

Autonomic Nervous System Monitoring of Patients with Excess Parasympathetic Responses to Sympathetic Challenges—Clinical Observations

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Abstract

A common assumption regarding the autonomic nervous system is that one branch either opposes the other or does not respond during physiological challenges. Recently, this assumption has been challenged based on clinical observations of unprovoked parasympathetic (P) excess (PE) during sympathetic (S) stimulation, an abnormal response. Over a three-year period, serial autonomic profiling of 1,340 patients was performed using the P and S method, which yields independent measures of P and S activity obtained from time–frequency analyses of respiratory activity and heart rate variability (ANX 3.0, ANSAR Medical Technologies, Inc., Philadelphia, PA). Within this cohort, patients with PE reported symptoms of sleep difficulties, poor peripheral circulation, general malaise, depression, frequent headache or migraines, gastrointestinal upset, and dizziness when standing. However, they demonstrated normal heart rate and blood pressure and no other apparent causes for their symptoms. The results of this study highlight the clinical effects of PE and indicate that, depending on patient history, carvedilol may be effective for patients with cardiovascular disease (CVD) and low-dose anticholinergics for patients without CVD. In cases where end-organ effects are not yet presented, patients may be weaned from therapy once PE is resolved.

Keywords

Autonomic nervous system (ANS), parasympathetic, parasympathetic excess/challenge, sympathetic, sympathetic excess/challenge, postural change, valsalva, beta-adrenergic antagonist, beta-blocker, cardiovascular disease, hypertensive, autonomic imbalance

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Non-invasive autonomic nervous system (ANS) assessment is often based on physiological challenges, such as the Valsalva maneuver and head-up postural change for the sympathetic nervous system (SNS) and deep breathing for the parasympathetic nervous system (PSNS). A common assumption about the ANS is that the predominant response is from stimulation of one ANS branch, and the opposing branch decreases its response or does not respond to the challenge. Partially responsible for this assumption is an incomplete understanding of the ANS.

In the past, measures of autonomic function have been based solely on heart rate variability (HRV), which yields mixed assessment of parasympathetic (P) and sympathetic (S) activity.¹ Therefore, these measures cannot provide complete information about the health of the ANS. Separate tests for S activity and P activity based on these measures also yield incomplete information because neither test accounts for the independent actions of the two ANS branches. The dynamic nature of the ANS and the continuous PSNS and SNS interactions dictate the requirement for simultaneous, independent measures of P and S activity. Only with such measures can the patient's autonomic activities, including responses to disease and common medications, be understood.

The failure of measures based solely on HRV^{2–4} can be attributed to a fundamental mathematical conundrum. Basic algebra dictates that a system (e.g. ANS) with two independent components requires two independent measures to be fully characterized. HRV alone is one such independent measure with multiple dependent measures. A solution to this conundrum was introduced in the 1996 Circulation Special Report, standardizing measures based solely on HRV.¹ The solution was validated by the Massachusetts Institute of Technology (MIT) and Harvard.^{5–8} It has recently been implemented for clinical use.^{9,10} The solution involves the introduction of a second measure of autonomic function—respiratory activity (RA). Analyzing RA concurrently with HRV offers two independent measures of the ANS and thus satisfies the fundamental algebraic requirement establishing independent, simultaneous measures of P and S activity. Analysis of RA concurrent with HRV is named the 'P and S method' in this article.

Clinical observations of unprovoked P excess (PE) with P and S measures are associated with abnormal clinical and pathophysiological responses. Chronic conditions such as diabetes,^{11–15} thyroid disease,¹⁶ kidney disease,¹⁷ cardiovascular disease (CVD),^{11,12} demyelinating and inflammatory neurological diseases,¹⁸ certain dementias,¹⁹ depression, and altered

psychological states¹⁹ can cause autonomic imbalance and associated P dysfunction. Severe acute conditions can precipitate PE, including trauma,²⁰ injury, infection, surgery, cancer, and myocardial infarction (MI). Preliminary evidence suggests that multiple pregnancies can cause PE in women, and severe or chronic exposure to chemicals, cold, and allergens can also affect PE. Stress, excess caffeine, nicotine, and other chemical^{21,22} and environmental exposures can also affect autonomic balance. PE may also be genetically mediated, as evidenced by colic in infants.

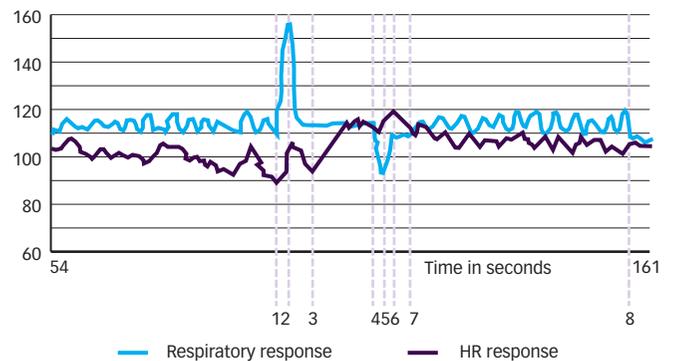
Establishing PE may help clarify a diagnosis when patients demonstrate multiple seemingly contradictory symptoms (e.g. hypertension with depression) and provide a more integrated approach to therapy. Disease can cause autonomic imbalance; for example, pain causes S excess that can lead to early hypertension. Disease can also be caused by autonomic imbalances. For example, dizziness on standing up (orthostasis or syncope) is caused by S abnormalities. Therefore, it seems reasonable to hypothesize that every autonomic imbalance is a separate and distinct dysfunction. A single agent can often address both the primary disease and autonomic disorders. PE can also be treated concurrently. Once the PE is corrected, the patient is more stable and the primary disease(s) can be treated more aggressively.

Measures of P and S activity are critical to understanding the true nature of autonomic dysfunction and its clinical implications. Simultaneous, independent documentation of P and S activity has provided more insight into many commonly observed clinical conditions. Such measures have identified failures in the reactive push-pull dynamics within the ANS. PE appears to be the primary autonomic disorder and the (reactionary) S abnormalities appear to be secondary. This article will discuss longitudinal studies showing PE, its correction, and outcomes.

Background

PE presents in response to an S challenge. For example, any type of P increase in response to head-up postural change (standing) is considered abnormal. Normally, P activity decreases first, potentiating the S increase that follows to perpetuate the expected vasoconstriction required to counter orthostasis. Stress responses such as short Valsalva maneuvers (<15 seconds) are expected to cause a decrease in average P activity. An increase in P activity to either of these S challenges appears to force a higher S response than typical for that patient and the condition. These relative S excesses (SE) are often experienced as increases in blood pressure (BP) or heart rate (HR), and as such may be treated as a primary SE. However, patient responses under these autonomic conditions are unexpected. By definition, PE is a dynamic autonomic imbalance and not a resting imbalance. Understanding the physiology of some commonly used clinical assessment challenges can help to elucidate PE and its clinical implications. The short Valsalva maneuver is normally a significant S challenge and should have little or no net P effect. Valsalva simulates normal stresses that occur daily, such as exercise, bowel movements, and domestic, environmental, and workplace-related stress. Clinically, Valsalva can help differentiate normalized hypertensives from those who are only normotensive at rest and still at risk for stroke or myocardial infarction (MI) due to SE from stress. The head-up postural change challenge is a challenge to both ANS branches, and a test of coordination between the two. As the P activity is expected to decrease and the S activity is expected to

Figure 1: Valsalva Maneuver—Sympathetic Challenge



A recording of normal subject data during the Valsalva challenge of the clinical exam (see 'Methods'). Instantaneous heart rate (HR) changes (in beats per minute; purple) and respiratory activity (RA; in volts; blue) are plotted against time. At (1) the short Valsalva is initiated by inhalation. At (2) the sudden increase in intrathoracic pressure stimulates the thoracic baroreceptors, causing a momentary parasympathetic (Vagal) response, followed by a drop in HR. Due to decreased venous return to the heart, sympathetic activity is stimulated and there is a gradual increase in HR starting at (3). Upon release of Valsalva during exhalation (4), there is an overshoot of blood pressure (BP) resulting from the sudden rush of blood back to the heart. This overshoot is compounded by the residual sympathetic activity (causing peripheral vasoconstriction) exaggerating the blood rush into the thorax and opposing venous return into the extremities. The deep inhalation (5) causes parasympathetic inhibition and a subsequent rise in HR. After the release of the Valsalva, HR and RA finish returning to normal (6). Normal sinus (HR) rhythm returns (7), synchronized with RA, and continues until the end of the recording (8).

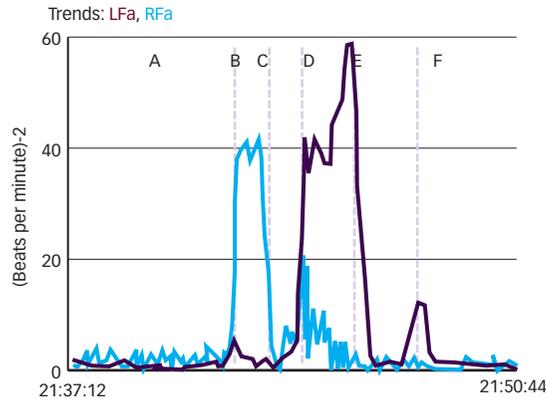
increase, the commonly perceived net effect is that postural change is an S challenge. It should be noted that the predominant S response to Valsalva is a beta-adrenergic response, and the predominant S response to postural change is an alpha-adrenergic response. In this way, it is possible to detect both an SE (in response to Valsalva) as well as an S insufficiency or S withdrawal (in response to postural change).

Normal Autonomic Nervous System Responses to a Valsalva Maneuver

Figure 1 depicts the instantaneous HR (purple) and respiratory (blue) responses of a normal subject during a short Valsalva. During a short Valsalva, there is a sudden increase in intrathoracic pressure. This mechanical pressure increase is falsely interpreted by the baroreceptors at the heart as a sudden increase in BP due to an increase in cardiac output. In actuality, the Valsalva lowers cardiac output by shunting blood away from the heart. The Valsalva is initiated by inhalation (see Figure 1, #1, respiratory response in blue), causing P (vagal) inhibition, immediately followed by an increase in HR (see Figure 1, #1, HR response in purple) from the cardiovagal inhibition as stretch receptors in the lungs are unloaded. The sudden increase in intrathoracic pressure stimulates the thoracic baroreceptors, which causes a momentary P response, followed by a drop in HR (see Figure 1, #2, HR response). As blood is shunted away from the thorax, two reflexes, the baroreceptor reflex and the venoarteriolar axon reflex, stimulate S activity. Due to decreased venous return to the heart and decreased cardiac output, aortic pressure reduces and the aortic baroreceptors are unloaded. In addition, there is no opposing peripheral vasoconstriction and no pre-existing S activity upon initiation of the Valsalva. Therefore, as blood is shunted freely into the peripheral vessels, the venoarteriolar axon reflex is initiated as transmural pressure within the blood vessels begins to exceed 25mmHg. As a result, S activity is stimulated and there is a gradual increase in HR (see Figure 1, #3, HR response).

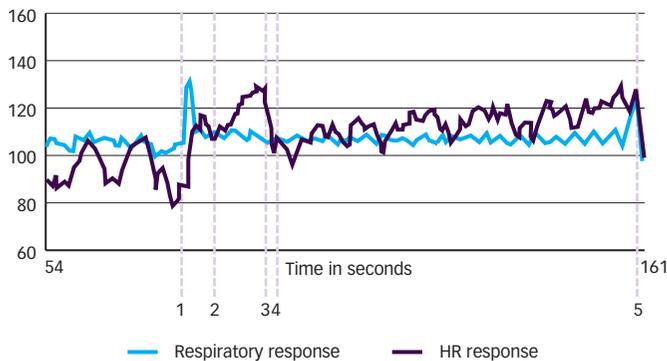
Figure 2: Frequency Domain with Respiration

Event	LFa ⁺	RFa ⁺	LFa/RFa
A Baseline	0.78	1.87	0.42
B Deep breathing	1.37	40.03	0.03
C Baseline	2.55	3.46	0.74
D Valsalva	48.27	2.36	20.46
E Baseline	0.77	0.84	0.91
F Stand	0.59	0.74	0.79



The table presents the averaged responses and the trends plot presents the instantaneous responses of the six phases of the clinical exam as listed (in order) in the second column of the table. The sympathetic responses are presented in the low frequency area (LFa) column in the table and as the purple trace in the trends plot. The parasympathetic responses are presented in the respiratory frequency area (RFa) column in the table and as the blue trace in the trends plot. Sympathovagal balance (SB) ($SB = LFa/RFa$) is the last column in the table. The letters on the graph represent the corresponding clinical exam phase as listed in the first column of the table. The data are from an otherwise normal, healthy 44-year-old female.

Figure 3: Stand—Sympathetic Challenge



A recording of normal subject data during the stand challenge of the clinical exam. Instantaneous heart rate (HR) changes (in beats per minute; purple) and respiratory activity (RA: in volts; blue) are plotted against time. At (1) the subject initiates a head-up posture that shifts blood from the thorax to the abdomen and lower extremities, with a corresponding decrease in cardiac output. These changes provide a strong sympathetic stimulus. The fluid shift when standing is immediate, and initiates an abrupt increase in HR due to a drop in parasympathetic activity (1 to 2), followed by a more gradual increase in HR due to an increase in sympathetic activity (2 to 3). The autonomics equilibrate at a new level supporting the head-up posture, and a new HR level is set (4) and maintained until the end of the postural change (5).

On release of the short Valsalva during exhalation (see *Figure 1*, #4, respiratory response), there is an overshoot of BP resulting from the sudden rush of blood back to the heart. This overshoot is compounded by the residual S activity (causing peripheral vasoconstriction) exaggerating both the blood rush into the thorax as well as the opposing venous return into the extremities. The baroreceptors in the thorax

sense this sudden stretch that causes a P surge to inhibit S activity. As a result, HR begins to return to normal. Immediately following the release of Valsalva, the HR continues to increase for a short period of time for two reasons. First, just as the S activity is slower to rise, it is also slower to fall. As a result, there is a short period of residual S activity. Second, it is the natural response on release of the Valsalva to inhale deeply (see *Figure 1*, #5, respiratory response), which causes P (vagal) inhibition and a subsequent rise in HR (see *Figure 1*, #5 HR response). After the release of the Valsalva, HR and RA finish returning to normal (see *Figure 1*, #7). Normal sinus rhythm, synchronized with the respiration, continues until the end of the recording (see *Figure 1*, #8).

Therefore, in normal subjects, short Valsalva maneuvers are expected to create a significant rise in S activity (compared with that at rest) with little if any overall increase in P activity (compared with that at rest), especially when averaged over the course of the Valsalva challenge (see *Figure 2*, section D). From the table in *Figure 2*, the subject's S activity (low frequency area [LFa]) increases 6,088% from baseline (A) to Valsalva (D), whereas the P activity (respiratory frequency area [RFa]) increases by only 26.2%. The trends plot in *Figure 2* shows the instantaneous values. A large surge in S activity (the purple trace) is observed during the Valsalva challenge (D: a series of five short Valsalvas) with a relatively small increase in P activity.

Normal Autonomic Nervous System Responses to a Rapid Postural Change

Postural change is not as stressful as a Valsalva maneuver. Therefore average or instantaneous S responses to standing (see *Figure 2*, F) should not be as great as those for Valsalva (see *Figure 2*, D). For postural change, a P decrease is expected. If, in fact, there is postural change SE or postural change PE, the physician is given insight into a possible cause of dizziness (possible syncope or orthostasis, respectively). Increases in P activity during postural change can counter the S surge, decreasing the expected vasoconstriction or possibly causing vasodilatation, leading to an inappropriate gravitational displacement of blood to the legs. Postural change poses a major challenge to circulatory homeostasis, mandating that the autonomic control center maintain blood pressure and cerebral perfusion irrespective of the effect of gravity.

Figure 3 depicts the instantaneous HR (purple) and RA (blue) responses of a normal subject during postural change. On assuming a head-up posture (see *Figure 3*, #1, respiratory response in blue), blood shifts from the thorax to the abdomen and lower extremities, with a corresponding decrease in cardiac output. These changes provide a strong S stimulus. The fluid shift during the postural change is immediate and accompanied by an initial increase in HR in the first three seconds (see *Figure 3*, #1 to #2, HR response in purple). This is followed by a more gradual increase occurring in the next three to 12 seconds (see *Figure 3*, #2 to #3, HR response).

As the S system takes three to five seconds to respond,²³ the initial HR increase cannot be due to S activity. Rather, it is due to a combination of P (vagal) inhibition and the exercise reflex. The exercise reflex is initiated as the leg muscles are engaged during postural change. The leg muscles manually clamp down on the peripheral blood vessels, helping to maintain blood in the abdomen and support the heart. This is supported

by P inhibition, potentiating the expected S surge by causing a relative S dominance. As the S system responds and initiates peripheral vasoconstriction, the gravitational effect on the blood while standing is opposed. The absolute amplitude of the S response is minimized by the P inhibition. Following the exercise reflex, an additional S stimulus, the venoarteriolar axon reflex, is engaged. This reflex is thought to account for 40% of the peripheral vascular resistance during stand.²³

S activation can be seen in *Figure 3* as a gradual increase in HR (see *Figure 3*, #2 to #3, HR response). S activation maintains cardiac-filling pressure by constricting the splanchnic (visceral) capacitance vessels. As peripheral vascular resistance increases, core S discharge stimulates the core P neurons. Finally, a saturation point is reached within the baroreceptors and the P system normalizes HR to a new baseline level (see *Figure 3*, #4, HR response). Hemodynamic postural change responses include a 10–30% increase in mean HR and a 0–10% increase in mean arterial pressure.²³ This is because the baroreceptors located in the carotid artery now sense a lower capillary pressure than that during sitting. This pressure differential provides the stimulus that maintains increased S activity while also maintaining upright posture. The net normal result is an expected decrease in P activity followed by an increase in S activity and an associated increase in HR, BP, and depth of respiration. PE blunts this feedback.

Methods

Serial autonomic profiling of 1,340 patients (746 females, 55.7%) was performed using the P and S method (ANX 3.0 Autonomic Monitor by ANSAR Medical Technologies, Inc., Philadelphia, PA) over a three-year period at six primary, ambulatory clinics located in six different states along the US east coast. Patients were followed as a matter of routine, based on their primary diagnosis. Electrocardiogram (ECG) and respiratory activity data (from impedance plethysmography) were concurrently collected, and analyzed independently and simultaneously to compute independent, simultaneous measures of P and S activity.^{9,10} ANS assessment was based on a clinical study that included (in order): five minutes of rest (initial baseline), one minute of relaxed paced breathing at six breaths per minute, one minute of rest to return to baseline, a series of five short Valsalva maneuvers in a period of one minute and 35 seconds, two minutes of rest, and a quick head-up postural change followed by five minutes of quiet head-up posture (standing). The results were analyzed and statistics were computed using SPSS v14.0.

Treatment Protocols

Treatment protocols were developed based on the following observations. The P system establishes and regulates metabolic thresholds to which the S system reacts or responds. The upper medullary brain stem nuclei, the nucleus solitarius, the dorsal nuclei of the vagus nerve, and surrounding small nuclei, which give rise to the vagus nerve, link the mind and body. These components are the core of the ANS. The lack of proper venous tone plays an important role in clinical manifestations of autonomic dysfunction, and supports a positive feedback loop for persistent autonomic imbalance leading to further symptoms. Abnormal S responses may be a secondary phenomenon and do not always require treatment. Various central nervous system drugs and vasoactive drugs (e.g. reticular activating system drugs and vasodilators) can interfere with ANS therapy and adversely affect the ANS. Three possible treatment protocols for PE

were developed. For patients with PE and CVD, including hypertension, low-dose carvedilol should be considered, dependent on patient history. If a beta-blocker is already on board, dose-equivalent carvedilol should be considered. The beta-adrenergic antagonist in carvedilol addresses CVD, and the alpha-adrenergic antagonist that is known to cross the blood–brain barrier, appears to indirectly address PE.^{24–28} For PE patients without CVD, low-dose anticholinergics (e.g. amitriptyline or nortriptyline, starting with 12.5mg daily at dinner, or duloxetine, starting with 10mg daily at dinner) can reduce systemic P activity. In many cases, PE masks S withdrawal, which has been linked to hypertension²⁹ and other symptoms. For S withdrawal, proper daily hydration is recommended, and the use of diuretics should be reconsidered. In patients with well-managed BP, clinicians should consider low-dose midodrine (starting with 2.5mg daily at dinner). Carvedilol with midodrine is often prescribed in patients with CVD and PE masked S withdrawal. For severe hypertensives with debilitating S withdrawal, the acetylcholinesterase inhibitor pyridostigmine should be considered.³⁰ Short-term therapy based on correction of PE or S withdrawal should be considered in all patients, with the exception of severe hypertensives. Treatment length is based on the duration of the disorder, and can be between six and 18 months. The ability to wean these medications is based on the plasticity of the patient's ANS. Patients presenting with end-organ effects may require continued maintenance dosing. Alternative therapies include exercise that does not incur any tissue damage, such as swimming, long gentle walks, rowing, simulated cross-country skiing, or exercise on elliptical machines. Running, weight-lifting, and most team sports should be avoided for the duration of the treatment period.

Results

Patients with PE often demonstrate normal HR and BP and no other cause is evident from the standard physical tests. In fact, 2.2% of the cohort was initially diagnosed as healthy. The average resting HR was 72.7bpm (± 13.1 bpm), and the average BP was 132.3/71.9mmHg. According to current American Heart Association guidelines,³¹ the patients in the cohort (age range 60–90 years) had mild hypertension (average BP 140.7/66.6mmHg).

PE appears to destabilize responses of patients to disease and therapy, and PE can be associated with difficult-to-control BP, blood glucose, and hormone levels (e.g. thyroid, estrogen, and growth hormones). Within this cohort, 58.5% have been diagnosed with hypertension, and 21.9% of those have difficult-to-control BP or labile hypertension. Patients diagnosed with diabetes, either type 1 or type 2, comprised 51.8% of the cohort, and 19.8% of that group reported difficult-to-control blood glucose. Individuals diagnosed with hypothyroid disorders comprised 15.3% of the cohort, with 8.1% reporting high levels of hormone replacement therapy and complaints of significant, continuing secondary symptoms. Of the females in the cohort, 19.1% reported menstrual or menopausal abnormalities.

PE can be associated with a host of symptoms, including:

- sleep difficulties (difficulty falling asleep or frequent waking at night, even to go to the bathroom; 13.7%), with 6% diagnosed with obstructive sleep apnea;
- evening edema, restless leg syndrome, varicose veins, or poor peripheral circulation (3% diagnosed with restless leg syndrome);

Autonomic Imbalance

- mild cognitive difficulties (thinking and memory, general malaise, chronic fatigue, 'difficulty getting started,' or attention-deficit disorder/attention-deficit-hyperactivity disorder [ADD/ADHD]; 14.4%);
- psychological symptoms (e.g. depression or anxiety or associated syndromes and disorders, or mood shifts; 14.9%);
- frequent headache or migraines (16.3%);
- gastrointestinal upset (e.g. constipation, abdominal cramps, nausea, irritable bowel, gastroesophageal reflux disorder [GERD], or acid reflux; 16.6%); or
- occasional to frequent dizziness on quick postural change, including standing (19.8%).

PE appears to mask S withdrawal when standing, and in pain patients the condition appears to underlie fibromyalgia (2%). PE can differentiate complex regional pain syndrome (CRPS) and vasovagal syncope, and a genetic predisposition has been suggested.

After treating for PE, more than half of the patients reported increased dizziness when standing, especially in patients with CVD. As a result, when PE patients are prescribed carvedilol, they are also given low-dose midodrine, depending on patient history. We have observed that correcting for this dynamic autonomic imbalance can reduce the severity of the primary disease or disorder, and in some cases, eliminate symptoms altogether.

Conclusion

The current working hypothesis is that PE during physiological challenges—Valsalva or postural change—is independent of the clinical state of the patient and, depending on history, can be treated independently of the primary disease. This dynamic autonomic imbalance has been found to have clinical relevance, in that when the imbalance is corrected, patients report relief from symptoms and their clinical status becomes more stable. Longitudinal studies have also shown that relieving PE can reduce or relieve other autonomic dysfunctions, also helping to stabilize the underlying disease (such as diabetes, hypertension, cardiomyopathy, or hypothyroidism).

PE may explain why many patients demonstrate vague diffuse symptoms. In most cases where PE has been resolved and the patients had a reasonable baseline ANS level with no end-organ effects, patients have been weaned from pharmaceutical therapy in ≤ 15 months. Our clinical observations show that the ANS of patients can be

retrained to function at a different 'set point' and left to carry on independent of clinical support. In some cases where end-organ effects either from the primary disease or from PE have not yet presented, such as thickening of heart muscle due to hypertension, patients may be able to stop lifelong therapy once the PE is resolved.

Many common chronic conditions such as hypertension, diabetes, thyroid disease, kidney disease, and CVD can cause autonomic imbalance. Severe acute conditions can also precipitate PE, including trauma, injury, infection, surgery, and cancer. When patients present with varied and multiple symptoms, identifying PE may help to clarify the diagnosis and provide direction for therapeutic options. Often a single agent or a combination of agents can address such autonomic disorders and treat PE. Correcting the underlying ANS for patients with other acute or chronic disease(s) facilitates more aggressive and targeted therapy. Once PE is corrected, clinicians are able to better manage the primary disease(s) and patients can become less symptomatic and have improved outcomes and quality of life. ■



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