

Autonomic Neuropathy Is Treatable

a report by

Aaron I Vinik, MD, PhD¹ and **Gary L Murray, MD²**

1. Director, Diabetes Research Institute, Strelitz Diabetes Center, and Scientific Director, Department of Medicine, and Professor of Medicine, Eastern Virginia Medical School; 2. Cardiologist, Memphis Cardiology PLC

Cardiovascular autonomic neuropathy (CAN) is associated with high risk of sudden cardiac death. In patients with diabetes, diabetic autonomic neuropathy (DAN) indicates an increased incidence of CAN, and is diagnosed based on the early symptoms of neuropathy and autonomic dysfunction. These symptoms may include orthostatic dizziness, gastrointestinal (GI) and genito-urinary (GU) symptoms, and hypoglycemia unawareness or unresponsiveness. In general, a diagnosis of DAN is made only after eliminating other causes of neuropathy.

DAN and CAN are preceded by autonomic dysfunction (see *Figure 1*), a progression of factors not limited to diabetes. The process of aging causes autonomic decline, which in turn leads to autonomic neuropathy. Chronic diseases such as diabetes accelerate the aging process and can cause early onset of autonomic neuropathy. Among individuals who do not have diabetes, the condition of DAN can be referred to as 'advanced autonomic dysfunction.'

Regardless of what the condition is called, and contrary to the common misperception, autonomic dysfunction is treatable. However, the earlier the autonomic dysfunction is detected, the greater the number of therapy options (see *Table 1*). Therefore, DAN or advanced autonomic dysfunction may be more difficult to treat. In other words, it is easier to correct early-stage autonomic dysfunction compared with advanced-stage autonomic neuropathic damage.



Aaron I Vinik, MD, PhD, FCP, FACP, is Director of the Diabetes Research Institute at the Strelitz Diabetes Center, and Scientific Director of the Department of Medicine and a Professor of Medicine at Eastern Virginia Medical School. He is one of the leading diabetes researchers in the world. His focus is the prevention and reversal of diabetic neuropathy and the development of islet cell regeneration research as a cure for diabetes. He spearheaded the discovery of ilotropan, a chemical substance that can reawaken a cell's potential to produce insulin,

and the gene INGP, the protein responsible for this reawakening. Dr Vinik has received research funding for his studies from the National Institutes of Health (NIH), the National Cancer Institute (NCI), the Kroc Foundation, the American Diabetes Association (ADA), and pharmaceutical industries.

E: vinikai@evms.edu



Gary L Murray, MD, FACC, FACA, FASNC, FASCI, FASA, is a cardiologist at Memphis Cardiology PLC. Dr Murray has practiced in Memphis, TN, for more than 21 years; he was the first nuclear cardiologist in Memphis and the first cardiologist in Memphis to perform peripheral angioplasty and stenting. Dr Murray has performed substantial original research and has published a variety of articles in peer-reviewed medical journals. He completed his residency and fellowship at the University of Tennessee Health Science Center and then served as Chief of Medical Services at Nellis Air Force Base.

The main function of the autonomic nervous system (ANS) is to maintain homeostasis, regardless of the conditions. The two main branches of the ANS, the parasympathetic and the sympathetic, can dynamically adjust their input to maintain homeostasis and apparent normalcy even in the face of degraded end-organ function. Often these ANS adjustments result in autonomic imbalance and begin to affect other systems within the body, including the cardiovascular system. This is, in part, the basis for the constellation of symptoms known to degrade quality of life in many chronic diseases. By the time symptoms present as a result of end-organ dysfunction or failure, the ANS has been out of balance for considerably longer.

Unfortunately, early signs of autonomic dysfunction are often not recognized due to two main reasons. First, the current understanding of the effects of the ANS and its interaction with other physiological systems is incomplete. Second, a reliable clinical tool to measure and monitor the ANS did not exist until recently, when the ability to measure both ANS branches simultaneously and independently was developed commercially (ANSAR Medical Technologies, Inc., Philadelphia, PA).^{1,2} Prior to this, autonomic neuropathy could be clinically diagnosed (orthostatic hypotension, gastroparesis, Shy-Drager, POTS, etc.) only at an advanced stage with dramatic symptoms. At this stage, it is usually much too late for anything but treatment of the symptoms. With simultaneous, independent measures of both ANS branches, these patients can be identified even when they are still asymptomatic, or mildly symptomatic, a fairly common situation usually accompanied by fatigue, light-headedness, palpitations, intractable hypertension, etc. Therapeutic intervention seems to improve outcomes by slowing or halting autonomic decline and the associated disease progression.

The history of non-invasive ANS monitoring in clinical practice is confusing. Traditionally, it has been based only on measures of heart rate variability (HRV). Measures of HRV, as defined in the 1996 *Circulation* standards article,³ are mixed or incomplete measures of the parasympathetics and the sympathetics. This is not surprising, as HRV by itself, regardless of how much it is dissected, is but one independent measure of a system (the ANS) that contains two components: the parasympathetics and the sympathetics. From a mathematical perspective, one measure is insufficient to fully characterize a two-component system. If one measure changes, it is impossible to determine which component changed without making assumptions or without additional information. This has resulted in a very low clinical acceptance rate for this method. Except in extreme cases, HRV alone provides no additional information. The use of HRV alone merely indicates the obvious: that the patient's ANS is functioning.

Investigators from the Massachusetts Institute of Technology (MIT) determined that a measure of respiratory activity that can conveniently be acquired in the

Table 1: Autonomic Imbalance (Autonomic Dysfunction) Can Be Treated Using Common Medications

Agent	Nervous System Affected	Primary Site of Action	Primary Effect
Beta-1 adrenergic antagonists*	↓ Sympathetics	Heart	↓ Heart rate
Alpha-1/2 antagonists*	↓ Sympathetics	Peripheral vasculature	↓ Blood pressure
Angiotensin–renin antagonists	↓ Sympathetics	Kidneys	↓ Blood pressure
Calcium channel antagonists	↓ Sympathetics	Heart	↓ Blood pressure
Beta-2 adrenergic agonists	↑ Sympathetics	Lungs	↑ Air flow
Alpha adrenergic agonists	↑ Sympathetics	Vasculature	Constrict vasculature
Cholinergic antagonists	↓ Parasympathetics	Entire body	↓ Parasympathetic activity
Cholinergic agonists	↑ Parasympathetics	Entire body	↑ Parasympathetic activity

* These categories can include combination alpha/beta antagonists such as Carvedilol.

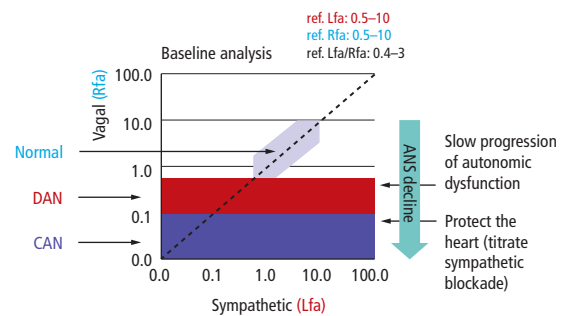
clinic (e.g. impedance plethysmography) is an appropriate second measure to use in conjunction with HRV. We now have the requisite two measures to fully characterize a two-component system. As a result, the sympathetics and parasympathetics can be measured both independently and simultaneously. With these two measures at their disposal, physicians are able to individualize treatment based on the patient's physiology. More importantly, physicians can now directly and objectively measure patients' responses to therapy.

To facilitate this insight, medical leadership including the American Diabetes Association (ADA),⁴ the American Heart Association,⁵ the American Academy of Neurology,⁶ the American Academy of Family Physicians,⁷ the Juvenile Diabetes Research Foundation International,⁵ and the National Institutes of Health⁵ have published recommendations for autonomic testing as part of the standard of care for chronic diseases. Autonomic neuropathy is a known risk factor for increased morbidity and mortality; in addition, chronic disease can lead to autonomic neuropathy. It is also well recognized that autonomic dysfunction precedes autonomic neuropathy, but is asymptomatic. Chronic disease should therefore indicate the need to test the parasympathetics and sympathetics. Additionally, chronic diseases, including diabetes, can lead to symptoms that disrupt quality of life for the average adult (e.g. GI upset, GU dysfunction, sleep difficulties, and orthostasis). If only diabetes led to a disruption of quality of life, the argument could be made that it was the disease; however, since many diseases involve these symptoms, the argument must be made for some underlying condition. Since both ANS branches are significantly involved in all of these functions, when these functions become compromised it is logical that autonomic dysfunction is part of the pathology.

With the ability to differentiate parasympathetic activity from sympathetic activity, and the ability to differentiate both from end-organ symptoms, more information about patients is available. Ultimately, the following questions can be answered:

- Is the patient responding to therapy in such a way as to appropriately limit stress (sympathetic) responses and thereby limit morbidity (i.e. maintain or improve quality of life)?
- Is the patient's heart sufficiently protected as to limit mortality (i.e. maintain longevity)?
- What is the autonomic pathophysiology? and
- What is the best choice of therapy for the individual patient?

We have the ability to measure the parasympathetics and the sympathetics independently and simultaneously, as well as the ability to determine whom to test. The question remains: How do we treat identified patients? Basic ANS therapy is straightforward. There are four autonomic imbalances and eight

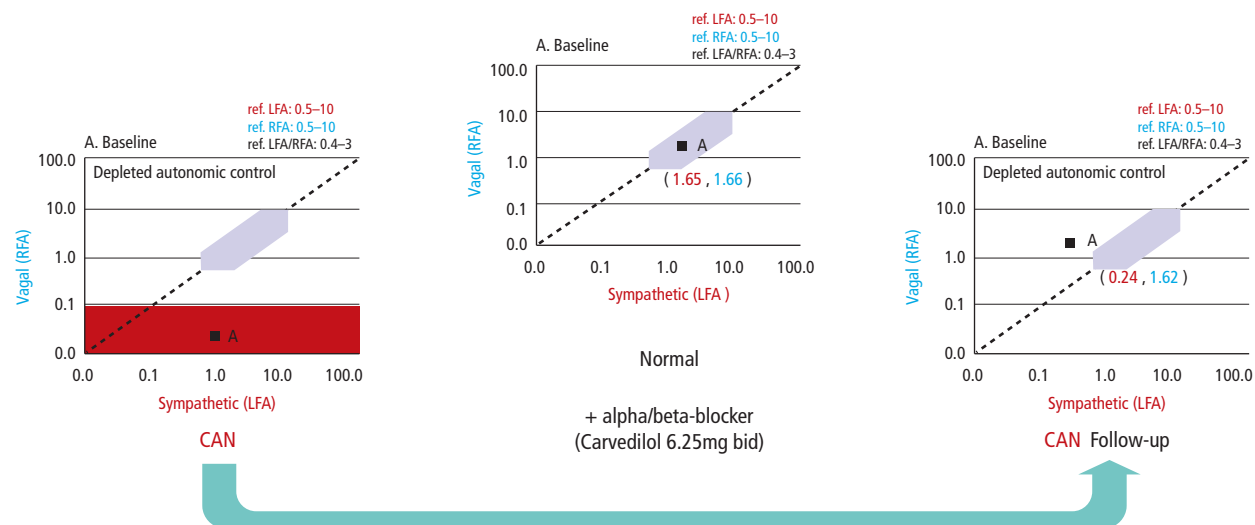
Figure 1: Autonomic Neuropathy

classes of medications for therapy (see Table 1). The four autonomic imbalances are high parasympathetic activity, low parasympathetic activity, high sympathetic activity, and low sympathetic activity.

The choice of a specific therapy option depends on the patient's specific medical history. For example, in the case of too little sympathetic activity upon standing (indicating possible orthostasis), vasopressor therapy (alpha-adrenergic agonists) would be contraindicated in the presence of supine hypertension or high blood pressure. In general, the first recommendation would be proper daily hydration and reduced intake of beverages containing caffeine, sugar, and alcohol. A second consideration would be an evaluation of the dosing of current diuretics. A third consideration would be mechanical intervention (e.g. compression stockings or counter-pulsation). A fourth option might be volume expansion. Finally, a vasopressor could also be considered (in the absence of supine hypertension or high blood pressure), or otherwise pyridostigmine bromide (Mestinon, Valeant Pharmaceuticals), a cholinergic agonist (see Table 1).

A common example in ANS monitoring is the use of a beta-1 adrenergic antagonist or a beta-blocker. With the use of independent, simultaneous measures of parasympathetic and sympathetic activity, physicians have discovered that in patients with chronic disease there is a clinical correlation between symptoms and excess parasympathetic activity during sympathetic challenges such as the Valsalva maneuver or a postural change test. This is especially true among patients with difficult-to-control blood sugar, blood pressure, or hormone levels. These are typically patients with symptoms of parasympathetic excess, including low energy, fatigue, depression-like symptoms, and sleep difficulties, and with symptoms of sympathetic excess, including high heart rate, hypertension, anxiety, or parasympathetic insufficiencies (e.g. gastroparesis). This combination of parasympathetic and sympathetic excess indicates that the ANS 'see-saw' as taught in medical

Figure 2: Cardiovascular Autonomic Neuropathy Is Treatable (Example—Patient with Poorly Controlled Diabetes)



school is broken: both ends are high. Physicians have also found that the combination alpha/beta-blocker Carvedilol™ treats this condition and can both reduce sympathetic excess with the beta component and indirectly reduce the parasympathetic excess with the central action of the alpha component. It is believed that the alpha component, in the presence of autonomic dysfunction or autonomic neuropathy, no longer acts as a post-ganglionic agent, but rather as a pre-ganglionic agent, exerting an indirect parasympathetic effect. In short, Carvedilol has been shown to treat autonomic neuropathy (history-dependent), thereby making the agent beneficial for patients with diabetes and other chronic diseases.

When Should Patients Be Tested and How Often?

Autonomic testing should begin when a chronic disease is diagnosed, because when a patient presents with a chronic disease the ANS is already dysfunctional. For example, in the case of type 2 diabetes, testing is recommended by the ADA at the time of diagnosis because the disease is known to have been present for many years without the patient's knowledge. Medicare will reimburse two tests per year to ensure early detection of additional autonomic pathology. Because the ANS appears to require two to three months to fully adapt to new therapy, depending on the patient's age and ANS status, follow-up testing at the three-month mark is reasonable (and reimbursed) to ensure proper patient response to therapy changes.

As the case study summarized in Figure 2 illustrates, CAN is treatable. An example of a normal patient's resting ANS is presented in the top middle plot. The plot presents parasympathetic (or vagal) activity on the ordinate and sympathetic activity on the abscissa. The gray area indicates the normal area as defined by normal parasympathetic and sympathetic activity. The diagonal broken line indicates perfect ANS balance (sympathetic-to-parasympathetic activity ratio of 1:1). ANS balance is also known as 'sympathovagal balance.' These data are obtained from the resting (baseline) segment of a standard autonomic function test that analyzes both HRV and respiratory activity (derived

using impedance plethysmography) to compute parasympathetic and sympathetic activity. The bottom two plots in the case illustrated are from a poorly controlled 63-year-old male with type 2 diabetes and no beta-blocker or antihypertensive agent on board. Upon first presentation, his resting heart rate was 83bpm and his blood pressure was 143/87mmHg. As the lower left plot shows, the patient's ANS was out of balance with the very low parasympathetic activity and normal sympathetic activity. Very low parasympathetic activity suggests insufficient parasympathetic protection to minimize the risk for sudden cardiac death. The 0.1bpm² level on the ordinate is associated with a threshold of high risk for sudden cardiac death according to the Framingham Heart Study. This patient was subsequently prescribed Carvedilol 6.25mg twice daily. Three-month follow-up results are presented in the lower right plot. The patient's resting heart rate is 84bpm and his blood pressure is 137/75mmHg. Although he still presents with autonomic dysfunction (depleted autonomic control or DAN), his ANS results are no longer in the high-risk region. His sympathetics are reduced, releasing his parasympathetics. The patient therefore no longer has CAN, and in fact his resting autonomic levels indicate that his sympathovagal balance is low. It is possible that the initial dose of Carvedilol was too high. Given that the patient is not exercise-intolerant, no change in therapy was made. Low-normal sympathovagal balance (in the range 0.4–1.0), an indicator of more parasympathetic activity, is recommended by the cardiology literature due to its association with reduced morbidity and mortality.^{1,2} The sympathovagal balance can now be titrated based on ANS monitoring (analyses of HRV with respiratory activity, according to the MIT approach).

There are substantial data from diabetic patients taking Carvedilol that support the results of this case study. With non-invasive, independent, simultaneous, quantitative measures of parasympathetic and sympathetic activity, CAN can be detected, identified earlier, treated specifically based on the patient's individual physiology, and monitored. This results in improved outcomes, a better quality of life, and preserved longevity through a reduction in morbidity and mortality. ■

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