IntelleWave is a fully automated cardiac monitoring device that provides quantitative assessment of the Autonomic Nervous System (ANS) on the basis of R-R interval variability and blood pressure analysis. The system is used to objectively confirm or exclude a Cardiovascular Autonomic Neuropathy (CAN), a Diabetic Autonomic Neuropathy (DAN), syncope, dizziness and other dysautonomia problems. It is able to distinguish between the early and late stages of autonomic neuropathy.

IntelleWave is distinguished by its accuracy and speed, high reliability and ease of operation. In addition, IntelleWave can provide up to 24 hours of “real-time” quantitative ANS assessment.

ANS status can be monitored in a variety of settings, i.e.:

- during anesthesia.
- in intensive care to see effectiveness of medication.
- using implantable devices.
- using ambulatory Holter – ANS status can be monitored during sleep studies to see the difference between “sleep time” and “awake time”.

The system provides instant assessment of QT-interval and ST-segment of the ECG data registered during the test (consisting of 448 QRS complexes), as well as complete interpretation of 2 tests – Orthostatic test and Valsalva maneuver combined with deep breathing. A variety of data collected during the test (R-R interval variability, blood pressure and ECG readings) enables clinicians to evaluate a patient’s ANS status.

Our system’s proprietary sophisticated algorithm based on artificial intelligence approach evaluates all components of the spectral analysis including shifting of these components during the test. The unique representation of results provided by IntelleWave allows physicians to recognize up to 81 different variations in the relationship between Sympathetic and Parasympathetic activities. The system uses Cartesian system of coordinates with high-frequency (HF) Parasympathetic intensity on the horizontal axis and low-frequency (LF) Sympathetic intensity on the vertical axis. The point of intersection is interpreted as the point of Autonomic Balance. The graphical image of this method is presented on the next page.

Please note that clinical decision about autonomic function can be made by combined analysis of HF(Parasympathetic) and LF(Sympathetic) relationship with blood pressure data.

An earlier version of the system was validated with excellent results by Columbia University.

### System Components

- PC-ECG wireless Acquisition Device or PC-ECG wire device.
- Automatic blood pressure-measuring device.
- Finger Pulse Oximeter.
- Mini notebook computer with integrated bluetooth and portable printer.
- ECG and R-R interval variability Analyzer Software for display, measurement and interpretation of test results.
Clusterization of the Autonomic Nervous System’s states

by Alexander Riftine, Ph.D
Common Reasons for Administering the ANS Test defined by American Medical Association

1. Presence of symptoms of Cardiovascular Autonomic Neuropathy (CAN) and/or Diabetic Autonomic Neuropathy (DAN).
2. Assessment and/or recognition of syncope.
4. Risk stratification of sudden cardiac death.

On the following pages please find samples of the test results and interpretations for the above mentioned cases and diagnoses.

Cardiovascular Autonomic Neuropathy (CAN) and Diabetic Autonomic Neuropathy (DAN)
The test is prescribed to a patient if symptoms of CAN or DAN are present.

The goal of administering the test in this case is to get objective data to confirm or exclude CAN or DAN diagnosis. Treatment protocol will depend on the stage of CAN.

The process of administering the test shall include the following steps:
- Prescribe the test only in the presence of CAN or DAN symptoms
- Use test results in clinical decision making
- Conduct a follow-up test to evaluate effectiveness of the prescribed treatment and make adjustments if necessary.

Guidelines for excluding CAN or DAN diagnosis
- The Parasympathetic level during Deep breathing in the Valsalva Maneuver Combined with Deep Breathing test is greater than +1 on the clusterization chart (see page 6).
  - The Valsalva Ratio is more than 1.7.
  - The 30/15 Ratio is less than 0.75.
  
  Note: The Valsalva Ratio and the 30/15 Ratio are calculated as a ratio of the minimum heart rate to the maximum heart rate during the Valsalva Maneuver and Orthostatic intervention.

Guidelines for Recognizing the CAN or DAN status
Guidelines for recognition of the early stage of CAN or DAN (see page 7):
- In the Orthostatic test and Valsalva Maneuver Combined with Deep Breathing test the PSNS level is -1 or -2 on the clusterization chart.
  - The Valsalva Ratio is less than 1.7.
  - The 30/15 Ratio is between 0.65 and 0.80.

Guidelines for recognition of the chronic stage of CAN or DAN (see pages 8-9):
- In the Orthostatic test and Valsalva Maneuver Combined with Deep Breathing test the PSNS level must be -3 or -4 on the clusterization chart.
  - The Valsalva Ratio is less than 1.3.
  - The 30/15 Ratio is more than 0.80.

Treatment protocol will depend on the test results. A follow-up test is administered upon completion of the course of treatment. Corrections in the treatment protocol can then be made based on results of the follow-up test.

Optimization of beta-blockers therapy
Side effects during use of beta-blockers are well known in medicine and described in the pharmaceutical guides. Therefore, the main problem related to beta-blockers therapy is optimization of use of different types of beta-blockers and their dosages.

While prescribing beta-blockers, physician is aiming to achieve not only clinical outcome, such as normalization of blood pressure and heart rate, but also take care of physiological aspect by optimizing the dose of beta-blockers in order to avoid side effects. Intellewave technology provides simple solution to help physicians to achieve such goals and avoid beta-blockers overdose.

To determine the optimal dose of beta-blockers, heart rate data is not sufficient, since it only indirectly provides information about the level of sympathetic activity. In order to confirm the case of overdose, it is essential for a physician to know not only the level of sympathetic activity, but also the level of parasympathetic activity.

Beta-blockers overdose exists only in case when the patient has low level of both sympathetic and parasympathetic activity (please refer to page 11 of the enclosed brochure to see the case of the patient with beta-blockers overdose). For instance, when a beta-blockers patient has low sympathetic activity (heart rate 45-50), but his parasympathetic activity is not lower than -1 (slight decrease of parasympathetic activity), such case cannot be qualified as overdose case. However, when a beta-blockers patient has sympathetic activity level from -2 to -4 and parasympathetic activity from -3 to -4, can be certainly confirmed as an overdose.

Intellewave system provides physician with objective quantitative information to confirm or exclude beta-blockers overdose case.
DEVICE CONFIGURATIONS

*Intellewave system 1.3* is available in two configurations:

1. **Intellewave Wireless**
   This option includes wireless BT3/6 bluetooth device produced by Corscience GMBX.

2. **Intellewave USB Connection**
   This option includes PC ECG device produced by Pulse Biomedical Inc.
INTELLEWAVE FEATURES

- Fully automated R-R interval variability analysis is performed without substantial human intervention.

**Three testing modalities are available:**
- Orthostatic intervention (lying-to-standing test) 7-8 min,
- Valsalva maneuver combined with deep breathing 7-8 min,
- Real-Time spectral analysis of R-R interval variability with clusterization of HF (Parasympathetic) and LF (Sympathetic) assessment (1 or 2 channels) up to 24 hours.

- Immediate results with automatic interpretation.

- ECG Graph with calculation of QT interval and ST segment. A compressed ECG tracing showing a continuous rhythm strip can be viewed at any time during the test. For convenience, the ECG rhythm strip is displayed on the screen. Additionally, one can select any section of this strip (e.g. a possible arrhythmic event) and retrieve full ECG readings for in-depth analysis of such event.

- Cluster Analysis of HRV: quantification and visual representation of relationships between High and Low Frequency components of R-R interval variability.

- Power spectral analysis of R-R interval variability; calculation of E/I Ratio, Valsalva Ratio, 30:15 Ratio and Heart Rate.

- Reliability of automatic HRV assessment was proved by Bland-Altman analysis with the Mean values of -0.07 for HF and -0.06 for LF and the Standard Deviation values of 0.77 for HF and 0.71 for LF.

- Patient data management capability, task selection, import/export of compatible database files.

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For accuracy of orthostatic intervention as well as for syncope prevention and/or recognition, optionally we include manual Tilt-Table as shown here.
Test Results to exclude CAN or DAN Diagnosis

Orthostatic test

Assessment of HRV changes during Orthostatic test

{| | Supine | Upright |
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<tbody>
<tr>
<td>BP</td>
<td>PP</td>
<td>MAP</td>
</tr>
<tr>
<td>120/80</td>
<td>40</td>
<td>100</td>
</tr>
</tbody>
</table>

Clusterization of High and Low Frequency Components

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<tr>
<th>HF/PSNS</th>
<th>LF/NSNS</th>
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<tbody>
<tr>
<td>0.63</td>
<td>1.5</td>
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</table>

CONCLUSION

SUPINE: HF/PSNS is decreased moderately while LF/NSNS is increased slightly
UPRIGHT: HF/PSNS is decreased significantly while LF/NSNS is increased moderately

Valsalva maneuver combined with Deep Breathing

Assessment of HRV changes during Valsalva Maneuver combined with Deep Breathing

{| | Normal Breathing | Deep Breathing |
<table>
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<tbody>
<tr>
<td>BP</td>
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<td>MAP</td>
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<td>130/80</td>
<td>50</td>
<td>105</td>
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<tr>
<td>135/90</td>
<td>40</td>
<td>112</td>
</tr>
</tbody>
</table>

Clusterization of High and Low Frequency Components

<table>
<thead>
<tr>
<th>HF/PSNS</th>
<th>LF/NSNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>2.4</td>
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</table>

CONCLUSION

NORMAL: HF/PSNS is decreased significantly while LF/NSNS is increased slightly
DEEP: HF/PSNS is increased significantly while LF/NSNS is increased sharply
Test Results of the early stage of CAN or DAN

Orthostatic test

Assessment of HRV changes during Orthostatic test

Valsalva maneuver combined with Deep Breathing

Assessment of HRV changes during Valsalva Maneuver combined with Deep Breathing
Test Results of the chronic stage of CAN or DAN

Orthostatic test

Assessment of HRV changes during Orthostatic test

Valsalva maneuver combined with Deep Breathing

Assessment of HRV changes during Valsalva Maneuver combined with Deep Breathing
Test Results of the chronic stage of CAN or DAN

Assessment of ANS functional state based on Heart Rate Variability analysis

Sympathetic activity is slightly elevated. Autonomic Nervous system activity is within the negative PSNS zone.

Deep breathing vs. Normal breathing shows no improvement by the Parasympathetic activity. Deep breathing vs. Normal breathing shows a slight decrease of the Sympathetic activity.

There is an evidence of significantly decreased sensitivity of Parasympathetic receptors. Deep breathing has slightly stabilized the Sympathetic function. There is a confirmation of the possibility of Cardiovascular autonomic neuropathy.

*Final decision can be made by combining with clinical data ONLY!
Risk Stratification for Primary SCD Prevention

Orthostatic test

Assessment of HRV changes during Orthostatic test

Valsalva maneuver combined with Deep Breathing

Assessment of HRV changes during Valsalva Maneuver combined with Deep Breathing
Overdose of beta-blockers

Orthostatic test

Valsalva maneuver combined with Deep Breathing

Assessment of HRV changes during Orthostatic test

Assessment of HRV changes during Valsalva Maneuver combined with Deep Breathing

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

Electrocardiographic Rhythm Strip

Clusterization of High and Low Frequency Components

CONCLUSION

IntellWave

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

Electrocardiographic Rhythm Strip

Clusterization of High and Low Frequency Components

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CONCLUSION
REAL-TIME HEART RATE VARIABILITY ANALYSIS
(every 2 - 4 minutes)
ORTHOSTATIC TEST-TO-TEST TRENDS OF HRV COMPONENTS
Additional information on Heart Rate Variability and Blood Pressure Analysis for Autonomic Nervous System testing and related issues

It has been shown in numerous published articles [1,2,3] that there is a high correlation (approximately 95%) between a high-frequency spectral function of R-R intervals variability and the PSNS activity and an almost 70% correlation between the low-frequency function of R-R intervals variability and the SNS activity. The remaining 30% of low-frequency activity relate to other regulatory mechanisms such as neuro-humoral, hormonal, thermoregulatory and baroreceptor mechanisms.

Thus, ANS activity cannot be fully assessed using HRV analysis alone. This challenge is addressed by combining HRV with blood pressure analysis since criteria for SNS confirmation by blood pressure response are well-known [4]. This solution is simple, and satisfies the American Medical Association requirements for ANS testing. However, in order to create reliable, reproducible and quantitative assessments, it is essential to consider the following:

**Method of data selection**

A majority of companies and scientific groups using HRV use the “5-minutes approach” as a method of data selection, but from the “Theory of Random Processes”, we learn that to make a statistical analysis of any random process we must take the same number of random events. This is one of the basic statements of the theory. In the case of HRV, the random event is the RR-interval. Each 5-minute set of such events consists of a different number of RR-intervals, even if it is the same person being tested in all measurements. As a result, those using the “5-minute” method, a “time-based” approach, can not get consistency and reproducibility for any HRV statistical analysis.

Currently, the only two other devices besides IntelleWave that use the “definite number of R-R intervals” as the data selection method are “HERO” and “ANSIscope”.

**Automatic detection of ectopic beats and artifacts to provide high quality HRV analysis**

Spectral analysis of R-R intervals is sensitive to any artifact or ectopic beat attained in the selected set of data. For instance, just one artifact in the center of the selected data segment dramatically increases the power of high frequency spectral function of R-R intervals variability making PSNS assessment completely wrong.

Most of companies who include HRV analysis in their product (all of the Holter-Monitors) provide artifact detection based on morphological analysis of ECG data which is very good for Holter application, but absolutely doesn’t work for HRV assessment in some clinical cases such as - “seek sinus syndrome” and complicated arrhythmias. For HRV assessment detection of artifact can be made only based on analysis different patterns of consecutive R-R intervals. During development of its algorithm, IntelleWave created >2000 patterns of relationships between consecutive R-R-intervals corresponding to different combinations of artifacts and ectopic beats. To organize the algorithm, IntelleWave used well-known Artificial Intelligence techniques actually the theory of Production that resulted in the development of fully automatic and highly accurate HRV assessment, unique to Intellewave.

**NOTE:** Instead of difficult automatic HF calculation in scientific literature we can find alternative solution to the problem of Autonomic assessment [5], which involves the use of two types of measurements as follows:
1. Traditional Spectral analysis of R-R interval variability (mostly for LF assessment, which is much easier than HF calculation) and
2. Respiration measurement to locate the frequency band of parasympathetic activity.

Physiologically this approach is based on the correlation of “breathing waves”, measured as respiration frequency, with the PSNS activity. This correlation does exist during spontaneous breathing but only in absolutely healthy subjects and is useful in fields such as Air Force and Navy but completely not applicable for patients with abnormal breathing and the elderly.

In matter of fact Dr. Cohen [9] suggests to use combination of HRV and respiration as an economical way to avoid difficult automatic HF calculation.

**Method of Spectral analysis of RR-intervals variability (Fourier transform) with the most effective mathematical filter to amplify High and Low-frequency components**

In the scientific literature we can find references on the “gold standard” in HRV analysis—the “Chronos algorithm” [1].

The IntelleWave algorithm (previous name Nerve Express) was validated at Columbia University with excellent agreement between the Nerve-Express algorithm and the “Chronos algorithm” which contains the best method of filtering HF and LF components.

**Sophisticated graphical clusterization of the relationship between High-Frequency (HF) and Low-Frequency (LF) components of HRV**

This stage has been developed to make the method useful not only for researchers but also for practitioners [6,7].

IntelleWave has done this by developing a proprietary algorithm based on Artificial Intelligence methods, in particular the Marvin Minsky’s Frame Theory.

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**Additional Advantages of Intellewave method**

Some of commercially available devices to assess CAN and DAN use just 3 very popular indices:

1. 30/15 ratio (after orthostatic intervention)
2. Valsalva Ratio (after Valsalva maneuver)
3. E/I Ratio (after Deep breathing)

**30/15 Ratio.** The main idea of this parameter is based on the theoretical suggestion that when a patient changes position from supine to upright, the highest heart rate will be on the 15th heart beat and the lowest heart rate will be on the 30th heart beat after the patient stands up (see Figure 1 below).

![Figure 1](image1)

**NOTE:** Each vertical line on this figure is corresponding to the time interval between consecutive heart beats.

Physiology of this parameter is well-known and is described in scientific literature [8].

The transition period between supine and upright is subdivided into 2 phases as shown in Figure 2 below.

![Figure 2](image2)

1st phase of transition from the moment of standing up to HR (max) – minimum R-R interval is highly correlated with the adaptation reserve of the myocardium [8] and is calculated as HR(Max)/HR (supine) ratio.
2nd phase is theoretically a 30/15 Ratio, but practically it must be calculated as a ratio of HR (min)/HR (max) or RR (max)/RR (min), because the possibility to match Heart Beat #15 with HR (max) and #30 with HR (min) can be just one of thousands of cases. Therefore, if we calculate 30/15 Ratio exactly as HR on beat 30 over HR on beat 15 we will never get an accurate assessment.

From a physiologic standpoint this ratio is consistent with a compensation response by the peripheral vascular system when a patient stands up. This parameter is, for example, very important for a patient with diabetic autonomic neuropathy (DAN).

NOTE: A simple calculation of 30/15 ratio as HR (min)/HR (max) is possible only when there is a previously completed detection of artifacts and ectopic beats in the transition period segment of R-R intervals. Intellewave solves this problem with its special approach to artifact detection during the transition period.

**Valsalva Ratio**

The classic response of heart rate during a Valsalva maneuver is to go up. As a result, R-R intervals become shorter and the Rhythmicographic strip begins to curve downward (see Figure 3 below).

After completing a Valsalva maneuver the heart rate slows down, the R-R intervals become longer, and the curve starts to go up. Valsalva ratio here is calculated as HR (max)/HR (min). However, in about 25-35% of cases humans demonstrate an opposite response [8]. At the beginning, the heart rate slows down and later increases (see Figure 4 below).


5. Benhur Aysin, Elif Aysin “Effect of Respiration in Heart Rate Variability (HRV) analysis.

