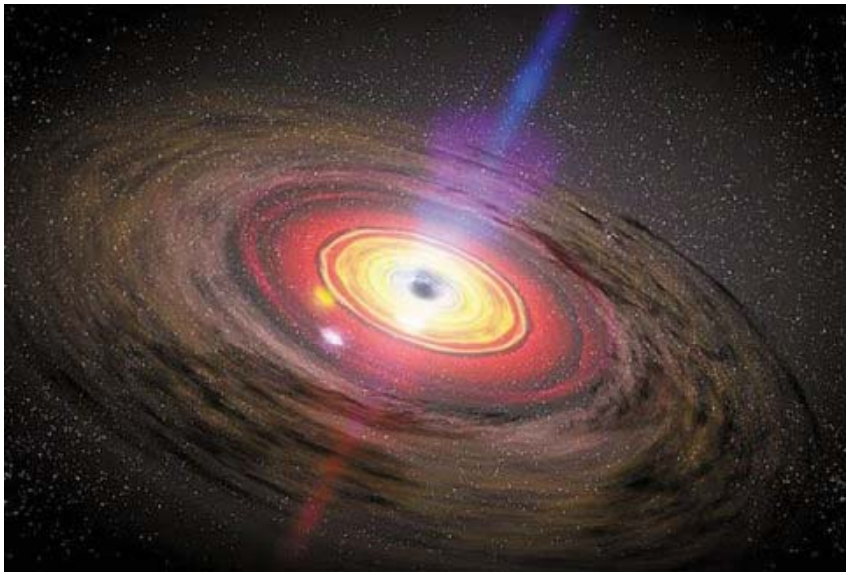
What is PD2i?

PD2i is a revolutionary method of analyzing the variations in R-R intervals in a non-linear fashion.

What is revolutionary about non-linear analysis?



Using linear techniques to measure non-linear complex human functions and organ interactions is like using geometry to measure a black hole.

What is PD2i?

PD2i is a measure of the degrees of freedom (cooperativity or independence) of the different elements of the autonomic nervous system (ANS) that control heart rate (sympathetic and parasympathetic). These elements, known as sensory-motor loops (SMLs), each react to specific sensory input, such as blood pH, body temperature, blood pressure, among others.

In chronic disease (e.g., congestive heart failure) or acute insult (e.g., trauma), the SMLs coordinate their behavior more; this results in the HRV signal showing lower degrees of freedom as the SMLs work more cooperatively, and is reflected in lower PD2i values.

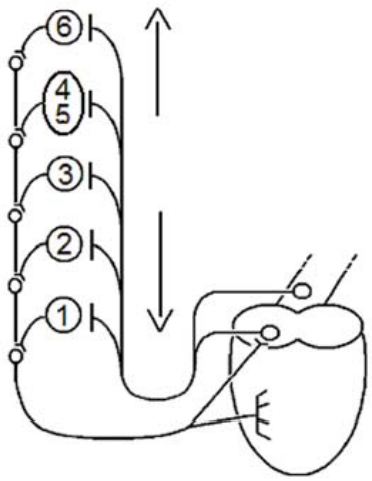
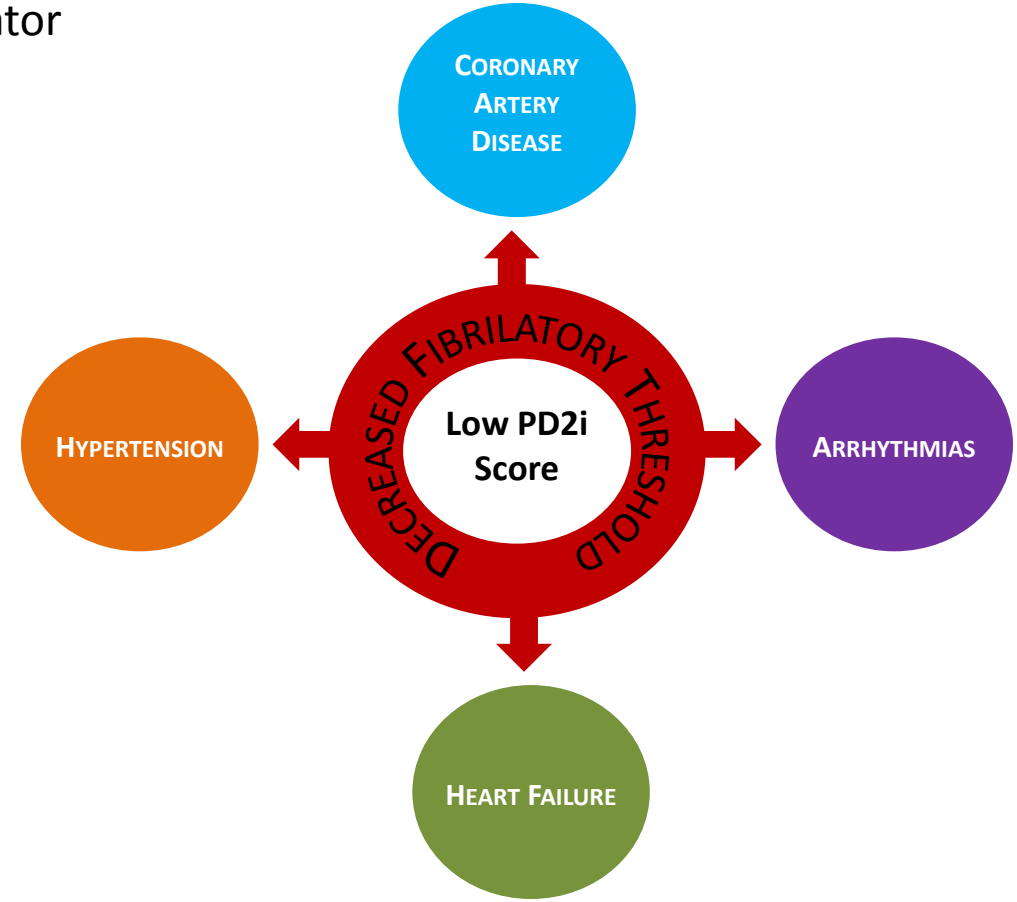


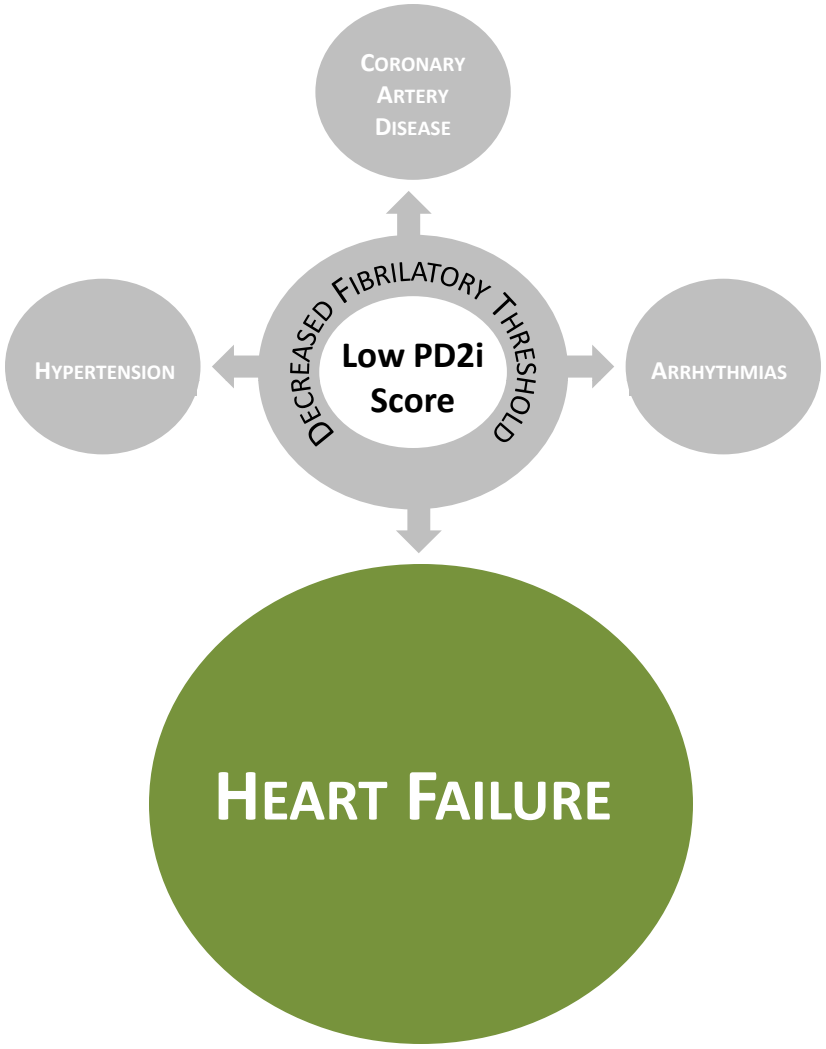
FIGURE 2. The sensory-motor loops of the brain-heart axis that compete with one another to control the heartbeat intervals.

Application of PD2i

The PD2i algorithm has been show in multiple studies to be an early indicator of future cardiovascular events

- Music Trial (Heart Failure)
- Risk stratification for arrhythmic death in an emergency department cohort (Chest Pain)
- Early detection of acute allograft rejection by linear and nonlinear analysis of heart rate variability





- Prognostic Significance of PD2i, Novel Risk Marker in Heart Failure Patients (MUSIC Trial) – American College Of Cardiology Poster Presentation 2011, Poster 1125-376

- The Role of Heart Rate Variability in Prognosis for Different Modes of Death in Chronic Heart Failure *PACE 2006; 29:892–904*

- Left Ventricular Systolic and Diastolic Function in Normotensive Type 1 Diabetic Patients With or Without Autonomic Neuropathy *DIABETES CARE, VOLUME 26, NUMBER 7, JULY 2003*

- Influence of cardiovascular autonomic neuropathy on atherogenesis and heart function in patients with Type 1 diabetes – DIABETES RESEARCH AND CLINICAL PRACTICE JULY, 7, 2008

Heart Failure

- **Diagnosis of CAN may be the earliest warning sign for diminishing cardiac function**

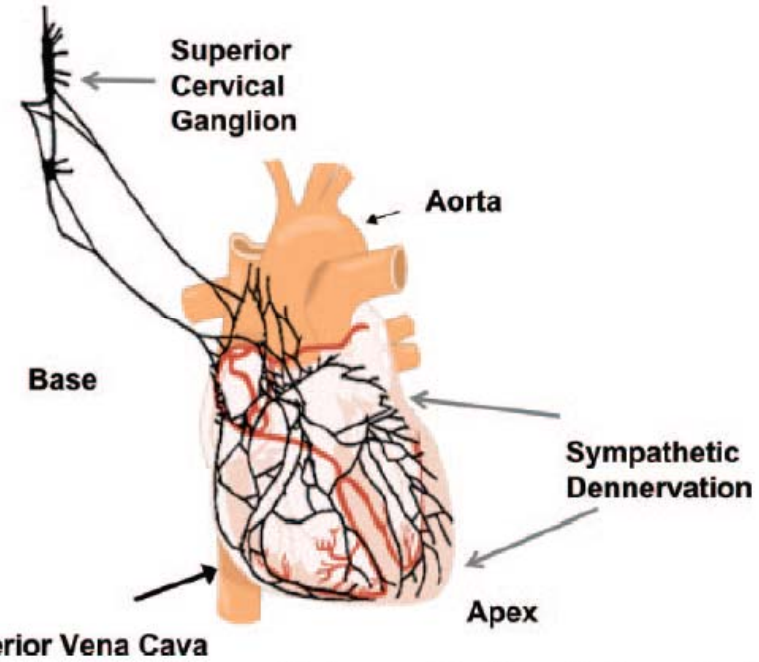


Figure 1—*The autonomic innervation of the heart and the effects of diabetes. It has been shown that in diabetes, in a fashion that parallels the development of peripheral neuropathy, which begins at the tip of the toes and can progress proximally, neuropathy affecting the heart begins at the apex of the ventricles and progresses toward the base.*

The presence of CAN was also linked to the development of diabetic cardiomyopathy in type 1 diabetes because in these patients LV dysfunction often precedes or occurs in the absence of significant coronary artery disease or hypertension. We have identified diastolic dysfunction early in the course of type 1 diabetes that correlated with abnormal cardiac sympathetic imaging.*

*Cardiac Autonomic Neuropathy in Diabetes: A clinical perspective - DIABETES CARE, VOLUME 33, NUMBER 2, FEBRUARY

VICOR TECHNOLOGIES, INC

MUSIC Trial

Basics:

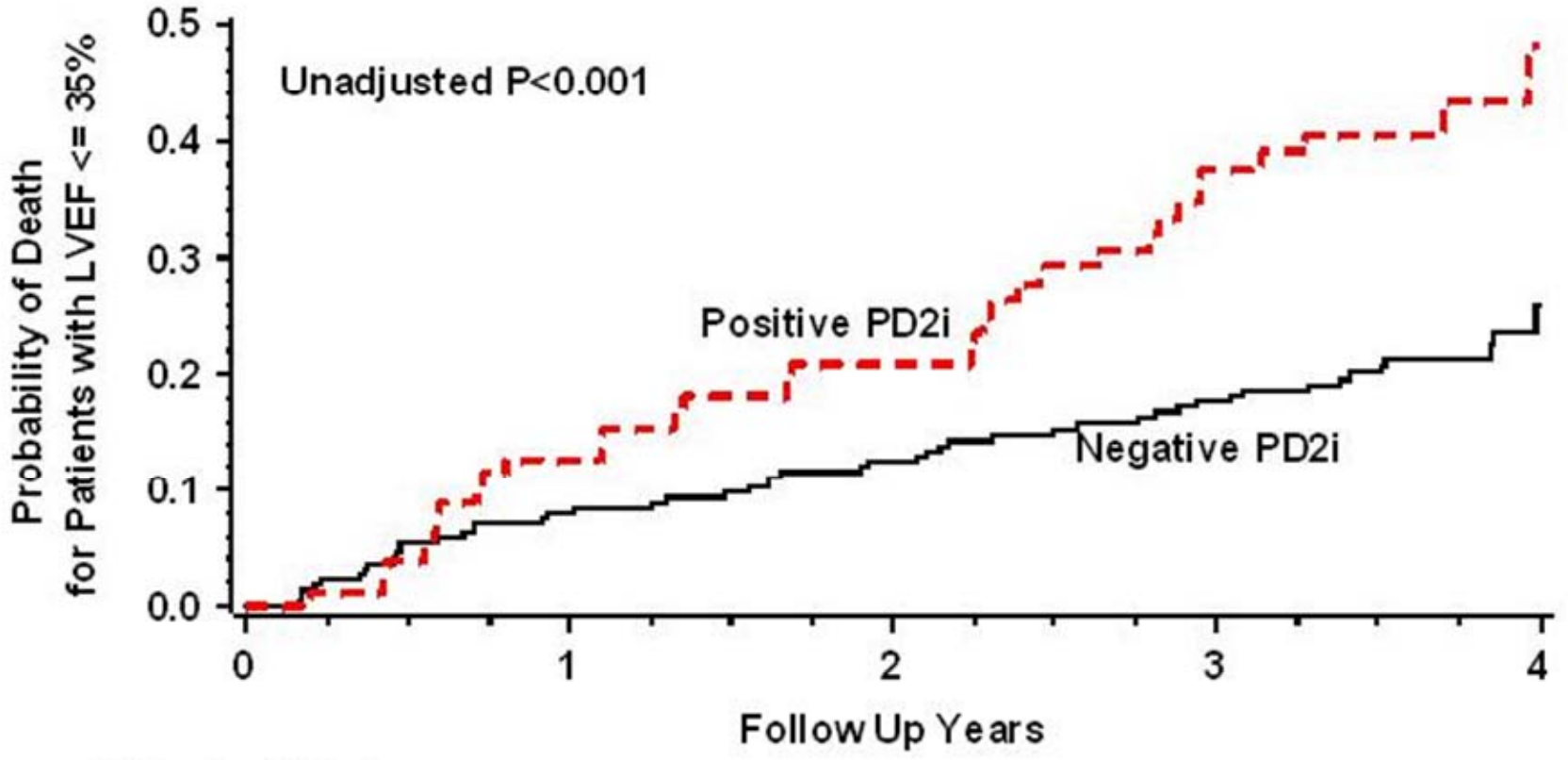
- 537 Chronic Heart Failure Patients Tested
- Primary Endpoint - Total Mortality
- Secondary Endpoint – Heart Failure
- Patient observed for an average of 44 months

Results:

- Low PD2i Score + EF ≤ 35% = 1.73 x Risk of Total Mortality

- Low PD2i Score + EF ≤ 35% = 2.34 Times Risk of Death due to Heart Failure

Heart Failure



Patients at Risk				
Negative PD2i 217	198 (0.08)	188 (0.13)	174 (0.18)	34 (0.26)
Positive PD2i 79	67 (0.13)	57 (0.21)	44 (0.38)	9 (0.48)

MUSIC Trial

Heart Failure

VICOR TECHNOLOGIES, INC

Implications of PD2i in Heart Failure

In the 2521-patient SCD-HeFT trial, primary-prevention ICDs in patients with stable NYHA class 2-3 HF and an LVEF ≤35% were associated with a 23% drop in five-year all-cause mortality compared with standard medical therapy only.

If you would consider implantation of an ICD based on risk reduction for patients with a low EF, would you be interested in learning more about a low cost, reimbursable test that if abnormal indicates a 2.34 x increased risk of death over 44 month for patients with and EF ≤ 35%???

MUSIC Trial

Heart Failure

VICOR TECHNOLOGIES, INC

➢**Diagnosis of CAN may provide the impetus for early evaluation of ventricular function in diabetics.**

Influence of cardiovascular autonomic neuropathy on atherogenesis and heart function in patients with Type 1 diabetes – DIABETES RESEARCH AND CLINICAL PRACTICE JULY, 7, 2008

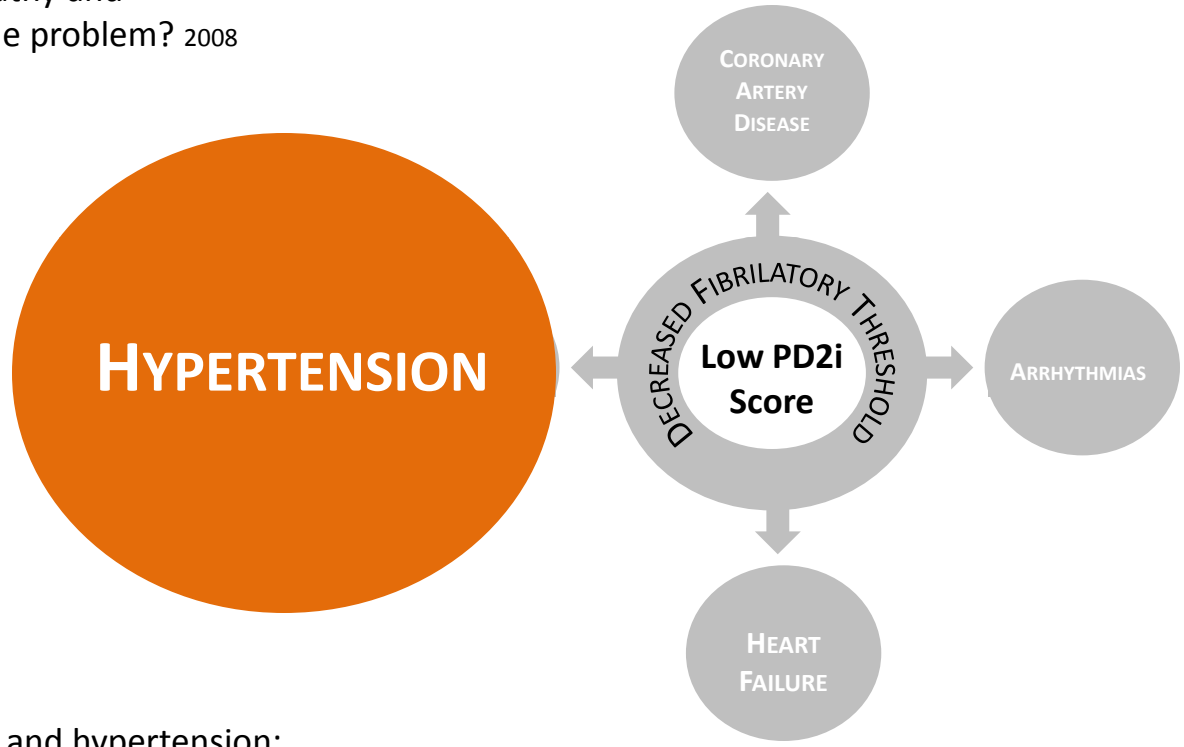
Our study clearly demonstrated that already **before patients develop clinical signs of heart failure, group with CAN differs** statistically significantly from the group without CAN in all selected parameters used for evaluation of the left heart function.

"CAN is associated with the impairment of systolic and diastolic left ventricle function and can thus be regarded as one of the risk factors of diabetic cardiomyopathy"

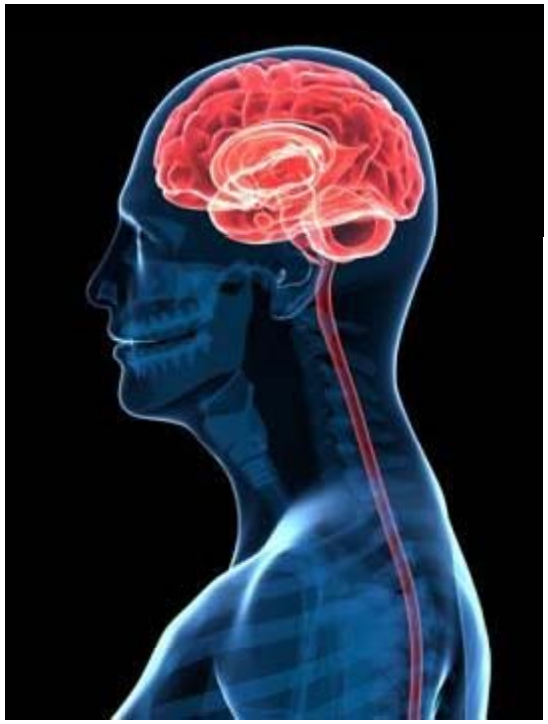
Hypertension

•Relationship between autonomic neuropathy and Hypertension - are we under estimating the problem? 2008 Diabetes UK. *Diabetic Medicine, 25, 863- 866*

•Treatment of hypertension in patients with diabetes mellitus: Relevance of sympathovagal balance and renal function – Clinical Research in cardiology, Volume 96, Number 10 (2007)



•Role of the brain in ventricular fibrillation and hypertension: From animal models to early human studies - CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 74 • SUPPLEMENT 1 FEBRUARY 2007



All Gas No Brake

The vagus nerve, the longest autonomic nerve, mediates 75% of all parasympathetic activity. Because neuropathy is seen first in the longest fibers, the earliest manifestations of autonomic neuropathy in diabetes tend to be associated with parasympathetic denervation.

Hypertension

VICOR TECHNOLOGIES, INC

➢**Identify potential non-dippers (nocturnal HTN) who are asymptomatic for HTN in office that may be candidates for evaluation 24-hr BP analysis**

Relationship between autonomic neuropathy and Hypertension - are we under estimating the problem?
2008 Diabetes UK. *Diabetic Medicine, 25, 863-866*

- Our results indicate that, by relying simply on clinic blood pressures, hypertension is frequently unrecognized and therefore untreated. Our study suggests that subjects with autonomic neuropathy should be screened aggressively for hypertension, including with 24-h blood pressure monitoring if necessary.

Hypertension

➢Diagnosis of CAN may suggest further evaluation of ventricular status

Cardiac Autonomic Neuropathy in Diabetes: A clinical perspective - DIABETES CARE, VOLUME 33, NUMBER 2, FEBRUARY 2010

Abnormal blood pressure regulation:
At night, nondiabetic subjects exhibit a predominance of vagal tone and decreased sympathetic tone, associated with reduction in nocturnal blood pressure.

In diabetic CAN this pattern is altered, resulting in sympathetic predominance during sleep and subsequent nocturnal hypertension.

These are associated with a higher frequency of left ventricular (LV) hypertrophy and both fatal and severe nonfatal cardiovascular events in diabetic CAN subjects