



Autonomic Testing Optimizes Therapy for Heart Failure and Related Cardiovascular Disorders

Nicholas L. DePace^{1,2} · Joe Colombo¹ · Kaushik Mandal³ · Howard J. Eisen³

Accepted: 23 August 2022

© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2022

Abstract

Purpose of Review Cardiovascular autonomic control is an intricately balanced dynamic process. Autonomic dysfunction, regardless of origin, promotes and sustains the disease processes, including in patients with heart failure (HF). Autonomic control is mediated through the two autonomic branches: parasympathetic and sympathetic (P&S). HF is arguably the disease that stands to most benefit from P&S manipulation to reduce mortality risk. This review article briefly summarizes some of the more common types of autonomic dysfunction (AD) that are found in heart failure, suggests a mechanism by which AD may contribute to HF, reviews AD involvement in common HF co-morbidities (e.g., ventricular arrhythmias, AFib, hypertension, and Cardiovascular Autonomic Neuropathy), and summarizes possible therapy options for treating AD in HF. **Recent Findings** Autonomic assessment is important in diagnosing and treating CHF, and its possible co-morbidities. Autonomic assessment may also have importance in predicting which patients may be susceptible to sudden cardiac death. This is important since most CHF patients with sudden cardiac death have preserved left ventricular ejection fraction and better discriminators are needed.

Summary Many life-threatening cardiovascular disorders will require invasive testing for precise diagnoses and therapy planning when modulating the ANS is important. In cases of non-life-threatening disorders, non-invasive ANS testing techniques, especially those that individually assess both ANS branches simultaneously and independently, are sufficient to diagnose and treat serially.

Keywords Heart failure · Parasympathetic · Sympathetic · Cardiovascular disease · Autonomic neuropathy · Quality of life

Abbreviations

AD	Autonomic dysfunction	HRV	Heart rate variability
AFib	Atrial fibrillation	HTN	Hypertension
ANS	Autonomic nervous system	MACE	Major adverse cardiovascular events
CAN	Cardiovascular autonomic neuropathy	NOH	Neurogenic orthostatic hypotension
CHF	Congestive heart failure	OIS	Orthostatic intolerance syndrome
LVEF	Left ventricular ejection fraction	P&S	PSNS & SNS
HF	Heart failure	PSNS	Parasympathetic nervous system
HFrEF	Heart failure with reduced ejection fraction	POTS	Postural orthostatic tachycardia syndrome
		QoL	Quality of life
		SNS	Sympathetic nervous system
		SB	Sympathovagal balance (= [resting SNS]/[resting PSNS])
		SCD	Sudden cardiac death

This article is part of the Topical Collection on *Heart Failure*

✉ Joe Colombo
dovetech@erols.com

¹ Franklin Cardiovascular Assoc., PA and Autonomic Dysfunction and POTS Center, Sicklerville, NJ, USA

² Pennsylvania Hospital, University of Pennsylvania Health System, Philadelphia, PA, USA

³ Penn State Milton S. Hershey Medical Center, Hershey, PA, USA

Introduction

Cardiovascular autonomic control is an intricately balanced, dynamic process. Autonomic dysfunction (AD, an imbalance between the parasympathetic and sympathetic (P&S) nervous

Table 1 Primary forms of autonomic dysfunction (AD) and their common presentations. See text for details

↑SNS (SE)	↓SNS (SW)	↑PSNS (PE)	↓↓PSNS (CAN)
<ul style="list-style-type: none"> • HTN • Tachy-Arrhythmia 	<ul style="list-style-type: none"> • OH • POTS 	<ul style="list-style-type: none"> • VVS • Hypotension 	<ul style="list-style-type: none"> • normal process of aging • predisposes to MACE, including Stroke or SCD
<ul style="list-style-type: none"> • (some forms of AFib, VT/ VF) • worsening HF 	<ul style="list-style-type: none"> • OIS 	<ul style="list-style-type: none"> • Depression • some forms of AFib 	

↑SNS, high sympathetics, including sympathetic excess (SE); ↓SNS, low sympathetics, including sympathetic withdrawal (SW); ↑PSNS, high parasympathetics, including parasympathetic excess (SE); ↓↓PSNS, very low parasympathetic activity, including CAN (a resting parasympathetic insufficiency); *AFib*, atrial fibrillation; *CAN*, cardiovascular autonomic neuropathy; *HF*, heart failure (including congestive HF); *HTN*, hypertension; *MACE*, major adverse cardiovascular events; *OH*, orthostatic hypotension; *OIS*, orthostatic intolerance syndrome; *POTS*, postural orthostatic tachycardia syndrome; *SCD*, sudden cardiac death; *VF*, ventricular fibrillation; *VT*, ventricular tachycardia; *VVS*, vasovagal syndrome

systems), either as a result of primary disorders of the autonomic nervous system (ANS) or secondary maladaptive P&S responses, as seen in patients with heart failure (HF), promotes and sustains disease processes. HF is arguably the disease that stands to most benefit from P&S manipulation to reduce mortality risk. AD results when the P&S are out of balance [1, 2]. This is the more common type of autonomic disorders. Most diseases and medications affect only one autonomic branch. However, P&S dysfunction is common [3]. Most types of AD are generally not life-threatening disorders, but significantly affect quality of life (QoL). Less common, but not rare, are the life-threatening forms of AD, such as cardiovascular autonomic neuropathy (CAN) [4]. CAN is defined as very low PSNS-activity and indicates risk of major adverse cardiovascular events (MACE). CAN with high SNS-activity indicates high risk of MACE, including sudden cardiac death (SCD) [5, 6••, 7•]. Rare autonomic disorders are Synuclein disorders which affect the ANS, such as Parkinson's disease, Lewy body dementia, multi-system atrophy, and primary autonomic failure, which may not be immediately life threatening but can abbreviate life expectancy. Synucleinopathies refer to a group of disorders characterized by misfolded α -Synuclein protein aggregates in the peripheral and central nervous systems. These disorders require more sophisticated and complex autonomic testing and work-up. These rare disorders are not the subject of this review.

By identifying AD, the goal is to normalize any objectively measured abnormalities (see Table 1) to restore the proper balance of PSNS- to SNS-activity in the body. There are four basic abnormalities. (1) Too much SNS-activity (see "↑SNS" in Table 1) promotes, high BP, provocation of tachy-arrhythmias, and worsening of HF. (2) Too much PSNS-activity (see "↑PSNS" in Table 1) predominantly promotes brady-arrhythmia, some forms of atrial fibrillation, hypotension, vagal syncope (parasympathetic and vagal are synonymous), and depression. Depression may predispose to coronary events. (3) Too little SNS-activity (see "↓SNS" in Table 1) especially upon standing predisposes to orthostatic drop in BP, or postural tachycardia,

and orthostatic intolerance syndromes. (4) Very low PSNS-activity (see "↓↓PSNS" in Table 1) defines CAN and predisposes to MACE endpoints and SCD, and is the most serious form of AD, see Appendix Figure.

In HF, AD may be involved early and if prolonged, may perhaps cause HF. For example, ↓SNS upon standing predisposes to orthostatic drop in BP upon standing due to insufficient vasoconstriction (an alpha-adrenergic response; adrenergic and sympathetic are synonymous). Prolonged ↓SNS upon standing may lead to poor cardiac perfusion and decreased diastolic BP. Decreased diastolic BP may lead to poor cerebral perfusion and increased systolic BP with ↑SNS (a beta-adrenergic response, releasing adrenaline to stimulate the heart). Decreased diastolic BP with increased systolic BP involves widened pulse pressure. Wide pulse pressure (>80 mmHg) is an indication of HF. Relieving ↓SNS (abnormal the alpha-adrenergic response), especially early, may prevent HF, before the ↑SNS (abnormal beta-adrenergic response) becomes a mortality risk involving prolonged ↑SNS which may lead to hypertension, arrhythmia, and SCD (or other MACE, including HF).

If within 3 months (it typically takes 3 months for the ANS to fully adapt to a new state, including titration of therapy), the patient's ANS is not moving towards balance at rest and normalization of response to challenge, then the patient is not responding to therapy as desired and secondary or alternate therapy plans should be considered. Autonomic therapy must be gentle. Too much therapy often causes imbalance in the opposite direction and often causes additional symptoms. Simply titrating more therapy is not typically a satisfactory solution to the lack of intended response. Often patients are intolerant or desensitized to primary therapy. Retesting in 3 months enables individualizing therapy. Testing at this time also helps to encourage the patient since little change in symptoms often occurs by that time, for the ANS must fully adapt before the organs are stabilized, before symptoms change significantly. We explain it to our patients as "braking a bad habit and establishing a good habit" before symptoms are fully relieved.

Autonomic Dysfunction

AD is a part of the aging process. Disease, disorder, injury, etc., serve to accelerate AD. Later stages of AD include advanced autonomic dysfunction (AAD) or diabetic autonomic neuropathy (DAN, AAD with the effects of Diabetes) and CAN. AAD or DAN are measured as \downarrow PSNS or \downarrow SNS and indicate increased morbidity risk. CAN is measured as $\downarrow\downarrow$ PSNS and indicates increased mortality risk, including risk of MACE or SCD event, especially in cases of $\downarrow\downarrow$ PSNS with \uparrow SNS. For example, with $\downarrow\downarrow$ PSNS, there may not be sufficient PSNS-activity to prevent a sympathetically mediated (\uparrow SNS) ventricular tachy-rhythm from becoming ventricular fibrillation. Sympatholytics (e.g., beta-blockers, renin-angiotensin system blockers) help to limit \uparrow SNS to establish balance and help the parasympathetics to prevent the deleterious effects of \uparrow SNS).

$\downarrow\downarrow$ PSNS and \uparrow SNS are not synonymous. For example, in older patients, $\downarrow\downarrow$ PSNS & \downarrow SNS may be normal and may not need significant therapy, as long as SB is within normal limits (CAN with low-normal SB: $0.4 < SB < 1.0$, as recommended for older or chronic disease patients; SB recommended for younger patients is $1.0 < SB < 3.0$ [3, 5, 6••]). Whereas, in most patients (especially younger patients), $\downarrow\downarrow$ PSNS & \uparrow SNS often does need significant therapy and is predictive of MACE.

AD may result from many types of insults, including 1) significant one-time traumas (mental or physical), 2) long-standing chronic diseases or multiple, 3) repetitive smaller traumas, 4) severe infections (causing oxidative stress, including COVID-19), and 5) genetic disorders. All are treatable by restoring balance [8] (including long-COVID [9]). For some (e.g., the genetic disorder Ehlers Danlos Syndrome/Hypermobility), the treatment may be life-long to maintain quality of life and productivity, especially if there is no treatment for the underlying cause (as is the case for EDS/hypermobility). Otherwise, once proper balance (both at rest and in response to challenge) is established and stabilized, the nervous system will “remember” that state and often carry forward without therapy until some other clinical event happens.

Tests of Autonomic Dysfunction

Typical clinical tests of AD include tilt-table testing to test for syncope and orthostatic dysfunction, deep breathing, and Valsalva challenges to test PSNS and SNS responses, and sudomotor testing to test for peripheral autonomic neuropathy. The autonomic tests requiring radioactive agents and imaging are typically hospital- or research-based. All of these ANS tests test only one branch of the ANS or test both branches together and require assumption or approximation to theorize

activity in each branch together. Cardio-respiratory monitoring (aka., P&S monitoring) tests both ANS branches independently and simultaneously and is reproducible, repeatable, and noninvasive. Measuring both ANS branches separately, but at the same time provides more information for serious cardiac diseases, such as HF, especially those predisposed to SCD, lethal ventricular arrhythmias, CHF, and CAN. Tests that focus solely on the autonomic effects on the sinus node (e.g., HR-variability, HR-Turbulence, and beat-to-beat BP measures) were not significant predictors of HF and other MACE [10]. This is well supported. To a limit (e.g., arrhythmia), more HR-variability indicates greater health. More variability indicates more PSNS-activity. Generally, a little more PSNS-activity is cardio-protective [11] and is associated with healthier patients [5]. However, a little more PSNS-activity cannot be measured with ANS tests, except cardio-respiratory monitoring [3].

HR-variability reflects sinus node activity. Respiratory sinus arrhythmia also reflects sinus node activity. Both are independent measures of autonomic activity, HR-variability from the heart and respiratory activity from the lungs. With these two independent, simultaneous measures of the ANS the two independent branches of the ANS are fully, mathematically characterized, eliminating assumption and approximation [12]. These two measurements are incorporated into cardio-respiratory (or P&S) monitoring.

Tilt-table testing is a useful measure of vasomotor adrenergic (sympathetic) responses, usually used for unexplained syncope. Beat-to-beat BP and HR are assessed. A tilt duration of 5 min is sufficient to establish NOH. Evaluation of disorders of delayed orthostatic intolerance, including syncope, a longer duration of tilt is often necessary [13].

Sudomotor testing identifies small fiber disease (the small nerve fibers also include SNS-nerves) and peripheral autonomic neuropathy, often involved in generalized pain syndromes, poor wound healing, and thermoregulatory dysfunction. Sudomotor testing consists of two general types: 1) Quantitative Sudomotor Axon Reflex Test (QSART) and 2) thermoregulatory sweat test [14].

Pharmacological Therapy

Treating cardiac disease with \uparrow SNS is more difficult due to its associated abundance of neurohormones. Neurohormones work to maintain cardiovascular homeostasis through increased volume expansion, peripheral vaso-arterial constriction, and increased myocardial contractility. An overabundance of neurohormones may dysregulate P&S and CHF [15].

Pharmacologic agents relieve the deleterious effects of excessive sympathetic and renin-angiotensin system activation

(\uparrow SNS). However, this treatment corrects only some P&S imbalances, typically static or resting imbalances (e.g., CAN with \uparrow SNS). The remaining imbalances (typically dynamic imbalances, e.g., orthostatic dysfunction with \downarrow SNS) are disruptive and continue to contribute to HF pathophysiology, or require high dosing which does not correct the uncoupling of the P&S nervous systems. For example, with NOH, diastolic BP may drop below 60 mmHg causing cardiac hypo-perfusion. This coupled with high systolic BP, as compensation for the associated cerebral hypo-perfusion, may widen pulse pressure and underlie HF and coronary ischemia [16]. Wide pulse pressures [17] are adverse prognostic factors and may be due to dynamic P&S imbalances. Relieving \downarrow SNS may normalize pulse-pressure and resting BP [18]. Without \downarrow SNS as additional information, traditional sympatholytic therapy targeting reduction in systolic BP may exacerbate BP. Conversely, systolic BP may not respond to antihypertensive therapy if cardiac and cerebral hypo-perfusion persist. The hypertension may be secondary to, and compensatory for, cerebral hypo-perfusion and the associated lightheadedness upon standing.

Autonomic interventions are extremely useful, the most established being β -adrenergic and renin-angiotensin blockers (beta-blockers, ACE-Is, and ARBs). However, pharmacology may not be sufficient to prevent progression and adverse outcomes, especially with cardiomyopathies. Midodrine (a vasoconstrictor and α SNS-agonist) has been used for patients with low BP and HR with reduced EF (HF_{rEF}), who have been precluded from instituting β -blockers and renin-angiotensin system blockers. Midodrine raises BP so patients may tolerate conventional pharmacological therapy [19].

Non-pharmacological Therapy

Several experimental, autonomic modulation techniques maybe used for advanced HF management [20]: spinal cord stimulation, renal artery denervation, baroreceptor activation therapies (BAT), and left cardiac sympathetic denervation.

Vagal nerve stimulation (VNS) is included for treatment of HF [21]. P&S imbalance (e.g., CAN with \uparrow SNS) is an integral component of the pathophysiology of HF. No mortality benefit was noted with VNS; however, VNS did improve their six-minute walk and QoL scores. The efficacy of VNS is mixed, indicating the need for better measures of PSNS-activity. This illustrates the complexity of the ANS, and the degree of modulation and specificity that may be necessary. The same complexity has been found with the other experimental, autonomic modulation techniques [15].

Another stimulator, BAT (which decreases SNS- and increases PSNS-activity), demonstrated improved QoL, 6-min walk, and NT-proBNP scores in HF_{rEF} [22•]. This confirms

that P&S modulation in systolic CHF patients improves QoL, exercise capacity, and biomarkers. This is extremely important because greater than 70% of patients with HF_{rEF} are ineligible for cardiac resynchronization therapy [23].

Congestive Heart Failure and Sudden Cardiac Death

SCD may be due to CHF, a sudden ischemic event, or other chronic cardiac condition where P&S imbalance is present. It was believed that medications could prevent SCD, especially in patients with left ventricular systolic dysfunction. Now devices such as defibrillators may be more important in preventing SCD from advanced structural heart disease. Renal sympathetic denervation may have beneficial effect in CHF patients [24]: For HF_{rEF}, these studies demonstrated improved symptoms and LVEF. For CHF with preserved LVEF, renal sympathetic denervation is associated with improved surrogate endpoints. Autonomic testing may provide more information to help improve the benefits of SNS-denervation. Most people have SCD, but do not have low LVEFs. Therefore, LVEF may not be a sensitive marker for SCD. It is hoped that P&S testing may describe additional information that may better discriminate those at risk for SCD and other MACE endpoints, specifically CAN with high SB (\uparrow SNS at rest) [6••, 25].

A recent study of patients with chronic CHF [26] demonstrates that Splanchnic nerve block reduced exercise intolerance, and resting pulmonary artery and wedge pressures, produced favorable effects on cardiac output and exercise capacity. Splanchnic nerve block predominately reduces systolic function by preventing the sympathetically innervated splanchnic nervous system from being activated. This helps to redistribute blood volume centrally, into the thorax. The study concluded that targeting the splanchnic autonomic nervous system may present a potential therapeutic target not currently used in HF treatment.

For severe heart disease, PSNS- or SNS-agents may improve management of chronic HF, arrhythmias, and hypertension [6••]. It is hoped that (1) identification of P&S abnormalities and (2) measures to improve these abnormalities, whether pharmacologic or interventional, may identify high-risk patients for SCD and enable the prevention of SCD. For example, \uparrow SNS may contribute to the pathogenesis of CHF [27] via downregulation of beta 1 receptors, exerting direct toxic effects on the myocardium, and contributing to myocardial remodeling and life-threatening arrhythmias. Beta-1 adrenergic blockers reduce morbidity and mortality in HF. Identification of CAN (\downarrow PSNS), especially with \uparrow SNS, may identify a higher risk subset of patients, especially with low LVEFs, who may benefit from cardio-protective measures, such as defibrillators, to prevent SCD.

Implications of Autonomic Dysfunction in Cardiovascular Conditions

Ventricular Arrhythmias

CAN and \uparrow SNS are associated with the cardiac electrophysiology and arrhythmogenesis of ventricular arrhythmias, especially in patients with myocardial ischemia. This may cause SCD. Novel autonomic neuromodulation may be beneficial for malignant ventricular arrhythmias [28]. SNS-activity increases just prior to the onset of ventricular tachy-arrhythmias [29], and \uparrow SNS indicates risk, given history. Cardiac baroreceptor stimulation, spinal cord stimulation, stellate ganglion modulation, electromagnetic fields, optogenetics, selective ablation of the ligament of Marshall, cervical vagal nerve stimulation, transcutaneous vagal nerve stimulation, and renal sympathetic denervation have all been tested to modulate the ANS to reduce ventricular arrhythmias. The outcome depends on the level of the cardiac neural axis in the patient's intrinsic cardiac status [30]. Stellate ganglion blocks may be useful in treating ventricular tachycardia and ventricular storm in some subsets of patients [31]. Other ventricular tachycardia substrates or mid-myocardial intra-septal is not easily catheter treated with ablation. Left stellate ganglion block may be useful, particularly in some with advanced HF on life support [32]. Bilateral stellate ganglionectomy may significantly reduce the incidence of recurrent ventricular tachycardia and defibrillator shocks, independent of the cardiomyopathic substrate [33]. It resulted in a 10% decrease in ventricular tachycardia and shocks for patients with arrhythmogenic right ventricular dysrhythmia [34] and has been effective in catecholamine polymorphic ventricular tachycardia and long QT [35].

Atrial Fibrillation

AFib in healthy hearts is usually associated with \uparrow PSNS. AFib in diseased hearts is usually associated with \uparrow SNS. However, this may not be that simple [36]. Low HR and \downarrow PSNS are associated with higher incidents of AFib [37]. SNS-activation may induce heterogeneous changes with arrhythmogenesis which may lead to AFib [38]. Sympatholytics may relieve AFib provocation. Device-based treatment, such as renal denervation and pulmonary vein isolation with ganglionated plexi-ablation, may also be effective [39]. Injecting botulinum into epicardial fat pad during open-heart surgery reduced postoperative incidences of AFib for up to 3 years [40]. Stellate ganglion blockade may be an AFib treatment by increasing ventricular fibrillation threshold, thereby increasing AFib threshold [41]. High thoracic epidural anesthesia in postoperative patients may decrease incidence of AFib [42].

AFib demonstrates the usefulness of cardio-respiratory monitoring [43]. Approximately 80% of all AFib cases involve the ANS. Approximately 80% of the ANS-AFib cases involve \uparrow PSNS. The remaining 20% of the ANS-AFib patients appear to involve \uparrow SNS [44]. Thus, 64% of AFib involves \uparrow PSNS and suggests that the target of atrial ablation is more

often PSNS-innervation. These data beg a more specific measurement of P&S activity.

Sympathetic nerve stimulation may promote development of Afib in the lab. A recent study [45] demonstrated that renal denervation added to pulmonary vein isolation in patients with paroxysmal Afib with significant hypertension. Sympathetic stimulation reduced BP, cardiac hospitalizations, and recurrent Afib at 1 year compared to randomized controls. Autonomic modulation added to Afib pulmonary vein ablation may add to the effectiveness of the procedure on multiple fronts.

Hypertension

Carotid baroreceptor stimulation and renal denervation are two invasive, therapeutic approaches to resistant hypertension; however, recent results have been mixed [46]. The anti-hypertensive effect of renal denervation was accompanied by decreased SNS-activity, but minimal bradycardia in prior work [47]. \uparrow SNS is associated with hypertension. Most anti-hypertensives are known sympatholytics. Normalizing \uparrow SNS normalizes BP, assuming no other end-organ dysfunction (e.g., atherosclerosis). Normalizing resting \uparrow SNS, however, is not always sufficient. If \uparrow SNS persists with stress, MACE risk may persist, including risk of stroke. Dynamic autonomic dysfunctions, such as those leading to poor cerebral perfusion (e.g., NOH and Syncope) may result in \uparrow SNS and eventually hypertension as a compensatory mechanism against poor cerebral perfusion. Often these patients do not respond to antihypertension therapies where hypertension is assumed to be the primary disorder.

Stress in the Cardiovascular System

Acute stress elicits a typical cardiovascular response, a “defense reaction,” which involves \uparrow SNS with \uparrow PSNS which increases HR and SNS-activation. In contrast, the “defeat reaction” involves \uparrow SNS with \downarrow PSNS and reflects an ongoing reaction to chronic stress. While cortisol secretion occurs in both acute and chronic stress reactions in the “defeat reaction,” \downarrow PSNS & \uparrow SNS occurs to elevate BP without accompanying tachycardia. Persistent defense reactions lead to \uparrow PSNS-activity which may result in gastric hypersecretion and ulceration [48]. Aging is associated with \downarrow PSNS & \uparrow SNS and reduction in Baroreflex function which leads to greater BP-variability [49]. Aging also influences the adrenal- and \uparrow SNS-responses to mental stress. The adrenalin response is much lower in older men. Conversely, \uparrow SNS-response in the heart based on cardiac noradrenalin spillover, which is substantially higher in older men, could possibly be relevant in triggering cardiac arrhythmias and stress.

Oxidative stress, through degradation of the mitochondria, negatively affects the cardiovascular system [50, 51]. These effects are compounded by the negative effect of oxidative stress on the ANS. The effect of oxidative stress on the ANS causes AD which compromises the control of the cardiovascular system exacerbating the effect of oxidative stress on the cardiovascular system. Common sources of oxidative stress are viral infections

(including COVID-19), and all types of psychosocial stresses. The longer Vagus nerves (the majority of the PSNS outside the brain) are more significantly affected and earlier, than the SNS, which is a common cause of \uparrow SNS (high SB), leading to high BP, further exacerbating cardiovascular diseases such as HF.

Conclusions

Autonomic assessment is important in diagnosing and treating CHF, ventricular arrhythmias, AFib, hypertension, and CAN. Autonomic assessment may also predict which patients may be susceptible to MACE, including SCD. This is important since most CHF patients with SCD have preserved LVEF and better discriminators are needed. Many life-threatening cardiovascular disorders will require invasive testing within or proximal to the heart for precise diagnoses and therapy planning when modulating the P&S is important, with follow-up facilitated by P&S testing. In cases of non-life-threatening disorders, non-invasive ANS testing techniques, especially those that individually assess both ANS branches simultaneously and independently, are sufficient to diagnose and treat serially. [3, 52].

Each cardiac patient may be better approached individually with P&S tests, at the discretion of the clinician. For example, imaging studies requiring radioactive agents may best assess the need for a defibrillator in patients with dilated cardiomyopathy and low LVEF. Whereas cardio-respiratory monitoring (P&S monitoring [3]) provides more serially, easily obtained, non-invasive information, and appears most appropriate for risk stratification and follow-up therapy, especially in CHF patients, as well as other cardiac disorders. The ability to serially test patients with non-invasive P&S monitoring enables follow-up to the invasive testing, especially for the life-threatening AD cases that may require modulation of ANS function to maintain. More information from serial, non-invasive P&S testing also enables earlier diagnoses, treatment, and possible prevention of AD disorders that may lead to cardiac disorders as a means of maintaining quality of life. More research is needed in early assessment and treatment of AD in cardiac disease management, especially in risk stratifying CHF patients and treating those who may be at high risk of SCD. Simultaneous assessment of both autonomic branches may play a key role.

P&S Monitoring may provide more information that helps all physicians, helping family practitioners, internists, and specialists work together to manage and perhaps reduce cardiac disorders.

Appendix

Detailed description of Table 1 (with Figure)

Table 1 summarizes the four general types of AD: \uparrow SNS, \downarrow SNS, \uparrow PSNS, \downarrow PSNS. The see-saw model of autonomic interaction is implicit and is valid at rest and mostly in relatively

healthy individuals. Where the see-saw model of the ANS fails is during the challenge responses. The challenge responses are better modeled by the brakes & accelerator of a car. For example, a common AD is Sympathetic Withdrawal (SW, an abnormal alpha-adrenergic response to head-up postural change, including Stand, see " \downarrow SNS" in Table 1). SW occurs upon standing. It is often the first AD to present and the hardest to relieve. The normal stand response is like being in an automatic transmission car and reacting to a traffic light changing from red to green. The first action, once the light turns green, is to release the brakes. This minimizes and potentiates acceleration. This is similar to the P&S upon standing as well as other Sympathetic responses, including stress responses. Again, in the normal response to head-up, postural change (*i.e.*, Standing), first the Parasympathetics decrease to minimize and potentiate the Sympathetic response. Then the Sympathetics increase to drive vasoconstriction to move blood to the abdomen to help the heart fight gravity and properly perfuse the brain. The Parasympathetics change first also because they are able to react faster than the Sympathetics. Using the car model, you never want the accelerator to respond faster than the brakes, or else you may never stop the car. In the abnormal SW response, the body "forgets" to accelerate enabling blood to pool in the lower extremities, causing Orthostatic dysfunction.

Another common AD is Parasympathetic Excess (PE, an abnormal Parasympathetic response to a Sympathetic, or stress, challenge, see " \uparrow PSNS" in Table 1). This is like driving a car when "riding the brakes." Riding the brakes forces more acceleration (referred to as Sympathetic Excess, or SE) and more stress on the engine (due to over-revving) as well as more stress on the brakes. Often this is perceived as a primary Sympathetic dysfunction because "over-revving" the engine causes high BP, HR, and cardiac output, and may involve Anxiety, pain, inflammation, histaminergic reactions, and other stress responses, which are all Sympathetic responses. However, in these patients, treating the SE as the primary dysautonomia exacerbates the problem by enabling more Parasympathetic activity, or forcing the body to defeat the Sympathetic therapy. Remember medicine is able to only block 3 or 4 of the 7 pathways the body has to increase BP, for example, leaving the body these additional pathways to defeat therapy. In these patients, PE is the primary dysautonomia to be treated, and is generally treated with anti-cholinergics. Once the brakes are released (PE is relieved), then acceleration is normalized (SE is relieved, often organically), and then BP, HR or Cardiac Output are normalized (also organically, unless there are end-organ disorders).

The third common AD is SE (a beta-adrenergic response to Sympathetic challenge, see " \uparrow SNS" in Table 1). This is simply over-revving the engine causing high BP, HR, and cardiac output. In the previous case where SE and PE are demonstrated concurrently, SE was secondary. In this case, SE is primary and generally treated with Sympatholytics (*i.e.*, beta-blockers or renin-angiotensin blockers). With standing there are SE states that may occur, often indicating risk of Syncope. SE may occur

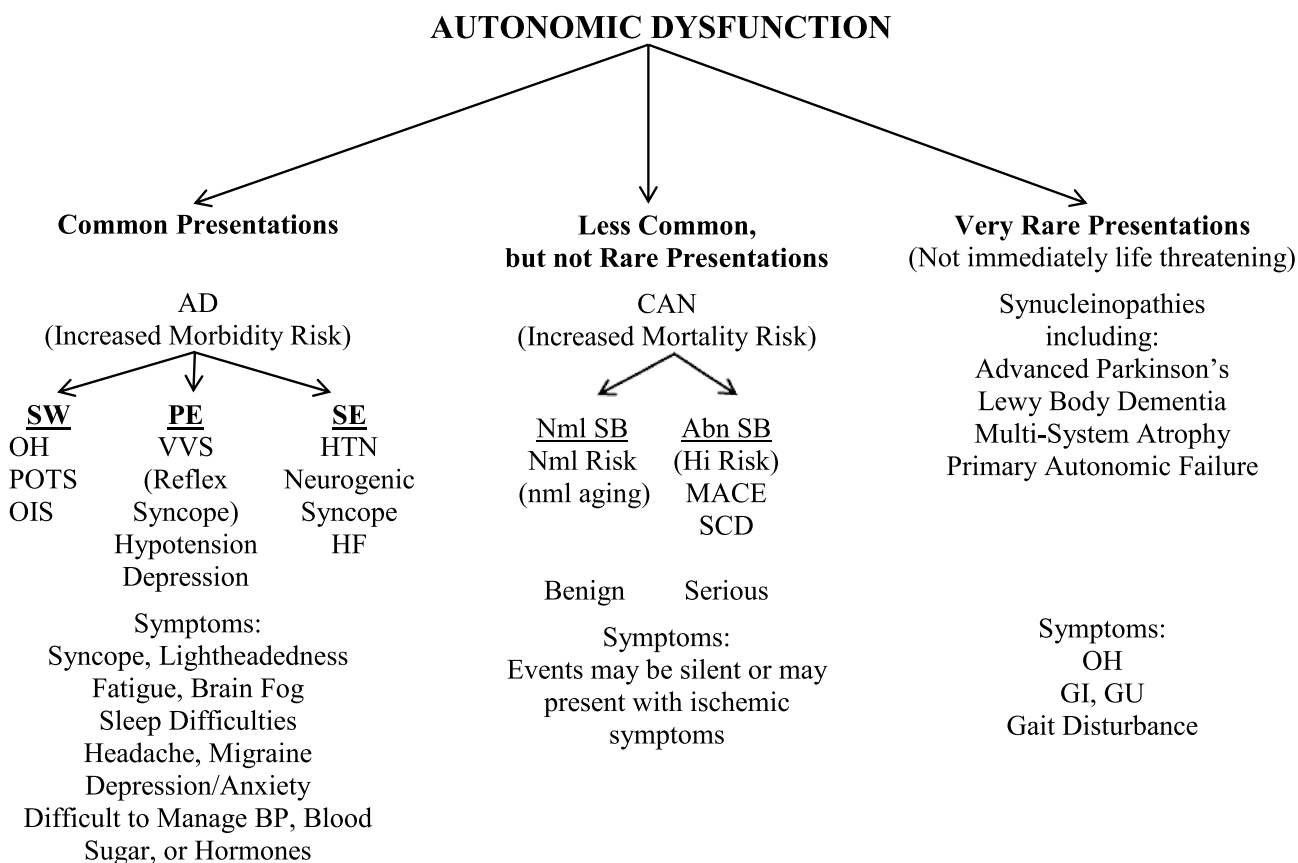
at rest or with other dynamic challenges, including stressors (exercise, cold pressor tests, or Valsalva responses), indicating risk of hypertension. In cases of resting SE or hypertension, with SW or NOH, the high, resting BP may be compensatory for, and secondary to, the abnormal stand response. As you see, there are several reasons for SE to be secondary. This may be a reason why many patients with hypertension are poorly managed.

The Parasympathetics, which are difficult to measure independently, may respond excessively (PE). Normally, the Parasympathetics decrease in response to stress (including standing, a stress to the ANS). This decrease minimizes and potentiates the needed SNS-reaction. PE is associated with Vagal symptoms, and forces an excessive or amplified SNS-reaction to stress¹, inflating histaminergic (Mast Cell), inflammatory, cardiovascular, stress hormone, pain, anxiety, and other stress responses. PE may occur

at rest or under dynamic or challenge conditions. In general, PE is associated with lightheadedness, depression, anxiety, fatigue, exercise intolerance, migraines or headaches, brain-fog, memory and cognitive difficulty, sleep difficulties, upper or lower GI upset, difficult to manage BP, blood glucose, or hormone levels, and in some cases may be a precursor to hypertension, since it provokes a secondary SE. SW, stand SE, and stand PE may be associated with hypovolemia. SW often involves elevated or high BP as a means of compensating for the associated reduced cerebral perfusion.

In general, the effects and recommended treatment of AD depends on when it is demonstrated (during which P&S test challenge), as well as the patient’s history. See the [Appendix Table](#) for more specific indications and therapy recommendations.

Appendix Figure



Appendix Figure: Summary diagram of Autonomic Dysfunction. See text for details. Abbreviations: AD, Autonomic Dysfunction; Adv., advanced; CAN, Cardiovascular Autonomic Neuropathy; GI, Gastro-intestinal; GU, Genitourinary; MSA, Multiple System Atrophy; PAF, Primary Autonomic Failure;

¹ Tobias H, Vinitzky A, Bulgarelli RJ, Ghosh-Dastidar S, Colombo J. Autonomic nervous system monitoring of patients with excess parasympathetic responses to sympathetic challenges – clinical observations. US Neurology. 2010; 5(2): 62-66.

Appendix Figure: Summary diagram of Autonomic Dysfunction. See text for details. Abbreviations: Abn, abnormal; AD, Autonomic Dysfunction; Adv., advanced; CAN, Cardiovascular Autonomic Neuropathy; GI, Gastro-intestinal; GU, Genitourinary; MSA, Multiple System Atrophy; Nml, normal; PAF, Primary Autonomic Failure;

Appendix Table

Appendix 1, Summary Table: Autonomic Dysfunction (P&S) testing indications and therapy recommendations. See text for details.

AUTONOMIC DYSFUNCTION	DIFFERENTIATING RESPONSES	INDICATIONS	GENERAL THERAPY RECOMMENDATIONS*
ARRHYTHMIA	Only SB is valid for interpretation		
	Low SB	Resting PE contributing to the arrhythmia	Relieve PE, anti-Cholinergics
	High SB	Resting SE contributing to the arrhythmia	Relieve SE, Sympatholytics
	Normal SB	No autonomic contribution to the arrhythmia	No autonomic therapy indicated
NO ARRHYTHMIA			
REST			
AAD (DAN)	Morbidity Risk		
	Low SB	PE, high Morbidity risk (<i>e.g.</i> , Hypotension, Vagally-mediated CVD, Depression)	Relieve PE, anti-Cholinergics
	High SB	SE, high Morbidity risk (<i>e.g.</i> , HTN, Sympathetically-mediated CVD, Anxiety)	Relieve SE, Sympatholytics
	Normal SB	Normal Morbidity risk	Treat remaining symptoms and maintain Normal SB
CAN	Mortality Risk		Complete cardiac work-up as soon as possible, if not recent.
	Low SB	PE, high Mortality risk (<i>e.g.</i> , Broken Heart Syndrome, Vagally-mediated CVD, SCD, Arrhythmia)	Relieve PE, anti-Cholinergics
	High SB	SE, high Mortality risk (<i>e.g.</i> , MACE, Sympathetically-mediated CVD, SCD, Arrhythmia)	Relieve SE, Sympatholytics
	Normal SB	Normal Mortality risk	Treat remaining symptoms and maintain Normal SB
CHALLENGE			
SW	BP decreases with Stand	NOH, fall risk indicator in older patients. Pre-clinical indication if SW with a BP response to Stand between 0/0 and 20/10 mmHg < resting BP	Fluids, Electrolytes, Compression garments, and low-dose Oral Vasoactives
	Excessive HR response with Stand	POTS, check for Vasovagal Syncope Pre-clinical indication if SW with a HR response to Stand < 30 bpm > resting HR	Fluids, Electrolytes, Compression garments, low-dose Oral Vasoactives, and low-dose Beta-Blocker
	DIFFERENTIATING RESPONSES	INDICATIONS	GENERAL THERAPY RECOMMENDATIONS*
SW	BP increases with Stand	OIS	low-dose Oral Vasoactives
	Long-standing with wide Pulse Pressure	Heart Failure	Treat both SW & HF
PE	with Valsalva or Stand	Typically causes patients to be difficult to control (<i>e.g.</i> , BP, blood glucose, hormone level, or depression/anxiety syndromes), or is associated with unexplained symptoms, including arrhythmia and seizure	If no SE, high SB, or high BP, Relieve PE with anti-Cholinergics If SE, high SB, or high BP is present, Relieve PE with Carvedilol to treat both PE & SE or high BP
	with Stand SE	Vasovagal Syncope, check for POTS; both may be treated concurrently	Treat PE as the primary Dysautonomia with low-dose anti-Cholinergics
SE	with Valsalva	Possible HTN, MACE, Stroke and CVD risk, even with (apparently) normal resting BP & SB	Relieve SE, titrate Sympatholytics
	with PE	Vasovagal Syncope, check for POTS; both may be treated concurrently	Treat PE as the primary Dysautonomia with low-dose anti-Cholinergics
	with Stand & a weak HR response to Stand	Neurogenic Syncope	Treat Syncope
	No PE & normal HR responses to Stand	Diagnosis by omission, possible Cardiogenic Syncope.	Requires further testing

AAD Advanced Autonomic Dysfunction (similar to DAN without the diabetes-related issues), BP Blood Pressure, CAN Cardiovascular Autonomic Neuropathy, CVD, Cardiovascular Diseases, DAN Diabetic Autonomic Neuropathy (AD, with diabetes-related issues), HR Heart

Rate, *HTN* Hypertension, *MACE* Major Adverse Cardiovascular Events including HF, SCD and Stroke, *n/a* not applicable, *NOH* Neurogenic Orthostatic Hypotension, *OIS* Orthostatic Intolerance Syndrome, *PE* Parasympathetic Excess, an excess PSNS-response to a stress, *e.g.*, Valsalva or stand, *POTS* Postural Orthostatic Tachycardia Syndrome, *SB* Sympathovagal Balance = [resting SNS-response]/[resting PSNS-response], *SCD* Sudden Cardiac Death, *SE* Sympathetic Excess, an excess SNS-response to a stress, *e.g.*, Valsalva or stand, *SW* Sympathetic Withdrawal, an insufficient SNS-response to head-up postural change, *e.g.*, Stand

* All general therapy recommendations are history dependent and low-dose. All may be treated simultaneously. However, treating primary autonomic dysfunctions first may reduce or eliminate the therapy need for secondary dysfunctions

Declarations

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any new unpublished studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. DePace NL, Mears JP, Yayac M, Colombo J. Cardiac autonomic testing and diagnosing heart disease. "A clinical perspective." *Heart Int.* 2014;9(2):37–44. <https://doi.org/10.5301/heartint.5000218>.
2. DePace NL, Mears JP, Yayac M, Colombo J. Cardiac autonomic testing and treating heart disease. "A clinical perspective." *Heart Int.* 2014;9(2):45–52. <https://doi.org/10.5301/heartint.5000216>.
3. Colombo J, Arora RR, DePace NL, Vinik AI. Clinical autonomic dysfunction: measurement, indications, therapies, and outcomes. Springer Science + Business Media, New York, NY, 2014.
4. Pop-Busui R, Braffett BH, Zinman B, Martin C, White NH, Herman WH, Genuth S, Gubitosi-Klug R. DCCT/EDIC Research Group Cardiovascular Autonomic Neuropathy and Cardiovascular Outcomes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study. *Diabetes Care.* 2017;40(1):94–100. <https://doi.org/10.2337/dc16-1397> (Epub 2016 Nov 1).
5. Curtis BM, O'Keefe JH. Autonomic tone as a cardiovascular risk factor: the dangers of chronic fight or flight. *Mayo Clin Proc.* 2002;77:45–54.
- 6.●● Murray GL, Colombo J. Routine measurements of cardiac parasympathetic and sympathetic nervous systems assists in primary and secondary risk stratification and management of cardiovascular clinic patients. *Clin Cardiol Cardiovasc Med.* 2019;3(1):27–33. <https://doi.org/10.33805/2639.6807.122>. **Documents that parasympathetic and sympathetic abnormalities, including high sympathovagal balance, autonomic neuropathy indices, and low sympathetic responses to head-up postural change are common. They cause and contribute to mortality and morbidity risk, and cost of medical care, including for CAD, chronic CHF and neurogenic orthostatic hypotension; however, they are treatable and treatment reduces the risks.**
- 7.● Murray LG, Colombo J. Maintenance (r) alpha lipoic acid reduces sudden cardiac death in geriatric diabetes mellitus II patients. 2020; *Clin Cardiol Cardiovasc Med* 4:6–12. **Documents a medication treatment of parasympathetic and sympathetic abnormalities, including cardiovascular autonomic neuropathy, high sympathovagal balance, and low sympathetic responses to head-up postural change that reduces the relative risk ratio for sudden cardiac death by 43%.**
8. Vinik AI, Murray GL. Autonomic neuropathy is treatable US *Endocrinol.* 2008;2:82–4.
9. Colombo J, Weintraub MI, Munoz R, Verma A, Ahmed G, Kaczmarek K, Santos L, DePace NL. Long-COVID and the autonomic nervous system: the journey from dysautonomia to therapeutic neuro-modulation, analysis of 152 patient retrospectives. *NeuroSci.* 2022;3(2):300–10. <https://doi.org/10.3390/neurosci3020021>.
10. Goldberger JJ, Arora R, Buckley U, Shivkumar K. Autonomic nervous system dysfunction: JACC focus seminar. *J Am Coll Cardiol.* 2019;73(10):1189–206. <https://doi.org/10.1016/j.jacc.2018.12.064>.
11. Umetani K, Singer DH, McCraty R, Atkinson M. Twenty-four hour time domain heart rate variability and heart rate: Relations to age and gender over nine decades. *JACC.* 1998;31(3):593–601.
12. Akselrod S. Spectral analysis of fluctuations in cardiovascular parameters: a quantitative tool for the investigation of autonomic control. *Trends Pharmacol Sci.* 1988;9:6–9.
13. Goldstein DS, Benth O, Park MY, Sharabi Y. Low-frequency power of heart rate variability is not a measure of cardiac sympathetic tone but may be a measure of modulation of cardiac autonomic outflows by baroreflexes. *Exp Physiol.* 2011;96(12):1255–61.
14. Cheshire WP. Autonomic history, examination, and laboratory evaluation in Autonomic Disorders. *Am Acad Neurol.* 2020;26(1):38.
15. Schwartz PJ, La Rovere MT, De Ferrari GM, Mann DL. Autonomic modulation for the management of patients with chronic heart failure. *Circulation: Heart Fail.* 2015;8:619–628.
16. Tsujimoto T, Kajio H. Low diastolic blood pressure and adverse outcomes in heart failure with preserved ejection fraction. *Int J Cardiol.* 2018;15(263):69–74. <https://doi.org/10.1016/j.ijcard.2018.04.031> (Epub 2018 Apr 9).
17. Al-Khalisy H, Nikiforov I, Jhaji M, Kodali N, Cheriya P. A widened pulse pressure: a potential valuable prognostic indicator of mortality in patients with sepsis. *J Community Hosp Intern Med Perspect.* 2015;5(6):29426. Published 2015 Dec 11. <https://doi.org/10.3402/jchimp.v5.29426>
18. Arora RR, Bulgarelli RJ, Ghosh-Dastidar S, Colombo J. Autonomic mechanisms and therapeutic implications of postural diabetic cardiovascular abnormalities. *J Diabetes Science and Technology.* 2008;2(4):568–71.
19. Gutman LB, Wilson BJ. The role of midodrine for hypotension outside of the intensive care unit. *J Popul Ther Clin Pharmacol.* 2017;24(3):e45–50. <https://doi.org/10.22374/1710-6222.24.3.4>.

20. Chatterjee NA, Singh JP. Novel interventional therapies to modulate the autonomic tone in heart failure. *JACC: Heart Fail.* 2015;3(10):786–802. <https://doi.org/10.1016/j.jchf.2015.05.008>.
21. Gold MR, Van Veldhuisen DJ, Hauptman PJ, Borggrefe M, Kubo SH, Lieberman RA, Milasinovic G, Berman BJ, Djordjevic S, Neelagaru S, Schwartz PJ, Starling RC, Mann DL. Vagus nerve stimulation for the treatment of heart failure: The INOVATE-HF Trial. *J Am Coll Cardiol.* 2016;68(2):149–58. <https://doi.org/10.1016/j.jacc.2016.03.525> (Epub 2016 Apr 4).
22. Zile MR, Lindenfeld J, Weaver FA, et al. Baroreflex activation therapy in patients with heart failure with reduced ejection fraction. *J Am Coll Cardiol.* 2020; 76(1):1–13. <https://doi.org/10.1016/j.jacc.2020.05.015>. **Documents a device treatment of parasympathetic and sympathetic abnormalities, that improves Quality of Life, six-minute walk, and NT-proBNP scores in heart failure.**
23. McAlister FA, et al. How many patients are eligible for cardiac resynchronization? Insights from two perspective cohorts. *Eur Heart J.* 2006;27:323–9.
24. Namas W, Koistinen J, Paana T, Karjalainen PP Renal sympathetic denervation for treatment of patients with heart failure: summary of the available evidence. *Ann Med.* 2017;49(5):384–95. <https://doi.org/10.1080/07853890.2017.1282168> (Epub 2017 Feb 1).
25. Murray GL, Colombo J. Ranolazine preserves and improves left ventricular ejection fraction and autonomic measures when added to guideline-driven therapy in chronic heart failure. *Heart International* 2014;9(2):66–73; published online 9/23/2014 6:53:43 AM. <https://doi.org/10.5301/heartint.5000219>.
26. Fudim M, Boortz-Marx RL, Ganesh A, DeVore AD, Patel CB, Rogers JG, Coburn A, Johnson I, Paul A, Coyne BJ, Rao SV, Gutierrez JA, Kiefer TL, Kong DF, Green CL, Jones WS, Felker GM, Hernandez AF, Patel MR. Splanchnic nerve block for chronic heart failure. *JACC Heart Fail.* 2020;8(9):742–52. <https://doi.org/10.1016/j.jchf.2020.04.010> (Epub 2020 Jun 10 PMID: 32535123).
27. Pepper GS, Lee RW. Sympathetic activation in heart failure and its treatment with beta-blockade. *Arch Intern Med.* 1999;159:225–34.
28. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Rev Esp Cardiol.* 2016;69:176. <https://doi.org/10.1016/j.rec.2016.01.001>.
29. Shusterman V, Aysin B, Gottipaty V, Weiss R, Brode S, Schwartzman D, et al. Autonomic nervous system activity and the spontaneous initiation of ventricular tachycardia. *ESVEM Investigators. Electrophysiologic study versus electrocardiographic monitoring trial.* *J Am Coll Cardiol.* 1998;32:1891–9.
30. Lai Y, Yu L, Jiang H. Autonomic neuromodulation for preventing and treating ventricular arrhythmias. *Front Physiol.* 2019;10:200. <https://doi.org/10.3389/fphys.2019.00200>.
31. Bradfield JS, Ajjola OA, Vaseghi M, Shivkumar K. Mechanisms and management of refractory ventricular arrhythmias in the age of autonomic modulation. *Heart Rhythm.* 2018;15(8):1252–60. <https://doi.org/10.1016/j.hrthm.2018.02.015> (Epub 2018 Feb 14).
32. Fudim M, Boortz-Marx R, Patel CB, Sun AY, Piccini JP. Autonomic modulation for the treatment of ventricular arrhythmias: therapeutic use of percutaneous stellate ganglion blocks. *J Cardiovasc Electrophysiol.* 2017;28:446–9. <https://doi.org/10.1111/jce.13152>.
33. Vaseghi M, Barwad P, CorralesMalavassi FJ, Tandri H, Mathuria N, Shah R, Sorg JM, Gima J, Mandal K, Saenz LC, Lokhandwala Y, Shivkumar K. Value of cardiac sympathetic denervation in structural heart disease and refractory ventricular arrhythmias and predictors of outcomes: an International Cardiac Sympathetic Denervation Collaborative Study (ICSDC). *Journal of American College of Cardiology.* 2017;69(25):3070–80.
34. Assis FR, Krishnan A, Zhou X, James CA, Murray B, Tichnell C, Berger R, Calkins H, Tandri H, Mandal K. Cardiac sympathectomy for refractory ventricular tachycardia in arrhythmogenic right ventricular cardiomyopathy. *Heart Rhythm* 2019;1697:1003–1010.
35. Collura CA, Johnson JN, Moir C, Ackerman MJ. Left cardiac sympathetic denervation for the treatment of long QT syndrome and catecholaminergic polymorphic ventricular tachycardia using video-assisted thoracic surgery. *Heart Rhythm.* 2009;6:752–9. <https://doi.org/10.1016/j.hrthm.2009.03.024>.
36. Tan AY, Chen PS, Chen LS, Fishbein MC. Autonomic nerves in pulmonary veins. *Heart Rhythm.* 2007;4(3 Suppl):S57–60. <https://doi.org/10.1016/j.hrthm.2006.12.011>.
37. Agarwal SK, Norby FL, Whitsel EA, Soliman EZ, Chen LY, Loefer LR, Fuster V, Heiss G, Coresh J, Alonso A. Cardiac autonomic dysfunction and incidence of AFib: Results From 20 Years Follow-Up. *J Am Coll Cardiol.* 2017;69(3):291–9. <https://doi.org/10.1016/j.jacc.2016.10.059>.
38. Carnagari R, Kiuchi MG, Ho JK, Matthews VB, Schlaich MP. Sympathetic nervous system activation and its modulation: role in AFib. *Front Neurosci.* 2019;12:1058. Published 2019 Jan 23. <https://doi.org/10.3389/fnins.2018.01058>.
39. Linz D, van Hunnik A, Hohl M, et al. Catheterbased renal denervation reduces atrial nerve sprouting and complexity of AFib in goats. *Circ Arrhythm Electrophysiol.* 2015;8:466–74.
40. Pokushalov E, Kozlov B, Romanov A, et al. Long-term suppression of AFib by botulinum toxin injection into epicardial fat pads in patients undergoing cardiac surgery: one-year follow-up of a randomized pilot study. *Circ Arrhythm Electrophysiol.* 2015;8:1334–41.
41. Schwartz PJ. Another role for the sympathetic nervous system in the long QT syndrome? *J Cardiovasc Electrophysiol.* 2001;12:500–2. <https://doi.org/10.1046/j.1540-8167.2001.00500.x>.
42. Svircevic V, Nierich AP, Moons KG, Diephuis JC, Ennema JJ, Brandon Bravo Bruinsma GJ, Kalkman CJ, van Dijk D. Thoracic epidural anesthesia for cardiac surgery: a randomized trial. *Anesthesiology.* 2011;114(2):262–70. <https://doi.org/10.1097/ALN.0b013e318201d2de>.
43. Goldberger JJ, Mitrani RD. Autonomic tone and AFib: a double-edged sword? *J Am Coll Cardiol.* 2017;69(3):300–2. <https://doi.org/10.1016/j.jacc.2016.11.021>.
44. Nanavati SH, Bulgarelli RJ, Vazquez-Tanus J, Ghosh-Dastidar S, Colombo J, Arora RR. Altered autonomic activity with AFib as demonstrated by non-invasive autonomic monitoring. *US Cardiology.* 2010;7(1):47–50.
45. Steinberg JS, Shabanov V, Ponomarev D, Losik D, Ivanickiy E, Kropotkin E, Polyakov K, Ptaszynski P, Keweloh B, Yao CJ, Pokushalov EA, Romanov AB. Effect of renal denervation and catheter ablation vs catheter ablation alone on atrial fibrillation recurrence among patients with paroxysmal atrial fibrillation and hypertension: the ERADICATE-AF randomized clinical trial. *JAMA.* 2020;323(3):248–55. <https://doi.org/10.1001/jama.2019.21187>. Erratum. In: *JAMA.* 2020Mar3;323(9):896.PMID: 31961420;PMCID:PMC6990678.
46. Mancia G, Grassi G. The autonomic nervous system and hypertension. *Circ Res.* 2014;114(11):1804–14. <https://doi.org/10.1161/CIRCRESAHA.114.302524>.
47. Heusser K, Tank J, Engeli S, Diedrich A, Menne J, Eckert S, Peters T, Sweep FC, Haller H, Pichlmaier AM, Luft FC, Jordan J. Carotid baroreceptor stimulation, sympathetic activity, baroreflex function, and blood pressure in hypertensive patients. *Hypertension.* 2010;55(3):619–26. <https://doi.org/10.1161/HYPERTENSIONAHA.109.140665> (Epub 2010 Jan 25).

48. Folkow B. Physiological aspects of the “defence” and “defeat” reactions. *Acta Physiol Scand Suppl.* 1997;640:34–7.
49. De Meersman RE, Stein PK. Vagal modulation and aging. *Biol Psychol.* 2007;74(2):165–73. <https://doi.org/10.1016/j.biopsycho.2006.04.008>.
50. Cox FF, Misiou A, Vierkant A, Ale-Agha N, Grandoch M, Haendeler J, Altschmied J. Protective effects of curcumin in cardiovascular diseases-impact on oxidative stress and mitochondria. *Cells.* 2022;11(3):342. <https://doi.org/10.3390/cells11030342>. PMID:35159155;PMCID:PMC8833931.
51. Shaito A, Aramouni K, Assaf R, Parenti A, Orekhov A, Yazbi AE, Pintus G, Eid AH. Oxidative stress-induced endothelial dysfunction in cardiovascular diseases. *Front Biosci (Landmark Ed).* 2022;27(3):105. <https://doi.org/10.31083/j.fbl2703105> (PMID: 35345337).
52. Vinik AI, Camacho PM, Davidson JA, Handelsman Y, Lando HM, Leddy AL, Reddy SK, Cook R, Spallone V, Tesfaye S, Ziegler D; Task Force to Develop an AACE Position Statement on Autonomic Testing. American Association Of Clinical Endocrinologists and American College Of Endocrinology position statement on testing for autonomic and somatic nerve dysfunction. *Endocr Pract.* 2017;23(12):1472–1478. <https://doi.org/10.4158/EP-2017-0053>.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.