# DRAFT: THE SYMPATHETIC INNERVATION OF THE HEART

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

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# INTRODUCTION

“Why did he die on Tuesday and not on Monday?” ~ Douglas Zipes

This question, asked over 30 years ago, remains unanswered in clinical medicine. Sudden cardiac death, particularly in the setting of ventricular fibrillation, ischemic heart disease, or heart failure, all serve as pathological examples that benefit from answering this question. To delve into it however requires an understanding of how the heart is acted upon by the surrounding world, and how the heart reacts in turn.

Animal life consists fundamentally of the adjustment of an organism to two primary conditions: pertaining to that of the external environment and pertaining to that of the internal environment. In vertebrates, the system that concerned itself with adjustment of an organism to its internal environment became known as the sympathetic nervous system.1

The sympathetic nervous system innervation of the heart and vasculature allow for the robust “fight-or-flight” response, allowing the body to augment its cardiac output and respond to stressors appropriately. However, alterations to sympathetic nerve activity (SNA) can lead to pathophysiological changes in cardiac function, while alterations in cardiac function can also lead to changes in SNA in a bidirectional manner. For example, high SNA can occur in trauma, psychological stress, or brain injury which in turn can affect the heart – from arrhythmia to stress cardiomyopathies. Cardiac disease, such as myocardial infarctions and heart failure, can reciprocally raise SNA.

In the following, we will first describe the historical importance of the sympathetic innervation of the heart and describe the relevant anatomy of the neurocardiac axis. We will highlight the physiology of cardiac reflexes that regular SNA and how derangements contribute to pathophysiological states of the cardiac substrate. We will finally describe clinical treatment paradigms and consideration for future directions in targeting sympathetic modulation.

# RELEVANT CARDIAC ANATOMY

The relationship of the heart to the sympathetic nervous system however was not clinically appreciated until Jonnesco performed the first cardiac sympathectomy, which protected a patient from recurrent angina pectoris and ventricular tachyarrhythmias.2 In humans, we describe these pathways that connect the brain, spinal cord, and heart the neurocardiac axis (Figure X).

The neural control of the heart is in part a product of its anatomy. The spinal cord houses the preganglionic neurons of the SNS within the intermediolateral cell columns at each vertebral level. Cardiac outflow occurs between the T1 and T6 vertebrae. Neurons exit through the ventral roots, merge into the white rami, and then join the sympathetic chain and the extracardiac ganglia, such as the stellate ganglion. These nerves have their own distinct cardiac rhythm and frequencies of oscillation that are transmitted to the postganglionic neurons of the heart. The have intrinsic periodicities that can match respiratory rates, in the 0.1 to 0.4 Hz range, as well as the oscillations seen in arterial blood pressure, known as Mayer waves.3 These nerves provide signals to the heart as part of a number of reflex arcs to maintain heart rate or blood pressure.

What happens when these nerves are transected, such as in a thoracic spinal cord injury? Without sympathetic input, the atrial and ventricular reflexes are diminished. The atria when dilated can signal through vagal afferents to increase SNA primarily through the Bainbridge reflex.4 The normal heart would increase sinoatrial node activity, increasing heart rate, and subsequently decrease atrial pressures. With this reflex destroyed, bradycardia would occur that could lead to worsened ventricular diastolic filling.4 Similarly, the ventricles have potent mechanical sensors that can trigger sympathetic outflow, such as increased contractility in response to increased pressure.5 Without this response, cardiac output diminishes. In a state of stress, such as hypoxemia or exercise, the loss of SNA is amplified and both chronotropy and inotropy are suppressed leading to bradycardia and systemic hypotension.6,7 This exemplifies not only the complexity of cardiac sympathetic innervation, but the importance of cardiovascular reflexes that are normally maintained and autoregulated.

**THE VENTRICULAR SUBSTRATE**

John MacWilliam proposed that ventricular fibrillation, historically known as delirium cordis or circus contraction, was the cause of sudden cardiac death in 1889.8 Since then, we have come to understand that the ventricular substrate has increased risk for fibrillation after being modified by disease, such as myocardial infarction or hypertrophy. In fact, Garrey found that a fibrillating ventricle required a minimum mass, and hearts less than 4 centimeters in size could not sustain ventricular fibrillation.9

The *nervous* heart can trigger sudden death. In the early 1970s, cases from across the world showed stressful events, from grief, anxiety, and anger lead to and potentially precipitated episodes of sudden death.10,11 Bernard Lown, considered the father of the coronary care unit, introduced a theory on the development of sudden death: 1) the mechanism of sudden death is ventricular fibrillation, 2) electrical instability precedes catastrophic arrhythmia, 3) ventricular beats predispose the vulnerable heart to ventricular fibrillation, and 4) transient nervous risk factors induce electrical instability.12 With this in mind, he proposed that in post-myocardial infarction, patients would most benefit from arrhythmia management and restful recoveries.13 The relationship to the sympathetic nervous system was elucidated through neurological testing, such as hypothalamic stimulation and stellate ganglion stimulation, both of which reduced the ventricular fibrillatory threshold.14

Psychological stress can also increase the rate of ventricular ectopy. Clinically, in patients with a predisposition to ventricular dysrhythmias, undergoing mental stress not only increases the frequency of ventricular beats but also the rate of ventricular and supraventricular tachycardia.12 This effect of sympathetic stimulation decreasing the ventricular threshold was abolished by beta blockade, a large part of why beta-blockers are protective in myocardial infarction. Similarly, in the nervous heart, stellate ganglion block and anti-anxiety medications can both be successful in decreasing ventricular ectopy.

# CORONARY BLOOD FLOW

In out-of-hospital cardiac arrests, ST-segment elevations after ventricular tachyarrhythmias have over a 70% chance of significant coronary artery disease,15 with a persistently elevated risk and require arrhythmia prophylaxis. Understanding how the coronary arteries are regulated reveals insight into their relationship with SNA and the subsequent risk for dysrhythmias.

The coronary arteries begin at the level of the cusps of the aorta, with large, epicardial, conduit vessels branching out and traversing through the myocardium to the endocardium. They are regulated through pressure changes and adrenergic signaling. The smaller arteries and arterioles, making up the resistance vessels within the myocardium, are more densely innervated than the larger, epicardial vessels. High pressures leads to sympathetic inhibition and subsequent vasodilation, while low pressures lead to sympathetic efferent outflow and subsequent vasoconstriction, all of which is more prominent in the resistance vessels than the epicardial vessels. Adrenergic receptors also lead to coronary vasomotor changes based on systemic catecholamines based on the type and density of receptors, such as β1 predominating the epicardial vessels, while resistance vessels have more β2 and α1 receptors. For example, in a transplanted heart, systemic nor epinephrine leads to vasodilation in the epicardial vessels in proportion to the amount of nerve terminals. This balance of pressure reflexes and adrenergic signaling help regulate the coronary blood flow to meet cardiac demands and myocardial contraction.

However, these systems were not built to respond to ischemia. In the setting of acute myocardial ischemia, the heart has an intense sympathetic response. The acute coronary occlusion leads to a strong cardiac sympathetic afferent response,16 which subsequently lowers the threshold for ventricular fibrillation as seen in **Figure X**. Of note, the fibrillatory threshold is protected during acute ischemia by the use adrenergic antagonists, such as propranolol, highlighting one of the mechanisms by which beta blockers provide mortality benefit. Transmural ischemia leads to the distal loss of efferent sympathetic nerves within 20 minutes and loss of afferent sympathetic and vagal nerves after approximately 90 minutes.17,18 The effects however are not just seen during the event, but ischemia and its changes can lead to more chronic changes in sympathetic regulation of the heart, including angina and persistent tachycardia.

# CHRONIC MYOCARDIAL ISCHEMIA

* 1. Douglas Zipes introduction to scars as a nidus for VT/VF
  2. Anatomy of myocardial innervation at histological layers, and again in overall density (MIBG)
  3. Cardiac remodeling after MI, including scar formation and physiology of VT/VF currents
  4. Chronic changes that lead to resting SNA tone after MI (Rosenberg and Dyx)

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# FIGURES

Figure X  
A close up of a map

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Figure X

A close up of text on a white background

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Figure X

A picture containing text, map

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