# SIGNIFICANCE

## B1. Ischemic Heart Disease Remains an Under Recognized Problem

IHD accounts for in 1 in every 7 deaths in the United States, with a prevalence of 3% or 7.9 million US adults.1 Over 700,000 new heart attacks occur annually, with annual costs of heart attacks ($12.1 billion) and IHD ($9.0 billion) being 2 of the 10 most expensive conditions treated in the US as of 2013. The estimated direct and indirect costs of IHD were $204 billion, and these medical costs are projected to double by the year 2030.1 However up to 20% of MIs are silent and up to 80% of IHD is unrecognized by standard ECG and clinical parameters.2 Although there has been a decline in cardiovascular mortality overall, the rate of out-of-hospital events has not decreased in proportion to the rate of in-hospital events.3 In addition, the majority of SCD still occur in those without previously diagnosed IHD.4 The above estimates underscore the current and emerging burden on the health care system and highlight a need for new strategies to identify IHD and prevent its associated complications.

## B2. Advances in Electrocardiography are Independent Prognostic of Cardiovascular Mortality

Historically, abnormal HRV after MI was associated with an increased mortality, and numerous other studies replicate its importance.5,6 Information contained within traditional HRV indices was thought to be explained by heart rate itself,7 but newer indices may capture additional information.8 A novel method for HRV analysis is througha non-linear method named *Dyx*, which uses the multipole method in Poincaré plots where RR intervals are plotted as a function of prior RR intervals.9–11 *Dyx* reflects how one beat accelerates or decelerates compared to the previous beat, which may more robustly signal autonomic tone. A recent study shows that after MI, low *Dyx* had a hazard ratio of 2.4 (CI 1.5 to 3.8) for mortality, even after adjusting for left ventricular ejection fraction.12 This suggests that advanced ECG analysis can convey information about autonomic function that is an independent marker for cardiovascular mortality.13 These important findings have helped to establish non-invasive means to measure ANS outflow, particularly in disease states, which has spurred research in HRV analysis. Interestingly, a recent task force noted that HRV analysis ﻿“seems to still suffer from the conceptual disconnect between clinical cardiologists on the one side and mathematicians and engineers on the other side.”13 Therefore, HRV analysis in cardiovascular disease represents an area of unmet and pressing need for translational research, which will hopefully improve our understanding of autonomic dysfunction and its complications.

## B3. Neurovisceral Dysfunction Potentially Alters the Autonomic Nervous System

The neurovisceral integration theory links cognitive and affective networks to autonomic regulation.14,15 This framework emphasizes that differential activation of brain structures, particularly the prefrontal cortex, cingulate cortex, and insula, are important in autonomic function. Maladaptive neuropsychological states, such as cognitive impairment and depression, can thus lead to neurovisceral dysfunction, which may alter the autonomic nervous system. Psychological stress, including depression, leads to changes in autonomic function that have historically known to increase to the risk of ventricular arrhythmia and SCD,16–18 and may be an independent risk factor for cardiovascular disease.19–21 Cognitive impairment, particularly as it relates to executive function, is also associated with abnormal HRV, and also leads to an increased odds of IHD independent of other cardiovascular risk factors.22,23 After ischemic stroke, when HRV is measured during cognitive performance tasks, patients with poorer performance have simultaneous findings of abnormal HRV.25 These interesting findings suggest that neurovisceral dysfunction may manifest as autonomic dysfunction as measured by HRV. Understanding this relationship is important because it will help identify patients at risk for neuropsychological disease, help target treatment and interventions early on, and may even serve as a tool to measure recovery.

## B4. Clinical Implications and Utility of Measuring Autonomic Dysfunction

Although numerous studies have suggested that autonomic dysfunction has independent prognostic value after MI, very few studies have examined the relationship of autonomic dysfunction preceding IHD. Traditional methods including exercise stress testing have limited sensitivity,32 but advances in ECG have led to novel risk markers for IHD that are in need of further investigation.33,34 Work by the lead mentor demonstrated that frontal T axis, QT interval, and heart rate from ECG could improve classification of the Framingham risk score by 24%,35 highlighting the importance of non-traditional ECG factors in risk prediction, particularly as they are low-cost and non-invasive. There is a single, recent study that examined *Dyx* in a moderate risk group without known IHD, and found that low *Dyx* predicted abnormal MPI with an improved sensitivity and specificity to exercise stress test.33 This applicant has shown that in a cohort of 276 individuals with no known IHD from the Emory Twin Study, low *Dyx* in morning hours had a 12-fold increase in the odds of abnormal MPI.36 These findings validate the prior work on *Dyx* but also strongly implicate the role of the circadian rhythm in autonomic balance, highlighting the importance of understanding HRV in the context of the time of day.37,38 In preliminary analysis of this cohort, additional HRV indices were also predictive of abnormal CAD in a subset of 31 individuals with depression, once again supporting the need to clarify the relationship of autonomic function within the neurocardiac axis. However, the coronary vasodilatory agents during MPI do not cause an increase in myocardial tissue demand nor do positive findings distinguish between epicardial and resistance vessels. Currently, no studies have evaluated autonomic dysfunction for its relationship to angiographic findings of obstructive CAD. Therefore, the role of autonomic dysfunction as a risk-stratification tool in those without known IHD represents a pressing area for translational research before application in a clinical context, and will help improve our understanding of non-traditional risk-factors in the pathogenesis of IHD. As ECG testing is readily available, measuring autonomic dysfunction as a risk-factor for IHD may help reduce the burden to the health-care system and allow for early intervention.

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