Measuring The Autonomic Nervous System

with therapy examples and sample studies

Joe Colombo, PhD
Why Monitor the ANS?
Leadership recommends* ANS monitoring

* AAN\(^1\), AHA\(^2,3\), ADA\(^2,3,4,5\), AAFP\(^6\), JDIF\(^2\), NIH\(^2\)


ANS & Early Disease

Autonomic Changes with Age

ANS dysfunction is asymptomatic

DAN presents

CAN presents

First presentation (intervention)

With permission from Vinik, et al., 2004
Why Monitor the ANS?

Chronic Disease →
Autonomic Dysfunction (PAN & DAN) →
Cardiovascular Autonomic Neuropathy (CAN) →
Death

\[ CAN = \text{Denervated Heart} \]

(No Parasympathetic Protection) =
Risk Of Sudden Death
Why Monitor the ANS?

Why wait for neuropathy to present?

• Autonomic Neuropathy does not happen over night
• Autonomic dysfunction precedes autonomic neuropathy
• Autonomic dysfunction is asymptomatic
History

• 1984 Acquired MIT Technology
• 1987 Technology Patented
• 1989 – 1992 Funded 18 Beta-Sites Nationwide
• 1992: Documented Beta-Site activity in Symposia co-sponsored by
  – Cleveland Clinic
  – Harvard Medical School
  – Johns Hopkins Medical School
History

- 1995 Received FDA Clearance
- 1997 Lobbied & had released CPT codes
  - 95921 & 95922
- 1999 Sole-source provider to US Government
- 2001 Released ANX-3.0 v. D
- 2004 Doubled sales over 2003

Over 450 Systems Placed Nationwide
ANS Testing: Clinical Challenges

Sympathetics:
Hand Grip
Short Valsalva Maneuvers
Postural Change
Cold Water
Sweat Response

Parasympathetics:
Deep Breathing
Postural Change
Long Valsalva Maneuvers
ANS Testing Augments:

- Nerve Conduction Velocity Studies
- Tilt Studies
- Sleep Studies
- Sex Function Tests
- Ambulatory BP
- Sitting-Standing BP

- Q-SART (Q-Sweat)
- Sudomotor Testing
- Thermal Studies
- Vestibular Tests
- Pain
- Stress-tests
- Holter-monitoring
Who To Test?

- ANS testing detects ANS imbalances in asymptomatic patients
  - Imbalances, whether the primary disorder or caused by a primary disorder, can cause secondary disorders which can cause further disorders and so on....
Who To Test?

- Patients with chronic, progressive diseases
- Patients with acute cardio-vascular diseases (Stroke)
  - Leadership recommends ANS monitoring
  - Medicare and third party payer reimburse; reliably
    - See lists of ICD-9 codes on next slides
Who To Test?
(A Partial List of ICD-9 Codes)

Neurology
307.4 Sleep Disorders
Manifestations of thiamine deficiency
332.0 Paralysis agitans
333 Parkinsonism & Huntington’s chorea
Other degenerative diseases of the basal ganglia,
  Olivopontocerebellar degeneration
333.9 Extrapyramidal disease & abn. movement
  disorders (incl., Stiff-man syndrome)
Cerebellar degeneration, Spinocerebellar & Amyotrophic
  diseases, Syringomyelia & Syringobulbia
336 Diseases of the spinal cord
337.0 Idiopathic peripheral autonomic neuropathy
337.9 Unspecified disorder of ANS
340 Multiple sclerosis
352.3 Disorders of Pneumogastric (10th) N.
Mononeuritis, Peripheral & Poly-Neuropathies, incl., DM
358.1 Myasthenic syndromes (Eaton-Lambert, LEMS)
372 Conjunctivitis
Chronic Pain
458 Orthostatic & Chronic Hypotension
596.54 Neurogenic bladder
Urogenital Dysfunctions
705.0 Anhidrosis
710.2 Sicca syndrome (Sjögren’s disease)
780.2 Syncope and collapse
780.71 Chronic fatigue syndrome
785.0 Tachycardia (postural)
796.1 Abnormal reflex
Migraines and other headaches
Internal Medicine
All of the rest, plus:
278.01 Morbid Obesity
279.3 AIDS
296 Depression or Bipolar Disease
300 Anxiety
309.81 Post-traumatic Stress Syndrome
314.0 Attention Deficit Disorder
729.1 Fibromyalgia

Who To Test?
(A Partial List of ICD-9 Codes)

**Cardiology**
- 401.0 - 405.99  Hypertension
- 412  Post-MI
- 413  Angina
- 414  Atherosclerosis
- 424  Mitral Valve Prolapse Syndrome
- 425.4  Cardiomyopathy
- 427  Cardiac Dysrhythmias
- 428  Congestive Heart Failure

**Pulmonology**
- 780.51, 780.53, 780.57  Sleep Apnea
- 493.90 - 493.93  Asthma
- 493.2  COPD

**Endocrinology**
- 244  Acquired Hypothyroidism
- 246  Thyroid Disorders
- 250.0 - 250.8  Diabetes
- 256.3  Premature Menopausal Symptoms
- 627  Menopausal Syndromes
ANS Testing

- Fully automated, any Technician can be trained and certified by Ansar in an hour
- The test itself is 15.5 minutes in duration
- Requires a plain straight-back chair, the test equipment, and a quiet room
- Technicians and nurses love it, one-on-one time with the patient and no interruptions
ANS Testing

- Six challenges include:
  A) resting (initial) baseline,
  B) the parasympathetic challenge of deep breathing,
  C) return to baseline,
  D) the sympathetic challenge of a series of short Valsalva maneuvers,
  E) return to baseline, and
  F) Quick postural change (seated to standing) followed by quiet standing
ANS Test Results

Multi-Parameter Graphical Report

** For Data Interpretation only, NOT A DIAGNOSIS, must be interpreted by a Physician **

Heart Rate

Breathing

Sympathetic Trend (LFA) vs. Parasympathetic Trend (RFA)

Current AIS Medication State

Notes

ANX 3.0

Copyright 2001

ANSAR

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Parametric Units: 3pm 1μu +ARR+2
Heart Rate Variability & Respirations


Classical HRV [Malek, Circulation]

Malek, 1996
Low, 1997
Uijtdehaage and Thayer, 2002
Williams and Lopes, 2002
Cammann and Michel, 2002
Vinik and Freeman, 2003

\[ \{ \text{HRV WITH RESPIRATIONS} \} \]

\[ \{ \text{RESPIRATIONS OMITTED} \} \]

\[ \{ \text{FOR ANS MONITORING HRV MUST INCLUDE RESPIRATIONS} \} \]
Heart Rate Variability & Respirations

• Heart Rate Variability (HRV) with Respiratory Activity (RA) = ANS testing
  – Consider healthy resting cardiogram:
    • Faster respiratory sinus arrhythmia (RSA) = Vagus (PSNS)
    • Slower mean heart rate (mHR) changes = SNS
  – Analyze separately (“peel apart”) = independent measures of both ANS branches

• Spectral analysis is the only method
HRV & RA = ANS

*RFa = Parasympathetic Measure

**LFa = Sympathetic Measure

LFa/RFa = Sympathovagal Balance

Normal, Healthy, Resting Cardiogram

Slower mHR

Faster RSA

Time (sec)

Time (sec)

September 2006

Ansar, Inc./jc
The Autonomic Nervous System

**Sympathetic**
- Dilates pupils
- Inhibits salivation
- Bronchial dilation
- Inhibits digestion
- Stimulates glucose release by liver
- Stimulates epinephrine & norepinephrine release
- Relaxes bladder
- Contracts rectum
- Orgasm ejaculation
- Peripheral vasoconstriction

**Parasympathetic**
- Constricts pupils
- Stimulates salivation
- Bronchial constriction
- Stimulates digestion
- Stimulates gallbladder
- Contracts bladder
- Relaxes rectum
- Vaginal lubrication
- Erection
- Peripheral vasodilation
Interpretation

• There are very few reasons why a test is not valid.

• In almost all cases, test anomalies still provide clinical information about both branches of the ANS, and that is the purpose of the test.
Therapy Summary

• Standard Practices titrated to the individual’s own needs at the time, considering
  – ANS imbalance
    • Standard therapies, perhaps lower doses, considering individual responses (balance)
    • Possible earlier detection of asymptomatic pts (DM, HTN)
    • Without end-organ effects ANS therapy may be short term

• Do not treat primary ANS imbalances without ANS symptoms
Follow-up Testing

• 10% to 15% changes are significant, less than 10% are significant if with symptoms
• Autonomic changes tend to take 4 to 6 weeks to complete
• Medicare pays for 2 test/yr, 3 if there are interventions
• Goal: slow or stay the progression of ANS decline and protect the heart
Why Monitor The ANS?

• Autonomic Neuropathy signs and symptoms are late in the progression
  – Chronic Progressive Disease is the indicator

• Early detection and correction of ANS imbalance (dysfunction) helps to:
  – Protect ANS and related organs
  – Keep patient stable
  – Prolong quality of life
Why Monitor The ANS?

• Differentiation or Early Detection of:
  – ANS involvement in Neurological (e.g., Parkinson’s) and Sleep disorders (incl., Circadian Rhythm & Limbic issues)
  – Orthostasis and its continuum
  – Syncope and its forms
  – ANS involvement in arrhythmias
  – CAD/CHF (Val Heft study)
  – Hypertension
    • Labile HTN, other difficult to control patients
  – Respiratory therapy effects on cardiovascular system
  – Autonomic Neuropathy
    – As well as Sudden Death
Why Monitor The ANS?

• Pain Therapy
  – Differentiate Psychosomatic, Autonomic, and CRPS
  – Objectively quantify pain levels
    • Use pain as a sympathetic stressor
  – Document rehabilitation
    • Customize titration of medication
      – Possibly decrease incidences of addiction
  – Maintain ANS balance to minimize presentation of secondary symptoms and syndromes.
Orthostasis
(ANS definition: Sympathetic Withdrawal upon standing with symptoms)
Orthostasis
(Examples)

• Orthostatic Hypotension
  – Clinical: Sympathetic Withdrawal plus 20 mmHg systolic and 10 mmHg diastolic BP decrease upon standing
  – Pre-clinical: Sympathetic Withdrawal plus any BP decrease upon standing

• Orthostasis (Orthostatic Intolerance)
  – Sympathetic Withdrawal plus normal BP change upon standing

• Postural Tachycardia Syndrome (POTS)
  – Clinical: Sympathetic Withdrawal plus 30 bpm increase in HR or HR > 120 bpm upon standing
  – Pre-clinical: Sympathetic Withdrawal plus excessive HR increase (>15%) upon standing
Orthostatic Hypotension + 
45 y/o Female

- Original Diagnosis (Dx) (before ANS testing):
  - Orthostasis (red circle) and
  - Low blood pressure upon standing (green circle)
- History:
  - Syncope (tilt positive seven years prior)
  - Pindolol on board
- Dx after ANS testing: Orthostasis (red circle)
- Therapy: initiate Midodrine
- Serial ANS testing (over a 4 month period):
  - Reversed Orthostasis with increasing BP upon standing
  - Patient reports more stable on therapy and no more dizziness
Orthostatic Hypotension

45 y/o Female

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<th>rangeHR'</th>
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Postural Orthostatic Tachycardia + (POTS)  56 y/o Male

- Original Dx: Orthostatic Hypotension due to drop in BP upon standing
- History: Frequent dizziness and vertigo upon standing
- Dx after ANS testing:
  - POTS:
    - Significant ectopy two minutes into stand challenge (presumably due to cardiac compensation for sympathetic withdrawal and venous insufficiency while standing (this is the source of the tachycardia)
    - Orthostasis (green circle)
  - Low baseline, PPS, and secondary Hypersympathetics
- Therapy: initiate Midodrine (2.5mg bid)
- Serial ANS testing (over a 6 month period):
  - Reversed the BP and HR abnormalities
  - Although some sympathetic withdrawal remains, patient reports significant reduction in dizziness
Postural Orthostatic Tachycardia (POTS) 56 y/o Male

September 2006
Syncope

- In younger patients with relatively healthy ANSs, Normal is $> 2:1$ LFa (red, sympathetic) Valsalva peak to first LFa Stand peak
- Abnormal suggests that it takes more sympathetic power to stand than it does to deal with a stressor like a series of Valsalva maneuvers
- Syncope does not require Orthostasis as a condition
Syncope

• Neurogenic vs Cardiogenic (ANS definition):
  – If HR increases from baseline to stand, then the nerves are working; therefore the Syncope is Cardiogenic
  – If HR does not change or decreases then the Syncope is Neurogenic

• In patients with autonomic dysfunction or depleted ANSs, Syncope can also be indicated by excess parasympathetic (Vagal) activity throughout the test
Treatment

Restoring autonomic balance improves outcomes, preserves quality of life*, and promotes longevity.

*(eating, sleeping, going to the bathroom, having sex)
TREATMENT & THERAPY

- Adrenergic agonists and antagonists
- Cholinergic agonists and antagonists
- Angiotensin-Renin agonists and antagonists
- Vasopressors
- Calcium Channel Blockers

*You are already treating your patient’s ANS. Now you can scientifically optimize therapy for the individual patient*
Treatment Titration

1. Appropriate for patient
2. Too low
3. Too high
End of Presentation

Thank you for your time and attention
Sample Normal Studies

Children:
3 year old male
7 y/o male

Teenagers:
13 y/o female
15 y/o female

Transition Years:
18 y/o female
21 y/o female

Adults:
34 y/o female
44 y/o female
60 y/o female
Normal Children
Normals Teenagers

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Normals: The Transition Years

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Normal Adults

34 y/o

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44 y/o

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Normal Adults

60 y/o

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Sample Longitudinal Studies

Diabetes
CRPS
CFS
Critical Care Medicine

Migraine
Fibromyalgia
PPS (ADD)
Type II Diabetes +
63 y/o Male

- Original Dx: Type II Diabetes and Hypertension
- History: Zocor
- Dx after ANS testing:
  - PPS & Orthostasis in addition to
  - Diabetes & Hypertension
- Therapy: Add Coreg
- Serial ANS testing (over a 12 month period):
  - Reverse Orthostasis, PPS and BP
Type II Diabetes
63 y/o Male
Sleep Apnea
55 y/o Female

• Original Dx: Hypertension, then Sleep Apnea
• History: Lasix, Toprol
• Dx after ANS testing:
  – PPS in addition to
  – Hypertension & Sleep Apnea
• Therapy: dc Toprol, add Coreg, Midodrine & CPAP
• Serial ANS testing (over a 6 month period):
  – Reduce PPS, Reduce Bx Ratio
Sleep Apnea
55 y/o Female

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Migraine Case Study
57 y/o Male

- 57-year-old, healthy, fit male, 5’7” tall, 160 lbs
- Hx: migraine without aura (IHS 1.1) since age 8
- Frequency: 0 to 3 per month (ave = 2-per-month)
- Characteristics:
  - Prodrome lasting several hours, w/ mood change, fatigue, yawning and polyuria
  - Initiate anteriorly (either side) and increase in severity over 1 to 2 hours.
  - Maximum intensity at 2 hours after onset if untreated, w/ throbbing pain & nausea (rarely vomiting) and photophobia; worsened by movement
Migraine Case Study
57 y/o Male

• Rx: highly responsive to (all 7) triptans
  – Comorbid conditions: mild controlled hypercholesterolemia (treated with atorvastatin 10 mg per day) and rare episodes of presyncope, secondary to orthostasis
  – No history of any cardiac problems, confirmed by an exercise stress test done 3 years prior; hypertension or diabetes
  – Family history: patient’s father had a history of migraine without aura. The patient’s sister also had occasional migraine. All three of the patient’s children had a history of migraine without aura.
Migraine Case Study

57 y/o Male

Interictal: 2 days before

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Fully Involved, Pre-Treatment, Severe Pain

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Migraine Case Study

57 y/o Male

Fully Involved, 70 min. Post-Treatment (Sumatriptan 6 mg, Sub-q), Symptom Free

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7 hrs. Post-Treatment, “Normal”

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Paradoxic Parasympathetic Syndrome (PPS, example: ADD) +
17 y/o Male

• Original Dx: ADD, Depression, high HR
• History: Adderol
• Dx after ANS testing:
  – PPS with secondary Hypersympathetics
  – Orthostasis and elevated BP
• Therapy:
  – Weaned from Adderol
  – Placed on Elavil (25mg QHS) to settle the Limbic and PPS, and
  – Midodrine (2.5mg BID) for Orthostasis
PPS

- Detected by measuring both ANS branches simultaneously and independently
- Destabilizes patient, both in response to
  - Disease (labile HTN, poorly controlled DM, unexplained seizures, Migraine, Hormonal disorders) and
  - Therapy (beta-blocker patients whose HR increases)
PPS

Abnormal Autonomic Response to Stimuli (e.g., PPS)

Increased Instability with Peripherally Acting Therapy Approaches
PPS

Cingulate Gyrus (Limbic System)

Limbic Input

Pons

Nucleus & Tractus Solitarius

Systemic Sympathetic Input

Medulla

Systemic Parasympathetic Outflow

Block with Tricyclics (use for depression, anxiety, emotional triggers, & sleep difficulties)

Block with centrally acting adrenergic antagonists (eg, Coreg if Diabetic or has heart disease)
PPS (ADD) +
17 y/o Male

• Serial ANS testing (over a 18 month period):
  – After first follow-up testing PPS was reversed (from an abnormal increase of 685.4% [1.03 to 8.09] to an acceptable increase of 61.14% [1.75 to 2.82])
  – Upon final follow-up testing, RFa increase from initial baseline to Valsalva acceptable, sympathetic withdrawal decreasing, HR and BP lower, and patient reporting feeling better, re-joining previous family and scholastic activities, and parents report grades improving
  – Midodrine was weaned after 6 months and Norpace expected to be weaned after 15 months
PPS (ADD)
17 y/o Male
The patient (38 y/o F) presents with RSD, ADD, HTN, & Gastric Disorder. She is on Neurontin, Methadone (pump) for pain and many others.

In general, she presents with elevated parasympathetic activity throughout most of the test characteristic of RSD. However, she shows weakness in the parasympathetics during deep breathing suggesting the first stages of chronic ANS dysfunction. Overall, based how “normal” her sympathetics seem she is well maintained.
Fibromyalgia
Typical First Presentations

KB1545F

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EG138M

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Chronic Fatigue Syndrome

Typical First Presentations

SC1669F

MH1667F

DK1671F
Critical Care Medicine

• 2002 ONR Technical Reports; Dr. Dutton
  – Naval Health Research Center, San Diego, CA
  – Wm. Beaumont Hospital, Detroit, MI
  – Cowley Shock Trauma Center, Baltimore, MD
    • Early detection of hypovolemia
    • Early detection of cardiac instability
    • Possible quantification of depth of anesthesia

• 2003 Critical Care Med. ANS & Trauma; Dr. Shoemaker USC, LA, CA
Critical Care Medicine

- 2004 Closed Head Injury
  - WC Shoemaker & PG Bernad GWU, DC
Critical Care Medicine

• 2005 CHEST Abstracts
  – ANS & Sepsis
    • Detect early onset of Sepsis
    • ANS role in Septic Shock
    • Gender Differences
  – ANS & Early Goal-Directed Therapy
    • Preliminary evidence: Enhanced outcomes

• Stroke
  – Acute v Chronic phases
  – Brain Stem v Hemispherical
Critical Care Medicine

– Penetrating Wounds
– Bunt Trauma

Sympathetic Activity in Blunt Trauma

Parasympathetic Activity in Blunt Trauma

- - - Non-Survivor
___ Survivor