

Excerpts from:

Clinical Autonomic Dysfunction Measurement, Indications, Therapies, and Outcomes

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PAINMANAGEMENT

There is increasing interest in the involvement of the SNS in the initiation and maintenance of chronic pain syndromes of different etiology. Epidemiological data show that stresses of different natures (*e.g.*, work-related and psychosocial), typically characterized by SNS activation, may be a co-factor in the development of the pain syndrome or negatively affect its time course. Besides its well-known action on muscle blood flow, the SNS is able to affect the contractility of muscle fibers to modulate the proprioceptive information arising from the muscle spindle receptors and, under certain conditions, to modulate nociceptive information. Furthermore, the activity of the SNS itself is in turn affected by muscle conditions, such as its current state of activity, or fatigue and pain signals originating in the muscle. [265]

Overview

Pain is a stress and the SNS responds to stress. Given this axiom, independent, simultaneous P&S Monitoring offers an objective, non-invasive means of:

1. Objectively quantifying pain level;
2. Differentiating non-physiologic pain (*e.g.*, psychosomatic), from physiologic pain (*e.g.*, somato-sensory), from chronic regional pain syndrome (CRPS, formerly reflex sympathetic dystrophy, or RSD);
3. Titrating (potentially addictive) pain therapy; and
4. Documenting rehabilitation.

From the five-minute resting baseline challenge, a patient's sympathetic level that day, is measured and compared to previous measures. If today's measure is higher, then the pain is higher, regardless of the patient's mental and emotional condition, and vice versa. Further, —High, □ —Normal, □ and —Low □ sympathetic measures are quantified and are pertinent. This augments and helps to specify the subjective criteria upon which a patient reports pain levels. [266]

Since pain is a sympathetic stimulus, if the sympathetic responses to all six Autonomic (P and S) Assessment challenges (see —Autonomic (P and S) Assessment □) are normal to low, then the pain is well managed (if the patient is medicated) or is not physiologic (if not medicated). In other words, the pain is not physiologic and there may be other issues, such as addiction. If there is SE to one or more of the challenges, then consider titrating pain therapy. However, normal to low sympathetic responses to resting baseline indicate that the patient is in balance and well managed at rest. Under these conditions, SE in response to Valsalva or PC (stand) challenge suggests activity-induced pain. SE in response to Valsalva suggests activity-induced pain in the upper body, and to Stand suggests activity-induced pain in the lower body. If the resting sympathetic activity is normal to low and the activity does not impede routine activities, perhaps additional pain therapy is not warranted.

SE with PE differentiates CRPS. For example, with plexus damage, SE indicates the presence of pain caused by tissue damage. However, tissue perfusion is also compromised. PE is associated with poor tissue perfusion. Therefore, SE with PE immediately differentiates —physiologic □ pain from CRPS, documenting CRPS (perhaps earlier), thereby enabling earlier therapy to help to reduce the potential for

long-term therapy, as is often the case with CRPS patients.

The purpose of pain therapy is to relieve pain, which relieves stress, which reduces sympathetic activity. As such, sympathetic levels may be used to titrate pain therapy, tailored to the patient's specific needs, helping to reduce the risk of dependency and over-dose.

Periodic and frequent independent, simultaneous P&S Monitoring documents the individual patient's changes in P and S activity. Given the initial diagnosis and considering any extant damage or disability, once the P and S challenge responses are normalized and P and S activity is balanced, the patient's autonomic recovery is complete. P&S Monitoring documents that the patient may be prepared to return to a normal lifestyle, including perhaps returning to the workplace; thereby, reducing workman's compensation claims. Independent, simultaneous P&S Monitoring has already stood up in courts of law.

In chronic pain, like other chronic diseases (see —Chronic Disease Affect on Autonomic Decline□), persistent SE accelerates the onset of secondary hypertension and other co-morbidities and ultimately CAN and sudden death.

Frequent and periodic independent, simultaneous P&S Monitoring detects, differentiates, and documents persistent or recurrent SE, guiding therapy to reduce morbidity and mortality risk, reduce medication load and hospitalization, and further reducing healthcare costs.

The following are excerpts from an article originally published online at pain.com [266].

Parasympathetic and Sympathetic Monitoring in Pain Management

Introduction

Chronic pain takes many forms, which often become associated with common comorbidities such as secondary hypertension, gastrointestinal upset, sleep disturbances, urogenital dysfunction, and dizziness. The role of early and focused intervention and preventive therapy in these patients is important to prevent long-term complications, compounded health risks, and higher health care costs. These comorbidities are also common in many other chronic diseases (*e.g.*, cardiovascular disease, diabetes, chronic pulmonary disorders, and progressive neurological diseases), and they are not limited to the elderly; they affect young patients as well. The disparate nature of these comorbidities and the fact that they are associated with many different processes suggests that there may be an underlying commonality that has largely been overlooked – the ANS.

The ANS has been overlooked due to the lack of simple, comfortable, noninvasive, and reliable tools to measure its two branches, the P and S nervous systems, independently and simultaneously. Tools now exist.

The ANS is involved in the way the body manages and responds to pain [267,268,269,270,271,272], including, neuropathic pain [273], migraine and headache [274,275,276], somatic pain [267], complex regional pain syndrome (CRPS) [277,278], fibromyalgia and related syndromes [279] (including chronic fatigue syndrome [CFS] [280,281], irritable bowel syndrome [282], and depression/anxiety disorders [165,283,284]), pain associated with rheumatoid arthritis [285,286], angina [287], and acute pain [288,289]. Treating pain can normalize autonomic function [290,291].

Autonomic Involvement in Pain Modalities and Management

The nociceptive and autonomic systems interact at the levels of the periphery, spinal cord, brainstem, and forebrain. Spinal and visceral afferents project information to spinothalamic neurons in the dorsal horn and then to neurons in the brain stem, including the nucleus tractus solitarius. These structures, in turn, project to areas at all levels of the central nervous system involved in reflex, homeostatic, and behavioral control of autonomic outflow and nociception.

Considering pain as the result of the interactions between the nociceptive and autonomic (specifically P and S) systems may document the complex pathophysiology of pain disorders and help customize therapy plans for individual patients [270]. Medications and therapies act on the P or the S branch of the ANS. Titrating therapy for the individual patient requires first-hand knowledge of the patient's P or S response to pain, disease or injury, therapy, and lifestyle.

The parasympathetics are involved in headache [274,276]. Based on HRV-alone measures, migraineurs with disabling attacks may be prone to ANS hypofunction [276]. These findings suggest that ANS dysfunction either may be a risk factor for migraine headaches or a consequence of frequent disabling attacks. HRV-alone measures are mixed or total ANS measures which do not allow further differentiation of these findings; specific P and S measures are needed.

Moreover, ANS dysfunction and migraine may share a common neural substrate [277], and headache and migraine pain may be accompanied by considerable autonomic reactions, which are dependent on sympathetic activity [273,274].

Based on autonomic innervation of cranial blood vessels, clinical and experimental observations in migraineurs suggest that a general hyperexcitability could develop along nociceptive trigeminal neurons, allowing the activation of

descending pathways that facilitate pain processing or the suppression of pathways that slow down pain transmission [267,273]. Progressive dysfunction of central pain systems secondary to the repetition of attacks of the originating headache have been implicated in slowly transforming the process from an episodic condition into a chronic condition [267].

Quality of life is significantly reduced among patients with neuropathic pain. Chronic pain patients have difficulty initiating and maintaining sleep, and sleep deprivation exacerbates pain [275]. Sleep deprivation is associated with anxiety and depression, both of which also make sleep disturbances worse. Depression and daytime sleepiness are associated with PE [284]. To effectively manage the chronic pain patient (including those with neuropathic pain), assessment and subsequent treatment of all comorbidities associated with the condition is necessary [275]. Recognition of an association between the diverse nature of comorbidities and the common underlying role of the P or S nervous systems facilitates the treatment of all comorbidities.

The sympathetics are involved in somatosensory pain and CRPS [267,273]. CRPS, for example, may develop as a complication of trauma to a plexus or plexus involvement in peripheral trauma. Sympathetic neurotransmitter release is compromised in the affected area, and signs of sympathetic deficit (*e.g.*, a warm flushed limb) often evolve into signs of sympathetic over-activity (*e.g.*, a cool moist limb) due to the development of adrenergic super-sensitivity. Because the parasympathetics are known to be involved in maintaining proper tissue perfusion [289], interactions between the P and the S can cause swings in sympathetic activation. Communication between sympathetic and the sensory neurons that signal pain may contribute to CRPS [274]. In addition, sympathetic activity may retard normal healing by aggravating inflammation-associated vascular disturbances. [274].

Fibromyalgia is a chronic, painful musculoskeletal disorder of unknown etiology or pathophysiology. Many studies have suggested ANS involvement in fibromyalgia syndrome and related disorders, including chronic fatigue syndrome (CFS), irritable bowel syndrome, and depression/anxiety disorders, and, via P and S dysfunction, the risk for cardiovascular morbidity and mortality [165,279]. A significant negative correlation between Hamilton Depression Scale scores and abnormal autonomic activity exists in patients with major depression, suggesting a direct association which may contribute to the higher cardiac morbidity and mortality [165]. Patients with stable coronary heart disease, or those with a recent acute coronary event, have been found to have lower HRV, as have depressed patients when compared with their non-depressed counterparts [284]. Anxiety disorders are associated with significantly lower HRV [283]. Patients with CFS show alterations in autonomic function, including orthostatic intolerance, which may be explained by cardiovascular deconditioning, a post-viral idiopathic autonomic neuropathy (AN), or both [280]. The presence of reduced HRV in CFS during sleep, coupled with higher norepinephrine levels and lower plasma aldosterone suggest a state of sympathetic dominance and neuroendocrine alterations [281].

Patients with rheumatic diseases often demonstrate with ANS-related dysfunctions. Clinically, these diseases are characterized by pain (*i.e.*, spontaneous, hyperalgesia, and allodynia), active movement disorders, including an increased physiologic tremor, abnormal regulation of blood flow and sweating, and edema and trophic changes of skin and subcutaneous tissues. The ANS is, in part, responsible for regulation of blood flow and sweating. Abnormal regulation is indicative of P and S imbalance. Alterations of P and S may also be involved in the pathogenesis of rheumatic diseases [286].

Based on clinical and experimental observations in critical care, including intensive care and surgery, the sympathetic is involved in pain following trauma [273,289]. Even in neonates, P and S imbalance is observed in response to painful procedures [272]. Pain therapies and anesthesia are also shown to affect autonomic activity. Low-dose fentanyl administration in healthy volunteers leads to sympathetic and overall ANS modulation decrease, with a trend toward vagal (parasympathetic) activation [290]. Similar reductions in sympathetic activity have been seen in response to other opioids and analgesic agents. P and S monitoring tools based on HRV and respiratory sinus arrhythmia (RSA) measurements are needed in pain-monitoring because a P and S imbalance results from pain [292].

Methods of ANS Measurements

Observing the marked vasomotor and sudomotor changes after traumatic nerve injury, it is apparent that the P and the S play an important role in pain modulation and perception [267]. HRV-alone cannot help to differentiate pain [293] because it is a mixed measure of P and S influences. Despite the debate on whether the role of the sympathetic in generating and sustaining certain pain syndromes is significant, specialists in pain management have sought tools for measuring the PSNS and the SNS. They have largely been overlooked, primarily due to the lack of simple, convenient, comfortable, reliable, and repeatable tools to independently and simultaneously measure both the PSNS and the SNS. Historically, HRV-alone has been attempted, but found to be inconsistent. HRV-alone measures general ANS function.

Simply measuring the ANS provides no additional clinical information. Knowing the individual P and S responses, in this case to pain and therapy, allows the physician to assess a patient's individual responses to disease, injury, therapy and lifestyle. We have found that P&S Monitoring enables: (1) objective, quantification of pain level; (2) differentiation non-physiologic (*i.e.*, psychosomatic) pain from physiologic (*i.e.*, somatosensory) pain, from pain syndromes complicated by comorbidity (*i.e.*, CRPS or Fibromyalgia); 3) customized therapy for the individual patient; and 4) documentation of the patient's rehabilitation.

Noninvasive, independent, simultaneous, quantitative measures of P and S are required for early and focused intervention and preventive therapy. Unfortunately, much of the literature discussing ANS monitoring is based on HRV-alone approaches as defined in the 1996 Standards article [9,10]. The studies that have found high correlations between HRV-alone measures and P or S functions have been very selective regarding their patient populations, and therefore highly specific as to the assumptions under which HRV-alone measures correlate. These assumptions, and therefore these studies, cannot be generalized to the greater patient population. These assumptions are misleading if they are not specifically met, and as a result, the measures are not valid. This is why the published HRV-alone studies do not generalize. P&S monitoring is proven to generalize [13,50,51,52,56,57].

For example, if HRV (*e.g.*, =S/P) doubles, two possibilities exist: either $_S^*$ (the sympathetic activity) doubles or $_P^*$ (the parasympathetic activity) is halved. Clinically, you may think that these are the same conditions, and HRV-alone measures would suggest that. They are not the same. If the sympathetics doubled and the parasympathetics stayed the same, perhaps (predicated on the fact that pain is a stressor and the S respond to stress) the pain has increased. The increased pain, in turn, is creating a pre-hypertensive state or, due to the persistence of pain, pre-existing hypertension has become worse. The sympathetic increases occur before BP rises (the sympathetics drive baroreceptor reflex which drives BP). SE, such as in pain, hypertension, COPD, and cardiovascular disease, may be treated with medication (additional pain therapy or sympathetic blockade, such as beta-blockers or anti-hypertensives) or perhaps, in the preclinical state, treated with lifestyle modification.

If the sympathetics stayed the same and the parasympathetics decreased by a factor of 2.0, several things may be indicated. First, there may not be increased pain and, therefore, no additional pain therapy may be needed.

Second, the parasympathetics may be too weak to protect the heart and prevent ventricular tachyarrhythmia. This may place the patient at risk for sudden cardiac death. Measuring a doubling in HRV-alone does not clearly define the patient's physiological or clinical state – P and S measurements do. This article highlights patient examples and suggests a P and S-based protocol to help guide patient management.

Clinical Examples

Since 1996 [63], autonomic testing for pain management has been recommended to identify and differentiate pain. P&S Monitoring also provides Holter-like results in an in-office study that takes about 15 minutes to perform. The study format, as recommended [4,81,71], includes six phases (see —Autonomic (P and S) Assessment□). The (initial baseline) rest responses determine 1) the balance between P and S, (=SB) which is a measure of patient response to injury and therapy, and 2) differentiates the severity of autonomic neuropathy, both chronic and acute. The resting responses are also used to quantify pain levels based on relative sympathetic responses from test to test. A Valsalva challenge SE helps to differentiate pain syndromes, including upper body from lower body pain. A PC (stand) challenge SE differentiates lower from upper body pain. PE during either the Valsalva or the PC differentiates CRPS from somatosensory pain.

Because P and S are already determined, these challenges are not required as a probe to differentiate the P from the S response (as in HRV-alone studies); rather, they are direct challenges to P or S. As a result, the data obtained are quantified response levels, valid for direct interpretation. The study becomes a model of a typical day in the patient's life; like a Holter monitor. In fact, pain management physicians prefer to witness the test, when possible, to watch the patient's —body language□ during the modeling of the patient's day. The deep breathing challenge simulates a patient's response to therapy, disease, lifestyle, after meals, and before retiring for the evening. The Valsalva challenge simulates a patient's response to exercise and stress. The stand challenge serves two purposes. It challenges the coordination of the P and S, highlighting possible risk of morbidity [65], and the PC challenge also differentiates orthostasis and its subforms, and possible syncope and its sub-forms. The PC challenge, when compared with resting baseline, is equivalent to a tilt-study [121]. The resting baseline period also serves two purposes. In determining the balance between P and S, it enables the customized titration of therapy, based on the patient's individual responses to therapy, disease, and lifestyle. Therapy may be considered as the counter-balance to disease or injury, and this balance is represented by the balance between the P and S. Therefore, when therapy is titrated to normalize SB, the resulting level

of therapy is thereby customized to the patient's individual needs. The resting period also quantifies mortality risk. Very low parasympathetic activity is associated with risk of sudden death (mortality) [64]. All data presented were collected from ambulatory pain clinics in Colorado, Maryland, New York, Pennsylvania, and Virginia, and one level-1, academic trauma center in California. The data were collected using the ANX-30 Autonomic Nervous System Monitor (ANSAR Medical Technologies, Inc., Philadelphia, PA).

Differentiating Pain

From an autonomic perspective, pain management is predicated on the fact that pain is a stressor and the sympathetics respond to stress [267]. The parasympathetics are responsible for proper tissue and brain perfusion [289]. Based on these predicates, P&S Monitoring differentiates non-physiologic (e.g., psychosomatic) pain, from physiologic (e.g., somatic or sympathetically-mediated) pain, from complex pain syndromes (e.g., CRPS

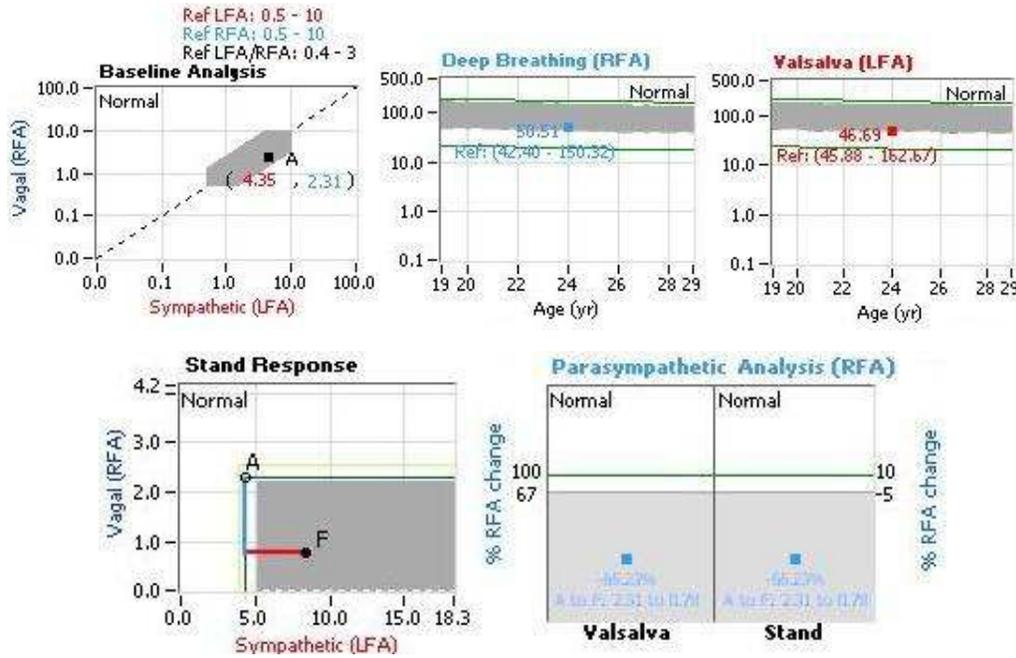


Figure 147: Sample non-physiologic pain responses. These are data from a 24 y/o pain patient with opiates already on board. The patient is well managed. The patient is requesting additional pain medication. These data indicate that the patient's request for additional therapy is not a physiologic response. See text for details.

or fibromyalgia). Because non-physiologic pain is perceived, and therefore cortical, the brainstem autonomic (e.g., sympathetic) measures are normal to low (see Figure 147). The graphs of Figure 147 are from a multi-parameter graph report (MPGR) which, in the MPGR, are presented all in one row. The graphs, from top, left to bottom, right in order, present: the (resting) (_A_) baseline P&S Monitoring results, the parasympathetic response to (_B_) deep breathing, the sympathetic response to (_D_) Valsalva, the P&S Monitoring responses to (_F, Stand_) PC, and the parasympathetic responses to Valsalva (left) and stand (right). The grey regions indicate normal responses. These are data from a 24 y/o pain patient with opiates already on board. The patient is well managed. The patient already has opiates on-board and is requesting additional pain medication. These data indicate that the patient's request for additional therapy is not a physiologic response. The fact that all indices are within normal limits, suggests that the patient is well managed and that the request for additional therapy is not based on a physiologic response.

For physiologic pain (e.g., somatic pain), one or more of the brainstem sympathetic measures are borderline high to high (see Figure 148). With complex pain syndromes, comorbidities are involved, induced by or exacerbated by autonomic dysfunction. For example, CRPS with plexus damage may involve circulatory deficits leading to

abnormal tissue perfusion, causing parasympathetic over-excitation (PE, see Figure 149). PE may heighten sympathetic activity, causing a heightened sensitivity to pain. PE is also associated with GI upset, sleep disturbances, fatigue, depression,

urogenital dysfunction, and dizziness. SE is associated with anxiety, hypertension, and heart disease. Based on resting sympathetic activity, pain levels are quantified. Even if a patient demonstrates autonomic neuropathy as measured by low autonomic levels, high sympathetic activity relative to parasympathetic activity will indicate a relative, resting SE (high SB) and possible pain. For a pain patient, high SB may suggest pain. If, upon follow-up, a pain patient demonstrates higher, absolute sympathetic activity, or high SB, then the percent increase indicates the percent increase in pain.

Also, based on balance (SB), therapy may be titrated. The goal of therapy is to remove the stress of pain and normalize P and S activity; in other words to balance disease or disorder – including pain – and adverse lifestyle. If the patients' SB is normal, then

they are well maintained at rest and may not need additional therapy. If P and S imbalance persists in a pain patient, whether at rest or during challenge, then additional pain therapy may be needed (history dependent). For example, SE during Valsalva indicates activity induced pain, typically upper body, including lower back. If (resting) SB is normal with Valsalva SE, then it needs to be known what types of activity may induce pain. If pain is affecting normal daily routine, then additional therapy is probably appropriate (see Figure 150). If, however, pain is affecting non-routine activity (e.g., recreational activity), then additional pain therapy may not be required, and the clinician may consider allowing the pain to limit the patient's activity until the affected area is healed.

Figure 150 displays sample baseline and follow-up trends plots for a 47y/o, female, chronic back pain patient with Oxycodone on board, requesting more pain medication. The trends plots show the six phases of the Autonomic (P and S) Assessment study indicated by the letters _A' through _F' (see —Autonomic (P and S) Assessment□). The left trends plot displays the patient's responses when reporting persistent pain and requesting more pain medication. The sympathetic (red) response to Valsalva (section D) is high (off the scale) indicating SE and supporting the request for more pain medication. The right trends plot displays the three month follow-up when the patient reports —pain free.□ This is a normal trends, plot (compare with Figure 151). Notice, even the follow-up assessment's resting baseline (section _A') and PC (section F) portions show less sympathetic activity with a more normal sympathetic response to PC at the beginning of the stand challenge.

Relieving all SE or PE suggests that all pain indices have been normalized. Relief may or may not involve prescription medications. PE includes low SB, or deep breathing Valsalva or stand PE. SE includes high SB, or Valsalva or stand SE. Figure 152 depicts examples of SE and PE. In this figure, sample trends plots from two CRPS patients are presented. The left panel presents a patient diagnosed with CRPS from a shoulder injury, including Brachial Plexus damage. The patient demonstrates resting and Valsalva (sections _A' and _D', respectively) PE and SE. The right panel presents a patient diagnosed with CRPS from a hip injury, including Femoral Plexus damage. The patient demonstrates Valsalva and stand (sections _D' and _F', respectively) PE and SE.

As a measure of normalizing P and S responses associated with pain relief, P&S assessment can document progress towards and successful rehabilitation. A caveat is that the stress of pain is additive to other SEs that may also be present. SE can result from hypertension, sleep apnea, anxiety, and other chronic diseases. Further, the affect of pain therapy is not to block sympathetic activity, it is only to reduce the stress of pain, thereby reducing sympathetic activity to what it would have been without the pain. Therefore, SEs and PEs must be considered in the context of the patient's history. SEs due to pain and SEs due to comorbidities are differentiated through titration of therapy and by observing the patient as P&S assessment is performed. Typically, if after three months upon follow-up P&S assessment there is no significant change in P and S activity levels after pain therapy was titrated higher, then the remaining autonomic imbalances are not a result of pain. To reduce the risk of morbidity and mortality, the clinician may consider titrating sympathetic blockade (e.g., beta-blocker or anti-hypertensive) or parasympathetic blockade (anti-cholinergics, tri-cyclic antidepressants, or SNRIs) to normalize SB and P and S challenge levels.

The three-month follow-up study for the patient with an injured brachial plexus (see Figure 152, left panel) is presented in Figure 153. The patient (38 y/o, female) also demonstrated hypertension, attention deficit disorder (ADD), and gastric disorder. She was prescribed gabapentin (Neurontin, Pfizer), non-steroidal anti-inflammatory drugs (NSAIDs), antihypertensives, and diuretics. Her previous history at the time of testing (see Table 41) documents a resting HR of 65 bpm and hypertension under control. Her resting BP was 123/66 mm Hg. From the first test (see Figure 152, left panel), her average resting autonomic state was normal (see Table 41): Resting sympathetics = 6.41 bpm² (normal resting sympathetics: 1.0 < LFa < 10.0 bpm²), Resting parasympathetics = 5.92 bpm² (normal resting

parasympathetics: $1.0 < \text{RFa} < 10.0 \text{ bpm}^2$), and $\text{SB} = 1.01 \text{ bpm}^2$ (normal $0.4 < \text{SB} < 3.0$). Her Valsalva state was high (see Table 41): sympathetic = 185.04 bpm^2 (normal Valsalva sympathetic for a 34 year-old: $13.81 < \text{LFa} < 151.87 \text{ bpm}^2$ [129]), and Valsalva parasympathetic = 63.27 bpm^2 (normal, age- and baseline-adjusted, Valsalva parasympathetic: $P < 35.7 \text{ bpm}^2$). PC was also problematic for this patient, due to her injury. She reports pain while trying to hold herself upright. Her PC autonomic state was abnormal (see Table 41): PC sympathetics = 11.52 bpm^2 (normal, baseline adjusted, PC sympathetics:

7.69 < S < 32.05 bpm²), and PC parasympathetics = 7.61 bpm² (normal, baseline adjusted, stand parasympathetics: P < 5.92 bpm²). In this case, the SE and PE associated with CRPS are found in both the patient's Valsalva and PC P and S responses. Her resting (baseline) responses are within normal limits. Follow-up testing (Figure 153 and Table 41) presents her responses after three months on a methadone pump, as prescribed based on her first test. Upon follow-up testing, her resting HR and BP are 62 bpm and 119/65 mm Hg, respectively, and she reports much less pain with more freedom to participate in physical therapy. Her resting sympathetic activity (2.51 bpm²) has decreased significantly, supporting her reports of relief. Her resting parasympathetic activity (4.39 bpm²) may still be higher than normal for her, as indicated by her low-normal SB (0.57). However, low-normal is more appropriate for geriatric patients, and high-normal is more appropriate for younger adults. This relative PE may be associated with persistent perfusion abnormalities from the plexus damage. All of the rest of her P&S responses are lower and normalized, suggesting relief from pain, both at rest and during activity. Also, from her follow-up test, the parasympathetic response to deep breathing (section B) is low, indicating the first signs of autonomic dysfunction, perhaps due to the chronic pain.

Fibromyalgia

Fibromyalgia, and related disorders, often present with PE, even if the pain is well managed and sympathetic activity is normal to low. PE is associated with persistent fatigue and day-time sleepiness, which are characteristic traits of fibromyalgia [165,279]. The PE associated with fibromyalgia generally presents during either Valsalva or PC challenge during the P&S assessment study. This heightened parasympathetic activity potentiates sympathetic activity, accentuating the fibromyalgia patient's sensitivity to painful stimuli. A sample patient (with both Valsalva and PC PE and SE) is presented in Figure 154, left panel. The patient, a 59 y/o male, initially demonstrates (Table 42) high resting HR and BP (122 bpm and 138/81 mm Hg BP, respectively) and normal resting P&S activity (resting sympathetics = 1.27 bpm², resting parasympathetics = 1.03 bpm², and SB = 1.27 bpm²). The patient's Valsalva responses are both high (sympathetics = 108.64 bpm², and parasympathetics = 12.85 bpm²) compared with normal 59 y/o subjects (7.44 < Valsalva sympathetics < 81.83 bpm² [129], and Valsalva parasympathetics < 6.18 bpm²). The patient's PC responses are also both high (PC sympathetics = 4.12 bpm², and PC parasympathetics = 1.36 bpm²) compared with normal (1.52 < PC sympathetics < 6.35 bpm², and PC parasympathetics < 1.03 bpm²). From these results, this average PC challenge response (averaged over the five-minute stand period) is within normal limits. However, the instantaneous peak sympathetic response (peak, red response in section _F' of left panel in Figure 154) is high (normally the PC peak response is less than 1/3 that for Valsalva). The peak Valsalva and PC responses must also be considered in this comparison because the time periods over which they are averaged are different.

The SNS is the reactionary nervous system and the PSNS establishes the metabolic threshold to which the SNS reacts; therefore, PE was selected as the primary indication. Low-dose amitriptyline (12.5 mg bid) was prescribed. Upon follow-up, the patient demonstrates (right panel of Figure 154 and Table 42) normal resting HR and BP (76 bpm and 112/79 mmHg BP, respectively) and normal P&S activity (resting sympathetics = 1.17 bpm², resting

parasympathetics = 1.10 bpm², and SB = 1.16 bpm²). In response to Valsalva the patient demonstrated normal activity (Valsalva sympathetics = 16.09 bpm², and Valsalva parasympathetics = 2.31 bpm²; normal ranges for a 59 y/o are: 7.44 < sympathetics < 81.83 bpm² [129], and parasympathetics < 6.60 bpm²). The patient's PC responses were also normal (sympathetics = 1.54 bpm², and parasympathetics = 0.43 bpm²; normal ranges for a 59 y/o are: 1.85 < sympathetics < 7.70 bpm², and sympathetics < 0.43 bpm²). The patient's response to the low-dose, antidepressant (anticholinergic) provides supporting evidence that PE was the primary indication, causing secondary SE and heightened pain perception.

Acute Pain

The next two examples are from patients admitted to the Emergency Department (ED) of a level-one, academic trauma center. The first patient neither requested nor rejected pain therapy. In both cases, the patients were titrated with 20% doses of morphine by body weight. The first patient (Figure 155) was a 57-year-old male, admitted with blunt trauma to the face and chest. From Figure 155, the patient's mean HR (purple trace) started near 100 bpm with a maximum of near 120 bpm prior to dosing. After dosing, his mean HR was maintained near 60 bpm. Prior to dosing, his sympathetic activity (red) was significant and was reduced to much lower levels a few minutes after dosing. The parasympathetic activity (blue) also diminished after dosing. The patient's lower physiologic levels were maintained for a couple of hours prior to higher sympathetic and HR activity returning. Just as the patient returned to expressing overt signs of pain, another 20% dose was administered. It was determined that the patient's physiologic pain threshold (lower than the level at which overt signs of pain were expressed) was near 10 bpm² (see, maintenance dosing). Additional 20% doses

were administered every two to three hours when the patient's sympathetic levels exceeded 10 bpm² and before the patient expressed pain. In this way, the patient was maintained comfortably for over 12 hours prior to surgery.

The second acute pain patient (a 40-year-old female, Figure 156) example is from the same trauma center as the first. She was admitted with blunt trauma to head, trunk, hips, and buttocks. This patient requested pain medication shortly after admission to the ED. She was also maintained comfortably on a 20% dose of morphine for six-hours prior to surgery. This patient was tested periodically, for ten-minutes at a time, and the average over that time was entered into her record for tracking purposes.

Figure 157: Sample non-diabetic, pain patient (21-year-old male) with a neck injury and diagnosed with CRPS. See text for details.

No Additional Therapy

Figure

The next example is of a non-diabetic, pain patient (21-year-old male) with a neck injury and diagnosed with CRPS (see Figure 157 and Figure 158). The patient presented for P&S Monitoring after six months of physical therapy completed and vicoprofen (hydrocodone and ibuprofen) on board. He was requesting more medication. As shown in his trends plot (Figure 157) and response plots (Figure 158), he demonstrates low-normal SB (0.49), low Valsalva sympathetic response (16.56 bpm²), and PC PE and SE. PC PE and SE is also associated with possible (preclinical) vasovagal syncope. Given that the patient had neck pain and no sign of pain at rest or Valsalva and a history of syncope, it is not likely the PC results are due to pain. This patient was not administered additional pain medication. Upon further testing, the patient was positive for and treated for syncope and continued physical therapy, then weaned from the vicoprofen.

The next two figures (Figure 159 and Figure 160) show a patient prescribed oxycodone, requesting a larger dose. The patient (49-year-old male) is a non-diabetic motor vehicle accident (MVA) victim with knee and shoulder injuries. His P&S assessment showed normal-to-low responses throughout the study, suggesting no physiologic evidence for persistent pain. The SW indicated from the stand challenge suggests possible orthostasis. The patient reported no dizziness upon standing, and no drop in BP was measured, suggesting that the possible orthostasis is preclinical.

Conclusion

P&S Monitoring has significantly advanced the quality of care and improved outcomes by enabling clinicians to quantify pain, differentiate pain syndromes, document rehabilitation, and titrate pain therapy. The P&S study provides Holter-like monitoring results. Pain management physicians observing patients undergoing the test, witness the patient's reactions to the DB, Valsalva, and PC challenges. This helps the physician gain more insight into the patient's condition. Based on data gained from the application of P&S Monitoring in pain management, a worksheet has been developed to assist in the assessment of patients using their P&S studies.

Whether or not the patient is medicated, the pertinent data from the P&S study includes high, normal, or low indications for: resting P and S activity, (resting) SB, Valsalva sympathetic, and Valsalva and PC parasympathetic responses as compared to rest. If the patient is not yet medicated, then Table 43 assists in differentiating the pain, and therapy would be titrated to normalizing the patient's SB. If resting P and S activity are normal or low, and SB is normal, and

while the perception of pain may be real, the pain is not physiologic. In these cases, perhaps addiction or other non-physiologic needs should be considered and alternate courses of therapy advised. In these cases, the test suggests that the pain is still perceived (at the cortical level), but at the brain stem (the P&S level), the pain is not registering. If resting sympathetic activity, or SB, or Valsalva sympathetic activity are high and no PE is indicated (either at Valsalva or PC), then the pain is physiologic (perceived at the level of the brain stem) and not complex (see Table 43). In these cases, given that pain is a stressor and the SNS deals with stress, the higher the sympathetics (at baseline or Valsalva), the

higher the pain level. If, in addition to high resting sympathetic activity, or SB, or Valsalva sympathetic activity, the Valsalva or PC parasympathetic activity is high, then complex pain syndromes, such as CRPS or fibromyalgia should be considered (see Table 43). In complex pain syndromes, while the (relative) SE indicates pain, the PE underlies the co-morbid disorders (*e.g.*, poor perfusion in CRPS or fatigue and sleep disorders in fibromyalgia). The PE potentiates the SE, causing heightened pain sensitivity. Often, the PE is considered the primary autonomic disorder. Especially with fibromyalgia, the efficacy of tricyclic antidepressants (anti-cholinergics, especially in low-dose) supports this claim. PE in CRPS patients has been important in the early differentiation of CRPS from non-CRPS patients, enabling early therapy for CRPS and improving outcomes.

If, upon baseline challenge, the patient is already medicated, then consider ???. If SB is normal, Valsalva sympathetic activity is normal or low, and there is no PE, then the patient should be considered as properly medicated. If SB is normal, with Valsalva SE or PE, then consider only titrating therapy a little higher. If SB is high, then therapy needs to be titrated higher. If SB is low then therapy needs to be titrated lower. PE (Valsalva or PC) can still differentiate complex pain syndromes from sympathetically-mediated or somatosensory pain conditions.

Upon follow-up testing, consider the Table on the next page. If SB is normal, resting P and S activity, and Valsalva sympathetic activity are normal to low, and there is no PE (or PE is decreasing), then consider the patient as properly titrated. If SB is normal, with Valsalva SE, then consider titrating pain therapy only a little more. If PE persists, but is lower, then perhaps the patient may be properly titrated and only a little more time is needed. If PE persists and is not lower, then perhaps PT also needs to be titrated higher, or an anti-cholinergic should be considered to help relieve the PE. If SB is normal and a resting SE persists or a high SB persists, then therapy needs to be titrated higher. If SB is low, then therapy may need to be titrated lower.

The ability to noninvasively quantify P and S activity has provided a breakthrough in pain management. From independent, simultaneous measures of P and S activity,

pain levels are quantified, pain syndromes are differentiated, and physiologic foundations are linked to the stress of pain and the co-morbid disorders associated with complex pain syndromes. The affects of chronic pain lead to autonomic imbalances which are associated with GI upset, sleep disturbances, secondary hypertension, orthostasis or syncope, and urogenital dysfunction. Secondary disorders such as these may now be measured and detected, perhaps prior to end-organ failure. In this way, the cascade of comorbidities that are often associated with chronic pain are ameliorated, improving outcomes, reducing medication load and hospitalizations, thereby reducing the cost of health care. Autonomic testing is indicated as part of the standard of care in pain management [63,294].

Nerve Conduction Velocity Studies and P&S Monitoring

Nerve Conduction Velocity (NCV) Testing and P&S Monitoring are complimentary tests. Anatomically, the nervous system is comprised of three main fiber types: A'-fibers, B'-fibers, and C' fibers. These are listed in order of diameter from largest to smallest. The A' and B' fibers are the larger fibers and tend to include the sensory and motor neurons. The C' fibers are significantly smaller and include the autonomic neurons. When, for NCV studies, the nerve bundle is stimulated with an electrical pulse, the electricity preferentially stimulates the larger fibers, leading to an overwhelming response from the sensory and motor neurons. While this helps to elucidate causes for paralysis, parasthesias, and pain, it does not elucidate autonomic function. Of course, paralysis, parasthesias, and pain definitely affect quality of life, however the P&S nervous systems control the heart and other organs. If heart and vascular control are compromised, mortality risk (as well as morbidity risk) is significantly higher. This is compounded by the asymptomatic nature of autonomic dysfunction or early autonomic neuropathy. Assuming that the P&S nervous systems follow a similar pathology time course is not very reliable. Just because the larger fibers may be dysfunctional does not mean the autonomic fibers follow the same course of pathology. For one thing, the myelin is different on the different types of neurons. Therefore, to objectively assess all branches of the nervous system, both NCV studies (to measure sensory and motor fibers) and P&S Monitoring are required.

Whiplash Associated Disorders

There is increasing interest about the possible involvement of the SNS in the initiation and maintenance of chronic muscle pain syndromes of different etiology [11,265]. Epidemiological data show that stresses of different natures (*e.g.*, work-related, psychosocial, pain, etc.) typically characterized by sympathetic activation, may be a co-factor in the development of the pain syndrome and/or negatively affect its time course [295,296,297]. Stress and increased sympathetic activity has also been shown to increase morbidity and mortality risk [64,65]. In spite of their clear traumatic origin, whiplash associated disorders (WAD) appear to share many common features with other chronic pain syndromes affecting the musculo-skeletal system [298]. These features do not only include symptoms, like type of pain or sensory and motor dysfunctions, but possibly also some of the pathophysiological mechanisms that may concur to establish the chronic pain syndrome. Besides its well-known action on muscle blood flow, the SNS is able to affect the contractility of muscle fibers, to modulate the proprioceptive information arising from the muscle spindle receptors and, under certain conditions, to modulate nociceptive information. Furthermore, the activity of the SNS itself is in turn affected by muscle conditions, such as its current state of activity, fatigue and pain signals originating in the muscle. The SNS may be involved in the development of WAD through several implicated, positive feedback loops. [265]

Published Case Study

This is a summary of a case study published in *Headache and Pain* [274]. The patient is a 57 y/o, healthy, fit male, with history of migraine without aura since age 8. The migraine frequency averages two per month. His prodrome lasts several hours, with mood change, fatigue, yawning and polyuria. It initiates anteriorly (either side), and increases in severity over 1 to 2 hours, with maximum intensity at two hours after onset if untreated. Maximum intensity is accompanied with throbbing pain and nausea (rarely vomiting) and photo/phonophobia, which is worsened by movement. The patient was highly responsive to triptans. His co-morbid conditions included mildly controlled hypercholesterolemia (atorvastatin 10 mg per day) and rare episodes of pre-syncope, secondary to orthostasis. He has no history of hypertension, diabetes, or cardiac problems, as confirmed by an exercise stress test three years prior. His family history includes his father with a history of migraine without aura, a sister with occasional migraine, and all three children with history of migraine without aura. Coincidentally, the patient had a P&S assessment two days prior to a migraine attack (see Figure 161, above, upper-left panel: —Interictal Period□). The patient typically would require hours of sleep to endure and recover from a migraine. Because the patient was driving to work as the prodrome started, he chose to drive to his doctor's office and agreed to be tested periodically throughout his migraine attack.

Figure 161 and Table 46 document the history of the patient's migraine that day. From the interictal period we are given his baseline, which includes PE as expected in migraineurs. His PE presents during the PC challenge (see Table 46). The results of his pre-treatment assessment are presented in the top row, right graph of Figure 161. This assessment was performed with the migraine fully-involved with severe pain, immediately prior to dosing. From Table 46 we see that his pre-treatment (relative) sympathetic activity, as measured by SB, is higher than the interictal SB indicating an increase in the (relative) sympathetic activity. This is confirmed by the increase in BP from the interictal study to the pre-treatment study. His Valsalva sympathetic activity has also increased (almost doubling) and Valsalva PE is present. The patient was then administered Sumatriptan (6 mg) given subcutaneously. Seventy minutes later he reported being symptom free, his resting HR and BP were below those for the interictal period, and his balance (SB) indicated parasympathetic dominant, perhaps associated with the healing process. However, from his 70-minute post-treatment assessment (see Figure 161, lower, left graph), his Valsalva sympathetic activity is still at the same level it was immediately prior to treatment. The Valsalva PE persists, and the PC PE returns. These abnormalities suggest that the P and S are still disordered from the migraine, even though the therapy has provided relief of symptoms. About seven hours after dosing, his P and S return to near his interictal state. Except for some motion artifact near the beginning and the end of the test seven hours after dosing (see the spikes in sections A and F in Figure 161, lower right panel), the last test is similar to the first. PE persists, and it is borderline with PC challenge (section F) and also demonstrated during the Valsalva challenge (section D). From Table 46, his seven hours post-treatment SB is similar to that for the interictal period, as is his Valsalva sympathetic response. His persistent (PC) PE may be what predisposes this patient to his migraines.

The following manuscripts were first published as articles in *Headache*, April 1992 [305], November 1992 [306], and Nov 1994 [307]. Excerpts of this manuscript are presented here. Autonomic impairment in migraine is well documented. In order to evaluate the autonomic control in migraine, P&S monitoring was performed on ten migraine patients, drug-free and during the inter-headache phase. They were compared to nine healthy controls and eight tension headache patients. Significant differences between control

subjects and patients with migraine were found. The migraine patients displayed markedly enhanced LFa (sympathetic) activity during day hours ($p < 0.01$) and especially at night ($p < 0.0006$). No significant change in the RFa (parasympathetic) was observed. Tension headache patients however, resembled the controls in that they did not display enhanced sympathetic activity. These enhancements are known to be related to vasomotor control, suggesting that the migraine patients are characterized by a clear sympathetic instability. This finding supports the hypothesis that migraine is of neural origin and is consistent with the observation of large variations in regional cerebral flow. P&S monitoring allows specificity and quantification of the associated autonomic imbalance as related to both the symptoms and efficacy of drug therapy in migraine.

Migraine patients seem to suffer from a continuous autonomic imbalance. Sympathetic instability, which exists during the headache free intervals, was observed in our previous study [305]. Propranolol, a beta adrenoceptor antagonist, is widely used in migraine prophylaxis. P&S monitoring was used to specify and quantitate propranolol efficacy in 10 migraine patients before and during the treatment with propranolol. They were compared to 10 healthy control patients and 6 migraine patients who were treated for several months with propranolol and then discontinued the medication.

Propranolol achieved a marked effect, when comparing the treated versus untreated migraine patients. A strong reduction (to normal level) in sympathetic activity was apparent in patients treated with propranolol. Subjects who had received propranolol in the past and discontinued the drug, displayed a carry-over effect of reduced fluctuations, even 2-3 months after its discontinuation. It seems that the propranolol efficacy in migraine is associated with the mechanism of stabilizing the fluctuations within the frequency band related to sympathetic activity (LFa), hereby moderating the vascular instability in migraine.

Abnormalities in autonomic control have been documented in migraine even during the headache-free interval. P&S monitoring was performed for each subject in a group of five migraine patients during the inter-headache period. In addition, shorter 5-minute-long recordings of blood flow (BF) and blood pressure (BP) were made in these patients in both supine and standing positions. Autonomic and hemodynamic assessment was performed in the migraine patients before and during the treatment with verapamil and compared to that of a healthy control group.

A characteristic autonomic abnormality is revealed in the group of untreated migraine patients in supine position: increased sympathetic sensitivity during the inter-headache phase. An exaggerated sympathetic (LFa) response is measured in the migraine patients during the transition from supine to standing position with a concomitant non-significant decrease in parasympathetic response. Under the influence of verapamil, the enhancement in sympathetic activity is reversed, as well as the exaggerated sympathetic response to standing.