# NOTES: THE SYMPATHETIC INNERVATION OF THE HEART

## Anatomy

1. Pre-ganglionic neurons
   1. Brain stem
      1. Medullary dorsolateral reticular formation
   2. Spinal cord
      1. Overview
         1. Lateral horns of the T1-T12 and L1-L3 spinal cord (thoracolumbar outflow)
         2. Synapse on sympathetic ganglia or on chromaffin cells of adrenal gland to release epinephrine (EPI)
         3. Cardiac nerves originate from T1-T6, exiting spinal cord from ventral roots into the white rami to join the sympathetic chain, including stellate ganglion (SG)
   3. Sympathovagal balance
      1. Vagal afferent stimuli, e.g. baroreceptors, can lead to central sympathetic efferent activity (either inhibition or excitation)
      2. Local neurotransmitter effects also present (e.g. galanin inhibits cholinergic nerves)
   4. Extracardiac
      1. Preganglionic neurons are found in the brain stem at the medullary dorsolateral reticular formation (mainly vagus), and the T1-T6 lateral horns of the spinal cord (sympathetic).
      2. Myocardium is directly innervated by sympathetic neurons, mainly found in cervical, stellate, and thoracic ganglia (both afferent and efferent paths are present)
2. Post-ganglionic neuron – sympathetic ganglia
   1. Overview
      1. Paravertebral
         1. Cervical region x 3, including left and right SG, thoracic region x 10-11, lumbar region x 4, sacral region x 4, coccyx x 1 (midline)
         2. SG nerves are purely sympathetic fibers
         3. Sympathetic nerves on the left mainly distribute to the epicardial surface of left ventricle, and endocardial surface of both ventricles(Stee, 1978)
      2. Prevertebral - axons are distributed to the 3 major gastrointestinal arteries arising from the aorta
      3. Neurotransmitter - predominantly nor epinephrine (NE)
   2. Firing rate
      1. Thoracic spinal segments have a distinct cardiac rhythm and other oscillatory frequencies that are reproduced in cardiac postganglionic neurons. Analyses shows there are periodicities from 2-6 Hz, 10 Hz, respiratory rates, and slower oscillations (~0.3 Hz) called Mayer waves.(Malpas, 1998)
      2. Afferent postganglionic neurons increase firing with increases in chamber pressure, and decrease discharge with decreased pressure. Similarly, higher firing rate with increase coronary flow, and decreased rate with decreased coronary flow (based on chamber). Ischemia only led to increase discharge of fibers when accompanied by heart failure.(A. Malliani, Recordati, & Schwartz, 1973)
3. Cardiac innervation
   1. Overview
      1. Sympathetic nerve fibers are located subepicardially and travel along major coronary arteries.
      2. Sympathetic fibers enter the heart close to the pulmonary vessels
      3. Ventricular sympathetic innervations is characterized by a gradient from base to apex, with highest NE concentration in apex.(Pierpont, DeMaster, Reynolds, Pederson, & Cohn, 1985)
      4. Majority of sympathetic postganglionic axons innervating the heart originate from cell bodies in the stellate ganglion
   2. Left versus right innervation
      1. In rat heart, NE concentration measurements show that left middle/inferior SG contributes to the RV(Pardini, Lund, & Schmid, 1989)
      2. Stellate ganglion
         1. RSG affects anterior/basal portion of ventricles; LSG has more effect on posterior/apical portion, as well as anterior LV wall (although both LSG/RSG contribute) (Vaseghi et al., 2012)
         2. LSG stimulation leads to increased inotropy due to effects at ventricle; RSG stimulation leads to chronotropy d/t atrial effects (Ajijola et al., 2015; Winter, Tanko, Brack, Coote, & Ng, 2012)
         3. Stimulation of the LSG leads to inotropic response.(Pardini et al., 1989) Stimulation of the RSG leads to chronotropic response.(Stee, 1978)
   3. Intrinsic cardiac plexus
      1. Postganglionic neurons interact with local plexus neurons, along with parasympathetic neuron interactions
      2. The majority of the ganglia are organized into ganglionated plexuses (GP) on the surface of the atria and ventricle, containing 200-1000 neurons each, that form synapses with sympathetic/parasympathetic fibers that enter the pericardial space.(Armour, Murphy, Yuan, Macdonald, & Hopkins, 1997)
      3. ﻿From the GP, they extend epicardially to innervate the atria, interatrial septum, and the ventricles.(Pauza, Skripka, Pauziene, & Stropus, 2000)
         1. Arterial
            1. Left coronary subplexus: arterial hilum by the pulmonary trunk
            2. Right coronary subplexus: arterial hilum by the aorta
         2. Venous
            1. Dorsal right atrial subplexus: right caudal vein or SVC and supplies the SA node and dorsum of RA
            2. Middle dorsal subplexus: branches from pulmonary veins into the coronary groove
            3. Left dorsal subplexus: terminates on dorsal left atrial and ventricular regions
            4. Ventral left atrial subplexus: begins by the left pulmonary vein and joins the ventral left atrial region
            5. Right ventral subplexus: ventromedial aspect of the SVC to the ventrial right atrium
      4. Majority of the GP neuronal bodies are on supraventricular tissues, laying flat on epicardial surface but also within fat pads on the heart hilum.(Wake & Brack, 2016) Most common locations include :
         1. Dorsal atria surface
         2. Base of aorta and pulmonary artery
         3. Dorsal and ventral to pulmonary veins
         4. Anterior ventricular surface
      5. The inferior wall of the left ventricle has a higher proportion of vagal afferent neurons, such that inferior ischemia, usually from the RCA system, leads to a cardioinhibitory pattern and subsequent sinus bradycardia. (Walker, Thames, Abboud, Mark, & Kloppenstein, 1978) In humans, imaging shows a consistent pattern of increased vagal innervation of the inferior wall, based on MIBG uptake in the myocardium. (Morozumi et al., 1997)
      6. Sympathetic nerves travel along major coronary arteries as a plexus, and decrease in proportion to vessel size to 2 single fibers at level of arterioles. (Dolezel, Gerová, Gero, Sládek, & Vasku, 1978)
   4. Sinoatrial and atrioventricular nodes
      1. Increased sympathetic efferent firing leads to increase in sinus rate and shortens AV nodal conduction. Also it shortens action potential duration (APD) and reduced transmural dispersion of repolarization.(Winter, Brack, & Ng, 2011; Winter, Tanko, Brack, Coote, & Ng, 2012)
   5. Efferent
      1. Postganglionic neurons are found in ganglionated plexuses (GPs) that are on epicardium, are location for the interaction between sympathetic and parasympathetic fibers as well as interneurons. Epicardiac GPs are consistent from heart to heart in humans.
      2. Generally, RA is innervated by 2 GPs, the LA by 3, the RV by 1, and the LV by 3. Highest density if GPs are near the hilum of the heart, mainly dorsal surface of the LA (contain up to 50% of cardiac ganglia). (Pauza, Skripka, Pauziene, & Stropus, 2000)
      3. Ventricular sympathetic innervations is characterized by a gradient from base to apex, with highest NE concentration in apex. (Pierpont, DeMaster, Reynolds, Pederson, & Cohn, 1985)
      4. Innervation is seen through all 4 chambers and endocardial/myocardial/epicardial layers, highest density in epicardium and decreasing to endocardium. Cholinergic nerves have a right-to-left density gradient in the endocardium only. Adrenergic nerves mainly found in atrial GP, also had right-to-left gradient only in endocardium. Epicardial tissue had ventricular-to-atrial gradient of adrenergic nerves. (Crick, Anderson, Ho, & Sheppard, 1999)
   6. Afferent
      1. Ventricular sensory neurons are mainly sympathetic afferents – triggered most powerfully by chemical stimuli (even after chemical removed), and mechanical stimuli. (Armour, Huang, Pelleg, & Sylvén, 1994)
4. Gross anatomy
   1. Right atrium
      1. The right atrial GP were sampled through epicardial fat biopsy during cardiothoracic surgery, and then visualized through immunofluorescent staining. Most neuronal somata contained ChAT and NOS. A subpopulation contained TH (noradrenergic markers). Although most neurons received cholinergic inputs, some were absent. (Hoover et al., 2009)
   2. Left ventricle
      1. The mid-myocardium has a higher-concentration of nitrergic (NOS) fibers compared to cholinergic (ChAT) by a factor of 8.
   3. Pulmonary veins
      1. Innervated by three epicardial GPs in humans: ﻿the dorsal right atrial, middle dorsal and left dorsal subplexuses, with an estimated 2000 neurons residing at the base of each PV. (Vaitkevicius et al., 2009)
5. Imaging techniques
   1. Fluorodopamine can be used to image sympathetic innervation of the heart. The predominance of visualization of tracer is the in the ventricles, homogenously, and slightly higher in the interventricular septum.(Armando et al., 2010)

## Chemical interactions

1. Choline acetyltransferase (ChAT)
   1. Cholinergic cell bodies predominate cardiac nerves. ChAT make up 60-100% of cardiac ganglia. ChAT somata most common in atria compared to rest of heart.
2. Tyrosine hydroxylase (TH) and nor epinephrine (NE)
   1. Neurons responsible for NE production. 10-20% of all neurons contain both TH and ChAT. Both left and right coronary plexuses are adrenergic. (Pauza et al., 2013; Pauziene et al., 2016)
   2. NE bind to both alpha and beta receptors – A2AR exist on varicosities on sympathetic neurons, leading to negative feedback to decrease NE release. (Shcherbakova et al., 2007)
3. Neuropeptide Y (NPY)
   1. Released along with NA, and attenuates effects of vagal bradycardia, through decrease in release of ACh.(Herring, Lokale, Danson, Heaton, & Paterson, 2008) Acutely potent coronary vasoconstrictor; may lead to angiogenesis in long-term. (Herring, 2015)
   2. NPY leads to mild constriction of epicardial arteries for all patients. In microvascular angina (clean LHC, +PET), NPY leads to transient myocardial ischemia. (Rosano et al., 2017)
4. Nitric oxide synthase (NOS)
   1. Makes NO, co-transmitter that modulates vagal effect to increase VF threshold (through modifying APD). Co-localizes with ChAT somata, present equally from endocardium to epicardium of LV, but density is basal > apical. (Brack, Patel, Coote, & Ng, 2007)
5. Galanin
   1. Galanin is released alongside NPY, acts by inhibiting cholinergic nerves to reduce ACh release. Galanin receptors (GalR1) are found on ChAT somata/synapses (may mediate the breaking of vagal bradycardia). (Herring et al., 2012)
   2. Galanin is co-expressed in ~5% of TH neurons in the stellate. After injury (e.g. ischemia), levels increase to almost all neurons after 3 days. (Herring et al., 2012)
   3. GalR1 is expressed at SA node.
6. Cardiomyocytes
   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).

Function

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.
3. 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)
4. 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. Sinoatrial and atrioventricular nodes
   1. Increased sympathetic efferent firing leads to increase in sinus rate and shortens AV nodal conduction. Also it shortens action potential duration (APD) and reduced transmural dispersion of repolarization.(Winter et al., 2011, 2012)
6. Atria
   1. Parasympathetic fibers have different effect in ventricles compared to atria. In the atria, it decrease action potential and reduce effective refractory period ( ERP), and enhance spatial electrophysiological heterogeneity.(Coote & Chauhan, 2016)
7. Ventricles
   1. Parasympathetic fibers have a potent anti-arrhythmic effect.
   2. Dogma previously taught that cardiotropic sympathetic ganglia resided in paravertebral chains and differentially innervated the left and right ventricle.
   3. RSG block or LSG stimulation both lead to prolonged QT and increased TW amplitude. LSG block or RSG stimulation have no measurable change in QT. RSG block leads to prolonged refractory period in anterior ventricle, while LSG block prolonged refractory period of posterior surface.
8. Ganglionated plexuses (GP)
   1. Multiple locations exist and depend on the animal model. When nicotine is injected into the RAGP, three changes can occurs: i) bradycardia followed by tachycardia; ii) bradycardia alone; iii) tachycardia alone. This suggests that a biphenotypic response is possible within a GP.(Cardinal, Pagé, Vermeulen, Ardell, & Armour, 2009)
   2. After using nicotine injections, and subsequently by blocking GP activity using hexamethonium, its suggested that GP have certain functions. The RA GP modulate vagal control, the IVC/LA GP AV modulates AV conduction, and the CMV (cranial medial ventricular) GP modulate LV inotropy.(Dickerson et al., 1998; Gatti et al., 1995; Gray, Johnson, Ardell, & Massari, 2004)
      1. However, ablation of a single GP doesn’t abolish its theoretical effect. For example, ablation of the RAGP leads to blunting of the initial tachycardic response, but doesn’t stop the prolonged secondary tachycardia that occurs. This is because the SA node is innervated by the RAGP and additional GPs.
   3. Communicating interneurons are also notable for transmitting afferent multimodal sensations into mechanical efferent signals that can induce atrial fibrillation.(Beaumont et al., 2013)
9. Coronary arteries
   1. Innervated by both adrenergic and cholinergic neurons. Smaller arteries/arterioles contain more nerve terminals than larger coronary arteries. (Lever, Ahmed, & Irvine, 1965)
   2. 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.

Reflex arches

1. Aortic arches (SNS inhibition)(Alberto Malliani, Pagani, Pizzinelli, Furlan, & Guzzetti, 1983)
   1. When the thoracic aortic diameter is increased, there is a reflex increase in aortic pressure
      1. An increase of the aortic segment by 9 mm from 16 mm, there was an increase in MAP by 31 mm Hg from 100 mm Hg, and an increase in HR by 20 bpm from 90 bpm. HR changes were due to vagolysis (after vagotomy, resting HR was higher and no further increase in HR occurred by aortic stretch).(Pagani, Pizzinelli, Bergamaschi, & Malliani, 1982)
2. Carotid baroreceptors (SNS inhibition)
   1. Including Bezold-Jarish reflex
   2. After stellate/spinal block, anesthesia-induced hypotension won’t correct for low-pressure baroreceptor stimuli (vagal afferent), leaving unopposed vagal tone. (Crystal & Salem, 2012)
3. Cardiovascular low-threshold polymodal receptors (SNS activation)
4. 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)

## Diseases

1. Heart failure
   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)
2. Atrial fibrillation (AF)
   1. GP around the PV are increased in activity during and preceding AF, and may be culprit. Thus ablations have a beneficial effect, although other GPs farther from the PV also show increased activity during AF. (Lu et al., 2009)
   2. Paroxysmal AF (pAF) can be induced by simultaneous discharge of both limbs of the ANS, as it leads to imbalance. Initially there is adrenergic surge, followed by vagal predominance. (Bettoni & Zimmermann, 2002) Thought to also play a role in termination of pAF… these are hearts that have no structural disease. (Tomita et al., 2003) pAF was triggered by rapid firing from within pulmonary veins, which is preceded by tachycardia-pause initiation leading to increased EAD. (Patterson et al., 2007)
   3. Extrinsic cardiac nervous system decreases AT/AF burden. When ablating GP that connects intrinsic to extrinsic, AT/AF went up chronically in a dog model. The “head” GP in dogs is by the SVC-Ao. (Lo et al., 2013)
3. Ventricular fibrillation
   1. Long QT syndromes: Increased beta-agonism leads to torsades de pointe (Tdp) d/t increased dispersion of depolarization or afterdepolarizations. (Shimizu & Antzelevitch, 1998)
   2. Sympathetic stimulation leads to decrease in VF threshold. (Lown, 1979; Opthof et al., 1991)
4. Myocardial ischemia (MI)
   1. MI lead to intrinsic cardiac neuronal remodeling. After MI, there is an immediate and persistent increase in neurons that express NOS. NA injections lead to increased intracardiac GP excitability, which was subsequently augmented post-MI. (Hardwick, Ryan, Beaumont, Ardell, & Southerland, 2014)
   2. 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)
   3. Transmural ischemia leads to sympathetic/vagal afferent denervation within 90 minutes after infarct. The afferents travel apical-to-basal, as nerves basal to infarct still functioned. (Barber, Mueller, Davies, Gill, & Zipes, 1985) Non-transmural ischemia maintains a response to bradykinin. (Inoue, Skale, & Zipes, 1988) Transmural ischemia leads to loss of efferent sympathetic nerves in non-infarcted apical regions within 20 minutes. (Inoue & Zipes, 1988)
   4. 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)
   5. 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)
   6. 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)
   7. Sympathetic efferent show different activity based on innervating ischemic vs non-ischemic territory. (Neely & Hageman, 1990)
   8. 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)
   9. 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)
   10. 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)
5. Stellate block
   1. After stellate/spinal block, anesthesia-induced hypotension won’t correct for low-pressure baroreceptor stimuli (vagal afferent), leaving unopposed vagal tone. (Crystal & Salem, 2012)
   2. Left versus right block (on healthy/controls) showed no change in EF. LSG block however led to increased LVEDP and LVESP compared to right. (Lobato, Kern, Paige, Brown, & Sulek, 2000)

# REFERENCES

Armando, I., Goldstein, D. S., Kirk, K. L., Dunn, B. B., Eisenhofer, G., Lenders, J., … Herscovitch, P. (2010). *Positron emission tomographic imaging of cardiac sympathetic Innervation using 6-[ 18 F]Fluorodopamine: Initial findings in humans*. *Journal of the American College of Cardiology* (Vol. 22). https://doi.org/10.1016/0735-1097(93)90786-z

Armour, J. A., Murphy, D. A., Yuan, B. X., Macdonald, S., & Hopkins, D. A. (1997). Gross and microscopic anatomy of the human intrinsic cardiac nervous system. *Anatomical Record*, *247*(2), 289–298. https://doi.org/10.1002/(SICI)1097-0185(199702)247:2<289::AID-AR15>3.0.CO;2-L

Barber, M. J., Mueller, T. M., Davies, B. G., Gill, R. M., & Zipes, D. P. (1985). Interruption of sympathetic and vagal-mediated afferent responses by transmural myocardial infarction. *Circulation*, *72*(3), 623–631.

Baumgart, D., Haude, M., Görge, G., Liu, F., Ge, J., Grosse-Eggebrecht, C., … Heusch, G. (1999). Augmented alpha-adrenergic constriction of atherosclerotic human coronary arteries. *Circulation*, *99*(16), 2090–2097.

Beau, S. L., Tolley, T. K., & Saffitz, J. E. (1993). Heterogeneous transmural distribution of β-adrenergic receptor subtypes in failing human hearts. *Circulation*, *88*(6), 2501–2509. https://doi.org/10.1161/01.CIR.88.6.2501

Beaumont, E., Salavatian, S., Southerland, E. M., Vinet, A., Jacquemet, V., Armour, J. A., & Ardell, J. L. (2013). Network interactions within the canine intrinsic cardiac nervous system: Implications for reflex control of regional cardiac function. *Journal of Physiology*, *591*(18), 4515–4533. https://doi.org/10.1113/jphysiol.2013.259382

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

Brack, K. E., Patel, V. H., Coote, J. H., & Ng, G. A. (2007). Nitric oxide mediates the vagal protective effect on ventricular fibrillation via effects on action potential duration restitution in the rabbit heart. *Journal of Physiology*, *583*(2), 695–704. https://doi.org/10.1113/jphysiol.2007.138461

Cardinal, R., Pagé, P., Vermeulen, M., Ardell, J. L., & Armour, J. A. (2009). Spatially divergent cardiac responses to nicotinic stimulation of ganglionated plexus neurons in the canine heart. *Autonomic Neuroscience: Basic and Clinical*, *145*(1–2), 55–62. https://doi.org/10.1016/j.autneu.2008.11.007

Cohn, P. F. (1980). Silent myocardial ischemia in patients with a defective anginal warning system. *The American Journal of Cardiology*, *45*(3), 697–702. https://doi.org/10.1016/S0002-9149(80)80024-5

Coote, J. H., & Chauhan, R. A. (2016). The sympathetic innervation of the heart: Important new insights. *Autonomic Neuroscience: Basic and Clinical*, *199*, 17–23. https://doi.org/10.1016/j.autneu.2016.08.014

Crystal, G. J., & Salem, M. R. (2012). The Bainbridge and the “Reverse” Bainbridge Reflexes. *Anesthesia & Analgesia*, *114*(3), 520–532. https://doi.org/10.1213/ane.0b013e3182312e21

Dickerson, L. W., Rodak, D. J., Fleming, T. J., Gatti, P. J., Massari, V. J., McKenzie, J. C., & Gillis, R. A. (1998). Parasympathetic neurons in the cranial medial ventricular fat pad on the dog heart selectively decrease ventricular contractility. *Journal of the Autonomic Nervous System*, *70*(1–2), 129–141. https://doi.org/10.1016/S0165-1838(98)00048-4

Drinkhill, M. J., Mcmahon, N. C., & Hainsworth, R. (1996). 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*, 261–269.

Gatti, P. J., Johnson, T. A., Phan, P., Jordan, I. K., Coleman, W., & Massari, V. J. (1995). The physiological and anatomical demonstration of functionally selective parasympathetic ganglia located in discrete fat pads on the feline myocardium. *Journal of the Autonomic Nervous System*, *51*(3), 255–259. https://doi.org/10.1016/0165-1838(94)00139-B

Gray, A. L., Johnson, T. A., Ardell, J. L., & Massari, V. J. (2004). Parasympathetic control of the heart. II. A novel interganglionic intrinsic cardiac circuit mediates neural control of heart rate. *Journal of Applied Physiology*, *96*(6), 2273–2278. https://doi.org/10.1152/japplphysiol.00616.2003

Hardwick, J. C., Ryan, S. E., Beaumont, E., Ardell, J. L., & Southerland, E. M. (2014). Dynamic remodeling of the guinea pig intrinsic cardiac plexus induced by chronic myocardial infarction. *Autonomic Neuroscience: Basic and Clinical*, *181*(1), 4–12. https://doi.org/10.1016/j.autneu.2013.10.008

Herring, N., Lokale, M. N., Danson, E. J., Heaton, D. A., & Paterson, D. J. (2008). Neuropeptide Y reduces acetylcholine release and vagal bradycardia via a Y2 receptor-mediated, protein kinase C-dependent pathway. *Journal of Molecular and Cellular Cardiology*, *44*(3), 477–485. https://doi.org/10.1016/j.yjmcc.2007.10.001

Hoover, D. B., Isaacs, E. R., Jacques, F., Hoard, J. L., Pagé, P., & Armour, J. A. (2009). Localization of multiple neurotransmitters in surgically derived specimens of human atrial ganglia. *Neuroscience*, *164*(3), 1170–1179. https://doi.org/10.1016/j.neuroscience.2009.09.001

Inoue, H., Skale, B. T., & Zipes, D. P. (1988). Effects of ischemia on cardiac afferent sympathetic and vagal reflexes in dog. *American Journal of Physiology-Heart and Circulatory Physiology*, *255*(1), H26–H35. https://doi.org/10.1152/ajpheart.1988.255.1.H26

Inoue, H., & Zipes, D. P. (1987). Results of sympathetic denervation in the canine heart: Supersensitivity that may be arrhythmogenic. *Circulation*, *75*(4), 877–887. https://doi.org/10.1161/01.CIR.75.4.877

Inoue, H., & Zipes, D. P. (1988). Time course of denervation of efferent sympathetic and vagal nerves after occlusion of the coronary artery in the canine heart. *Circulation Research*, *62*(6), 1111–1120.

Lever, J. D., Ahmed, M., & Irvine, G. (1965). Neuromuscular and intercellular relationships in the coronary arterioles. A morphological and quantitative study by light and electron microscopy. *Journal of Anatomy*, *99*(Pt 4), 829–840.

Levy, M. N. (1971). *Brief Reviews Sympathetlc-Parasympathetic Interactions in the Heart*. *Circulation Research An Official Journal of the American MI ear t Association*.

Liu, Y., Yue, W. S., Liao, S. Y., Zhang, Y., Au, K. W., Shuto, C., … Tse, H. F. (2012). Thoracic spinal cord stimulation improves cardiac contractile function and myocardial oxygen consumption in a porcine model of ischemic heart failure. *Journal of Cardiovascular Electrophysiology*, *23*(5), 534–540. https://doi.org/10.1111/j.1540-8167.2011.02230.x

Lo, L. W., Scherlag, B. J., Chang, H. Y., Lin, Y. J., Chen, S. A., & Po, S. S. (2013). Paradoxical long-term proarrhythmic effects after ablating the head station ganglionated plexi of the vagal innervation to the heart. *Heart Rhythm*, *10*(5), 751–757. https://doi.org/10.1016/j.hrthm.2013.01.030

Lobato, E. B., Kern, K. B., Paige, G. B., Brown, M., & Sulek, C. A. (2000). Differential effects of right versus left stellate ganglion block on left ventricular function in humans: an echocardiographic analysis. *Journal of Clinical Anesthesia*, *12*(4), 315–318.

Lown, B. (1979). Sudden cardiac death -- 1978. *Circulation*, *60*(7), 1593–1599. https://doi.org/10.1161/01.CIR.60.7.1593

Lu, Z., Scherlag, B. J., Lin, J., Yu, L., Guo, J. H., Niu, G., … Po, S. S. (2009). Autonomic mechanism for initiation of rapid firing from atria and pulmonary veins: Evidence by ablation of ganglionated plexi. *Cardiovascular Research*, *84*(2), 245–252. https://doi.org/10.1093/cvr/cvp194

Malliani, A., Recordati, G., & Schwartz, P. J. (1973). Nervous activity of afferent cardiac sympathetic fibres with atrial and ventricular endings. *The Journal of Physiology*, *229*(2), 457–469. https://doi.org/10.1113/jphysiol.1973.sp010147

Malliani, Alberto, Pagani, M., Pizzinelli, P., Furlan, R., & Guzzetti, S. (1983). Cardiovascular reflexes mediated by sympathetic afferent fibers. *Journal of the Autonomic Nervous System*, *7*(3–4), 295–301. https://doi.org/10.1016/0165-1838(83)90082-6

Malpas, S. (1998). The rhythmicity of sympathetic nerve activity. *Progress in Neurobiology*, *56*(1), 65–96. https://doi.org/10.1016/S0301-0082(98)00030-6

McMahon, N. C., Drinkhill, M. J., & Hainsworth, R. (1996). Vascular responses to stimulation of carotid, aortic and coronary artery baroreceptors with pulsatile and non-pulsatile pressures in anaesthetized dogs. *Experimental Physiology*, *81*(6), 969–981. https://doi.org/10.1113/expphysiol.1996.sp003997

Minisi, A J, & Thames, M. D. (1993). Distribution of left ventricular sympathetic afferents demonstrated by reflex responses to transmural myocardial ischemia and to intracoronary and epicardial bradykinin. *Circulation*, *87*(1), 240–246.

Minisi, Anthony J, & Thames, M. D. (1991). Activation of cardiac sympathetic afferents during coronary occlusion. Evidence for reflex activation of sympathetic nervous system during transmural myocardial ischemia in the dog. *Circulation*, *84*(1), 357–367. https://doi.org/10.1161/01.CIR.84.1.357

Murphree, S. S., & Saffitz, J. E. (1988). Delineation of the distribution of beta-adrenergic receptor subtypes in canine myocardium. *Circulation Research*, *63*(1), 117–125.

Opthof, T., Misier, A. R., Coronel, R., Vermeulen, J. T., Verberne, H. J., Frank, R. G., … Janse, M. J. (1991). Dispersion of refractoriness in canine ventricular myocardium. Effects of sympathetic stimulation. *Circulation Research*, *68*(5), 1204–1215.

Pagani, M., Pizzinelli, P., Bergamaschi, M., & Malliani, A. (1982). A positive feedback sympathetic pressor reflex during stretch of the thoracic aorta in conscious dogs. *Circulation Research*, *50*(1), 125–132.

Pagani, M., Pizzinelli, P., Furlan, R., Guzzetti, S., Rimoldi, O., & Malliani, A. (1981). A sympathetic hypertensive reflex from the heart of conscious dogs. *Clinical Science (London, England : 1979)*, *61 Suppl 7*, 181s-183s.

Pardini, B. J., Lund, D. D., & Schmid, P. G. (1989). Organization of the sympathetic postganglionic innervation of the rat heart. *Journal of the Autonomic Nervous System*, *28*(3), 193–201. https://doi.org/10.1016/0165-1838(89)90146-X

Parsons, R. L., Locknar, S. A., Young, B. A., Hoard, J. L., & Hoover, D. B. (2006). 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 and Tissue Research*, *323*(2), 197–209. https://doi.org/10.1007/s00441-005-0074-3

Patterson, E., Jackman, W. M., Beckman, K. J., Lazzara, R., Lockwood, D., Scherlag, B. J., … Po, S. (2007). Spontaneous pulmonary vein firing in man: relationship to tachycardia-pause early afterdepolarizations and triggered arrhythmia in canine pulmonary veins in vitro. *Journal of Cardiovascular Electrophysiology*, *18*(10), 1067–1075. https://doi.org/10.1111/j.1540-8167.2007.00909.x

Pauza, D. H., Saburkina, I., Rysevaite, K., Inokaitis, H., Jokubauskas, M., Jalife, J., & Pauziene, N. (2013). Neuroanatomy of the murine cardiac conduction system. *Autonomic Neuroscience*, *176*(1–2), 32–47. https://doi.org/10.1016/j.autneu.2013.01.006

Pauza, D. H., Skripka, V., Pauziene, N., & Stropus, R. (2000). Morphology, distribution, and variability of the epicardiac neural ganglionated subplexuses in the human heart. *Anatomical Record*, *259*(4), 353–382. https://doi.org/10.1002/1097-0185(20000801)259:4<353::AID-AR10>3.0.CO;2-R

Pauziene, N., Alaburda, P., Rysevaite-Kyguoliene, K., Pauza, A. G., Inokaitis, H., Masaityte, A., … Pauza, D. H. (2016). Innervation of the rabbit cardiac ventricles. *Journal of Anatomy*, *228*(1), 26–46. https://doi.org/10.1111/joa.12400

Pierpont, G. L., DeMaster, E. G., Reynolds, S., Pederson, J., & Cohn, J. N. (1985). Ventricular myocardial catecholamines in primates. *The Journal of Laboratory and Clinical Medicine*, *106*(2), 205–210.

Shimizu, W., & Antzelevitch, C. (1998). 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*, *98*(21), 2314–2322.

Singh, S., Sayers, S., Walter, J. S., Thomas, D., Dieter, R. S., Nee, L. M., & Wurster, R. D. (2013). Hypertrophy of neurons within cardiac ganglia in human, canine, and rat heart failure: the potential role of nerve growth factor. *Journal of the American Heart Association*, *2*(4). https://doi.org/10.1161/JAHA.113.000210

Stee, E. W. Van. (1978). Autonomic Innervation of the Heart. *Environmental Health Perspectives*, *26*, 151. https://doi.org/10.2307/3428837

Tomita, T., Takei, M., Saikawa, Y., Hanaoka, T., Uchikawa, S.-I., Tsutsui, H., … Kubo, K. (2003). Role of autonomic tone in the initiation and termination of paroxysmal atrial fibrillation in patients without structural heart disease. *Journal of Cardiovascular Electrophysiology*, *14*(6), 559–564.

Vaitkevicius, R., Saburkina, I., Rysevaite, K., Vaitkeviciene, I., Pauziene, N., Zaliunas, R., … Pauza, D. H. (2009). Nerve Supply of the Human Pulmonary Veins: An Anatomical Study. *Heart Rhythm*, *6*(2), 221–228. https://doi.org/10.1016/j.hrthm.2008.10.027

Wake, E., & Brack, K. (2016). Characterization of the intrinsic cardiac nervous system. *Autonomic Neuroscience: Basic and Clinical*. https://doi.org/10.1016/j.autneu.2016.08.006

Wang, H. J., Rozanski, G. J., & Zucker, I. H. (2017). Cardiac sympathetic afferent reflex control of cardiac function in normal and chronic heart failure states. *Journal of Physiology*, *595*(8), 2519–2534. https://doi.org/10.1113/JP273764

Winter, J., Brack, K. E., & Ng, G. A. (2011). The acute inotropic effects of cardiac contractility modulation (CCM) are associated with action potential duration shortening and mediated by β1-adrenoceptor signalling. *Journal of Molecular and Cellular Cardiology*, *51*(2), 252–262. https://doi.org/10.1016/j.yjmcc.2011.04.010

Winter, J., Tanko, A. S., Brack, K. E., Coote, J. H., & Ng, G. A. (2012). Differential cardiac responses to unilateral sympathetic nerve stimulation in the isolated innervated rabbit heart. *Autonomic Neuroscience: Basic and Clinical*, *166*(1–2), 4–14. https://doi.org/10.1016/j.autneu.2011.08.004