# DRAFT: THE SYMPATHETIC INNERVATION OF THE HEART

Title: The Sympathetic Innervation of the Heart – a Clinical Review

Authors: Anish Shah, MD; Amit Shah, MD, MSCR; Puja Mehta, MD; Marc Thames, MD

Affiliations: Emory University School of Medicine, Atlanta, Georgia

# 

# INTRODUCTION

The human sympathetic nervous system, the master and commander of the “fight or flight” response, has not adapted adequately to human disease. It is the culprit in multiple pathological states, particularly that of the heart. The sympathetic innervation of the heart is part of the connection between the brain and the heart and it is inherent to physiology and pathophysiology of cardiac autonomic function. The purpose of this review article is to teach clinicians the importance of the sympathetic nervous system in both normal and pathophysiological states, share how pathology stems from inappropriate responses by the autonomic nervous system, and to explore the anatomy and physiology of sympathetic outflow to the heart. The reader should be able to (1) understand the relevant anatomy of the sympathetic nervous system as it innervates the heart, (2) understand the effects of sympathetic tone on the heart, such as chronotropy, inotropy, lusitropy, and dromotropy, and (3) understand how sympathetic dysfunction plays a role in pathological states such as ventricular dysrhythmias, myocardial infarctions, and cardiomyopathies.

# ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

## Overview

The neural control of the heart is in part a product of its anatomy. The structure, sometimes described as the neurocardiac axis, has three distinct levels: the brain and spinal cord, the thoracic and extracardiac ganglia (EC), and the intrinsic cardiac nervous system (IC).1 These levels send information through afferent and efferent limbs of both the sympathetic and parasympathetic nervous systems, and at each level interactions occur that affect the autonomic state.

## Brain and spinal cord level

The spinal cord houses the preganglionic neurons of the SNS within the lateral horns at each vertebral level. Cardiac outflow occurs between the T1 and T6 vertebrae. The neurons exit through the ventral roots that merge into the white rami, which join the sympathetic chain and the ganglia of the EC. In contrast, the vagal preganglionic neurons are in the brain stem, mainly the medullary dorsolateral reticular formation. The thoracic spinal segments have a distinct cardiac rhythm and other frequencies of oscillation that are transmitted to the postganglionic neurons in the heart. The distinct periodicities include 10 Hz, 2-6 Hz, respiratory rates, and slower firing that matches the speed of arterial blood pressure oscillations (Mayer waves).2

Although there is some automaticity of the firing rate of the SNS neurons within the spinal cord, there are many higher orders of influence that affect the activity of the preganglionic cell bodies. For example, nervous activity such as a panic attack, can lead to increased autonomic outflow, but so can events liked traumatic brain injury that leads to hyperactivation and sympathetic storm. Other peripheral and systemic reflexes are also integrated at the level of the spinal cord, such as vasovagal syncope, the mesenteric ganglia response to stress (lumbosacral outflow).

## Thoracic, extracardiac level

The thoracic ganglia that make up the EC contain neurons that directly innervate the myocardium. Both afferent and efferent pathways are present. The most well-studied is of course the stellate ganglia, which carries both preganglionic fibers and postganglionic neurons to the heart. The right stellate ganglia (RSG) and the left stellate ganglia (LSG) are seen to have differences in function based on the location of their nerve endings. Of the ventricles, the RSG is directed towards the anterior and basal aspects, while the LSG is directed towards the posterior and apical aspects. Both ganglia however dually innervate the anterior left ventricular (LV) wall.3 The RSG in particular in addition has predominance in the atria, compared to the LSG. The postganglionic fibers from the thoracic ganglia, as well as the preganglionic fibers from the spinal cord, terminate within a complex neural network of ganglionated plexuses (GPs) within the heart that compose the IC.

## Intrinsic cardiac level

The postganglionic neurons of the IC are found in the GPs, which are the location for the interaction between preganglionic fibers, parasympathetic fibers, and cardiac interneurons. The majority of GPs contain 200-1000 neurons each, and form synapses with sympathetic and parasympathetic fibers that enter the pericardial space.4 The highest density of GPs are near the hilum of the heart, with up to 50% of cardiac ganglia on the dorsal surface of the LA.5 Sympathetic nerves also travel along the major coronary arteries as a plexus, and decrease in proportion to vessel size to 2 single fibers at level of arterioles.6

The GPs extend epicardially to innervate the atria, interatrial septum, and ventricles, but sympathetic innervation is not uniform. Early studies looked at tyrosine hydroxylase, the enzyme that produces nor epinephrine (NE), to help identify important sympathetic nerves and fibers. The ventricles showed a gradient from base to apex, with the lowest concentration in the apex of the heart.7 Another way that the innervation has been studied is by using radiolabeled metaiodobenzylguanidine (MIBG), a catecholamine analog. Studies showed that the inferior wall of the LV had less uptake than the anterior region. 8,9 In contrast, the inferior LV wall has a higher proportion of vagal afferent neurons.10

The layers of the heart also showed differences in sympathetic density. The highest is in the epicardium, and it decreases reaching towards the endocardium. Within the endocardium, there is a right-to-left decreasing gradient of sympathetic innervation, proportional to the density of cholinergic (vagal nerves).11 Within the epicardium, there is also ventricle-to-atrium decreasing gradient of innervation. Within the ventricles, sympathetic afferent neurons are the main sensory neurons. They are triggered by predominately chemical stimuli, but also by mechanical stimuli.12

# VENTRICULAR FIBRILLATORY THRESHOLD

1. Ventricular fibrillatory threshold
   1. Pertinent history of SCD
      1. SCD occurs with increased sympathetic tone
         1. Historical studies about emotional and stress triggers
      2. Lown et al showed increased SNS leads to VT/VF in humans
      3. Increased PVC during times of stress and increased SNS activity in human recordings
      4. VF threshold is modulated by different factors (mainly SNS activity)
         1. Increased likelihood of ventricular dysrhythmias of the heart
   2. Normal effects of sympathetic tone through stellate ganglia stimulation
      1. Increased SNS (e.g. stellate stimulation) leads to increased inotropy/lusitropy
      2. RSG stimulation leads to increased SA firing, thus increased chronotropy/dromotropy
      3. Increased stimulation leads to increased episodes of VT/VF (excluding effects of ischemia)
      4. Paroxysmal atrial fibrillation (pAF)
         1. pAF induced by initial adrenergic surge, followed by vagal predominance. 13,14 Mediated by increased PV firing from tachycardia-pause initiations which lead to increased EAD. 15
         2. Extrinsic cardiac (EC) after
      5. VT/VF
         1. Stimulation of the stellate ganglion in canine models had increased chance of causing ventricular fibrillation particularly after coronary occlusion.16 Stellate ganglion thought to be carrying efferent sympathetic fibers. After stellate ganglionectomy, the VF threshold increased to 11% from 31% (compared to control VF rate). 17 Unilateral stellectomy may have compensatory contralateral activation, and then are agonized by vagal activity.18
      6. Long QT syndromes
         1. Increased beta-agonism leads to torsades de pointe (Tdp) d/t increased dispersion of depolarization or afterdepolarizations. 19

Sudden cardiac death is the most draft event that is triggered by the sympathetic nervous system. Understanding the pathology of SCD

# CORONARY PERFUSION

## Coronary perfusion

1. Coronary perfusion
   * 1. Coronary baroreceptor
        1. Baroreceptor reflex vagally mediated: high coronary pressure leads to sympathetic inhibition, but low pressures lead to delayed/slow efferent sympathetic outflow/vasoconstriction. 20,21
     2. Coronary blood flow
        1. Sympathetic coronary vasoconstriction can be attenuated/blocked by adenosine. 22
        2. Increased sympathetic tone leads to increased coronary vasodilation based on NE content of sympathetic nerve terminals (LAD > LCx > RCA), but only in cardiac transplant patients. 23 Suggest EC influences on IC may exist.
        3. Innervated by both adrenergic and cholinergic neurons. Smaller arteries/arterioles contain more nerve terminals than larger coronary arteries. 24
        4. B1AR predominantly in larger coronary conduit arteries (B1AR:B2AR in ~2:1 ratio) > 100 µm, while in smaller coronary arteries < 100 µm, B1AR ~= B2AR. 25 B1AR stimulation leads to vasodilation, while A1AR leads to vasoconstriction. 26 May exist to limit large vessel “steal” during ischemia.

## Myocardial infarction and ischemia

Coronary perfusion

* 1. Myocardial infarction/ischemia
     1. Advent of MI can change and increase VT/VF events
     2. Infarction leads to rewiring of the heart, including NE release
     3. Beta blockers, CCU “quiet and calm” can prevent sympathetic dysregulation
  2. Cardiac innervation heterogeneity
     1. Localized changes occur after infarct, included denervation
        1. FIGURE: myocardial ischemia leads to interdigitations of non-ischemic regions
     2. Scar tissue development becomes a nidus for VT/VF
        1. Benefit of epicardial ablation at times
     3. Adrenergic receptor dysregulation after ischemia

1. Ventricular wall
   1. Transmural infarct leads to sympathetic denervation (subendocardial ischemia may only damage vagal afferent). 27,28 Afferent sympathetic/vagal denervation occurs within 90 minutes after infarct at site, which travel apical-to-basal. 29 Non-transmural ischemia retains response to stimuli. 30 Transmural ischemia leads to apical loss of efferent sympathetic nerves within 20 minutes. 31
   2. Areas of cardiac tissue that have lost sympathetic innervation have supersensitive shortening of ERP to stimuli (e.g. NE or cervical ganglia stimulation), and have increased VF events. 32
   3. Sympathetic efferent show different activity based on innervating ischemic vs non-ischemic territory. 33
   4. Transmural ischemia, hitting epicardial layer (without collaterals like in dogs), triggers sympathetic afferent activity = leads to excitatory outflow. 34. Left ventricular wall has asymmetric sympathovagal innervation: vagal afferent preferentially distribute to inferior-posterior LV wall, sympathetic afferent are equally distributed (tested by inducing ischemia). 35
   5. Ischemia leads to IC neuronal remodeling, with immediate/persistent increase in NOS-neurons, with hypersensitivity to NE stimuli (increase GP excitability, augmented post-MI). 36
   6. Response to ischemia can be denervation vs. hyperinnervation, leads to heterogenous sympathetic fibers (increased arrhythmogenesis). 37 Nerve sprouting theory: increased sympathetic neurons lead to increased VT/VF in ischemia (induced by nerve growth factor in LSG), and in chronic myocardial ischemia, higher amount of LSG sympathetic nerve sprouting occurs. 38,39

# EFFECT OF CATECHOLAMINES

1. Catecholamine-based necrosis
   1. Malignant effects of catecholamines
      1. Takotsubo to discuss apical ballooning
         1. Mortality with Takotsubo is same with traditional AcS
      2. Wellen’s T waves occur in setting of significant apical NE levels
         1. Stress events
         2. Cerebral injury
      3. Effect of adrenergic receptor density on apex of the heart

## Neurotransmitters

* 1. Important neurotransmitters that mediate sympathetic tone
     1. Sympathetic signals
        1. NE
           1. Alpha and beta adrenergic receptors have differential preference of location
        2. Galanin
        3. NPY
     2. Parasympathetic signals
        1. Ach
        2. NOS
     3. TABLE: Describe individual neurohormones and effect on heart

Although NE is the typical mediator of adrenergic fibers, the other relevant neurohormones have an important role in their interactions. Through immunofluorescent staining, multiple neuronal somata have been identified. Choline acetyltransferase (ChAT) produced acetylcholine (ACh), which are typically cardioinhibitory. Cholinergic cell bodies predominate cardiac nerves, making anywhere from 60% to 100% of cardiac ganglia. ChAT somata are also more common in the atria than the rest of the heart. In the presence of NE, the inhibitory effects of ACh are exaggerated in a phenomenon called accentuated antagonism.40,41 Nitric oxide synthase (NOS) produces nitric oxide (NO), and colocalizes with ChAT somata. Its present equally from endocardium to epicardium, but the density favors the base versus the apex.42 As it is also a co-transmitter that modulates the vagal effect of increasing the VF threshold, through modifying action potential duration (APD). Vasoactive intestinal peptide (VIP) is also co-released with ACh, however neuronal somata containing VIP are scarce within the IC. All of the nerve fibers reaching into the cardiac ganglia however are reactive for VIP which likely comes from central sources.43,44

TH is responsible for NE production, but surprisingly 10-20% of all neurons contain both TH and ChAT.45 Both the left and right coronary plexuses however are mainly adrenergic.46 Alongside NE, neuropeptide Y (NPY) is co-released. At the level of the synapse, NPY attenuates the effect of vagal tone by decreasing ACh release.47 It also functions as a potent coronary vasoconstrictor acutely, however may lead to angiogenesis in the long-term.48 NPY, in human studies, leads to mild constriction of epicardial arteries for all patients. However, in those with microvascular angina, defined by normal left heart catherization but abnormal myocardial perfusion, NPY leads to transient myocardial ischemia.49 Galanin is also released alongside NPY, and it acts by inhibiting cholinergic nerves to reduce ACh release. Galanin receptors (GalR1) are found on ChAT somata and synapses, and may mediate the breaking of vagal bradycardia as it is expressed strongly at the sinoatrial (SA) node.50 Galanin is normally only co-expressed in ~5% of TH somata in the stellate, however after injury, its levels are increased to almost all neurons within 72 hours.50

The direct effect of sympathetic firing is through the release of NE, which can bind to four different adrenergic receptors (AR). B1 and B2 adrenergic recept

* + 1. B1 and B2 adrenergic receptors are present in cardiac myocytes at sympathetic synaptic terminals; B1AR accumulate at synapses, while B2AR undergo endocytosis/internalization. 51 Beta-agonists lead to increase in cardiac mass through increased size of cardiac myocytes. 52,53
    2. Almost all cardiomyocytes are in contact with sympathetic neurons (similar proportion to contact c- capillaries). 54 Basal/trophic sympathetic release leads to cardiomyocyte eutrophy (loss of beta-agonism leads to atrophy).

## Cardiomyopathy

1. Increased sympathetic tone in ischemic HF models (porcine) improves myocardial contraction, decreased oxygen consumption, decreases intraventricular desynchrony, all without elevation of NE. 55
2. After developing late-stage HF, neuronal bodies become hypertrophied and edematous. They become less excitable and may lead to vagal withdrawal. 56
3. In both ischemic and dilated CM…B1 receptor downregulation (proportion of subtypes are the same compared to healthy). Transmural distribution is different, c- lower B1 receptors found in subendocardium. 57
4. Cardiac sympathetic afferent reflex (CSAR) causes minimal increase in contractility, but has increased peripheral vasoconstriction (compared to rat controls). CSAR can be inhibited by epicardial lidocaine – decreased contractility more in HF rats than control (also caused drop in LVEDP paradoxically). 58
   1. Myocardial contractility
      1. NE release by the heavily sympathetically-innervated myocardium leads to Ca++ channel activity and ryanodine receptor (RyR), which leads to increased cytosolic Ca++. Effect is increased inotropy/lusitropy. 59 Sympathetic stimuli with NE at SA node also leads to increased myocardial interstitial levels of NE, which lead to ventricular inotropy.
5. Electrical conduction
   * 1. Chronotropy/dromotropy
        1. SA node firing rate depends on “funny current”, which has inward-rectifying Na+ current that leads to depolarization through the hyperpolarization-activated cyclic nucleotide-gated channel (HCN). Sympathetic tone leads to dromotropy/chronotropy through increased HCN activity, spontaneous SA depolarization rate, and sarcoplasmic reticulum release of Ca++, as well increased depolarization through other neuronal bundles (e.g. His bundle, AV node, etc). 52,60
     2. Repolarization
        1. Effective refractory period (ERP) are shorted by sympathetic excitation, while sympathetic inhibition prolongs ERP… similar in endocardium/epicardium. 61 Transmural dispersion of repolarization also shortened by sympathetic activity, prolonged by beta-blockade. 62

# CONCLUSION

* Review objectives
* Summary statement

# REFERENCES

1. Ardell JL, Armour JA. Neurocardiology: Structure-Based function. *Compr Physiol*. 2016;6(4):1635-1653. doi:10.1002/cphy.c150046

2. Malpas S. The rhythmicity of sympathetic nerve activity. *Prog Neurobiol*. 1998;56(1):65-96. doi:10.1016/S0301-0082(98)00030-6

3. Vaseghi M, Zhou W, Shi J, et al. Sympathetic innervation of the anterior left ventricular wall by the right and left stellate ganglia. *Hear Rhythm*. 2012;9(8):1303-1309. doi:10.1016/j.hrthm.2012.03.052

4. Armour JA, Murphy DA, Yuan BX, Macdonald S, Hopkins DA. Gross and microscopic anatomy of the human intrinsic cardiac nervous system. *Anat Rec*. 1997;247(2):289-298. doi:10.1002/(SICI)1097-0185(199702)247:2<289::AID-AR15>3.0.CO;2-L

5. Pauza DH, Skripka V, Pauziene N, Stropus R. Morphology, distribution, and variability of the epicardiac neural ganglionated subplexuses in the human heart. *Anat Rec*. 2000;259(4):353-382. doi:10.1002/1097-0185(20000801)259:4<353::AID-AR10>3.0.CO;2-R

6. Dolezel S, Gerová M, Gero J, Sládek T, Vasku J. Adrenergic innervation of the coronary arteries and the myocardium. *Acta Anat (Basel)*. 1978;100(3):306-316.

7. Pierpont GL, DeMaster EG, Reynolds S, Pederson J, Cohn JN. Ventricular myocardial catecholamines in primates. *J Lab Clin Med*. 1985;106(2):205-210.

8. Momose M, Tyndale-Hines L, Bengel FM, Schwaiger M. How heterogeneous is the cardiac autonomic innervation? *Basic Res Cardiol*. 2001;96(6):539-546. doi:10.1007/s003950170004

9. Morozumi T, Kusuoka H, Fukuchi K, et al. Myocardial iodine-123-metaiodobenzylguanidine images and autonomic nerve activity in normal subjects. *J Nucl Med*. 1997;38(1):49-52.

10. Walker JL, Thames MD, Abboud FM, Mark AL, Kloppenstein HS. Preferential distribution of inhibitory cardiac receptors in the left ventricle of the dog. *Am J Physiol*. 1978;235(2):H188-H192. doi:10.1152/ajpheart.1978.235.2.H188

11. Crick SJ, Anderson RH, Ho SY, Sheppard MN. Localisation and quantitation of autonomic innervation in the porcine heart II: endocardium, myocardium and epicardium. *J Anat*. 1999;195 ( Pt 3(3):359-373. doi:10.1046/j.1469-7580.1999.19530359.x

12. Armour JA, Huang MH, Pelleg A, Sylvén C. Responsiveness of in situ canine nodose ganglion afferent neurones to epicardial mechanical or chemical stimuli. *Cardiovasc Res*. 1994;28(8):1218-1225. doi:10.1093/cvr/28.8.1218

13. Bettoni M, Zimmermann M. Autonomic tone variations before the onset of paroxysmal atrial fibrillation. *Circulation*. 2002;105(23):2753-2759.

14. Tomita T, Takei M, Saikawa Y, et al. Role of autonomic tone in the initiation and termination of paroxysmal atrial fibrillation in patients without structural heart disease. *J Cardiovasc Electrophysiol*. 2003;14(6):559-564.

15. Patterson E, Jackman WM, Beckman KJ, et al. Spontaneous pulmonary vein firing in man: relationship to tachycardia-pause early afterdepolarizations and triggered arrhythmia in canine pulmonary veins in vitro. *J Cardiovasc Electrophysiol*. 2007;18(10):1067-1075. doi:10.1111/j.1540-8167.2007.00909.x

16. Harris AS, Otero H, Bocage AJ. The induction of arrhythmias by sympathetic activity before and after occlusion of a coronary artery in the canine heart. *J Electrocardiol*. 1971;4(1):34-43. doi:10.1016/S0022-0736(71)80048-1

17. Kliks BR, Burgess MJ, Abildskov JA. Influence of sympathetic tone on ventricular fibrillation threshold during experimental coronary occlusion. *Am J Cardiol*. 1975;36(1):45-49. doi:10.1016/0002-9149(75)90866-8

18. Schwartz PJ, Verrier RL, Lown B. Effect of stellectomy and vagotomy on ventricular refractoriness in dogs. *Circ Res*. 1977;40(6):536-540. doi:10.1161/01.RES.40.6.536

19. Shimizu W, Antzelevitch C. Cellular basis for the ECG features of the LQT1 form of the long-QT syndrome: effects of beta-adrenergic agonists and antagonists and sodium channel blockers on transmural dispersion of repolarization and torsade de pointes. *Circulation*. 1998;98(21):2314-2322.

20. McMahon NC, Drinkhill MJ, Hainsworth R. Vascular responses to stimulation of carotid, aortic and coronary artery baroreceptors with pulsatile and non-pulsatile pressures in anaesthetized dogs. *Exp Physiol*. 1996;81(6):969-981. doi:10.1113/expphysiol.1996.sp003997

21. Drinkhill MJ, Mcmahon NC, Hainsworth R. Delayed sympathetic efferent responses to coronary baroreceptor unloading in anaesthetized dogs independent control of pressures to the aortic root , including the coronary arteries , the aortic arch and the carotid sinuses . Electrophysiological recordin. *Physiology*. 1996:261-269.

22. Abe T, Morgan DA, Gutterman DD. Role of adenosine receptor subtypes in neural stunning of sympathetic coronary innervation. *Am J Physiol Circ Physiol*. 1997;272(1):H25-H34. doi:10.1152/ajpheart.1997.272.1.H25

23. Di Carli MF, Tobes MC, Mangner T, et al. Effects of Cardiac Sympathetic Innervation on Coronary Blood Flow. *N Engl J Med*. 2002;336(17):1208-1216. doi:10.1056/nejm199704243361703

24. Lever JD, Ahmed M, Irvine G. Neuromuscular and intercellular relationships in the coronary arterioles. A morphological and quantitative study by light and electron microscopy. *J Anat*. 1965;99(Pt 4):829-840.

25. Murphree SS, Saffitz JE. Delineation of the distribution of beta-adrenergic receptor subtypes in canine myocardium. *Circ Res*. 1988;63(1):117-125.

26. Baumgart D, Haude M, Görge G, et al. Augmented alpha-adrenergic constriction of atherosclerotic human coronary arteries. *Circulation*. 1999;99(16):2090-2097.

27. Zipes DP. Influence of myocardial ischemia and infarction on autonomic innervation of heart. *Circulation*. 1990;82(4):1095-1105. doi:10.1161/01.CIR.82.4.1095

28. Herre JM, Wetstein L, Lin YL, Mills AS, Dae M, Thames MD. Effect of transmural versus nontransmural myocardial infarction on inducibility of ventricular arrhythmias during sympathetic stimulation in dogs. *J Am Coll Cardiol*. 1988;11(2):414-421. doi:10.1016/0735-1097(88)90110-6

29. Barber MJ, Mueller TM, Davies BG, Gill RM, Zipes DP. Interruption of sympathetic and vagal-mediated afferent responses by transmural myocardial infarction. *Circulation*. 1985;72(3):623-631.

30. Inoue H, Skale BT, Zipes DP. Effects of ischemia on cardiac afferent sympathetic and vagal reflexes in dog. *Am J Physiol Circ Physiol*. 1988;255(1):H26-H35. doi:10.1152/ajpheart.1988.255.1.H26

31. Inoue H, Zipes DP. Time course of denervation of efferent sympathetic and vagal nerves after occlusion of the coronary artery in the canine heart. *Circ Res*. 1988;62(6):1111-1120.

32. Inoue H, Zipes DP. Results of sympathetic denervation in the canine heart: Supersensitivity that may be arrhythmogenic. *Circulation*. 1987;75(4):877-887. doi:10.1161/01.CIR.75.4.877

33. Neely BH, Hageman GR. Differential cardiac sympathetic activity during acute myocardial ischemia. *Am J Physiol*. 1990;258(5 Pt 2):H1534-41. doi:10.1152/ajpheart.1990.258.5.H1534

34. Minisi AJ, Thames MD. Activation of cardiac sympathetic afferents during coronary occlusion. Evidence for reflex activation of sympathetic nervous system during transmural myocardial ischemia in the dog. *Circulation*. 1991;84(1):357-367. doi:10.1161/01.CIR.84.1.357

35. Minisi AJ, Thames MD. Distribution of left ventricular sympathetic afferents demonstrated by reflex responses to transmural myocardial ischemia and to intracoronary and epicardial bradykinin. *Circulation*. 1993;87(1):240-246.

36. Hardwick JC, Ryan SE, Beaumont E, Ardell JL, Southerland EM. Dynamic remodeling of the guinea pig intrinsic cardiac plexus induced by chronic myocardial infarction. *Auton Neurosci Basic Clin*. 2014;181(1):4-12. doi:10.1016/j.autneu.2013.10.008

37. Huang WA, Boyle NG, Vaseghi M. Cardiac Innervation and the Autonomic Nervous System in Sudden Cardiac Death. *Card Electrophysiol Clin*. 2017;9(4):665-679. doi:10.1016/j.ccep.2017.08.002

38. Cao J-M, Chen LS, KenKnight BH, et al. Nerve Sprouting and Sudden Cardiac Death. *Circ Res*. 2000;86(7):816-821. doi:10.1161/01.RES.86.7.816

39. Chen PS, Chen LS, Cao JM, Sharifi B, Karagueuzian HS, Fishbein MC. Sympathetic nerve sprouting, electrical remodeling and the mechanisms of sudden cardiac death. *Cardiovasc Res*. 2001;50(2):409-416. doi:10.1016/s0008-6363(00)00308-4

40. Stramba-Badiale M, Vanoli E, De Ferrari GM, Cerati D, Foreman RD, Schwartz PJ. Sympathetic-parasympathetic interaction and accentuated antagonism in conscious dogs. *Am J Physiol Circ Physiol*. 1991;260(2):H335-H340. doi:10.1152/ajpheart.1991.260.2.H335

41. Levy MN. *Brief Reviews Sympathetlc-Parasympathetic Interactions in the Heart*.; 1971.

42. Brack KE, Patel VH, Coote JH, Ng GA. Nitric oxide mediates the vagal protective effect on ventricular fibrillation via effects on action potential duration restitution in the rabbit heart. *J Physiol*. 2007;583(2):695-704. doi:10.1113/jphysiol.2007.138461

43. Hoover DB, Isaacs ER, Jacques F, Hoard JL, Pagé P, Armour JA. Localization of multiple neurotransmitters in surgically derived specimens of human atrial ganglia. *Neuroscience*. 2009;164(3):1170-1179. doi:10.1016/j.neuroscience.2009.09.001

44. Parsons RL, Locknar SA, Young BA, Hoard JL, Hoover DB. Presence and co-localization of vasoactive intestinal polypeptide with neuronal nitric oxide synthase in cells and nerve fibers within guinea pig intrinsic cardiac ganglia and cardiac tissue. *Cell Tissue Res*. 2006;323(2):197-209. doi:10.1007/s00441-005-0074-3

45. Pauza DH, Saburkina I, Rysevaite K, et al. Neuroanatomy of the murine cardiac conduction system. *Auton Neurosci*. 2013;176(1-2):32-47. doi:10.1016/j.autneu.2013.01.006

46. Pauziene N, Alaburda P, Rysevaite-Kyguoliene K, et al. Innervation of the rabbit cardiac ventricles. *J Anat*. 2016;228(1):26-46. doi:10.1111/joa.12400

47. Herring N, Lokale MN, Danson EJ, Heaton DA, Paterson DJ. Neuropeptide Y reduces acetylcholine release and vagal bradycardia via a Y2 receptor-mediated, protein kinase C-dependent pathway. *J Mol Cell Cardiol*. 2008;44(3):477-485. doi:10.1016/j.yjmcc.2007.10.001

48. Herring N. Autonomic control of the heart: Going beyond the classical neurotransmitters. *Exp Physiol*. 2015;100(4):354-358. doi:10.1113/expphysiol.2014.080184

49. Rosano GMC, Tousoulis D, McFadden E, Clarke J, Davies GJ, Kaski JC. Effects of neuropeptide Y on coronary artery vasomotion in patients with microvascular angina. *Int J Cardiol*. 2017;238:123-127. doi:10.1016/j.ijcard.2017.03.024

50. Herring N, Cranley J, Lokale MN, et al. The cardiac sympathetic co-transmitter galanin reduces acetylcholine release and vagal bradycardia: Implications for neural control of cardiac excitability. *J Mol Cell Cardiol*. 2012;52(3):667-676. doi:10.1016/j.yjmcc.2011.11.016

51. Shcherbakova OG, Hurt CM, Xiang Y, et al. Organization of β-adrenoceptor signaling compartments by sympathetic innervation of cardiac myocytes. *J Cell Biol*. 2007;176(4):521-533. doi:10.1083/jcb.200604167

52. Franzoso M, Zaglia T, Mongillo M. Putting together the clues of the everlasting neuro-cardiac liaison. *Biochim Biophys Acta - Mol Cell Res*. 2016;1863(7):1904-1915. doi:10.1016/j.bbamcr.2016.01.009

53. Zaglia T, Milan G, Franzoso M, et al. Cardiac sympathetic neurons provide trophic signal to the heart via β2-adrenoceptor-dependent regulation of proteolysis. *Cardiovasc Res*. 2013;97(2):240-250. doi:10.1093/cvr/cvs320

54. Hirsch E, Hilfiker-Kleiner D, Balligand J-L, et al. Interaction of the heart and its close and distant neighbours: report of the Meeting of the ESC Working Groups Myocardial Function and Cellular Biology. *Cardiovasc Res*. 2013;99(4):595-599. doi:10.1093/cvr/cvt179

55. Liu Y, Yue WS, Liao SY, et al. Thoracic spinal cord stimulation improves cardiac contractile function and myocardial oxygen consumption in a porcine model of ischemic heart failure. *J Cardiovasc Electrophysiol*. 2012;23(5):534-540. doi:10.1111/j.1540-8167.2011.02230.x

56. Singh S, Sayers S, Walter JS, et al. Hypertrophy of neurons within cardiac ganglia in human, canine, and rat heart failure: the potential role of nerve growth factor. *J Am Heart Assoc*. 2013;2(4). doi:10.1161/JAHA.113.000210

57. Beau SL, Tolley TK, Saffitz JE. Heterogeneous transmural distribution of β-adrenergic receptor subtypes in failing human hearts. *Circulation*. 1993;88(6):2501-2509. doi:10.1161/01.CIR.88.6.2501

58. Wang HJ, Rozanski GJ, Zucker IH. Cardiac sympathetic afferent reflex control of cardiac function in normal and chronic heart failure states. *J Physiol*. 2017;595(8):2519-2534. doi:10.1113/JP273764

59. Shan J, Kushnir A, Betzenhauser MJ, et al. Phosphorylation of the ryanodine receptor mediates the cardiac fight or flight response in mice. *J Clin Invest*. 2010;120(12):4388-4398. doi:10.1172/JCI32726

60. Liao Z, Lockhead D, Larson ED, Proenza C. Phosphorylation and modulation of hyperpolarization-activated HCN4 channels by protein kinase A in the mouse sinoatrial node. *J Gen Physiol*. 2010;136(3):247-258. doi:10.1085/jgp.201010488

61. Martins JB, Zipes DP. Effects of sympathetic and vagal nerves on recovery properties of the endocardium and epicardium of the canine left ventricle. *Circ Res*. 1980;46(1):100-110. doi:10.1161/01.RES.46.1.100

62. Dukes ID, Vaughan Williams EM. Effects of selective alpha 1‐, alpha 2‐, beta 1‐and beta 2‐adrenoceptor stimulation on potentials and contractions in the rabbit heart. *J Physiol*. 1984;355(1):523-546. doi:10.1113/jphysiol.1984.sp015436