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

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.

[figure: innervation of the heart anatomy]

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).

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.

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

Over 100 years ago, John MacWilliam proposed that VF was the mechanism behind SCD, and subsequently Thomas Jonnesco demonstrated that cardiac sympathectomy was protective against ventricular arrhythmias.[13,14] Other corroborative studies by Bernard Lown showed that vagus nerve stimulation decreased the vulnerability of the heart to VF while vagotomy increased it.[15,16] This adequately argues that sympathetic tone is in part culpable for VF/VT events.

[figure of VF threshold and vagotomy]

The unopposed sympathetic nerve is pathologic. Stimulation of the SNS however can occur from higher nervous factors. An excellent example is how the frequency of premature ventricular contractions increased under psychological stress, suggesting that even transient nervous factors lead to electrical instability.[17] These extrasystole beats can be reduced by the introduction of beta-adrenergic blockade.[18] Empiric and anecdotal evidence provided the initial insight into how sudden death was triggered by psychological stress. Engel described several categories of traumatic life settings that precipitated sudden death, from the loss of a loved one, acute grief, personal danger, and even triumph. This pattern was found to play out in a larger scale, with case series by Greene and Rahe that demonstrated hundreds of episodes of sudden death preceded acute and chronic emotional events.[19,20]

[figure: PVC frequency increased with stress]

The evolutionary purpose of sympathetic outflow to the heart allows for a by-product, the decrease in the VF threshold that is seen with stellate stimulation . Its physiologic role however is related to the original “fight or flight” response. Studies focused on the stellate ganglia helped to delineate the specific actions the SNS had upon the heart. The basic responses of the heart are inotropy (increased “squeeze”), lusitropy (improved relaxation), chronotropy (increased sinoatrial firing), and dromotropy (improved nerve conduction). There is an element of handed-ness to the innervation, such that the right and left stellate ganglia have differing effects, in

part because of location of innervation. The RSG has an higher amount of atrial innervation, including the SA node, and leads to changes in chronotropy. The LSG innervates the ventricles predominantly, leading to an increase in inotropy. The relationship is complex, as right stellectomy can lead to compensatory contralateral activation.[15] Bilateral stellectomy though has a well-established effect of increased the resilience of the heart to VT and VF.[21]

CORONARY PERFUSION

In an out-of-hospital cardiac arrests, ST-segment elevations after VT or VF event have over a 70% chance of significant coronary artery disease (CAD).[22] Even after an MI, Dr. Bernard Lown noted that patients were at significant risk for SCD and would benefit from a coronary care unit that focused on prophylaxis of arrhythmias. How do acute infarction and chronic ischemia generate malignant rhythms? There are acute responses and delayed reorganization of the SNS that explain these findings.

Knowledge of coronary blood flow regulation is important in understanding the pathogenesis of VT and VF. The most prominent regulators of the coronary arteries is based on pressure changes. High pressure leads to sympathetic inhibition, while low pressures causes increased sympathetic efferent outflow which leads to vasoconstriction.[23,24] The coronary arteries are innervated by both adrenergic and cholinergic neurons, with an increase in the amount of nerve terminals in the smaller arteries and arterioles.[25] The beta-1 adrenergic receptors (B1AR) predominate the larger conduit arteries while the smaller vessels have a higher proportion of B2AR and alpha-1 adrenergic receptors (A1AR).[26,27] For example, in cardiac transplant patients, as they have no connection between the EC and IC, systemic NE leads to coronary vasodilation in the large vessels (e.g. left anterior descending) in proportion to the concentration of sympathetic nerve terminals.[28] However, in the event of ischemia or increased workflow, coronary vasoconstriction can be attenuated by the metabolic waste productions like adenosine.[29] These differences in proportions of receptors are responsible for balancing perfusion through local vasodilation and vasoconstriction in the healthy heart, as a response to cardiac demand and myocardial contraction. These systems were not built to respond to ischemia.

[figure: coronary perfusion and VF threshold]

The heart responds to acute changes in coronary perfusion with an intense sympathetic response, which subsequently lowers the VF threshold. Transmural infarcts lead to sympathetic denervation, while subendocardial ischemia will likely only impact the vagal afferent nerve endings.[30,31] This was studied by looking at the response of nerves to epicardial stimuli. Non-transmural ischemia still allowed for a response to

chemical stimuli, but transmural ischemia lead to apical loss of efferent sympathetic nerves within 20 minutes.[32] After 90 minutes, afferent sympathetic and vagal nerves also became denervated.[33] During these ischemic events, there is an increase in sympathetic excitatory outflow.[34].

[figure: zipes myocardial innervation]

However there remains a prolonged risk for arrhythmias after reperfusion. There is differential, heterogenous innervation of sympathetic fibers in the cardiac tissue that become a nidus for arrhythmogenesis. Initially after ischemia, IC neuronal remodeling occurs. There is an immediate and persistent increase in nitric oxide synthase (NOS) containing neurons and a hypersensitivity to NE stimuli leading to generalized excitability.[35] The non-ischemic and ischemic territories develop differential sympathetic efferent activity after events as well.[36] Both denervation and hyperinnervation are the response, and at the boundary of preserved and ischemic myocardium there becomes an interdigitation of innervated and denervated tissue.[37] The nerve-sprouting that occurs is due to an increase in activity of left stellate ganglia in the setting of chronic myocardial ischemia.[38,39]

Not only does myocardial ischemia and infarction lead to changes in innervation, but also in receptor density and response, which we will discuss in the next section.

EFFECT OF CATECHOLAMINES

The expected physiologic response to increased demands, through physical or psychological arousal, is an augmented cardiac output upwards of 10 L/min mediated through local neurotransmitters. Myocardial contractility is increased through the effect of NE on heavily sympathetically-innervated myocardium, which leads to ventricular inotropy and lusitropy through increased cytosolic calcium.[40] The effect of NE at the SA and AV node leads to increases in chronotropy (heart rate) and dromotropy (speed of conduction).[41,42] However, at supraphysiologic levels, pathology develops.

Takotsubo cardiomyopathy, the “broken heart” syndrome, is a clinical entity well-known for the role of SNS overactivity, characterized by apical hypokinesis. Situations that cause sympathetic hyperactivation, from elevated intracranial pressure, pheochromocytoma crises, and emotionally devastating events, cause both increased systemic and cardiac sympathetic outflow can lead to a stress cardiomyopathy.[43,44] But is it systemic NE or local NE that leads to these findings? There are two paths the sympathetic branch takes to reach the apex of the heart – through the coronary artery system and direct innervation of the myocardium. Understanding the location and density of adrenergic receptors helps to theorize how catecholamine-excess states leads to cardiac pathology. Above, we discussed the receptor locations within the coronary arteries, and here we will discuss the importance of receptor location in the myocardium.

Almost all cardiomyocytes are in contact with sympathetic neurons, as sympathetic stimulation leads to normal cardiomyocyte growth.[42,45,46] B1AR and B2AR are both present in cardiac myocytes at sympathetic nerve terminals. B1AR accumulate at synapses, while B2AR undergo endocytosis after stimulation.[47] These signals help regulate the contractility of myocytes. The density of adrenergic receptors and NE is greatest at the base of the heart, with decreasing concentrations moving towards the apex.[7,8] Cardiac myocyte toxicity occurs under excessive or prolonged catecholamine exposure, and is seen in Takotsubo syndrome with contraction band necrosis on histology. The preference for the apex could occur through either the coronary adrenergic system, or through the cardiomyoctes themselves. An older theory posited that multivessel coronary vasospasm could lead to apical toxicity, however A1AR and B1AR within the coronary vessels do not cause cardiomyocyte

necrosis, which is seen in Takotsubo syndrome with contraction band necrosis.[48,49] The apex may be more vulnerable to NE overactivation due to the scarcity of available adrenergic receptors, leading to relatively "earlier" saturation of receptors compared to more proximal parts of the heart.

The adrenergic and vagal neurotransmitters interact locally, with each branch of the ANS modulating the other. Choline acetyltransferase (ChAT) somata produce acetylcholine (ACh), which are typically vagal and cardioinhibitory. Cholinergic cells predominate the 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.[50,51] 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.[52] As it is also a co-transmitter that modulates the vagal effect of increasing the VF threshold, through modifying action potential duration (APD). TH is responsible for NE production, but surprisingly 10-20% of all neurons contain both TH and ChAT.[53] Both the left and right coronary plexuses however are mainly adrenergic.[54] 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.[55] It also functions as a potent coronary vasoconstrictor acutely, however may lead to angiogenesis in the long-term.[56] 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.[57] 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.[58] 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.[58]

Understanding both the receptor responses and the neurotransmitters themselves serve to provide a structure to more complex disease states, such as cardiomyopathy. The increased sympathetic tone seen in acute ischemic heart failure models show an improved myocardial contraction, decreased oxygen consumption, decreases intraventricular desynchrony, all without elevation of NE.[59] But, through prolonged exposure to

elevated levels of NE, the neuronal bodies become hypertrophied and edematous. They become less excitable and eventually lead to vagal withdrawal.[60] In all types of dilated cardiomyopathy, the B1AR are downregulated eventually, such that the cardiac sympathetic afferent reflexes causes minimal increases in contractility.[61] Systemically however, this leads to increased vasoconstriction, leading to the high systemic vascular resistance or afterload that is seen in the end-stage heart failure population.[62]

CONCLUSION

The sympathetic outflow to the heart has important implications both acutely and chronically. The most drastic effect of SNS pathology is the triggering of ventricular fibrillation, and understanding the anatomical considerations leads to an understanding of pathogenesis and treatment strategies (i.e. epicardial scar ablation, stellate ganglion blocks, etcetera). Understanding the innervation of the coronary arteries and cardiomyocytes helps to explain the effect of local neurotransmitters both in the acute setting of ischemia or infarction and also the pathogenesis of cardiomyopathies. This review serves to contextualize the sympathetic nervous system to a clinical audience, allowing a better and more nuanced understanding of the importance of this branch of the autonomic nervous system in cardiac pathology.

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