# DRAFT: THE SYMPATHETIC INNERVATION OF THE HEART

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

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# 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

1. Spinal cord level
   * 1. Spinal cord anatomy of preganglionic neurons location, and both proximal and distal connections to brain and postganglionic neurons
        1. Automaticity and firing of these SNS neurons
     2. Effect of cerebral/nervous influences on these preganglionic cell bodies
        1. Examples include sympathetic storm from TBI, which leads to hyperactivation
        2. Nervous activity (e.g. panic attack) on the preganglionic bodies (what is the connection/mechanism of communicatin)
     3. Integration of systemic/peripheral reflex arcs into the spinal cord
        1. Examples include vasovagal syncope, mesenteric ganglia response to stress, etc (lumbosacral outflow)

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

1. Thoracic, extracardiac level
   * 1. Anatomy of the thoracic ganglia
        1. Preganglionic fibers exit from DRG and enter white rami, then eventually form sympathetic chain and thoracic ganglia
        2. T1 to T6 specifically are responsible for cardiac outflow
     2. Stellate ganglia
        1. Historic examples include stellectomy/ganglion block to help decrease VT/VF burden
        2. Innervation of the heart is different between LSG and RSG, to some degree

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

1. Intrinsic cardiac level
   * 1. Sympathetic nervous system is within GPs around epicardium of heart, particularly in epicardial fat pads.
     2. Innervation of the cardiac chambers and wall
        1. Epicardium is highest density of nerve fibers, which decrease as going into endocardium
        2. Atria have different right-to-left innervation of both adrenergic and cholinergic nerves
        3. Ventricles have a base-to-apex density gradient of adrenergic fibers, but barely any vagal fibers (except inferior wall)
     3. Coronary artery innervation goes from a plexus around major/large arteries, and decreases in size until it is only 1-2 nerves at level of arteriole

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 GPs themselves are mainly found in epicardial and hilar fat pads in a consistent pattern within humans.5 The right atrium (RA) is innervated by two GPs, the left atrium (LA) by three, the right ventricle (RV) by one, the left ventricle (LV) by three. 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.6 The GPs extend epicardially to innervate the atria, interatrial septum, and ventricles. Three GPs and subplexuses innervate the pulmonary veins, with about 2000 neurons residing at the base of each vein.7 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.8

Adrenergic fibers are seen in all four chambers and layers of the heart, but sympathetic innervation is not uniform. In initial studies, the enzyme responsible for nor epinephrine (NE) production, tyrosine hydroxylase (TH), was stained to identify sympathetic somata and fibers. The ventricles themselves show a gradient from base to apex, with the highest NE concentration in the apex.9 Using radiolabeled metaiodobenzylguanidine, a catecholamine analog, its seen that the inferior wall of the LV has less uptake than the anterior region.10,11 In contrast, the inferior wall of the LV has a higher proportion of vagal afferent neurons.12 The RA itself shows only a small subpopulation of adrenergic fibers. This was determined by GP epicardial fat biopsy during cardiothoracic surgery, with immunofluorescent staining showing a majority population of parasympathetic markers.13 The highest density is found in the epicardium, decreasing towards the endocardium. Within the endocardium, adrenergic nerves found in the atrium show an right-to-left decreasing gradient, which mimics the density of cholinergic (vagal) nerves.14 Within the epicardium, there is also ventricle-to-atrium decreasing gradient of innervation. Within the ventricles, sympathetic afferent neurons are main sensory neurons. They are triggered by predominately chemical stimuli, but also by mechanical stimuli.15

# 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. (Bettoni & Zimmermann, 2002; Tomita et al., 2003) Mediated by increased PV firing from tachycardia-pause initiations which lead to increased EAD. (Patterson et al., 2007)
         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.(Harris, Otero, & Bocage, 1971) 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). (Kliks, Burgess, & Abildskov, 1975) Unilateral stellectomy may have compensatory contralateral activation, and then are agonized by vagal activity.(Schwartz, Verrier, & Lown, 1977)
      6. Long QT syndromes
         1. Increased beta-agonism leads to torsades de pointe (Tdp) d/t increased dispersion of depolarization or afterdepolarizations. (Shimizu & Antzelevitch, 1998)

# 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. (Drinkhill, Mcmahon, & Hainsworth, 1996; McMahon, Drinkhill, & Hainsworth, 1996)
     2. Coronary blood flow
        1. Sympathetic coronary vasoconstriction can be attenuated/blocked by adenosine. (Abe, Morgan, & Gutterman, 1997)
        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. (Di Carli et al., 2002) 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. (Lever, Ahmed, & Irvine, 1965)
        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. (Murphree & Saffitz, 1988) B1AR stimulation leads to vasodilation, while A1AR leads to vasoconstriction. (Baumgart et al., 1999) 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). (Herre et al., 1988; Zipes, 1990) Afferent sympathetic/vagal denervation occurs within 90 minutes after infarct at site, which travel apical-to-basal. (Barber, Mueller, Davies, Gill, & Zipes, 1985) Non-transmural ischemia retains response to stimuli. (Inoue, Skale, & Zipes, 1988) Transmural ischemia leads to apical loss of efferent sympathetic nerves within 20 minutes. (Inoue & Zipes, 1988)
   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. (Inoue & Zipes, 1987)
   3. Sympathetic efferent show different activity based on innervating ischemic vs non-ischemic territory. (Neely & Hageman, 1990)
   4. Transmural ischemia, hitting epicardial layer (without collaterals like in dogs), triggers sympathetic afferent activity = leads to excitatory outflow. (Anthony J Minisi & Thames, 1991). 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). (A J Minisi & Thames, 1993)
   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). (Hardwick, Ryan, Beaumont, Ardell, & Southerland, 2014)
   6. Response to ischemia can be denervation vs. hyperinnervation, leads to heterogenous sympathetic fibers (increased arrhythmogenesis). (Huang, Boyle, & Vaseghi, 2017) 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. (Cao et al., 2000; Chen et al., 2001)

# 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.16,17 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.18 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.13,19

TH is responsible for NE production, but surprisingly 10-20% of all neurons contain both TH and ChAT.20 Both the left and right coronary plexuses however are mainly adrenergic.21 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.22 It also functions as a potent coronary vasoconstrictor acutely, however may lead to angiogenesis in the long-term.23 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.24 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.25 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.25

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. (Shcherbakova et al., 2007) Beta-agonists lead to increase in cardiac mass through increased size of cardiac myocytes. (Franzoso, Zaglia, & Mongillo, 2016; Zaglia et al., 2013)
    2. Almost all cardiomyocytes are in contact with sympathetic neurons (similar proportion to contact c- capillaries). (Hirsch et al., 2013) 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. (Liu et al., 2012)
2. After developing late-stage HF, neuronal bodies become hypertrophied and edematous. They become less excitable and may lead to vagal withdrawal. (Singh et al., 2013)
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. (Beau, Tolley, & Saffitz, 1993)
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). (Wang, Rozanski, & Zucker, 2017)
   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. (Shan et al., 2010) 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). (Franzoso et al., 2016; Liao, Lockhead, Larson, & Proenza, 2010)
     2. Repolarization
        1. Effective refractory period (ERP) are shorted by sympathetic excitation, while sympathetic inhibition prolongs ERP… similar in endocardium/epicardium. (Martins & Zipes, 1980) Transmural dispersion of repolarization also shortened by sympathetic activity, prolonged by beta-blockade. (Dukes & Vaughan Williams, 1984)

# CONCLUSION

* Review objectives
* Summary statement

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