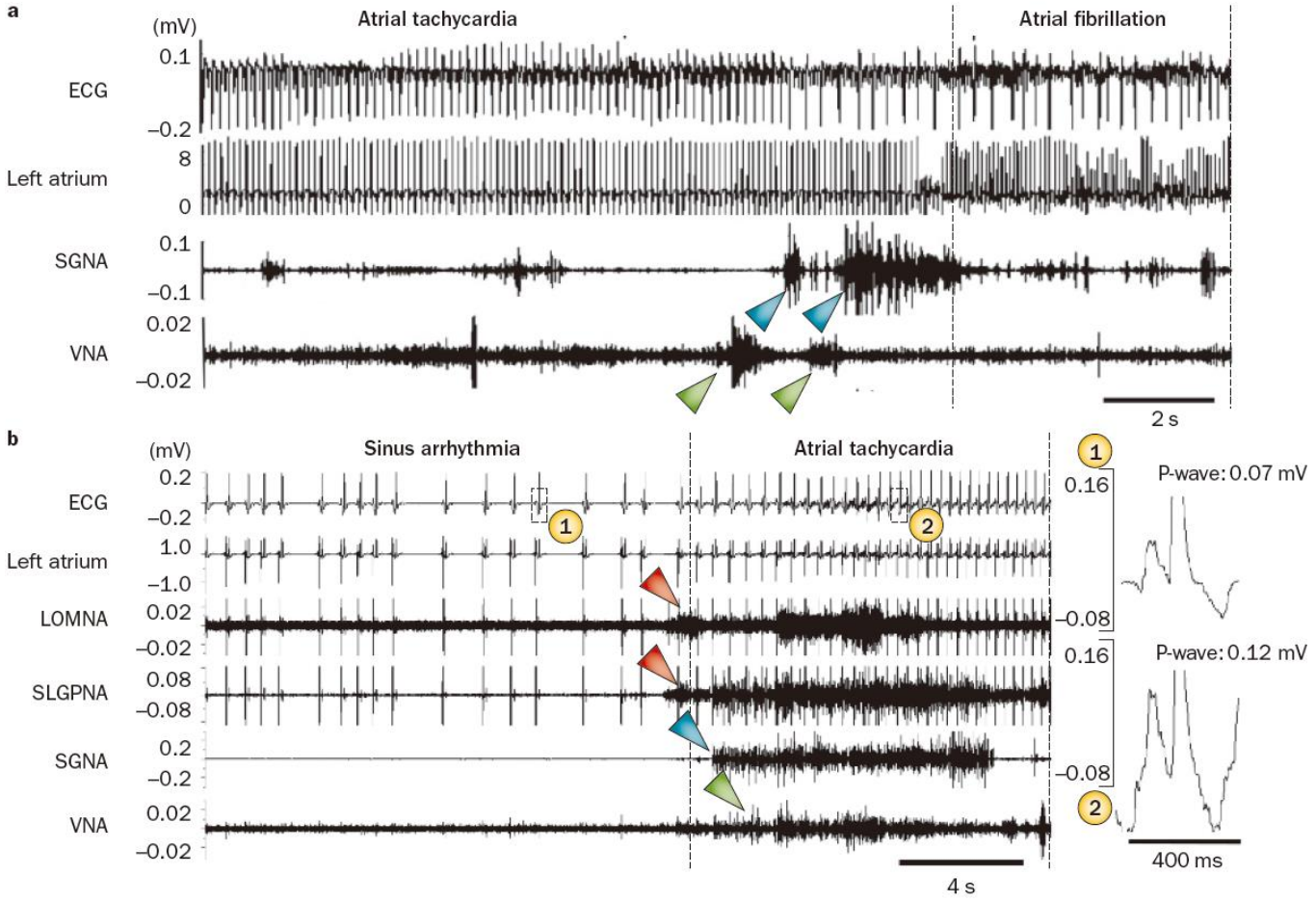






Tan, A. Y. et al. Circulation, 2008;118:918–925
Choi, E. K. et al. Circulation 2010;121:2615–2623

# The autonomic nervous system and paroxysmal atrial tachyarrhythmias

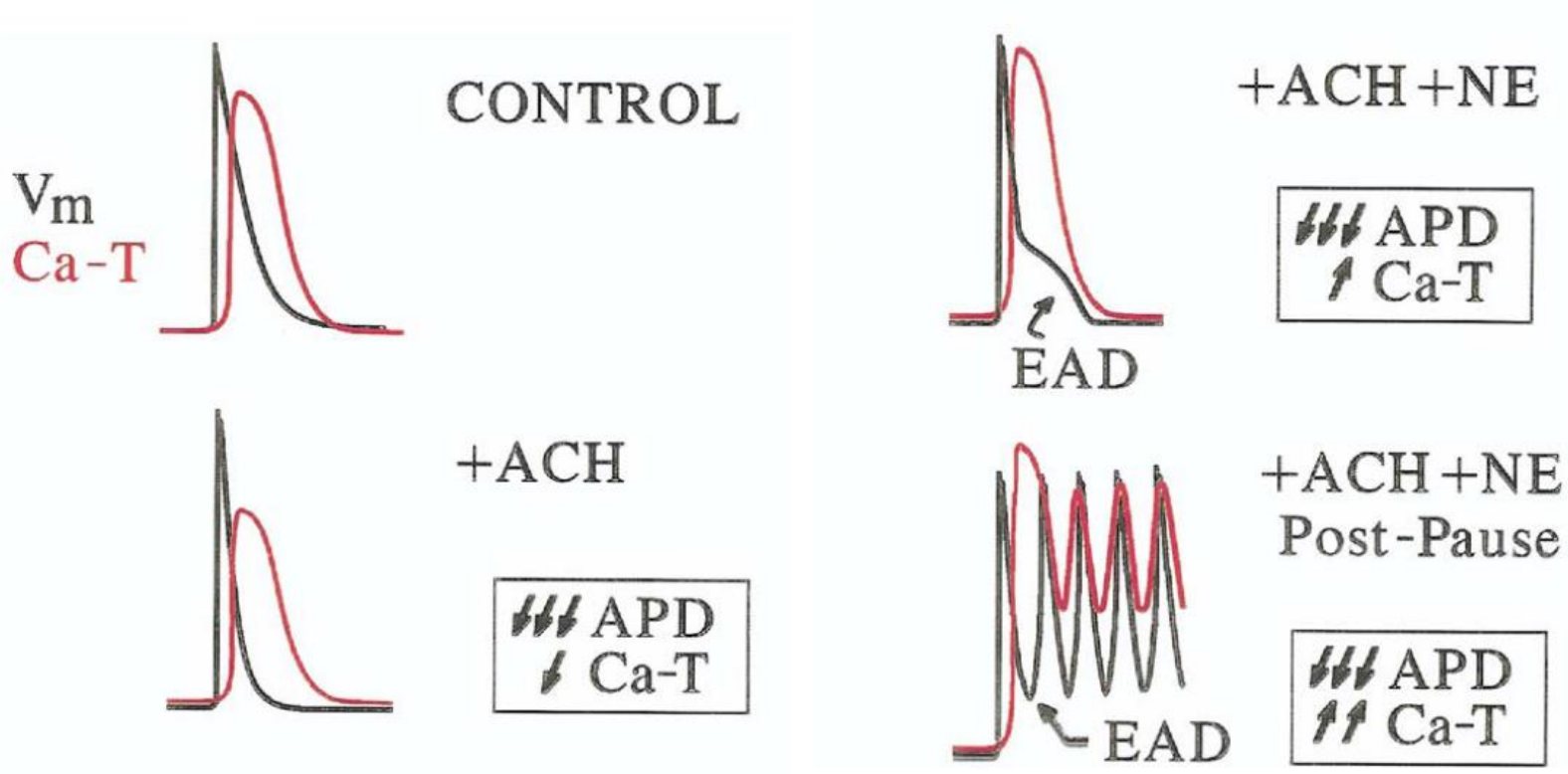





Tan, A. Y. et al. Circulation, 2008;118:918–925
Choi, E. K. et al. Circulation 2010;121:2615–2623

# Sodium-Calcium Exchange Initiated by the $Ca^{2+}$ Transient

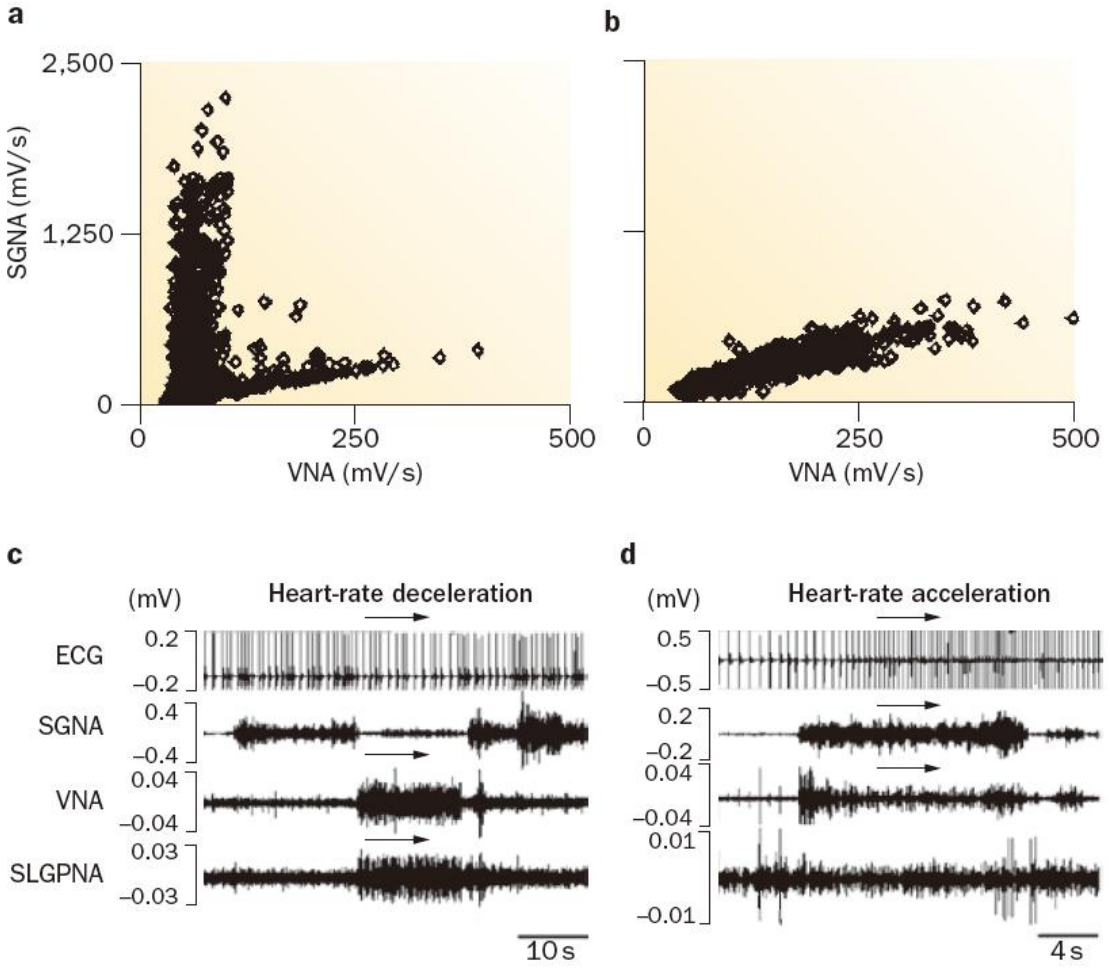
## :An Arrhythmia Trigger Within Pulmonary Veins






Patterson E, et al. J Am Coll Cardiol 2006;47:1196–206

# ANS and persistent atrial fibrillation

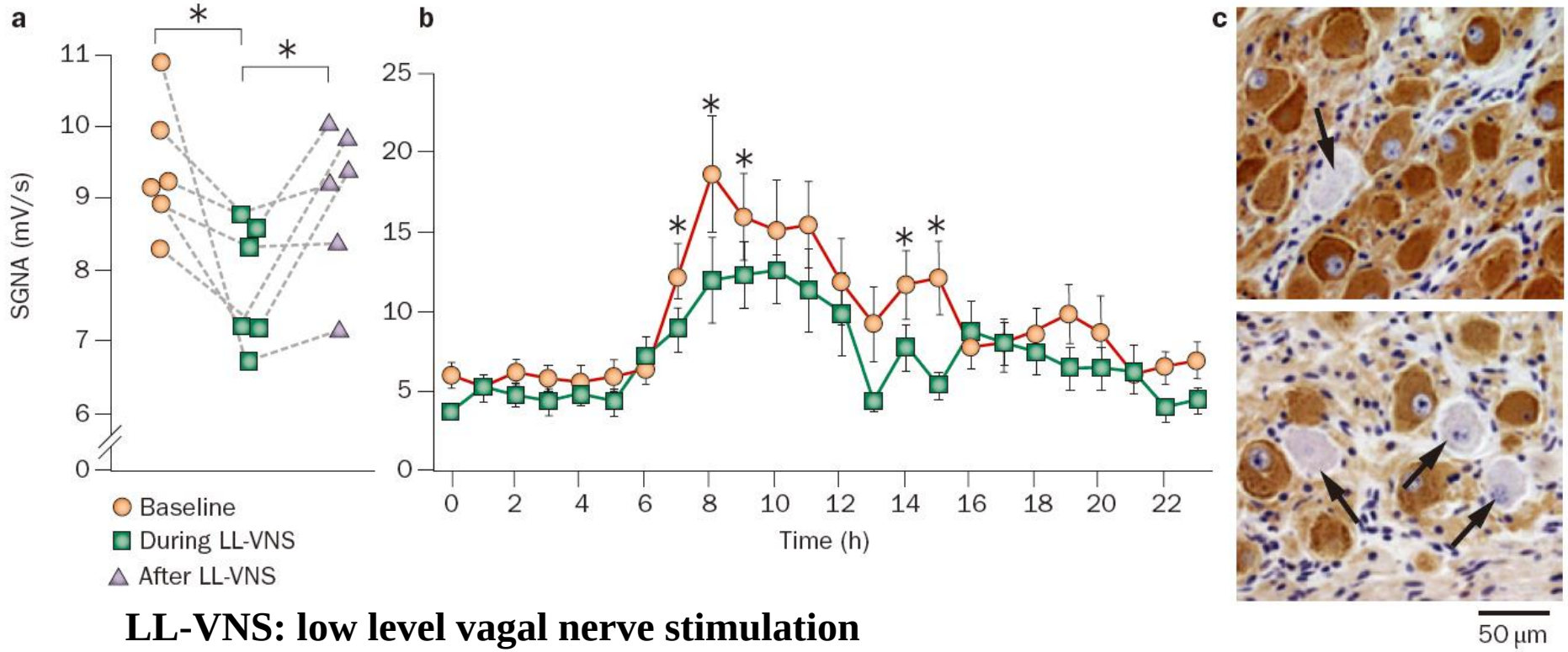





Shen M, et al. Heart Rhythm 2011;8:583–589

# LL-VNS and nerve activity of the left stellate ganglion

**TH immunostaining of left stellate ganglion**




**LL-VNS: low level vagal nerve stimulation**
**SGNA: stellate ganglion nerve activity**



**Shen et al. Circulation 2011;123, 2204–2212**

# Nerve Sprouting and Sympathetic Hyperinnervation in a Canine Model of Atrial Fibrillation Produced by Prolonged Right Atrial Pacing

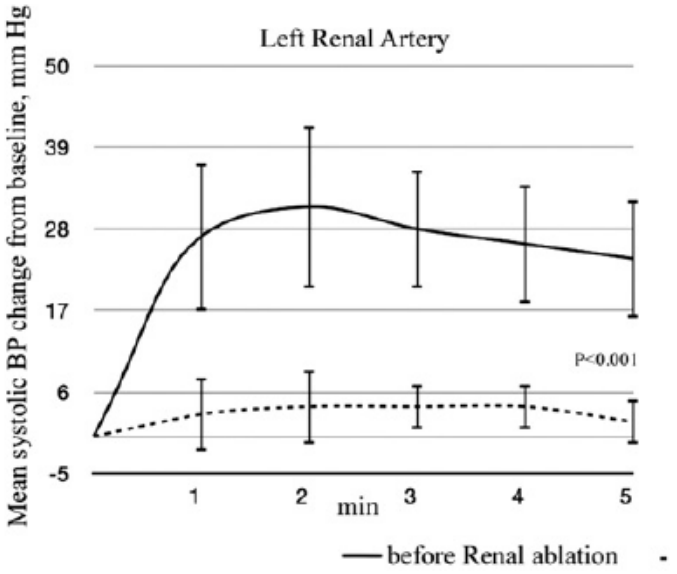
Che-Ming Chang, MD; Tsu-Juey Wu, MD; Shengmei Zhou, MD; Rahul N. Doshi, MD; Moon-Hyoung Lee, MD; Toshihiko Ohara, MD; Michael C. Fishbein, MD; Hrayr S. Karagueuzian, PhD; Peng-Sheng Chen, MD; Lan S. Chen, MD

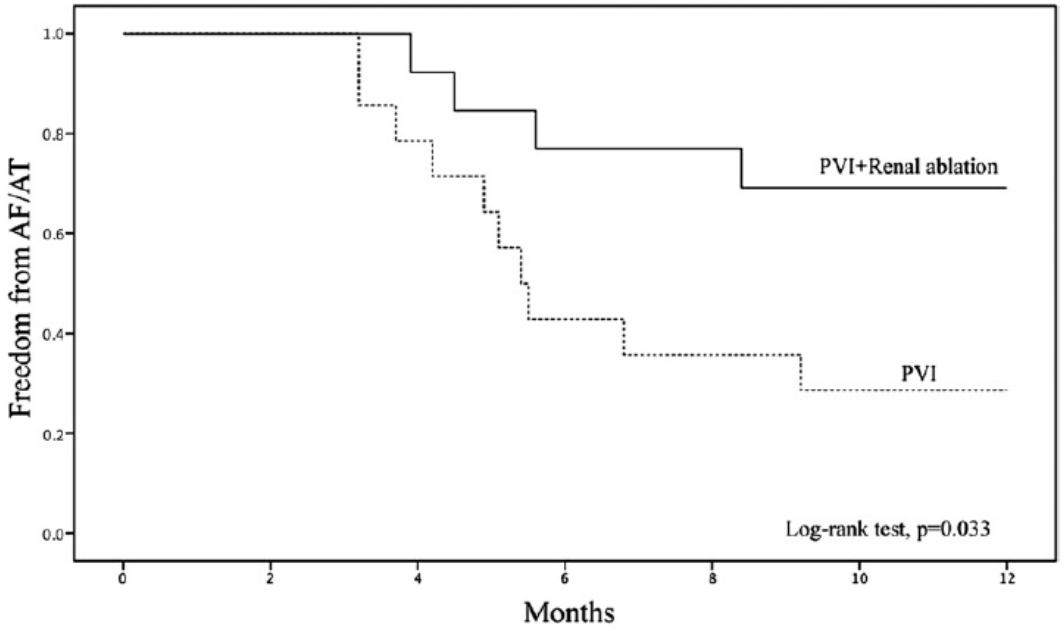
***Background***—Long-term rapid atrial pacing may result in atrial fibrillation (AF) in dogs. Whether there is histological evidence for neural remodeling is unclear.

***Method and Results***—We performed rapid right atrial pacing in 6 dogs for 111±76 days to induce sustained AF. Tissues from 6 healthy dogs were used as controls. Immunocytochemical staining of cardiac nerves was performed using anti–growth-associated protein 43 (GAP43) and anti–tyrosine hydroxylase (TH) antibodies. In dogs with AF, the density of GAP43-positive and TH-positive nerves in the right atrium was 470±406 and 231±126 per $mm^2$, respectively, which was significantly ($P<0.001$) higher than the nerve density in control tissues (25±32 and 88±40 per $mm^2$, respectively). The density of GAP43-positive and TH-positive nerves in the atrial septum was 317±36 and 155±85 per $mm^2$, respectively, and was significantly ($P<0.001$) higher than the nerve density in control tissues (9±13 and 30±7 per $mm^2$, respectively). Similarly, the density of GAP43-positive and TH-positive nerves in the left atrium of dogs with AF was 119±61 and 91±40 per $mm^2$, respectively, which was significantly ($P<0.001$) higher than the nerve density in control tissues (10±15 and 38±39 per $mm^2$, respectively). Furthermore, in dogs with AF, the right atrium had a significantly higher nerve density than the left atrium. Microscopic examinations revealed an inhomogeneous distribution of cardiac nerves within each sampling site.

***Conclusions***—Significant nerve sprouting and sympathetic hyperinnervation are present in a canine model of sustained AF produced by prolonged right atrial pacing. The magnitude of nerve sprouting and hyperinnervation was higher in the right atrium than in the left atrium. **(*Circulation.* 2001;103:22-25.)**

# Renal Denervation and AF




**Twenty-seven patients were enrolled, and 14 were randomized to PVI only, and 13 were randomized to PVI with renal artery denervation.**



**Pokushalov E, et al. J Am Coll Cardiol 2012;60:1163–70**

# Ventricular arrhythmia & Renal denervation

YONSEI UNIVERSITY COLLEGE OF MEDICINE
SEVERANCE CARDIOVASCULAR HOSPITAL

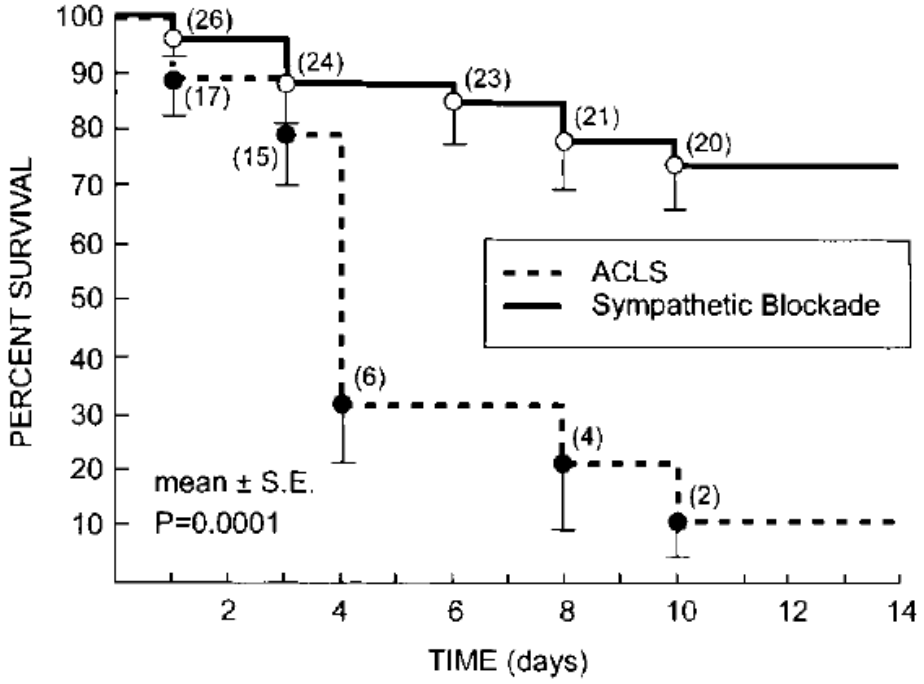
# Nerve Sprouting and Sudden Cardiac Death

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.)**

# Treating Electrical Storm

## Sympathetic blockade vs. ACLS therapy




**Sympathetic blockade treatment: (n=25)**

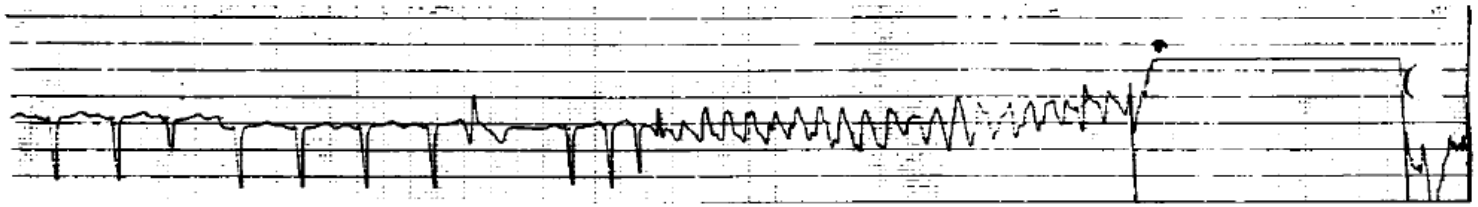
**6 left stellate ganglionic blockade,**

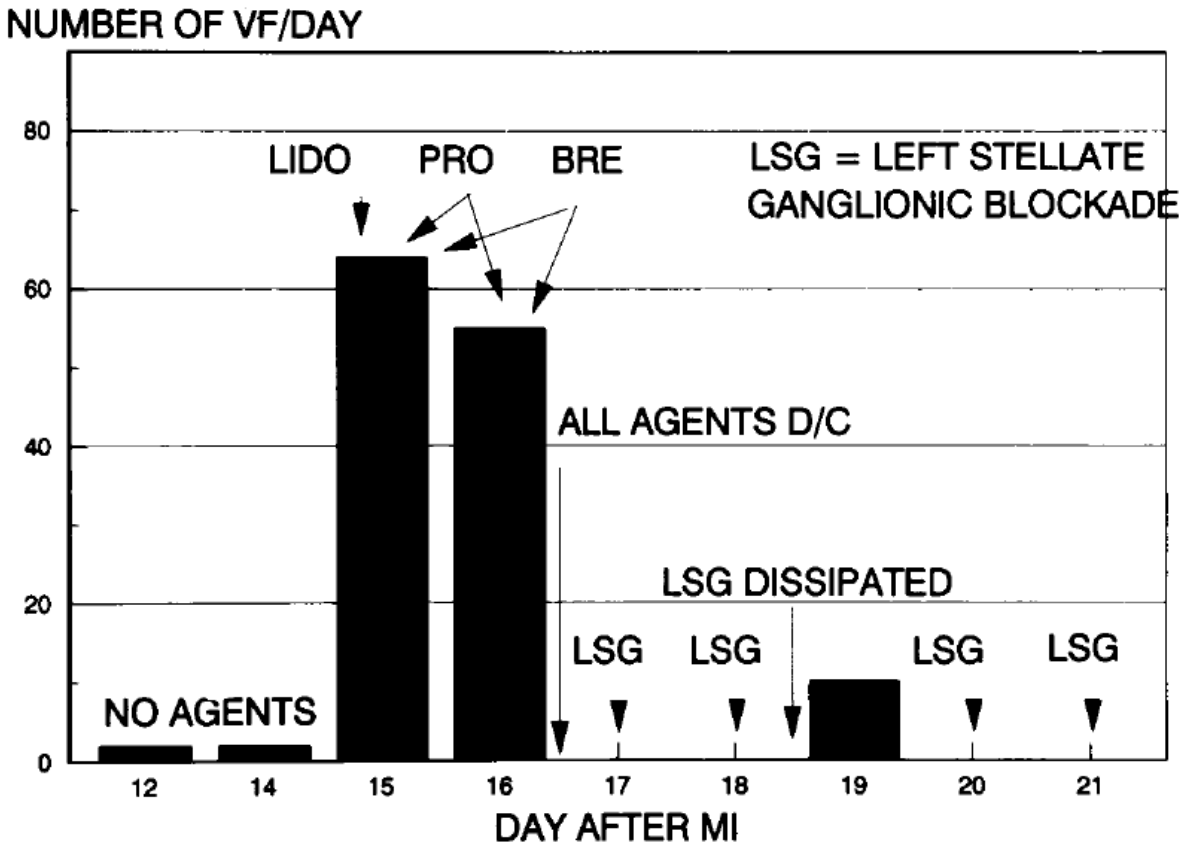
**7 esmolol,**

**14 propranolol**



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








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

# Neuraxial Modulation for Refractory Ventricular Arrhythmias

## Value of Thoracic Epidural Anesthesia and Surgical Left Cardiac

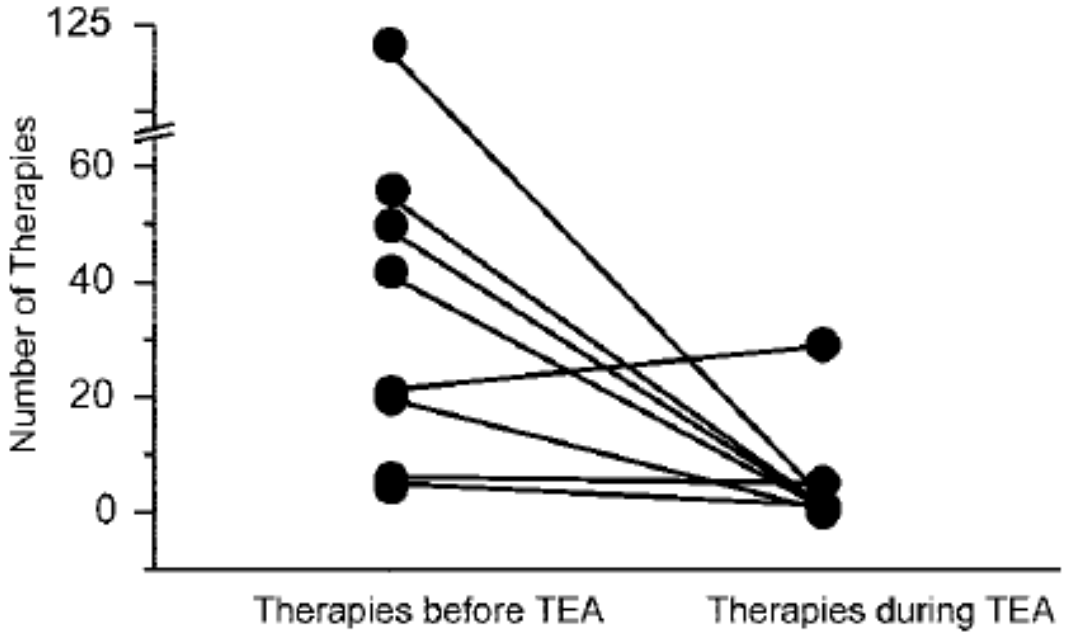



**Figure 2.** Effect of TEA. Line graph demonstrating number of VT therapies both before and during TEA infusion.

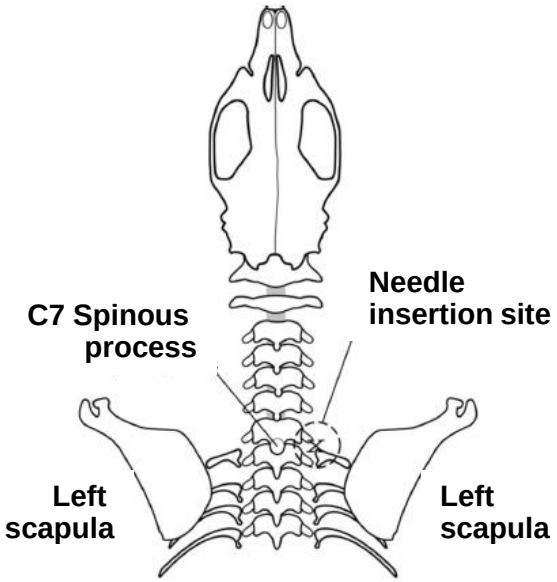

*Backgrou* hythmias. The purpos sympathetic denerv ase.

*Methods* 13 men) who underv and catheter ablatic ximal medical therap e ranged from 5 to 2( vent LCSD (3 patien patients had a large ( ither resolved within ients survived to hospital discharge (2 TEA alone, 3 TEA/LCSD combined, and 4 LCSD alone), 1 of the TEA alone patients underwent an urgent cardiac transplantation.

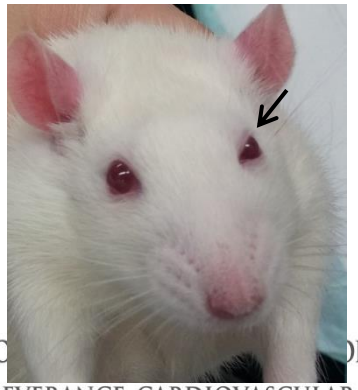
*Conclusions*—Initiation of TEA and LCSD in patients with refractory VT was associated with a subsequent decrease in arrhythmia burden in 6 (75%) of 8 patients (68% confidence interval 51% to 91%) and 5 (56%) of 9 patients (68% confidence interval 34% to 75%), respectively. These data suggest that TEA and LCSD may be effective additions to the management of refractory ventricular arrhythmias in structural heart disease when other treatment modalities have failed or may serve as a bridge to more definitive therapy. (*Circulation*. **2010;121:2255-2262.**)

# Left Stellate Ganglion Block Suppress CaMKII activation and Arrhythmia in Autoimmune Myocarditis Model

A




B



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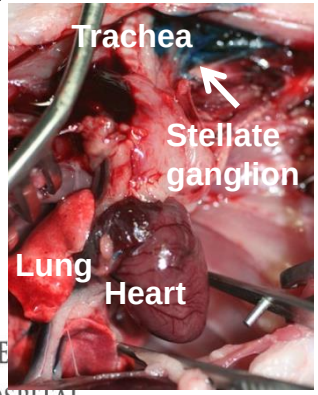
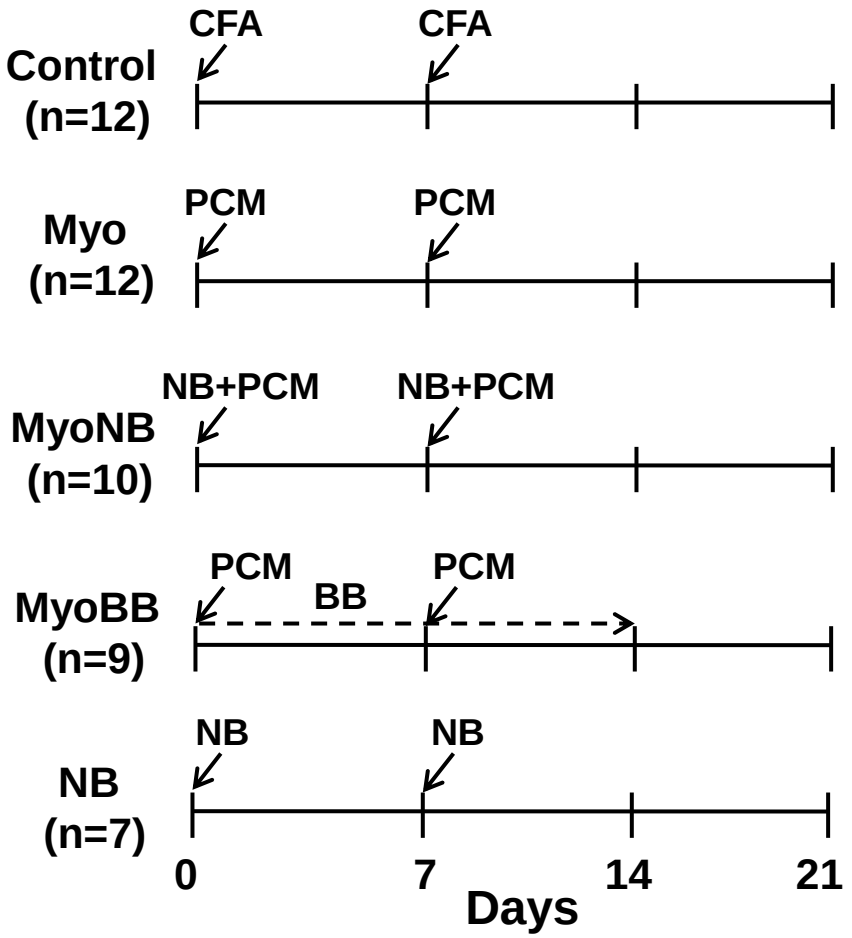
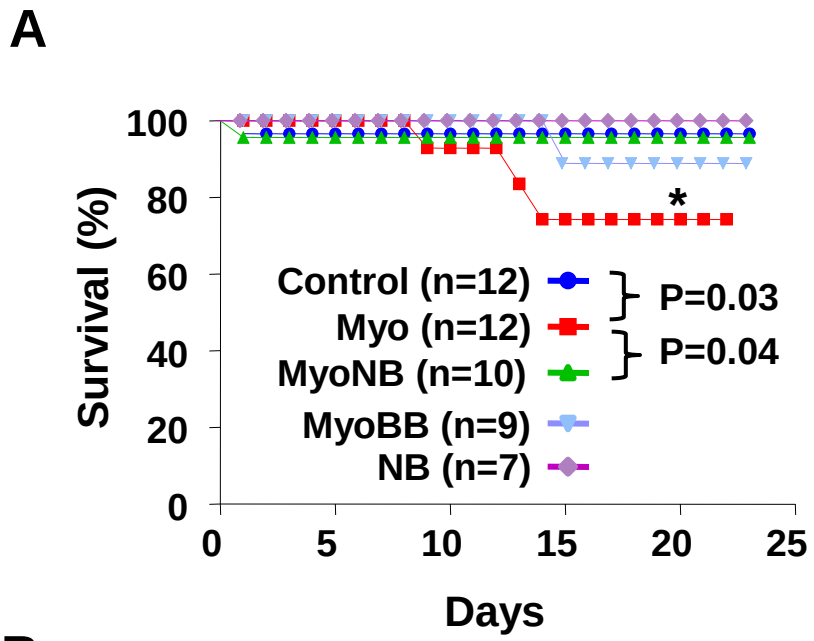


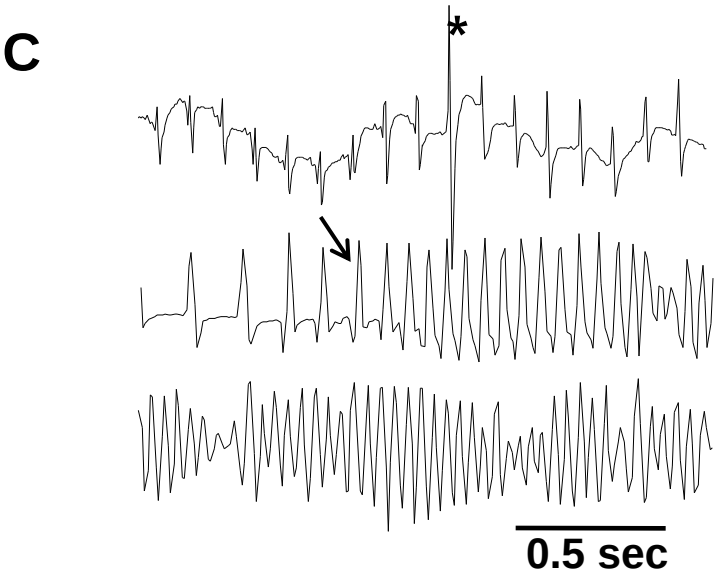

D

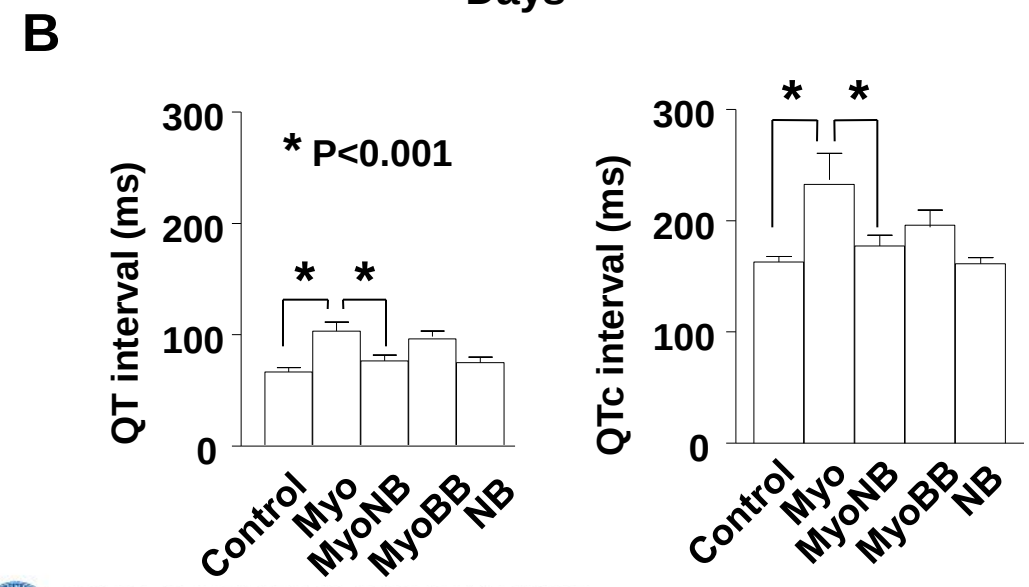


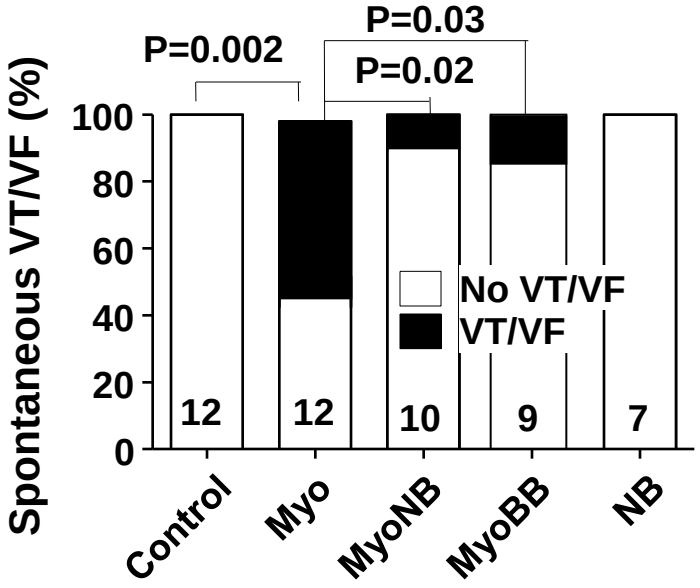

Park H, et al. APHRS 2013

# Figure 3






Park H, et al. APHRS 2013

# Carvediolol Reduced Arrhythmia

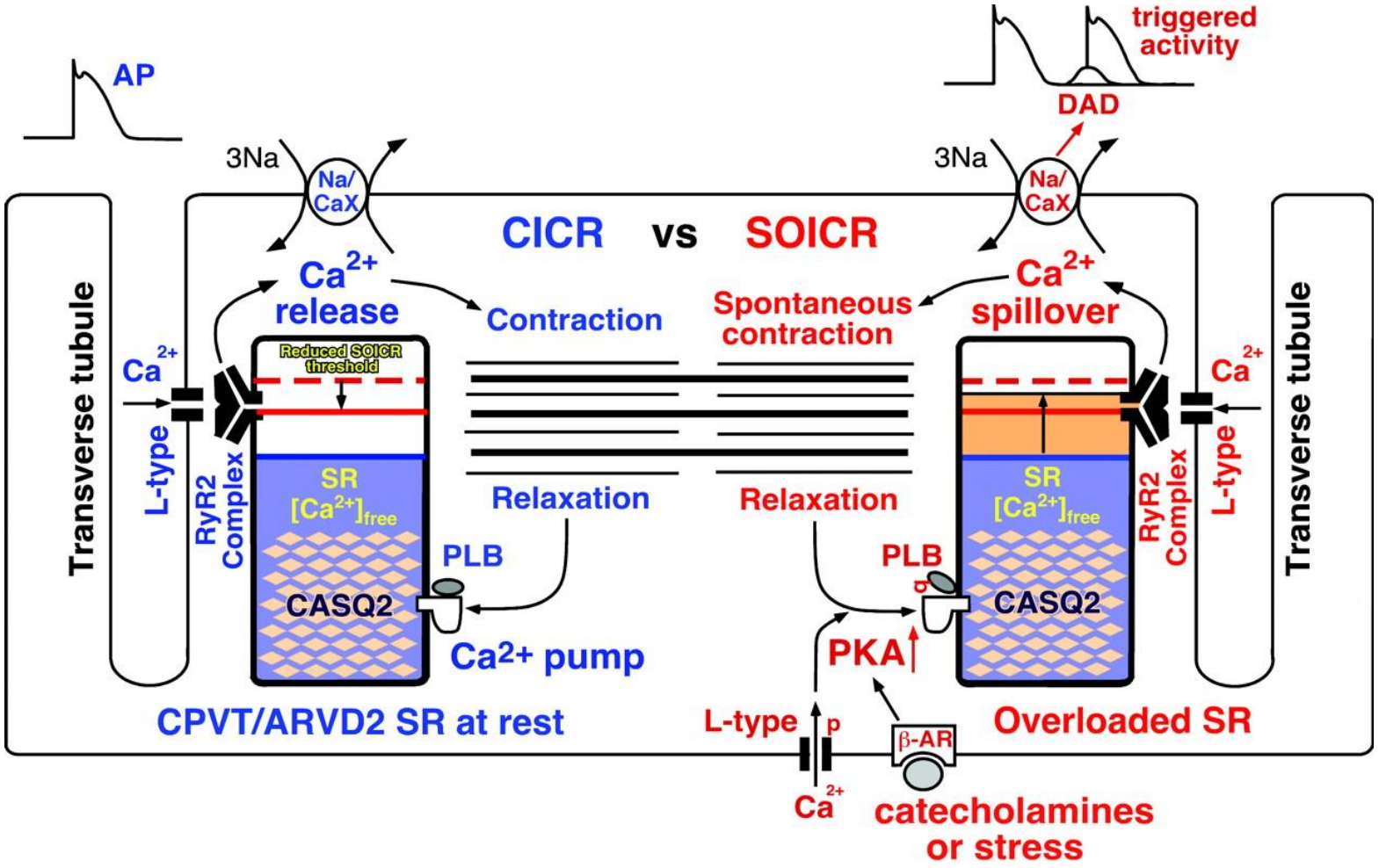
| Outcome | Subjects With Event Carvedilol (n = 975)/ Placebo (n = 984) | Carvedilol/Placebo Hazard Ratio (95% CI) | Log-Rank p Value |
|---|---|---|---|
| Death or SV arrhythmia | 133/187 | 0.70 (0.56, 0.88) | 0.0016 |
| Death or SV arrhythmia (excluding patients with a history of AF/AFL) | 112/152 | 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

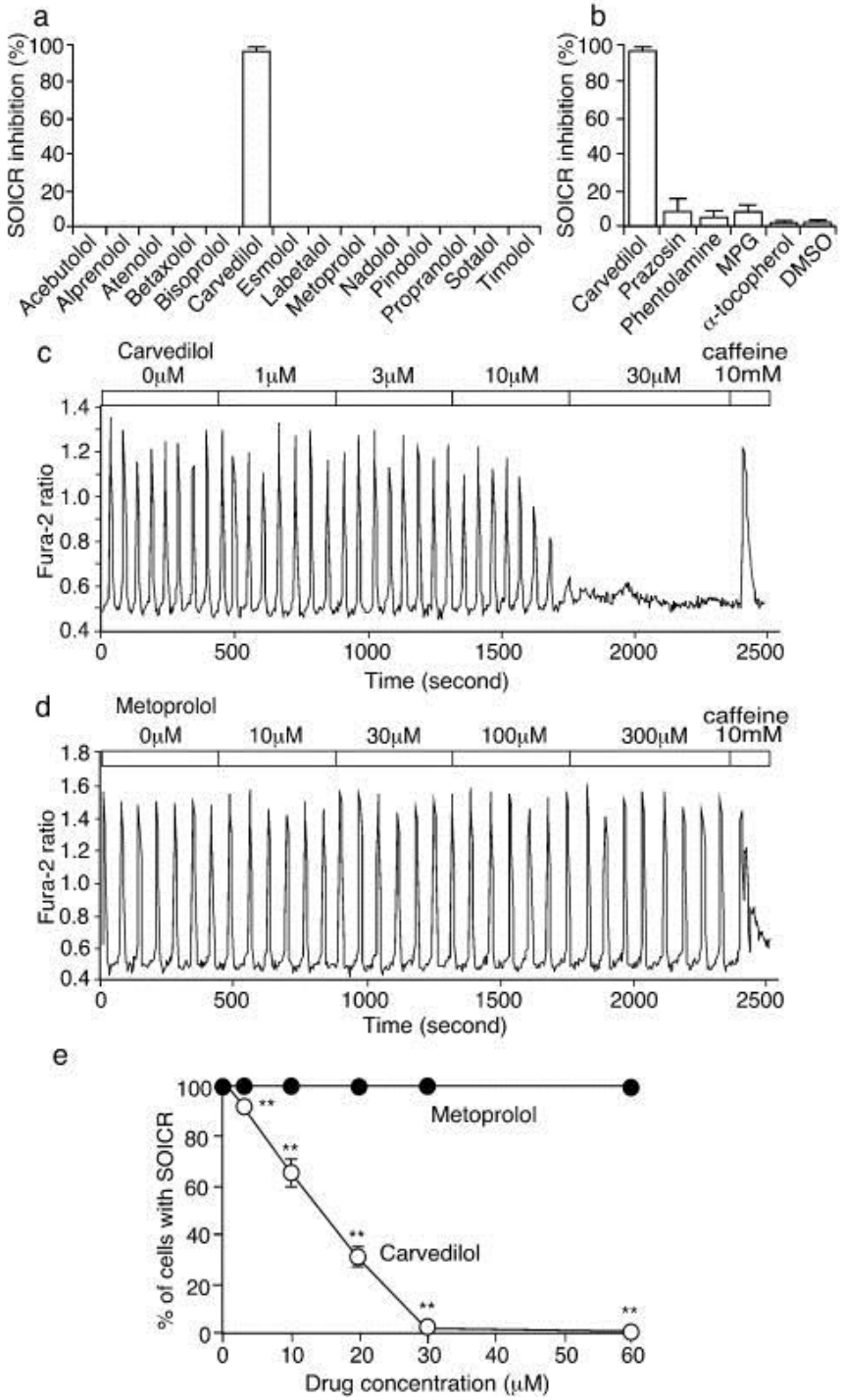
Qiang Zhou[1,2,8], Jianmin Xiao[1,8], Dawei Jiang[1], Ruiwu Wang[1], Kannan Vembaiyan[3], Aixia Wang[3], Chris D Smith[3], Cuihong Xie[1,2,8], Wenqian Chen[1], Jingqun Zhang[2], Xixi Tian[1], Peter P Jones[1,8], Xiaowei Zhong[1], Ang Guo[4], Haiyan Chen[2], Lin Zhang[1], Weizhong Zhu[5], Dongmei Yang[6], 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 inhibits SOICR in HEK293 cells




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

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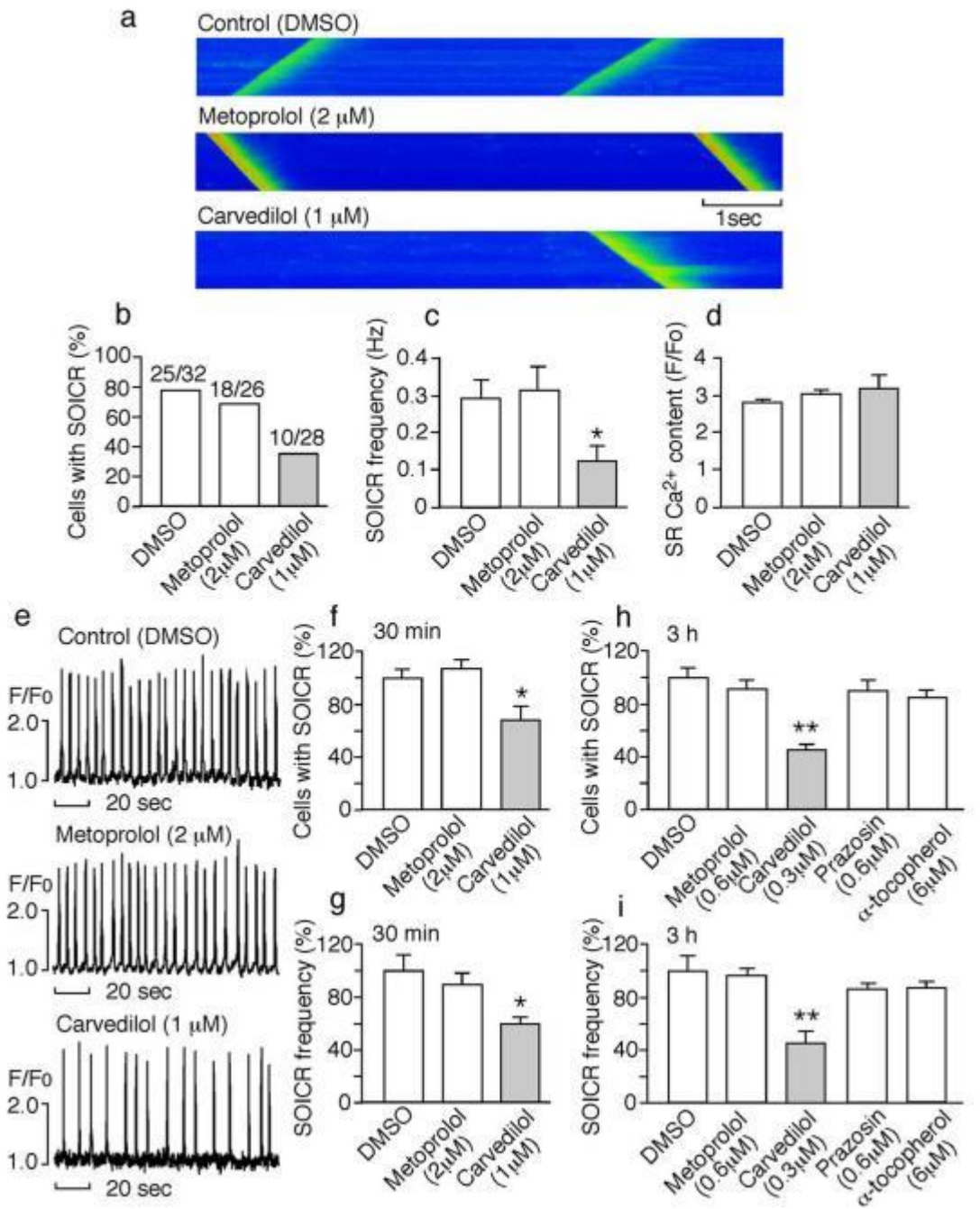
SEVERANCE CARDIOVASCULAR HOSPITAL

# Carvedilol suppresses SOICR in mouse ventricular myocytes




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

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

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**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.

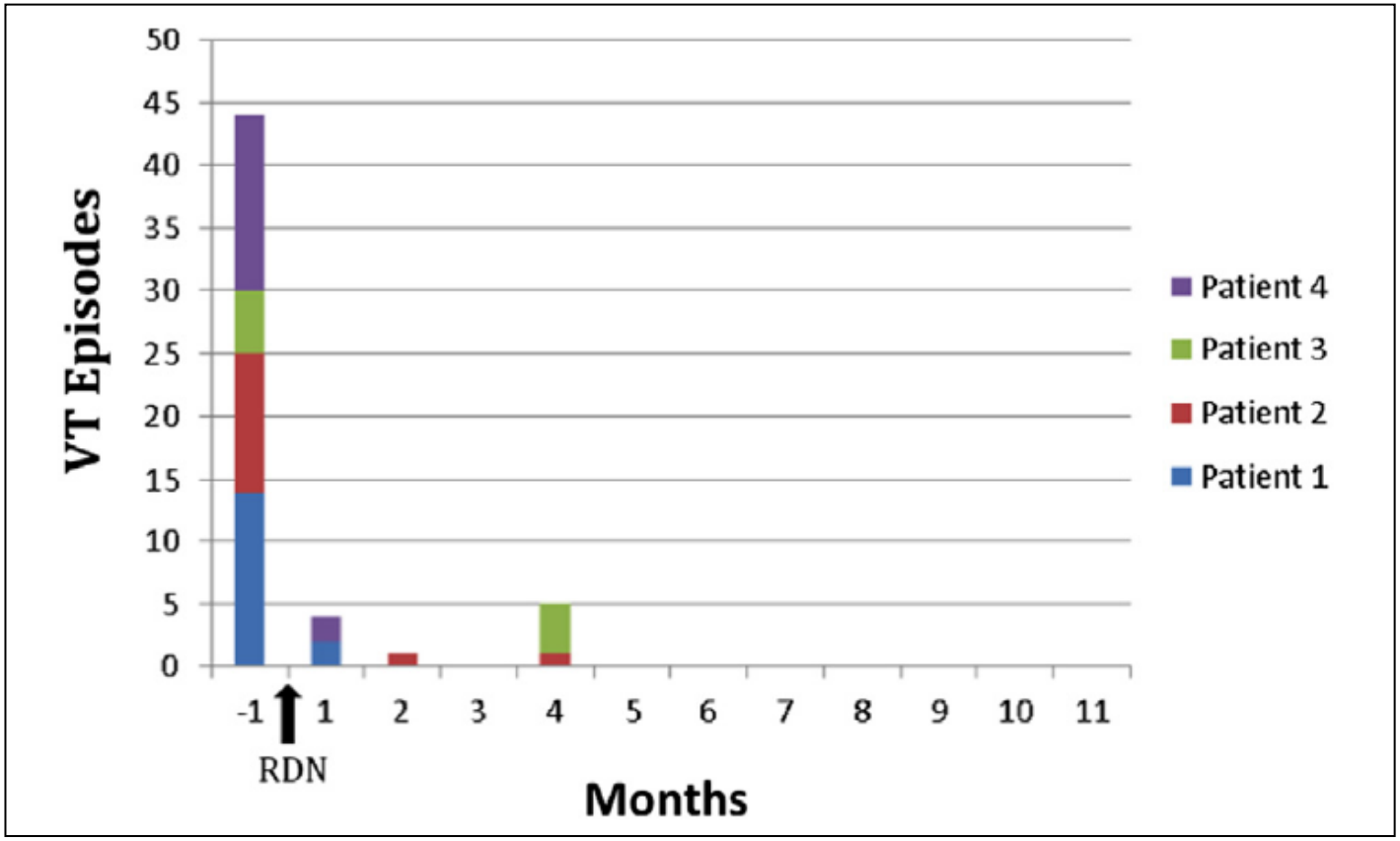
**RESULTS** RDN was well tolerated acutely and demonstrated no clinically significant complications during follow-up of 8.8 ± 2.6 months (range 5.0–11.0 months). No hemodynamic deterioration or worsening of renal function was observed. The number of VT episodes was decreased from 11.0 ± 4.2 (5.0–14.0) 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

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



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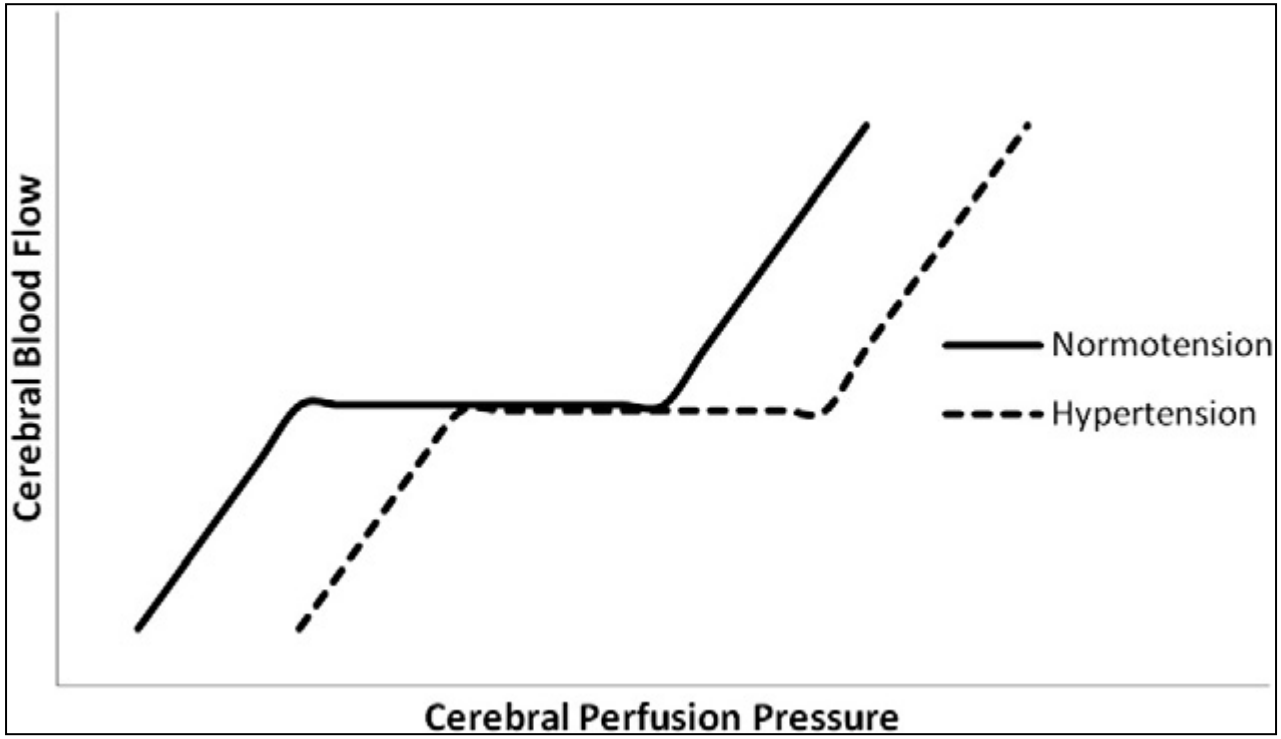
# Take-Home Message

- 부정맥은 autonomic nerve의 활성과 밀접한 관련을 가지고 있다.
- Autonomic nerve의 조절은 부정맥 치료에 중요한 modality이다.
- Renal denervation은 최근 AF, VT의 치료에 도움을 주는 것으로 보고 되었다. 하지만 치료 효과에 대하여는 많은 연구가 필요하다.

# There is a theoretical concern that attenuating the renal sympathetic nerves might cause orthostatic hypotension or syncope.



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# Thank you for your attention!