The section headers below contain a couplet of words. The first word in the couplet indicates whether or not the patient’s condition falls within the paradigm of the automated interpretation software. The second word in the couplet indicates whether or not the patient’s ANS is normal. On average, our physicians find that the “Normal-Normals” account for up to 5% of their population. They find that the “Normal-Abnormals” account for about 85% of their population, and the “Abnormal-Abnormals” account for about 10% of their population.

Interpretation for the majority of the patients seen has been reduced to the understanding of five results from the test. These results have been presented in the “response plots” which comprise the second row of graphs on the ANX-3.0 graph report. The response plots all include a gray area that indicates (age and gender matched) normal values from nationwide studies. Your patient’s response is plotted against this background. The source of the patient values is from the table at the bottom of the graph report. See Appendix I for a graphical display of the source of the patient values on the response plots.

Included at the end is an example showing the utility of the “Current ANS Medication State” chart on the multi-parameter graph report. This chart indicates the net, overall influence that ANS medications may have on the patient’s ANS. The medications included in this analysis are those that are indicated in the Physician’s Desk Reference as being ANS active. For instance, it is believed that serotonin re-uptake inhibitors (SSRIs) are ANS active. However, they not indicated in the PDR as such. So, until that status changes or some publications are found that confirms this belief, they are not included. To enter the ANS active drugs that the patient may be on, there are pull-down menus programmed into the software that the person administering the test can click on and enter. The computer will note the net, overall influence, and then this influence can be correlated with the initial (resting) baseline response plot to determine if the medication is properly titrated. The example (Figure 14) is provided at the end of this document after the initial (resting) baseline response plot (Figure 13) is introduced.

**NORMAL-NORMAL**

All ANS parameters are normal. The patient’s ANS is in balance. Everyone is doing a good job. Congratulations. Retest in six months.

Appendix IV includes examples of normal patients from childhood to adult. Note the child and teenage, since they are still developing, have much higher parasympathetic activity throughout the test than do the normal adults.

**NORMAL-ABNORMAL**

These patients fall within the paradigm of the software that automates the interpretation process. Simply read the “Summary Diagnostic Implications” and correlate with the “Recommended Therapy Options” for treating ANS dysfunctions. For these patients the software provides you access to the knowledge base developed from a data base of over 10,000 patient studies, including 3,000 patients studied longitudinally, from over 36 physicians over the past six years. The Summary Diagnostic Implications is like these doctors speaking to you through the software. The Recommended Therapy Options have been found to work in the patient populations of these physicians. The six steps to the automated interpretation (see Figure 1) are listed in Appendix II with some questions to ask the patient in certain cases to verify an indication. Below are some abbreviations and related jargon that we define and that are used as
pointers to the Recommended Therapy Options. Since Ansar’s technology is not approved as a diagnostic, we cannot print the Recommended Therapy Options on the same page as the Summary Diagnostic Implications.

ABNORMAL-ABNORMAL

These are the issues that the FDA insists that the physician needs to consider more closely with the patient’s history. These issues center mostly around ectopic beats suggesting possible arrhythmias and possible respiratory or pulmonary difficulties. There are 14 individual rules to complete the interpretation options. These 14 rules are addressed below.

MOST FREQUENTLY USED DRUG CATEGORIES FOR ANS THERAPY

- Beta 1 Adrenergic Blockers (Anatgonists)
- Beta 2 Adrenergic Agonists
- Alpha Adrenergic Agonists
- Anti-Cholinergics (Cholinergic Anatgonists)
- Angiotensin Blockers (Anatgonists)
- Calcium Channel Blockers (Anatgonists)

Beta 1 Adrenergic Blockers (Anatgonists) Work on the Heart

Beta 1 Adrenergic receptors are typically found on the heart and is a means for the sympathetic (adrenergic) nervous system to control heart rate. Therefore, Beta 1 Adrenergic Blockers block these receptors and limit heart rate. From an autonomic perspective, there are two classes of these drugs: peripherally acting (e.g., Metaprolol, Toprol, Atenolol, and Propanolol), and centrally acting (e.g., Acebutolol and Coreg). (Actually, Acebutolol and Coreg are known as cocktails, they contain more than one agent, and only one of their agents actually crosses into the brain.) The centrally acting Beta-Blockers, have a component that works in the brain stem and one or more components that work on the connection between the sympathetic nerves and the heart.

Beta 2 Adrenergic Agonists Work in the Lungs

Beta 2 Adrenergic receptors are typically found on the smooth muscles that control the diameter of the bronchi in the lungs. Beta 2 Adrenergic Agonists stimulate these receptors to relax, opening airways and allowing more oxygen into the lungs. These drugs are typically used by asthmatics and other pulmonary patients as inhalants to treat the symptoms of spasmodic or constricted airways.

Alpha Adrenergic Agonists

Alpha Adrenergic receptors are typically found on the smooth muscles that control the diameter of the vasculature. Alpha Adrenergic Agonists (e.g., Midodrine, a.k.a. ProAmatine) stimulate
these receptors to constrict the vasculature and reduce the diameter and forcing blood to return to
the heart.

**Anti-Cholinergics (Cholinergic Antagonists)**

The cholinergic system is another name for the parasympathetic nervous system which is
comprised mostly of the Vagus Nerve. Anti-Cholinergics (e.g., Clonadine, and the side-effects
of Tricyclic Anti-Depressants like Elavil or Amatriptyline and Nortriptyline) are drugs that limit
the activity of the parasympathetic nervous system. These drugs help to treat disorders like
depression, gastrointestinal upset, and fibromyalgia.

**Angiotensin Blockers (Antagonists)**

The angiotensin-renin system is a part of the sympathetic nervous system that works with the
kidneys to help control blood pressure. Angiotensin Blockers (e.g., Angiotensin Converting
Enzyme Inhibitors (ACE-Is) like Captopril, Benazepril, and Lisinopril; and Angiotensin II
Receptor Blockers (ARBs) like Avapro or Irbesartan, Cozaar or Losartan and Diovan or
Valsartan).

**Calcium Channel Blockers (Antagonists)**

Calcium Channel are gated tunnels in the walls of cells that help to initiate the electrical activity
in the cell that allows it to function. In the case of the cardiac muscles cells of the heart, it causes
contraction. Calcium Channel Blockers (e.g., Almodipine or Norvasc, Diltiazem or Cardizem,
Vascor, and Verapamil) limit the ability of the “gate” to open, thereby limiting the ability of the
cell to function. In this case, they limit the contraction of the cardiac muscles, which limits the
force of contraction of the heart, thereby limiting or reducing blood pressure.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Associated Nervous System</th>
<th>Primary Site of Action</th>
<th>Primary Effect</th>
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<tbody>
<tr>
<td>Beta 1 Blockers</td>
<td>Sympathetics</td>
<td>Heart - Chronotropy</td>
<td>↓ Heart Rate</td>
</tr>
<tr>
<td>Beta-2 Agonists</td>
<td>Sympathetics</td>
<td>Lungs</td>
<td>↑ Air Flow</td>
</tr>
<tr>
<td>Alpha Agonists</td>
<td>Sympathetics</td>
<td>Vasculature</td>
<td>Constrict Vasculature</td>
</tr>
<tr>
<td>Anti-Cholinergics</td>
<td>Parasympathetics</td>
<td>Entire Body</td>
<td>↓ Parasympathetic activity</td>
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<tr>
<td>Angiotensin Blockers</td>
<td>Sympathetics</td>
<td>Kidneys</td>
<td>↓ Blood Pressure</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>Sympathetics</td>
<td>Heart - Ionotropy</td>
<td>↓ Blood Pressure</td>
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</table>
The Need For Central Vs Peripheral Therapeutic Action

In general, there is an oppositional or See-Saw relationship between the two autonomic branches: sympathetics (red) and parasympathetics (blue). Normal balance and normal responses to sympathetic and parasympathetic responses are shown below in the first three diagrams. The fourth diagram models the abnormal condition known as paradoxic parasympathetic syndrome (PPS). The paradox is that the parasympathetics are abnormally responding (abnormally increasing) to a sympathetic challenge.

Clinically, this serves to destabilize patients’ responses to disease and therapy. It destabilizes because rather than falling away first, the parasympathetics are increasing, forcing a the sympathetics to increase more than usual. These frequency, excessive sympathetics surges can lead to hypertensive states and all of the secondary conditions that result.

PPS is found in over 50% of our database (over 12,000 patient studies), and seems to be associated with three or more of the following symptoms:

- Difficulty falling asleep (can take up to several hours) or wake frequently during the night;
- Poor circulation;
- Restless leg syndrome or night-time edema;
- GI upset (GERD, frequent diarrhea or constipation);
- Depression, anxiety, panic-attacks or bipolar-like symptoms;
- Frequent morning migraines or headaches;
- Frequent morning cognitive difficulties (memory, function);
- Chronic pain syndromes (including Fibromyalgia);
- Syndromes that include chronic fatigue;
- (If 35-45 y/o female) menopause-like symptoms; or
- Frequent dizziness upon standing.

Therapeutically, the difficulty is that these surges look like a primary sympathetic abnormality when EKG, heart rate, or blood pressure is measured. If treated as such using typical anti-adrenergic therapy like (peripheral) beta-blockers (e.g., Toprol, Metaprolol), the anti-adrenergic therapy (1) reduces any endogenous sympathetic opposition, thereby (2) further strengthening the parasympathetics, which then (3) respond even more abnormally, ultimately (4) forcing the sympathetics to respond even more. The sympathetics respond even more because the brain still demands its blood and since the therapy does not block all sympathetic channels, the body can find alternate pathways to deliver blood to the brain; thus defeating the efficacy of the therapy.

As examples, typically patients with:

- PPS and hypertension are found to have labile or poorly controlled blood pressures;
- PPS and diabetes are found to have poorly controlled blood sugars;
- PPS and are on hormone replacement therapy (e.g., thyroid or estrogen) are found to be on large dosages of hormone replacement still not feel completely normal;
- PPS and on beta-adrenergic blockers and still their heart rate increases; and
- PPS and on angiotensin blockers and still their blood pressure increases.
This is modeled in the fourth and fifth diagrams. In the fourth diagram when PPS is present the see-saw lifts off the fulcrum in response to a sympathetic stimulus. If a peripheral adrenergic agent is taken, the parasympathetics are strengthened and the see-saw becomes more unstable and becomes vertical in the extreme.

The solution to PPS is to “grab” the see-saw in the center and “bring it back down to earth”. This requires centrally acting agents that can directly or indirectly reduce parasympathetic outflow from the Vagal nuclei in the Medulla of the brain stem. There are two options for which we have statistically relevant data: Coreg or the Tricyclic Anti-depressants (Amatriptyline or Elavil, and Nortripyline). One of the triple cocktail of Coreg crosses the blood-brain barrier and reduces systemic sympathetic input to the Vagal nuclei at the site of feedback. By reducing the input, the output is reduced indirectly resolving the dynamic parasympathetic excess PPS. The Tricyclic Anti-depressants have an anti-cholinergic side-effect and help to reduce the dynamic parasympathetic excess PPS directly. Of course, since Coreg also includes beta 1 adrenergic blockade, it also serves to protect the heart as indicated for diabetics with heart disease and heart failure patients. Similarly, since the Tricyclics also help to reduce limbic activity, they also help to indirectly reduce dynamic parasympathetic outflow and help to resolve any depression that may be involved.

Therapy recommendations include:

- For cardiac patients on a peripheral beta-blocker(s), switch to dose equivalent Coreg, titrate as needed, retest in 2 to 3 months. If symptoms abate, consider d/c in 12-15 months, otherwise continue as maintenance dosing.
- For cardiac patients not on peripheral beta-blocker(s), initiate Coreg 6.25 mg bid and titrate as needed.
- For non-cardiac patients, presenting with symptoms of sleep difficulties, pain, depression, anxiety, bi-polar disorder, or other limbic issues, initiate Amytriptaline or Nortryptaline 10 mg 12 hours before waking, titrate to no more than 25 mg bid. If more is needed, add Coreg starting at 3.125 mg bid.
- For non-cardiac patient without above the symptoms, start on Coreg 3.125 mg bid titrate to no more than 12.5 mg bid. If more is needed, add the Amytriptaline or Nortryptaline.

In general, the intent is to use low dose to reduce the potential for side-effects and retrain the nervous system to carry forward on its own. This includes the possibility for weaning the patient from autonomic therapy after the patient demonstrates autonomic stability. However, this may not be possible due to end organ effects which may require the patient to stay on maintenance dosing of autonomic therapy.

One last note, if the subject only has PPS upon Valsalva and not upon standing, and the subject has no chronic disease or any of the symptoms associated with PPS, do not treat. These subjects are associated with individuals whose lifestyles have already compensated for the PPS. Simply note the PPS and should some other clinical event occur, treat the patient in light of the PPS. This may possibly require using a centrally acting agent rather than a peripherally acting agent.
Diagram 1: Sympathetics (red) and Parasympathetics (blue) in normal balance (at rest).

Diagram 2: A normal autonomic response to a sympathetic (red) challenge. As the sympathetics increase the parasympathetics fall away. In many cases, since the sympathetics are slower than the parasympathetics to respond, the parasympathetics fall away first then the sympathetics increase. The parasympathetics falling away creates an apparent sympathetic increase and reduces the need for the sympathetics to respond as much when they do respond. Having the sympathetics slower to respond is preferred. If the sympathetics are modeled by the accelerator on your car and the parasympathetics as the brakes. It is preferred that the ability to slow or stop is faster than the ability to accelerate. If the opposite were the case, the car could accelerate beyond the ability of the brakes to slow the car. In the human this could result in a heart attack.

Diagram 3: A normal autonomic response to a parasympathetic (blue) challenge. As the parasympathetics increase the sympathetics fall away.
Diagram 4: An abnormal autonomic response to a sympathetic (red) challenge. As the sympathetics increase the parasympathetics also increase (rather than fall away). This is PPS. This causes patients to be unstable in their response to both disease and therapy (the see-saw is off the ground). Clinically, this is typically viewed as a primary, excess sympathetic disorder due to the fact that the sympathetics are so elevated and the resulting blood pressure and heart rate responses are also elevated. But, because the parasympathetics are increasing abnormally, the sympathetic excess is actually secondary, in response to the parasympathetic increase. Remember, the parasympathetic set the threshold around which the sympathetics must surge to respond to short-term metabolic needs.

As shown in Diagram 5, when PPS is treated as a primary sympathetic excess using typical anti-adrenergic agents (peripheral beta-blockers), some of the endogenous sympathetic parasympathetics to become relatively stronger, ways to help deliver blood to the brain and defeat primary sympathetic (red) excess, exacerbates PPS. Peripheral beta-blockers will suppress the sympathetics, further strengthening the parasympathetic, which the sympathetics will still have to overcome to help deliver blood to the brain.

So, as stated above, the therapy for PPS “grab the see-saw” at its center, “level it”, and “return it to the ground.” The agents that Coreg, Elavil, and Nortriptyline. See above for a more complete description, and the of action.

As shown in the figure below, typical blockers, angiotensin blockers, and many sympathetic pathways outside the central nervous system. This has little effect on correcting PPS. It is like “kinking” one parasympathetic system. Coreg is one component that crosses the blood-brain barrier, reducing sympathetic input to the parasympathetic system. This action is like “kinking” the “hose” that leads to the nozzle the peripheral anti-adrenergics (peripheral beta-calculator channel blockers) work on one of the central nervous system. The fact that it also protects the heart means that it can serve
ABNORMAL – ABNORMAL RULES

Rule #1: FRF Is Out of Range

The FRF is the Fundamental Respiratory Frequency. It is equivalent to the inverse of the breathing rate in a normal healthy individual. The expected value of the deep breathing FRF is 0.1 Hz (6 breaths per minute). The accepted range is 0.09 Hz to 0.15 Hz (see Figure 2). There are two reasons why the FRF may be out of range. First the patient was hyperventilating causing a sympathetic, rather than a parasympathetic, challenge. If this is the case, then this portion of the exam must be repeated. The other reason is that the patient is experiencing upper respiratory or pulmonary difficulties that cause the Vagus (parasympathetics) to “struggle” to ventilate the patient. This extra effort causes higher frequency components that elevate the FRF. Upper respiratory or pulmonary causes of elevated FRF can include: cold, flu, bronchitis, allergies,

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**Interpretation Summary**

1. Is HR normal?
   - Consider the HR Plot

2. Obtain overall impression of ANS responsiveness
   - Consider the Trends Plot

3. Quantify responsiveness
   - Consider the Deep Breathing and Valsalva Response Plots

4. Consider total ANS issues
   - Stand and PPS Response Plots

5. Consider Medication State

6. Determine Therapy
   - Baseline Response Plot

---

*Figure 1: Summary of Six Steps to Interpretation*
congested sinuses, asthma, COPD, and emphysema. We have also seen a couple of cases where the breathing pattern looks like that of Cheyenne-Stokes Syndrome (Multiple System Atrophe). For these issues, treat the respiratory or pulmonary disorder to ease the patient’s ability to breath and re-test in eight weeks to titrate and consider the remainder of the ANS.

Hyperventilation is defined as an increase in FRF. So, as long as the FRF decreases (by 10% or more), then the test is considered valid and billable. For this issue, help the patient to relax, and re-test.

### The Final Check for QA

<table>
<thead>
<tr>
<th>Event</th>
<th>FRF''</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Baseline</td>
<td>0.36</td>
</tr>
<tr>
<td>B Deep Breathing</td>
<td>0.13</td>
</tr>
</tbody>
</table>

- From whatever their respiratory frequency (FRF) is at rest (A), there should be a significant decrease to deep breathing (B). The target is 0.1 to 0.15 Hz.
- If the FRF stays the same or increases it maybe due to hyperventilation (rather than relaxational deep breathing) which is a sympathetic challenge and defeats the purpose of the challenge

Ansar/jc

**Figure 2:** Implications for Fundamental Respiratory Frequency (FRF) out of range.

**Excessive Ectopy**

Occurrence of ectopy is recorded throughout the test. Ectopic beats can be isolated, one or two at a time, or can form patterns, three or more in sequence. If there are less than three in
sequence, the FDA permits a correction for them by approved interpolation methods. If there are three or more they cannot be corrected and must be presented. When presented they effect the results by artificially inflating the corresponding ANS results so as to make those results unintelligible. So there are two issues at hand here: ectopic beats throughout the entire test and ectopic beats isolated to one or two of the clinical study segments (see Figures 3 & 4). Both will be addressed here.

**Heart Rate Plot Determines how to Interpret the Results**

**Normal?** -or- **Abnormal?**

---

**Figure 3:** The difference between normal heart rate and ectopic heart beats throughout the test

Excessive ectopy is defined as more than 50 total ectopic beats (whether isolated and corrected or not) in the 15 minutes of the test. There are two issues with ectopy. First, the source of the ectopy can be muscle or other artifact. In this case, the test must be repeated. If it is due to some sort of arrhythmia, the test is still interpretable and billable, just not in the way the software was programmed. In general, the test with ectopic heart beats suggesting possible arrhythmia indicates that a 12-lead EKG needs to be ordered to determine the cause of the arrhythmia.
Then, after 8 weeks of intervention to clear the arrhythmia, re-test to read the ANS completely and then intervene for the ANS as appropriate.

**HR: How Abnormal?**

- Ectopy all the way through, or
- Spotty

Either way, test still provides clinically relevant information about both ANS branches and is billable under both CPT codes

*Ansar/jc*

**Figure 4:** The difference between ectopic heart beats throughout the test and isolated to a challenge

As a reminder, the test consists of six challenges, which are in order: 1) a five minute, resting, initial baseline, 2) a one minute parasympathetic challenge of paced, rhythmic, deep breathing, 3) a one minute (second) baseline – the Valsalva baseline, 4) a 1:35 minute Valsalva challenge which consists of a series of five short Valsalvas (no more than 15 seconds in duration) with short rests in between each, 5) a two minute (third) baseline – the stand baseline, and 6) a five minute postural change (stand) challenge which consists of a rapid change in posture, followed by approximately five minutes of quiet upright posture.

**Rule #2: Ectopy Throughout**
Ectopy throughout (see Figure 5) is defined as ectopy during the initial baseline and two or more of the challenges, or more, up to ectopy throughout the entire test as is typically seen in patients with atrial fibrillation. In this case, the only number in the test that has any clinical significance is the initial baseline LFa/RFa Ratio (yes, even if the initial baseline has ectopy in it as well). This number can help to differentiate whether or not there is a neurogenic (an autonomic) component to the ectopy (arrhythmia):

- If the baseline ratio is normal (between 0.4 and 3.0) then there is no autonomic component to the ectopy. Treat as usual.

### Abnormal HR

- Artificially inflates ANS (LFa & RFa) values
- If all the way through:

  - In these cases other physicians have found that the only valid value is the initial baseline (resting) Ratio

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<th>RFa+</th>
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<td>A Baseline</td>
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<tr>
<td>B Deep Breathing</td>
<td>72.98</td>
<td>80.23</td>
<td>0.91</td>
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<tr>
<td>C Baseline</td>
<td>237.17</td>
<td>215.85</td>
<td>1.10</td>
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<tr>
<td>D Valsalva</td>
<td>157.37</td>
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</tr>
<tr>
<td>E Baseline</td>
<td>37.94</td>
<td>168.03</td>
<td>0.23</td>
</tr>
<tr>
<td>F Stand</td>
<td>59.86</td>
<td>176.66</td>
<td>0.34</td>
</tr>
</tbody>
</table>

**Figure 5**: Interpretation of a ANS test with ectopy throughout. Note the Heart Rate plot (the Cardiogram) is shown in Figure 4. Here the resulting Trends plot is presented.
• If the value of the Ratio is high (greater than 3.0) then there may be a sympathetic component to the ectopy. Treat with sympathetic blockade (adrenergic antagonist; e.g., Beta blocker, ACE-I, ARB, or Calcium Channel Blocker) and re-test in eight weeks to titrate and consider the remainder of the ANS.

• If the value is low (less than 0.4) then there may be a sympathetic component to the ectopy. Treat with parasympathetic blockade (cholinergic antagonist; e.g., Tricyclic Anti-depressant) and re-test in eight weeks to titrate and consider the remainder of the ANS.

As an example, we have data from a 76 year old female who had a ten year history of atrial fibrillation with Digoxyn therapy onboard. When we first tested her, he baseline ratio was 0.38, with over 300 ectopic beats. We added 10 mg Nortriptyline in the evening and retested in eight weeks to titrate and consider the remainder of the ANS. Her second test showed no ectopy and a 12-lead EKG showed normal sinus rhythm. She was given a full cardiac work-up which returned negative. She remains on a maintenance level of Digoxyn and the Nortriptyline was weaned after nine months to ensure that the autonemics stabilized.

**Spotty Ectopy**

Due to the design of the clinical exam, ectopy in specific sections of the test still provide clinically relevant information, and as a result, enable billing for the test. The sections discussed below can be taken in any combination. Ectopy can be identified in the Heart Rate (HR) graph (the cardiogram) on the Multi-Parameter Graphical Report, or it can be identified as an abnormally high computed HR range (‘rangeHR’ equal to maximum heart beat interval minus the minimum heart beat interval during that phase of the exam) from the ANS Test Results Report. Normal for ‘rangeHR’ is between 15 and 50 beats per minute for all phases of the clinical exam.

**Rule #3: Ectopy At The Very Beginning Of The Test**

Ectopy at the very beginning of the test typically indicates “White Coat Hypertension” or its pre-clinical form, especially if there is no ectopy anywhere else (see Figure 6). Here ectopy can be indicated as spike activity on the cardiogram (HR graph) or as the ‘rangeHR’ greater than 50 for the initial (resting) baseline. White coat hypertension is also confirmed by a blood pressure pattern throughout the test that constantly decreases without regard to the expected changes due to the various challenges.

Treat for the mild hypersympathetic condition, retest in eight weeks to titrate and consider the remainder of the ANS. Meanwhile, to read the rest of the test with ectopy only in the initial baseline, use an average of the other two baseline periods to estimate what the initial baseline would have been without the ectopy. Then re-assess the ANS Test Results with this more appropriate baseline. Typically, the software should compute this average, indicate this action, and interpret the results accordingly.

**Rule #4: Ectopy During Deep Breathing or Stand Baseline**

Deep breathing is a parasympathetic challenge (if performed correctly, see FRF Out of Range). Stand Baseline is also considered an parasympathetic stimulus in that it typically includes a parasympathetic rebound from the sympathetic challenge of Valsalva. Although the deep breathing challenge is typically the stronger of the two. Ectopy during either of these periods can indicate that there is a parasympathetic trigger to the ectopy (see Figure 7). Here ectopy can
be indicated as spike activity on the cardiogram (HR graph) or as the ‘rangeHR’ greater than 50 for the deep breathing period. If this is the case, treat the hyper-parasympathetics (possibly with a Tricyclic – using its anti-cholinergic side-effect) to clear the ectopy. Re-test in eight weeks to titrate and consider the remainder of the ANS. Meanwhile, if this is the only segment of the test presenting ectopy, the rest of the test can be read according to the software.

Abnormal HR

- If the initial baseline (A) contains the abnormality, use one, or the other, or the average, of the two other baselines for comparison and read the test as usual

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<td>9</td>
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6 Oct 05

Figure 6: Spotty ectopy at the beginning of the clinical exam suggests possible "white coat hypertension syndrome"
Abnormal HR

- If the deep breathing (B) contains the abnormality then the patient’s parasympathetic nervous system, when stressed can induce arrhythmia
- This can be corrected with cholinergic-antagonists

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Figure 7: Spotty ectopy during the deep breathing portion of the clinical exam suggests a possible parasympathetic trigger to the ectopy. There can also a parasympathetic rebound after the Valsalva challenge (during stand baseline). Ectopy here can also suggest a possible parasympathetic trigger.

Rule #5: Ectopy During Valsalva or Valsalva Baseline

Valsalva is a sympathetic challenge. Valsalva Baseline is also considered an sympathetic stimulus in that it typically includes a sympathetic rebound from the parasympathetic challenge of deep breathing. Although the Valsalva challenge is typically the stronger of the two. Here ectopy can be indicated as spike activity on the cardiogram (HR graph) or as the ‘rangeHR’ greater than 50 for the Valsalva period. Ectopy during either of these periods can indicate that there is a sympathetic trigger to the ectopy (see Figure 8). If this is the case, treat the hyper-sympathetics (possibly with a Beta-blocker, ACE-I, ARB, or Calcium Channel Blocker) to clear the ectopy. Re-test in eight weeks to titrate and consider the remainder of the ANS. Meanwhile,
Abnormal HR

- If the Valsalva (D) period contains the abnormality then the patient’s sympathetic nervous system, when stressed can induce arrhythmia
- This can be corrected with adrenergic-antagonists

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<td>6.54</td>
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**Figure 8**: Spotty ectopy during the Valsalva portion of the clinical exam suggests a possible sympathetic trigger to the ectopy. There can also be a sympathetic rebound after the deep breathing challenge (during Valsalva baseline) Another sympathetic stimulus is during the stand challenge, especially during the initial gravitational response and later after the exercise reflex is over (see also Rule #6 and Figures 9 & 10). Ectopy during any of these periods can also suggest a possible sympathetic trigger.

if this is the only segment of the test presenting ectopy, the rest of the test can be read according to the software.

**Rule #6: Ectopy During Stand**

Stand is also a sympathetic challenge, but there are two periods of interest during the stand challenge: 1) immediately upon assuming an upright posture, and 2) after about two or three minutes of quiet upright posture (see Figure 9). The former reveals the immediate sympathetic
Abnormal HR

- If the stand period (F) contains the abnormality then gravitational challenges can induce arrhythmia and the patient probably has postural tachycardia syndrome (POTS)

- This can be corrected by treating the Orthostasis

**Figure 9**: Spotty ectopy two to three minutes into the stand portion of the clinical exam suggests a possible sympathetic trigger to the ectopy and after the exercise reflex is over when the sympathetics are expected to help constrict the vasculature in the lower extremities. Therefore, this particular placement of ectopy suggests possible postural orthostatic tachycardia syndrome (POTS).

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<td>93</td>
<td>717.99</td>
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response to gravity. If there is ectopy here is usually accompanied by ectopy during the stronger Valsalva maneuver. The latter reveals the sympathetic response to the end of the exercise reflex when a sympathetic surge is expected to help maintain venous sufficiency. Here ectopy can be indicated as spike activity on the cardiogram (HR graph) or as the ‘rangeHR’ greater than 50 for the stand challenge. If ectopy occurs only during the gravitational response, then see Rule #5.

The opposite of a sympathetic surge is a sympathetic withdrawal. This is abnormal. So, if venous insufficiency should result, the heart may have to work harder to maintain proper blood flow to the brain. During this time of stress, ectopy can occur. If this is the case, treat for
Postural Orthostatic Tachycardia Syndrome (POTS) by considering an sympathetic stimulant (an alpha-adrenergic agonist), re-test in eight weeks to titrate to read the remainder of the test. Meanwhile, if this is the only segment of the test presenting ectopy, the rest of the test can be read according to the software.

Rule #7: Hyperactivity in the Deep Breathing Response

The deep breathing response plot shows the parasympathetic (Vagal or RFa) response to the deep breathing challenge. If this response is abnormally high, it can also indicate respiratory or pulmonary issues (see Figure 10). Treat the parasympathetic excess with anti-cholinergics or adrenergic stimulants.

Parasympathetic Response to Deep Breathing

- Indicates ANS dysfunction
- If all others are normal, suggests earliest onset of peripheral autonomic neuropathy [AAN, 2004]

• Possibly indicates respiratory difficulties or early onset of parasympathetic excess

Figure 10: Hyperactivity in the parasympathetic response to deep breathing indicates the early onset of parasympathetic excess and can suggest possible upper respiratory or pulmonary difficulties.
Rule #8: Hyperactivity in the Valsalva Response

The Valsalva response plot shows the sympathetic (LFa) response to the Valsalva challenge. If this response is abnormally high, it can indicate pre-clinical or clinical hypertension issues (check resting blood pressure to determine if clinical or not; see Figure 11). Treat the sympathetic excess with sympathetic blockade. Note if paradoxic-parasympathetic syndrome (PPS) presents central sympathetic blockade is recommended.

Sympathetic Response to Valsalva

- Low
  • Indicates moderate ANS dysfunction, including late peripheral autonomic dysfunction

- Normal
  • Suggests pre-clinical hypertension if BP is normal or underlying cause if BP is high

- High
  • If PPS, hypersympathetics are secondary

Figure 11: Hyperactivity in the sympathetic response to Valsalva indicates the early onset of sympathetic excess and can suggest possible clinical or pre-clinical hypertension.

Rule #9: Hypoactivity in Either the Deep Breathing or Valsalva Response

Hypoactivity in the deep breathing plot (see Figure 10) tends to occur first followed by hypoactivity in the Valsalva response (see Figure 11). The former alone suggest the earliest
onset of autonomic dysfunction. This is listed as “mild acute ANS dysfunction” on the Recommended Therapy Options report (see Appendix III). The two together suggest moderate acute ANS dysfunction (as indicated on the Recommended Therapy Options report).

**Syncope**

Syncope is another cause of dizziness. Syncope is differentiated from Orthostasis as a heart muscle (cardiogenic syncope) or the nerves controlling the heart muscle (neurogenic syncope) issue versus a venous (vascular insufficiency) or the nerve controlling the veins (sympathetic withdrawal) issue. Venous issues are indicated by sympathetic withdrawal.

Syncope is indicated by more of a sympathetic response to stand than that to Valsalva (see Figure 12). In other words, if in the Trends plot (in the absence of ectopy) the peak sympathetic response to stand is equal to or greater than the peak sympathetic response to Valsalva Syncope is present. Normally, the ratio of these two peaks are 3:1 or greater (peak Valsalva response to peak stand response). If this ratio is less than 2:1 (including negative or reversed) then Syncope is indicated. Physiologically, it should not take more sympathetic activity to stand than it does to perform a Valsalva.

**Rule #10: Cardiogenic Syncope**

If syncope presents and the change in heart rate from rest to stand is normal, then the nerves are functioning but the heart is not. This suggests cardiogenic syncope. Treat the sympathetics based on patient history. Re-test in eight weeks to titrate and consider the remainder of the ANS.

**Rule #11: Neurogenic Syncope**

If syncope presents and the change in heart rate from rest to stand is abnormally low, then the nerves are not functioning. This suggests neurogenic syncope. Treat with current syncope therapy. Re-test in eight weeks to titrate and consider the remainder of the ANS.

**Rule #12: Vasovagal Syncope**

If the peaks of the Trends plot are less than 5 bpm², then the RFa column in the Table at the bottom of the Multi-Parameter Graphical Report should be consulted. If four of the six measures are greater than the sympathetics, or three are and PPS is present, then Vasovagal Syncope is indicated. Treat with current syncope therapy and consider anti-cholinergic therapy if not already.

**Structural ANS Deficits**

The above issues have focused on functional ANS deficits. They assume that the ANS is still functional just not functioning normally. Therefore, the deficits can be treated with pharmaceutical therapies, lifestyle modifications, exercise, diet and the like. Structural deficits are indicated when the onset of neuropathy presents. This includes symptoms of gastrointestinal upset (e.g., GERD, Irritable Bowel Syndrome, Diarrhea, or Constipation), or bladder control problems, or sexual dysfunction (these three help to define quality of life), slow wound healing, etc.
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

Figure 12: Syncope can be detected by the pattern in the Trends Plot. It is nonsensical for the system to require more sympathetic activity to stand as compared to performing Valsalva maneuvers. Once Syncope is detected, the cardiogenic and neurogenic forms are differentiated by considering the heart rate. If heart rate increases upon standing as expected (the nerves are working) is must be cardiogenic. If heart rate does not increase normally, the it must at least be neurogenic. This finding correlates with positive tilt-studies in more than 95% of the patients tested using both measures.

Rule #13: If Autonomic Neuropathy Presents Treat Structural Deficits

For peripheral autonomic neuropathy, diabetic autonomic neuropathy or cardiac autonomic neuropathy, treat with current therapy. Also, alpha-lipoic acid has shown some effect, especially early when its anti-oxidant behavior may help protect the nerves. Prophylactic application, after chronic disease has been diagnosed and before autonomic neuropathy presents, of alpha-lipoic acid has also shown some benefit.
Rule #14: Critically Low Parasympathetic Activity Levels

Parasympathetic levels are indicated by the RFa measure. The RFa equal to 0.1 bpm\(^2\) level is determined as the mathematical equivalent to the Framingham Heart Study threshold for high risk of sudden cardiac death (see Figure 13). For acute patients (post-MIs and post-CABGs) the same five year time course can be followed. For chronic patients, it has been found that these patients are chronically at risk as long as the RFa remains below 0.1 bpm\(^2\). In these cases, treat the lack of parasympathetic protection for the heart (protection from sustained tachycardia and worse) with sympathetic blockade. This should return the RFa to greater than 0.1 bpm\(^2\) (or at least cause the RFa to be greater than the LFa – in this case the Ratio could be between 0.4 and 1.0 as recommended for geriatrics with heart disease). Re-test in eight weeks to titrate and consider the remainder of the ANS.

AN EXAMPLE OF THE UTILITY OF THE CURRENT ANS MEDICATION STATE CHART

Consider the Val Heft study which states that 35% of level III and level IV (on the New York scale) congestive heart failure (CHF) patients on the recommended triple adrenergic blockade are over blocked. In this cohort, the results of this triple blockade is that the patient reports excessive fatigue and secondary syndromes related to (relatively) excessively high parasympathetic levels (e.g., upper- and lower-GI upset, bladder and sexual dysfunction). Furthermore, cardiac patients are typically treated with anti-depressants as recommended. Let us assume for the sake of this illustration that it is a Tricyclic Anti-depressant (e.g., Amitriptyline or Nortriptyline). The net, general ANS influence of three adrenergic antagonists and one cholinergic antagonist (the anti-cholinergic “side-effects” of the Tricyclic) is the influence of two adrenergic antagonists. This is indicated in Figure 14.

To continue this illustration, there are three possible results from the CHF therapy considered above:

- The resting state is in balance or normal: If the patient’s (resting) initial baseline response indicates normal (point A is in the gray area, Area 7 in Figure 13) or the resting sympathovagal balance (the resting LFa/RFa ratio) is in range (normal is between 0.4 and 3.0) as indicated by point A in Figure 13 being near the diagonal broken line, the therapy and dosage is appropriate for that patient.

- The resting state is out of balance with abnormally high sympathetic levels: If the resting response indicates sympathetic dominance (point A in Figure 13 is in either area 2, 4 or 6) then the results suggest that there is not enough adrenergic blockade on board. Titrating the dosage higher or adding more adrenergic blockade (in the form of ACE-Is, ARBs, or calcium channel blockers) will help to normalize the patient’s resting response (bring the sympathovagal balance, the LFa/RFa ratio, into the normal range).

- The resting state is out of balance with abnormally high parasympathetic levels: If the resting response indicates parasympathetic (or Vagal) dominance (point A in Figure 13 is in either area 1, 3 or 5) then the results suggest that there is too much adrenergic blockade on board. Titrating the dosage lower or discontinuing one adrenergic blocker will help to normalize the patient’s resting response (bring the sympathovagal balance, the LFa/RFa ratio, into the normal range).
Figure 13: Indications from the initial baseline analysis. This includes indications of cardiac stress (areas 5 & 6 from this figure), areas of parasympathetic excess (area 3), and areas of sympathetic excess (area 4). The area below the line RFa = 0.1 bpm$^2$ represents the high risk of sudden cardiac death region. For this the goal of therapy should be to get the RFa above 0.1 bpm$^2$ to protect the heart. This area also suggests cardiac autonomic neuropathy (CAN). The area just above this, between RFa = 0.1 bpm$^2$ and RFa = 0.5 bpm$^2$ suggests diabetic autonomic neuropathy (DAN) in patients with Diabetes Mellitus.
**Figure 14**: An example of a ValHeft qualified patient on triple adrenergic blockade and a Tricyclic anti-depressant. Correlate this figure with the initial baseline response plot presented in Figure 13. See text for details.

Note, if the patient is in area 2 or in area 4 below RFa = 0.1 bpm^2 of Figure 13 and the result of titration is only to place the patient in area 1 of Figure 13. This may be all that is possible due to the depleted nature of the patient’s ANS and the presence of CAN. Area 1 of Figure 13 is preferred over area 2 or in area 4 below RFa = 0.1 bpm^2 since it suggests that the patient has some remaining (relative) parasympathetic dominance to help to protect the heart; even if it is clinically induced.
APPENDIX I: THE SOURCE OF PATIENT VALUES IN THE RESPONSE PLOTS FROM THE ANX-3.0 GRAPH REPORT

Initial Baseline Response

- The Initial Baseline (Resting) Response plot
  - Displays resting tone or power in each ANS branch
    - Parasympathetic, RFa, or Vagal
    - Sympathetic or LFa
  - Displays balance between the two ANS branches
  - Indicates
    1. Effectiveness of therapy and medication
    2. Potential for arrhythmias
    3. Quantification of risk of sudden death

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Deep Breathing Response

- The Deep Breathing Response plot
  - Displays the (age adjusted) ability of the parasympathetic’s (RFa) to respond to a challenge
  - Too high indicates Hypervagotonia (possible respiratory distress)
  - Too low can indicate parasympathetic neuropathy

- If everything else is in normal range and this is still too low, this is now accepted as the earliest indication of peripheral autonomic neuropathy

<table>
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<th>RFa+</th>
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Valsalva Response

- The Valsalva Response plot
  - Displays the (age adjusted) ability of the sympathetic’s (LFa) to respond to a challenge
  - Too high indicates Hypersympathetics (possible cardiac distress)
  - Too low can indicate sympathetic neuropathy
Stand Response

- The Stand Response plot
  - Displays ability of both ANS branches to respond in a coordinated fashion
  - Indicates
    1. Sympathetic withdrawal = the physiologic definition of Orthostasis
    2. One component of Paradoxic Parasympathetic Syndrome

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<tr>
<td>F Stand</td>
<td>0.59</td>
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Paradoxic-Parasympathetic Response

- PPS is defined as an abnormal increase in parasympathetic activity in response to a sympathetic challenge (Valsalva and Stand)
  - Valsalva: an RFa increase > 100% (2x)
  - Stand: and RFa increase > 10%

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APPENDIX II: AUTOMATED SIX STEP INTERPRETATION FOR “NORMAL-ABNORMALS”

See file ‘INTERPRETATION.doc’
APPENDIX III: RECOMMENDED THERAPY OPTIONS REPORT

See file ‘TherapyOptionsH+.doc’

The therapy options, as well as the interpretation paradigm detailed in the text, are predicated on a knowledge-based developed from a data-base of 10,000 patient studies, including 3,000 patients studied longitudinally to validate the interpretation and confirm clinical efficacy of the therapy options.
APPENDIX IV: EXAMPLE NORMAL PATIENTS

Example normal patients from early childhood (3 years old) to later adult (60 years old).

Note the child and teenage, since they are still developing, have much higher parasympathetic activity throughout the test than do the normal adults.

Test Date: 6/8/01

Test Date: 7/3/01

Test Date: 10/9/01

Figure A4.1: An example of a normal 3 year old, male child.

Figure A4.2: An example of a normal 7 year old male child.

Figure A4.3: An example of a normal 13 year old female teenager.
Figure A4.4: An example of a normal 15 year old female teenager.

Figure A4.5: An example of a normal 21 year old female. Note that during the “transition years” patients can still look like teenagers, or as seen in Figure A4.6, like adults.

Figure A4.6: An example of a normal 18 year old female. Note that during the “transition years” patients can look like adults, or as seen in Figure A4.5, like teenagers.
Figure A4.7: An example of a normal 34 year old female adult.

Figure A4.8: An example of a normal 44 year old female adult.

Figure A4.9: An example of a normal 60 year old female adult.