INTELLEWAVE

Heart Rate Variability Testing With Clusterization of Spectral Function Components

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INTELLEWAVE INC.

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Intellewave HRV System is a fully automated cardiac monitoring device that provides real-time quantitative assessment of Heart Rate Variability analysis.

Intellewave System HRV testing allows physicians to monitor physiological activity and assess the state of a patient's autonomic status through analysis of Spectral Function Components of R-R intervals Variability. On the one hand, HRV testing with Intellewave System enables a physician to detect specific types of autonomic dysfunction linked to a multitude of clinical diagnoses. On the other hand, Intellewave System is a tool for overall, general assessment of patient's physiology, and as a physiologic monitor it provides a comprehensive, in-depth patient evaluation, which standard medical practice is often missing. Such an ability to assess patent's physiology determines the wide range of Intellewave system clinical applications and distinguishes it favorably from all other diagnostic devices based on analysis of Integrated low-frequency (LF) and Integrated high-frequency (HF) components.

Intellewave System's proprietary algorithm (US Patent 7,826,892 B2) uses novel artificial intelligence techniques to provide clusterization of Integrated HF and Integrated LF components of spectral function. This unique representation of test results allows physicians to recognize up to 81 variations of the relationship between Integrated LF and Integrated HF components. For visualization of test results Intellewave system uses Cartesian system of coordinates with high-frequency (HF) intensity on the horizontal axis and low-frequency (LF) intensity on the vertical axis.

NOTE: *The final decision about autonomic function can be made only by a physician and is based on the combined analysis of HF and LF relationships, and blood pressure data.*

The system includes Electrocardiogram and Blood pressure measuring device. A variety of data collected during the test (HRV, blood pressure and Electrocardiogram readings) enables doctors to evaluate (more accurately) patients' Autonomic Nervous System activity/status. The Intellewave system is distinguished by its high accuracy, speed and reliability, and is very easy to operate.

An earlier version of the Intellewave HRV System was validated with excellent results by Columbia University studies in 1998, 1999 and 2001.

System Components

- ECG wired USB device or optionally wireless Acquisition Device.
- Automatic USB connected blood pressure-measuring device.
- Computer with integrated Bluetooth and a portable printer.
- ECG and R-R interval variability Analyzer Software

DEVICE CONFIGURATIONS:

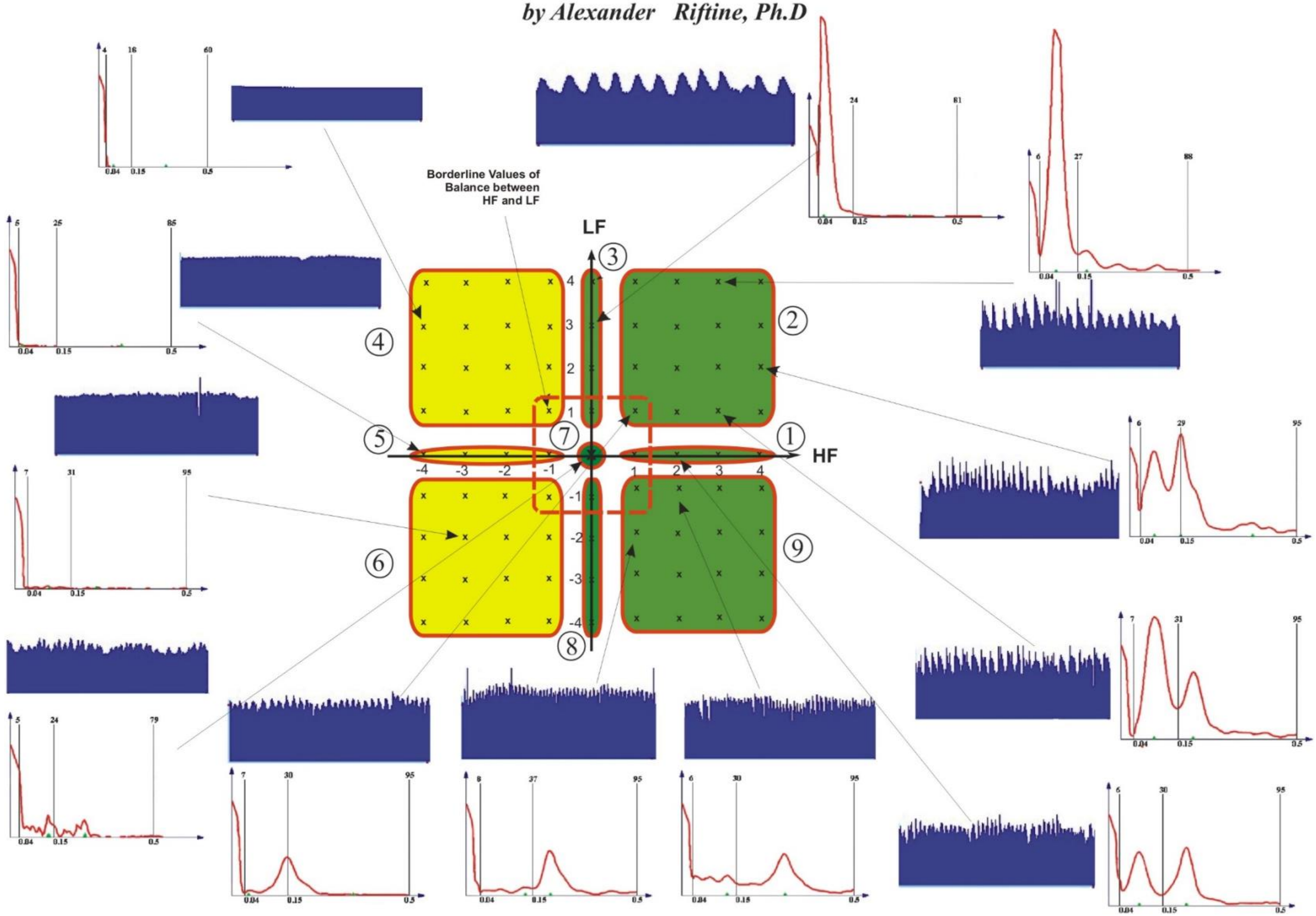
Intellewave system 1.5 included:

1. Lap-top computer with preinstalled software of ECG and R-R intervals variability analysis;
2. PBI QRS-card ECG device with optionally USB or Bluetooth wireless connections;
3. Fully automatic USB connected Blood Pressure device Meditech ABPM-05.

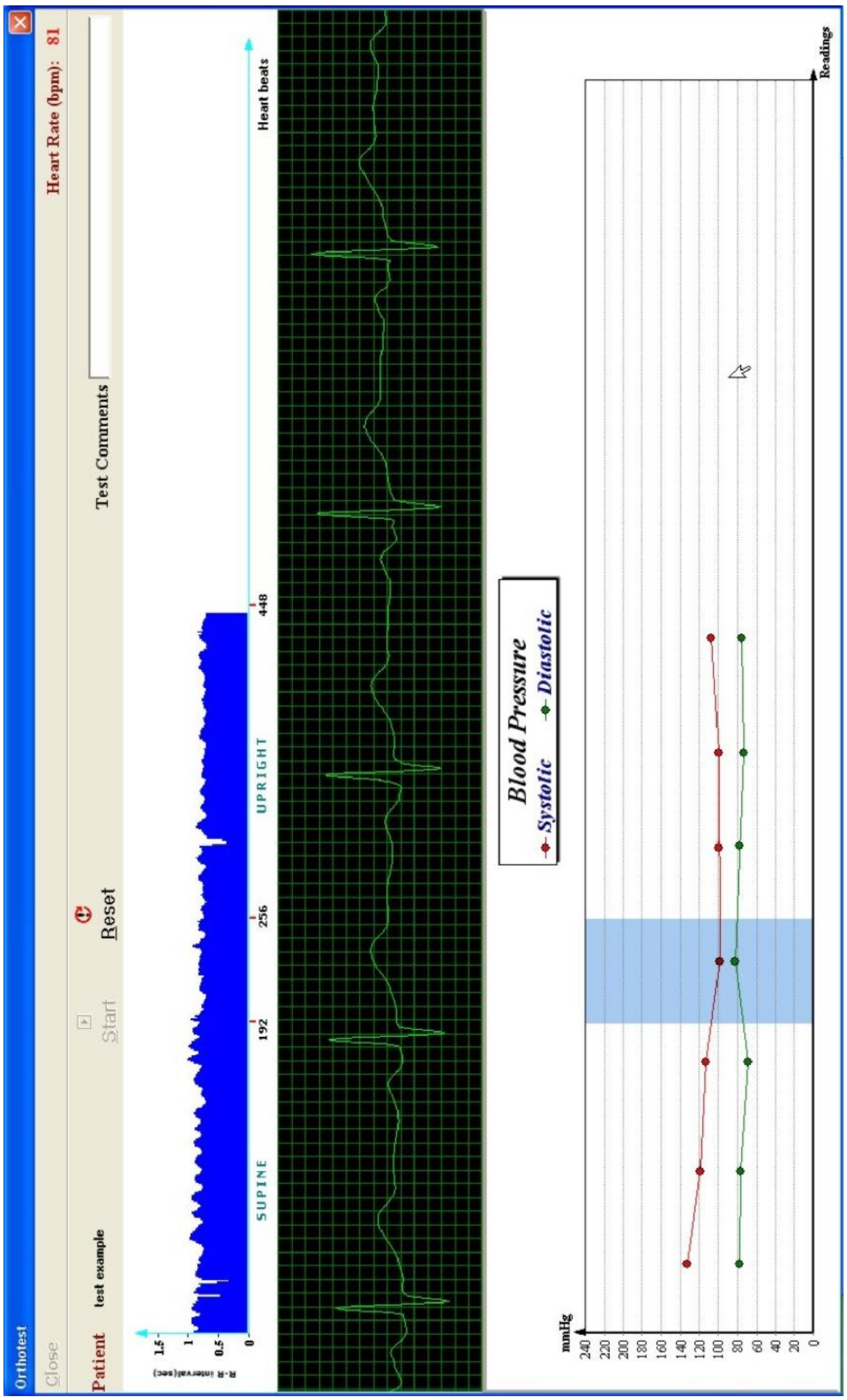
System configuration.

Clusterization of the High and Low frequency components of HRV

by Alexander Riftine, Ph.D



Data input visualization (ECG, R-R intervals variability, Blood Pressure) during the HRV test.

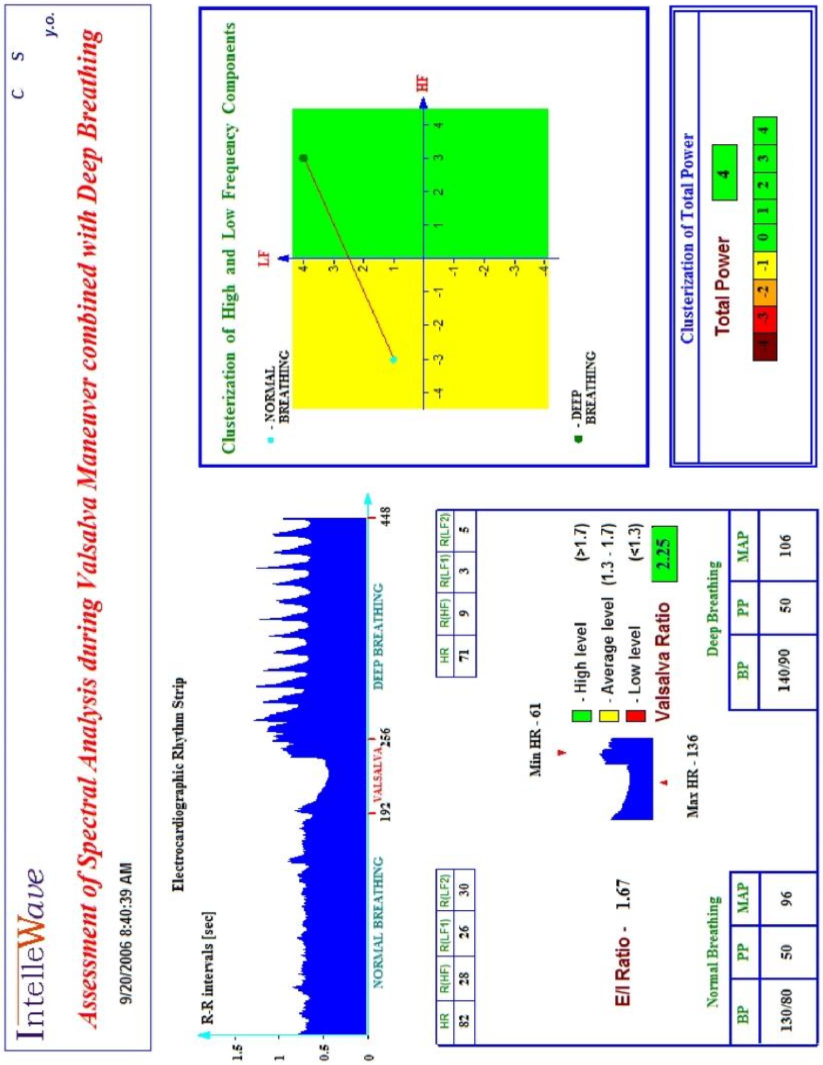


In the medical field Intellewave System is used by physicians to objectively confirm or exclude cases of Cardiovascular Autonomic Neuropathy (CAN), Diabetic Autonomic Neuropathy (DAN) and other diseases or malfunctions of the Autonomic Nervous System (ANS). For example, information provided by Intellewave system gives a physician an ability to recognize cases of Beta-Blockers overdose or Risk of Sudden Cardiac Arrest. Moreover, the new version 1.5 includes Real-Time Autonomic assessment during Tilt-Table testing. Intellewave System can also monitor ANS activity by a "real-time" (up to 24 hrs) quantitative assessment of Spectral function components.

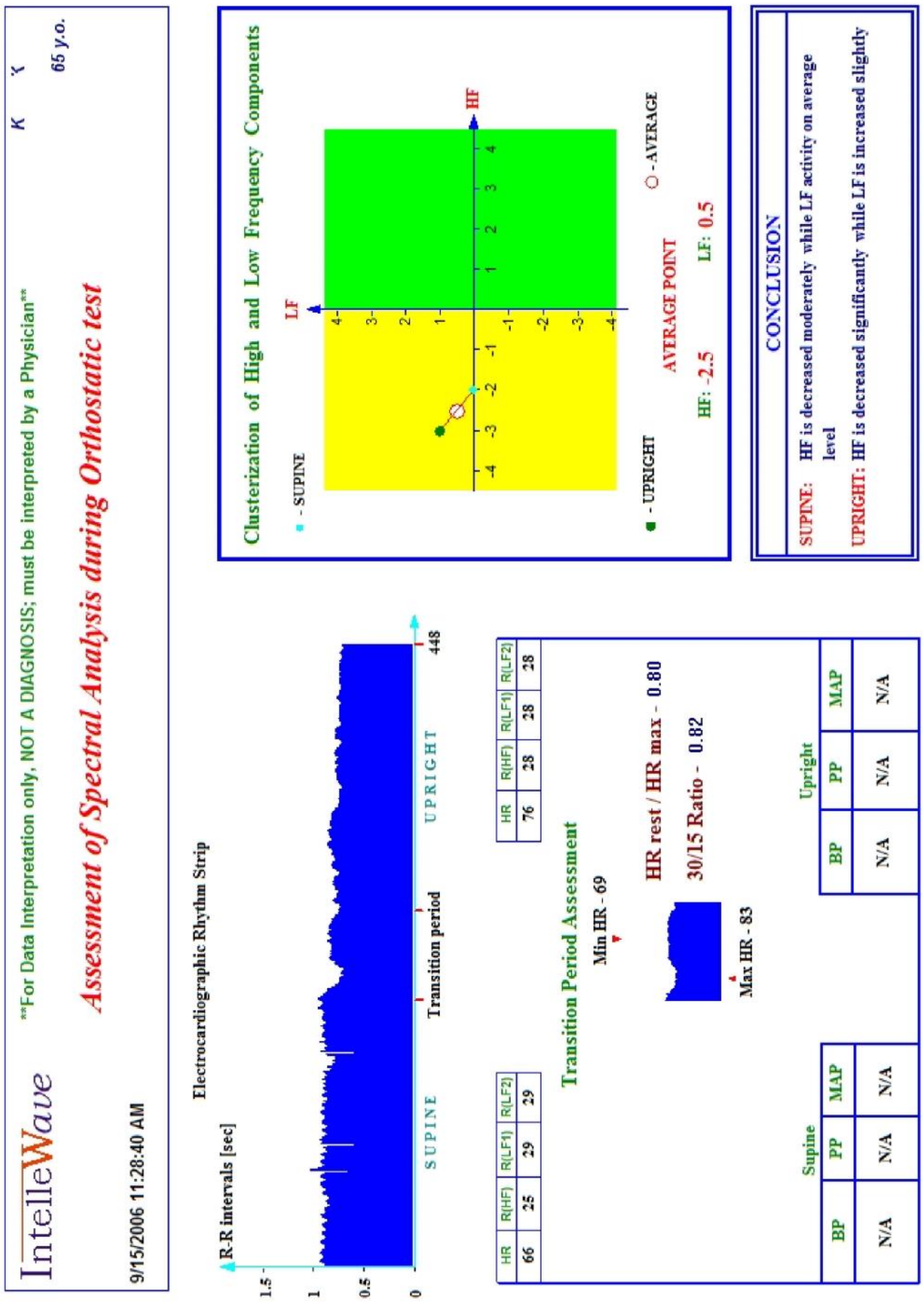
NOTE: *All clinical correlations of HRV analysis data is made by a physician only*.

Below you can find some samples of different clinical cases:

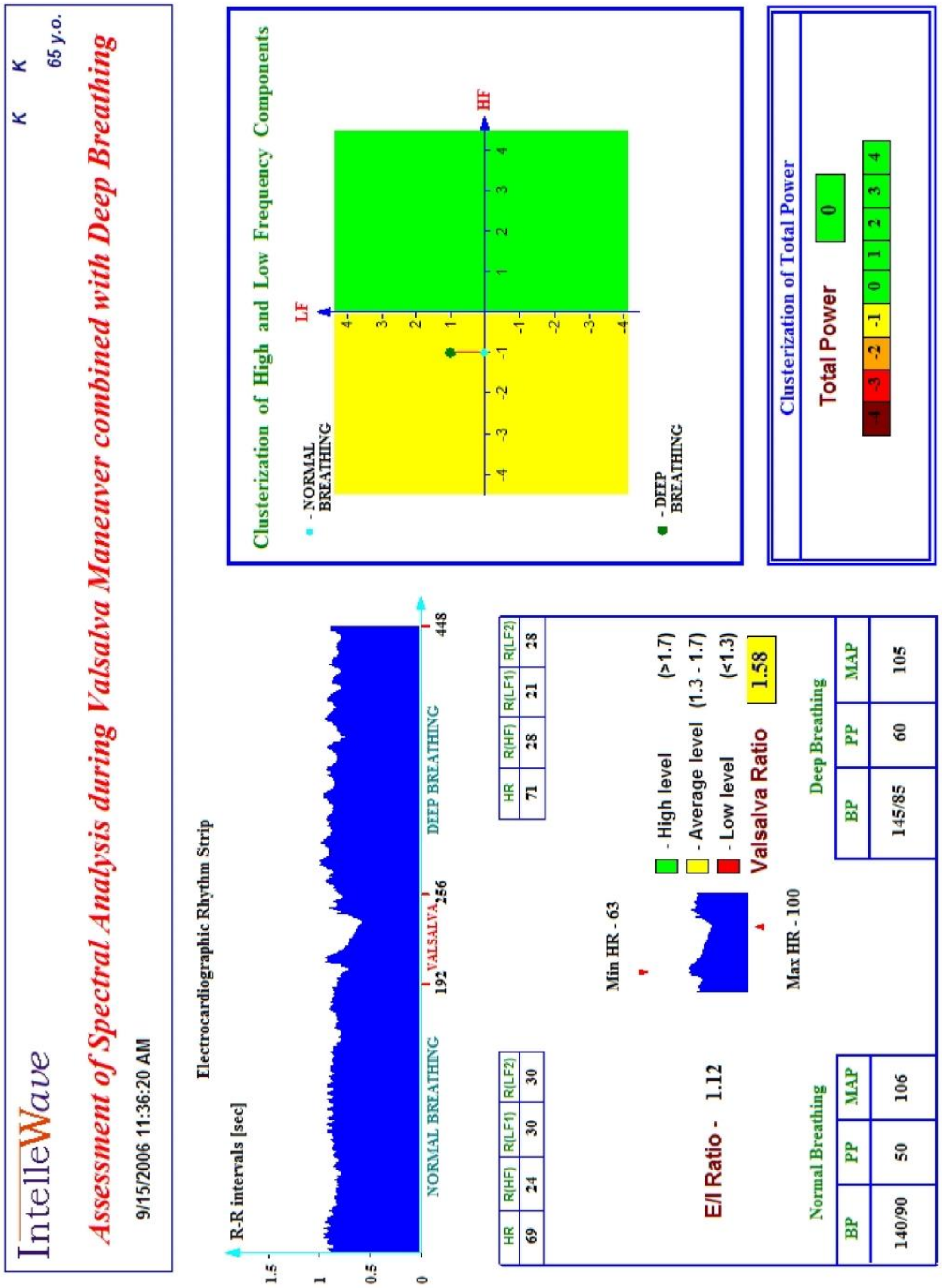
1. <u>Example of excluding CAN Case (Cardiovascular Autonomic Neuropathy)</u> during Valsalva maneuver combined with Deep Breathing you can see on a picture below.



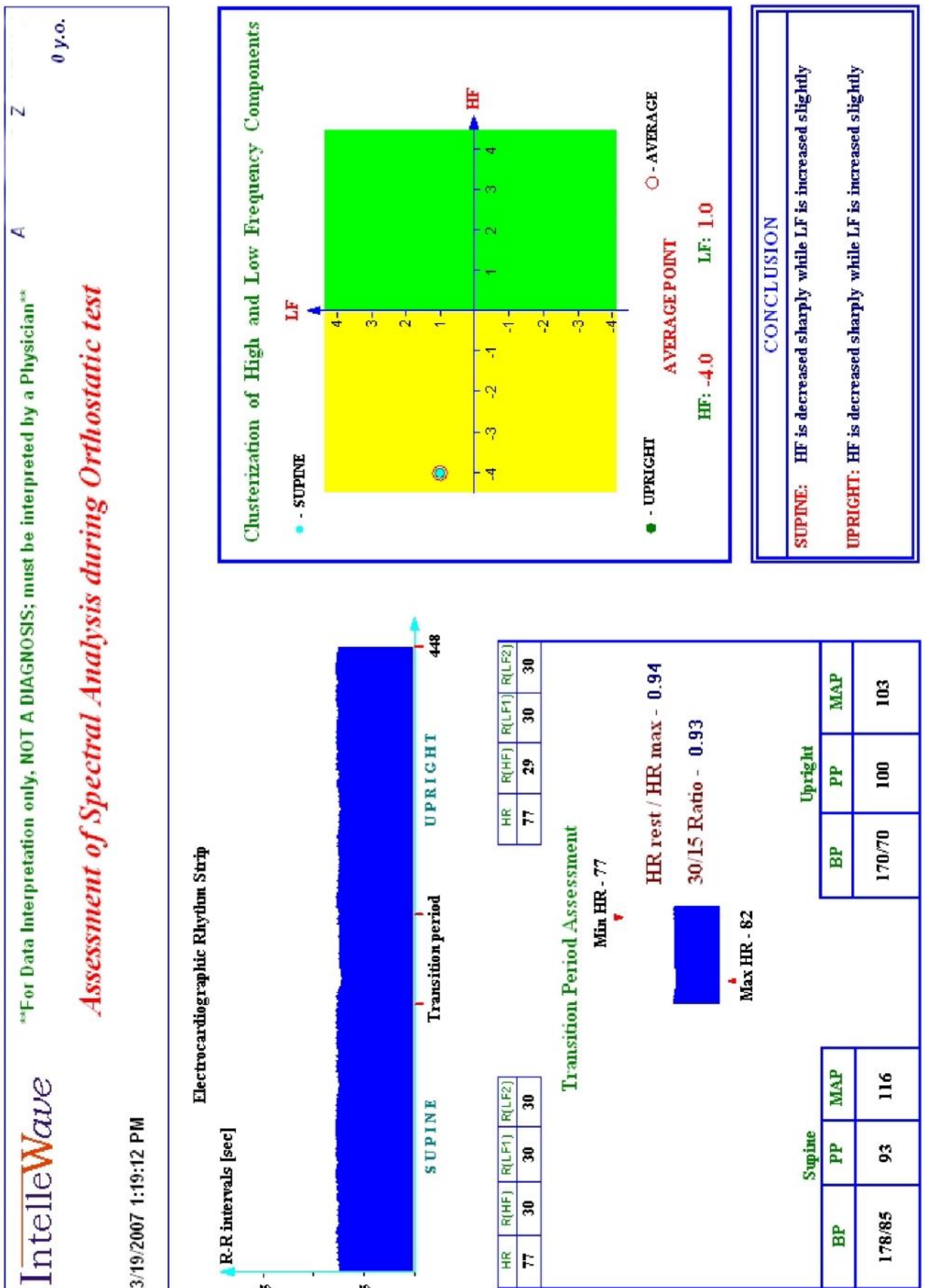
Example of excluding CAN Case (Cardiovascular Autonomic Neuropathy) during Valsalva maneuver combined with Deep Breathing



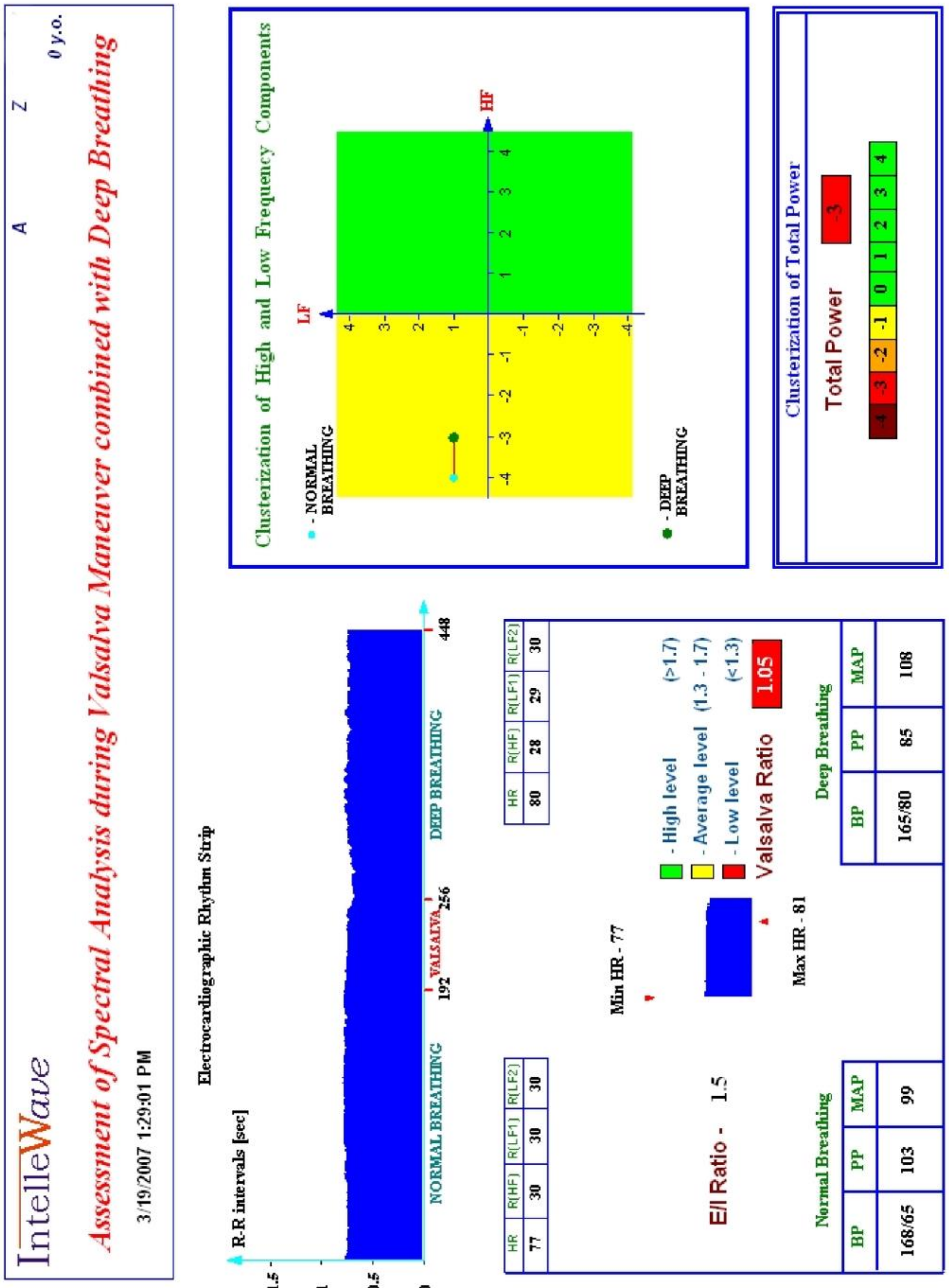
Orthostatic test results of the early stage of CAN or DAN cases



<u>Valsalva maneuver combined with Deep Breathing, test results of the early stage of CAN or DAN cases</u>



<u>Orthostatic test results of the chronic stage of CAN case</u>



HR	R(HF)	R(LF1)	R(LF2)
77	30	30	30

HR	R(HF)	R(LF1)	R(LF2)
80	28	29	30

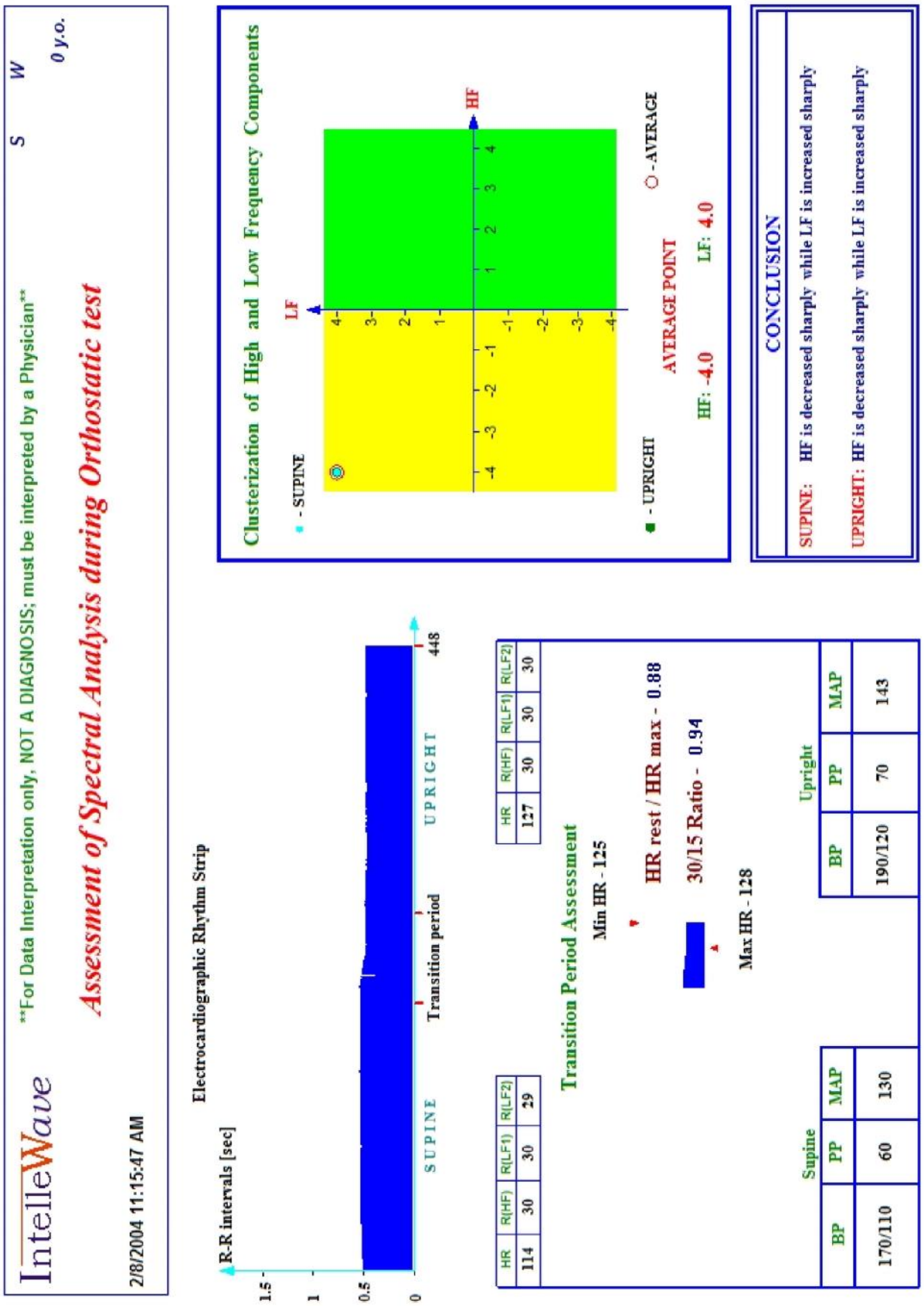
Normal Breathing

BP	PP	MAP
168/65	103	99

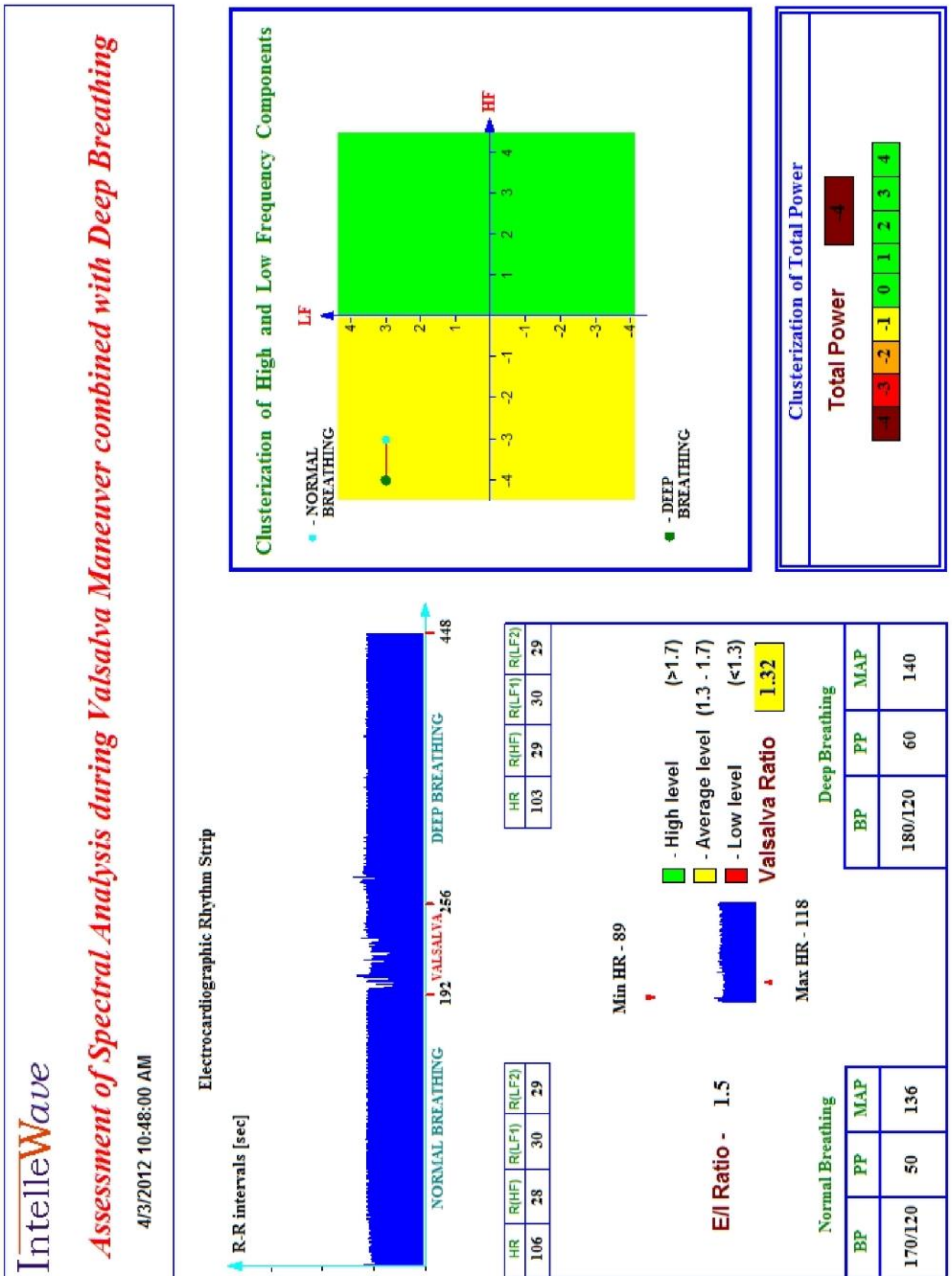
Deep Breathing

BP	PP	MAP
165/80	85	108

<u>Valsalva maneuver combined with Deep Breathing. Test Results of the chronic stage of CAN case</u>

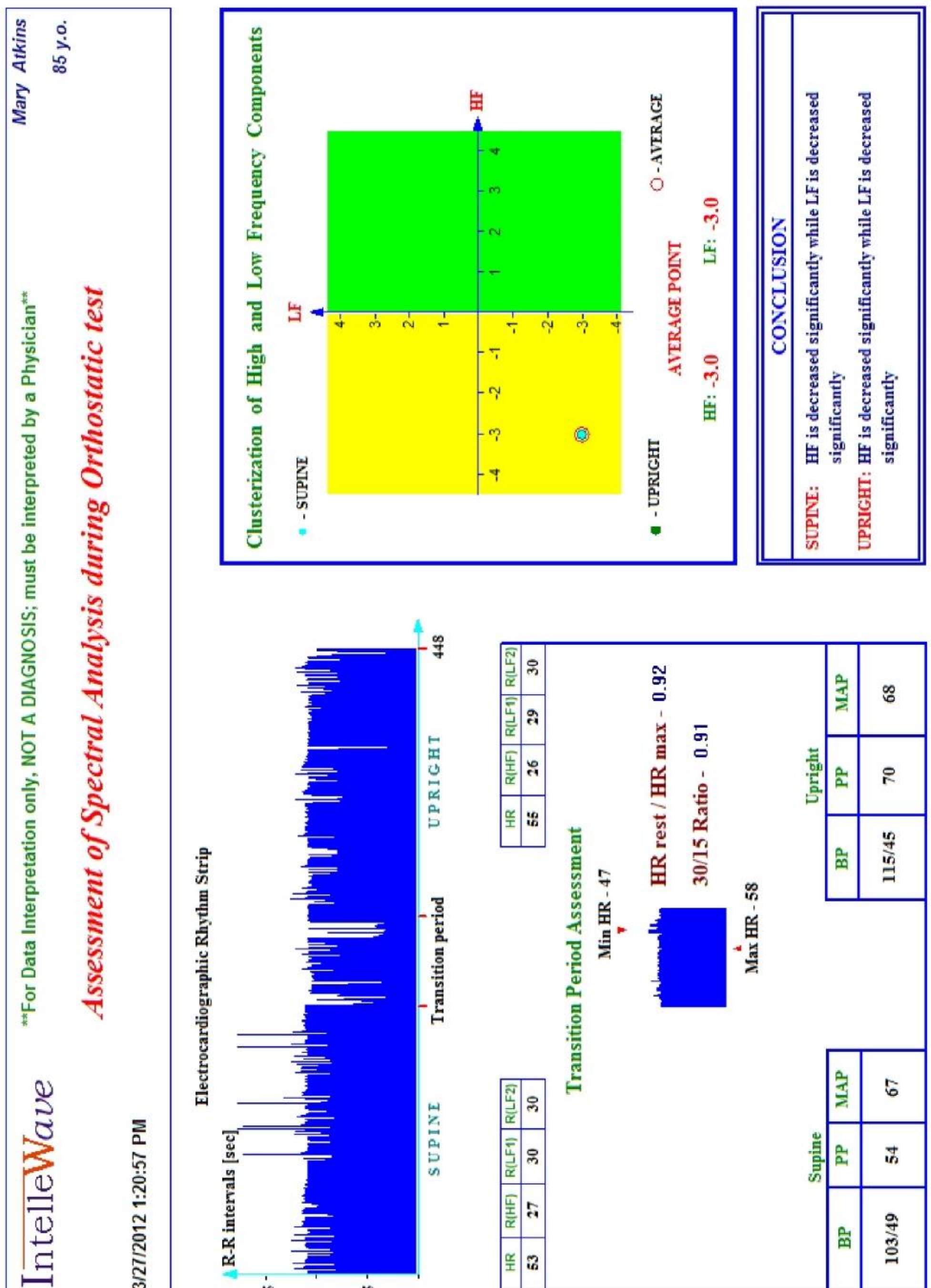


Risk Stratification for Primary SCD Prevention - Orthostatic test

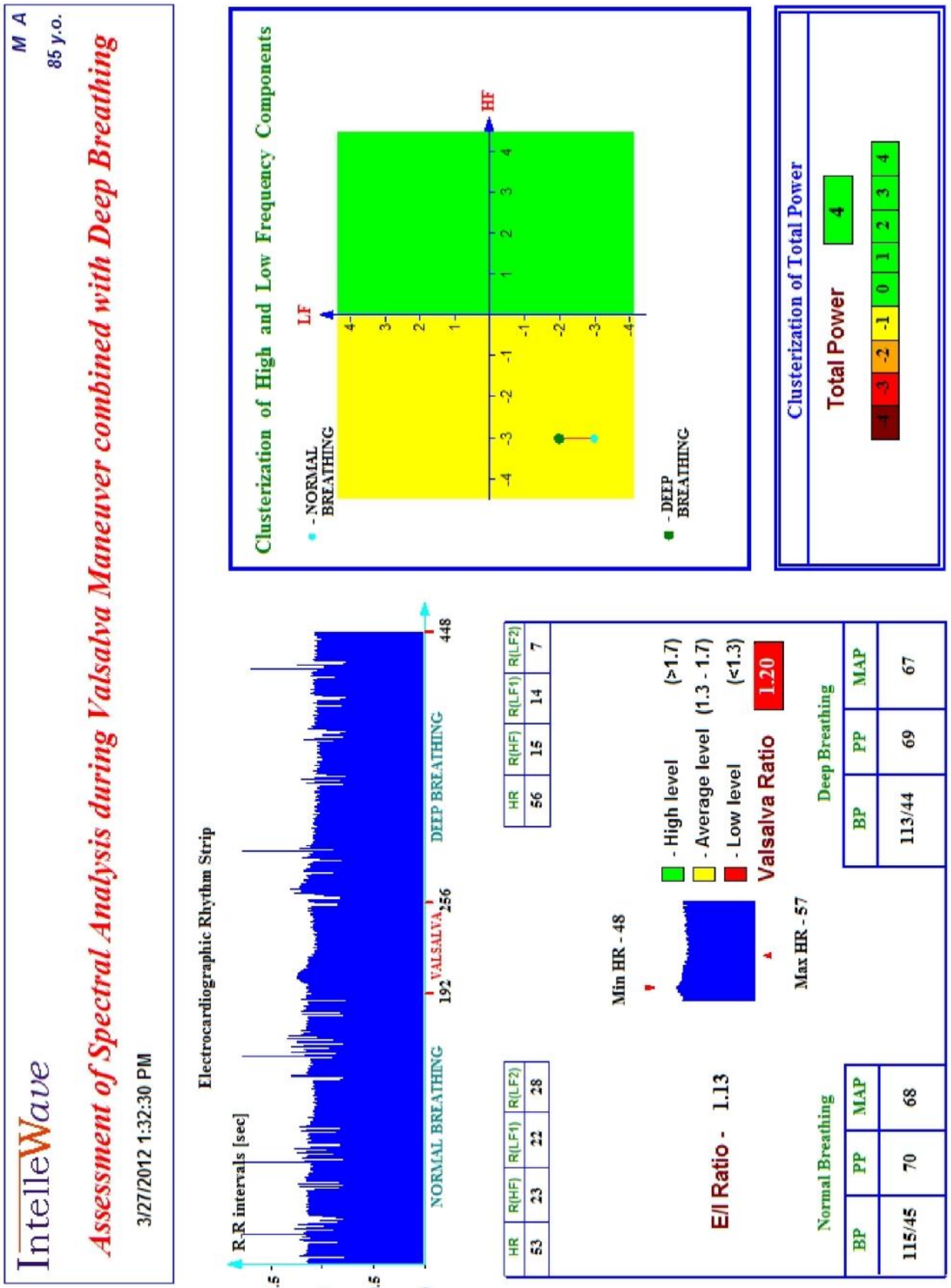


<u>Risk Stratification for Primary SCD Prevention -</u>

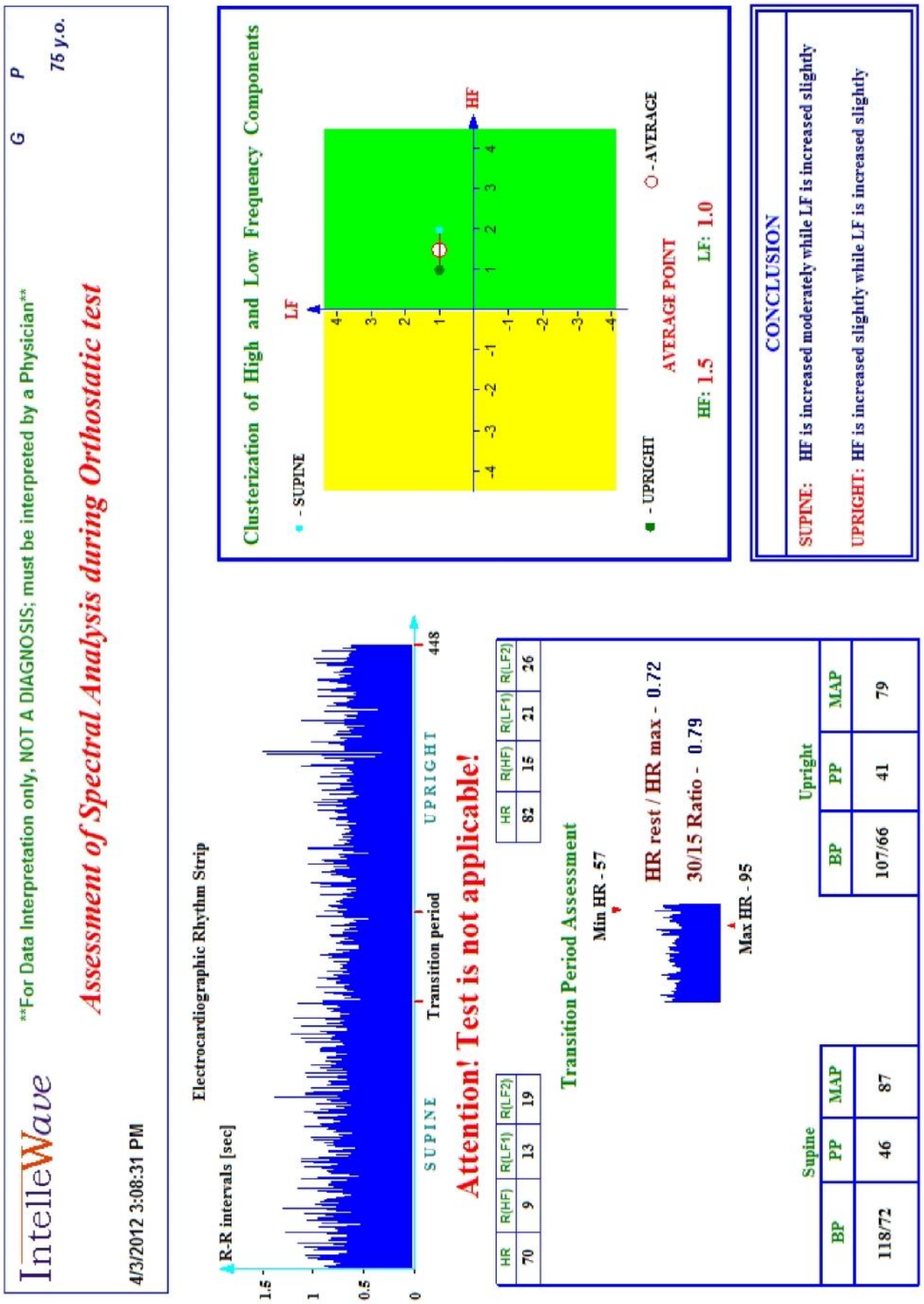
<u>Valsalva maneuver combined with Deep Breathing</u>



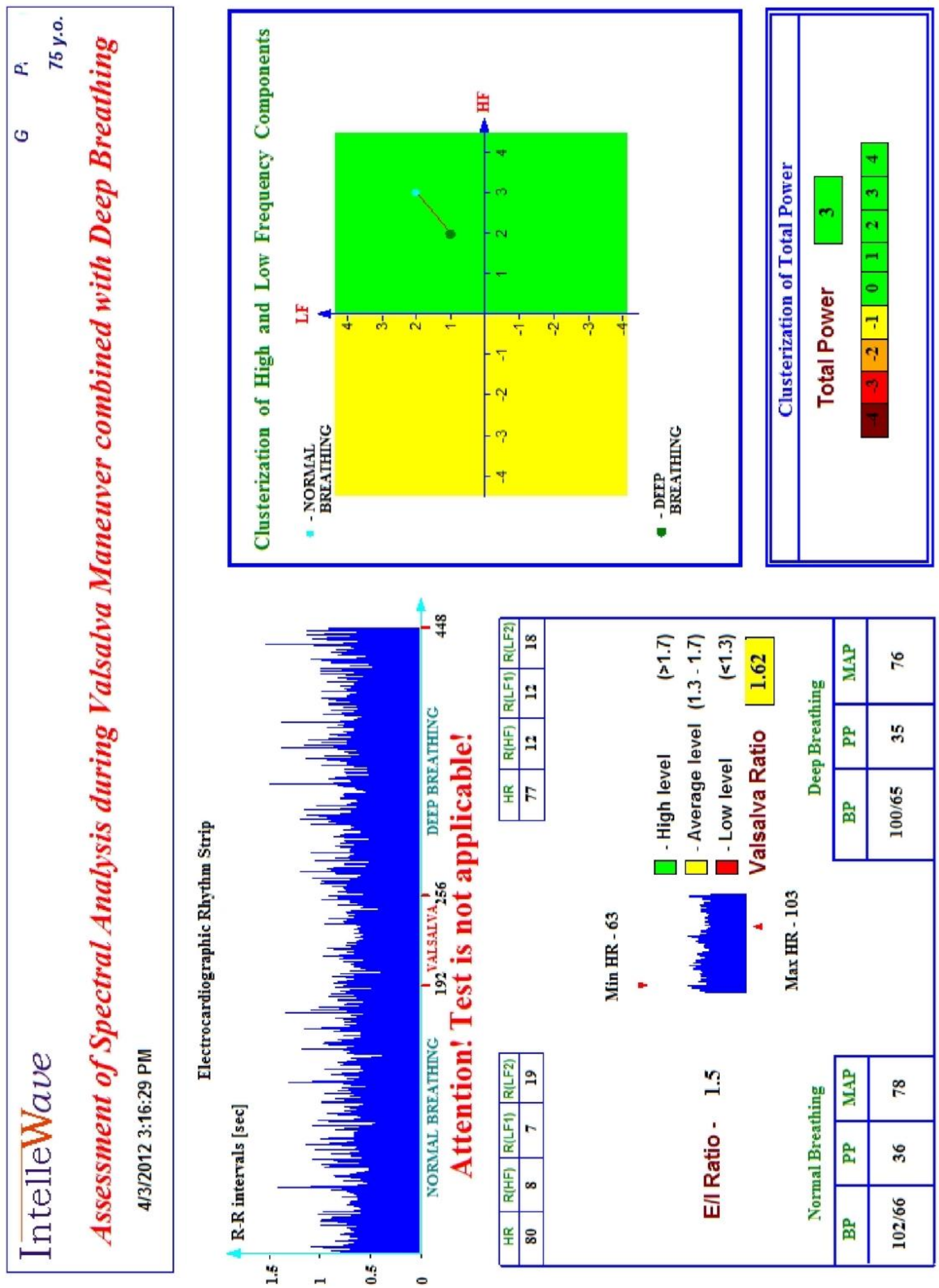
Overdose of Beta-blockers - Orthostatic test



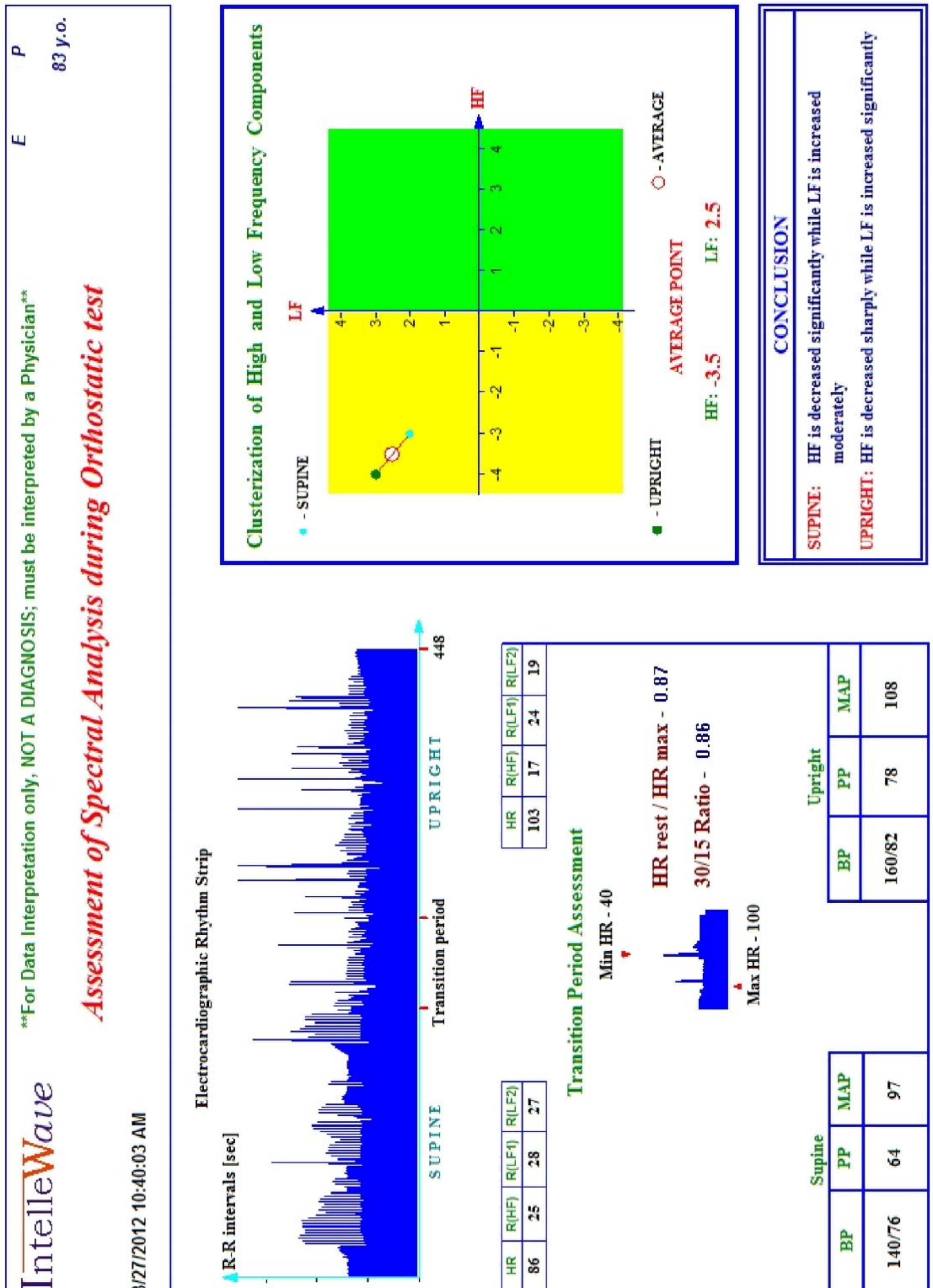
<u>Overdose of Beta-blockers - Valsalva maneuver combined with Deep Breathing</u>



Atrial Fibrillation case - Orthostatic test



<u>Atrial Fibrillation case - Valsalva maneuver combined with Deep Breathing</u>



<u>Case of Chronic stage of CAN with a number of PVC's and SVT - Orthostatic test</u>

IntelleWave

E P

83 y.o.

Assessment of Spectral Analysis during Valsalva Maneuver combined with Deep Breathing

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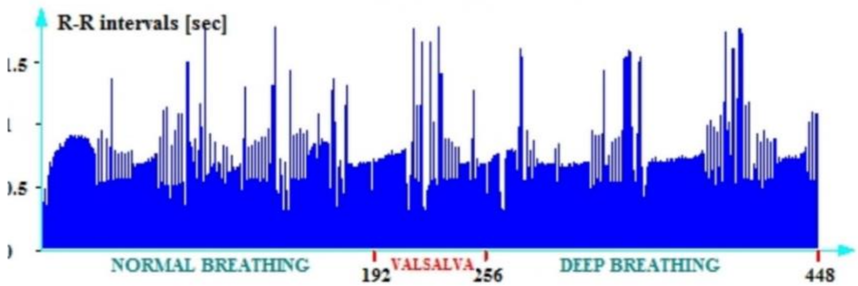
Electrocardiographic Rhythm Strip



HR	R(HF)	R(LF1)	R(LF2)
80	24	22	15

HR	R(HF)	R(LF1)	R(LF2)
83	27	28	29

E/I Ratio - 1.02

Min HR - 73

Max HR - 89

- High level (>1.7)
- Average level (1.3 - 1.7)
- Low level (<1.3)

Valsalva Ratio 1.22

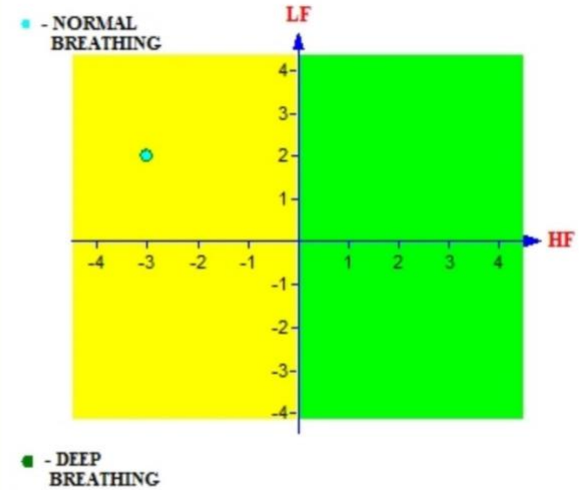
Normal Breathing

BP	PP	MAP
160/82	78	108

Deep Breathing

BP	PP	MAP
140/72	68	94

Clusterization of High and Low Frequency Components



Clusterization of Total Power

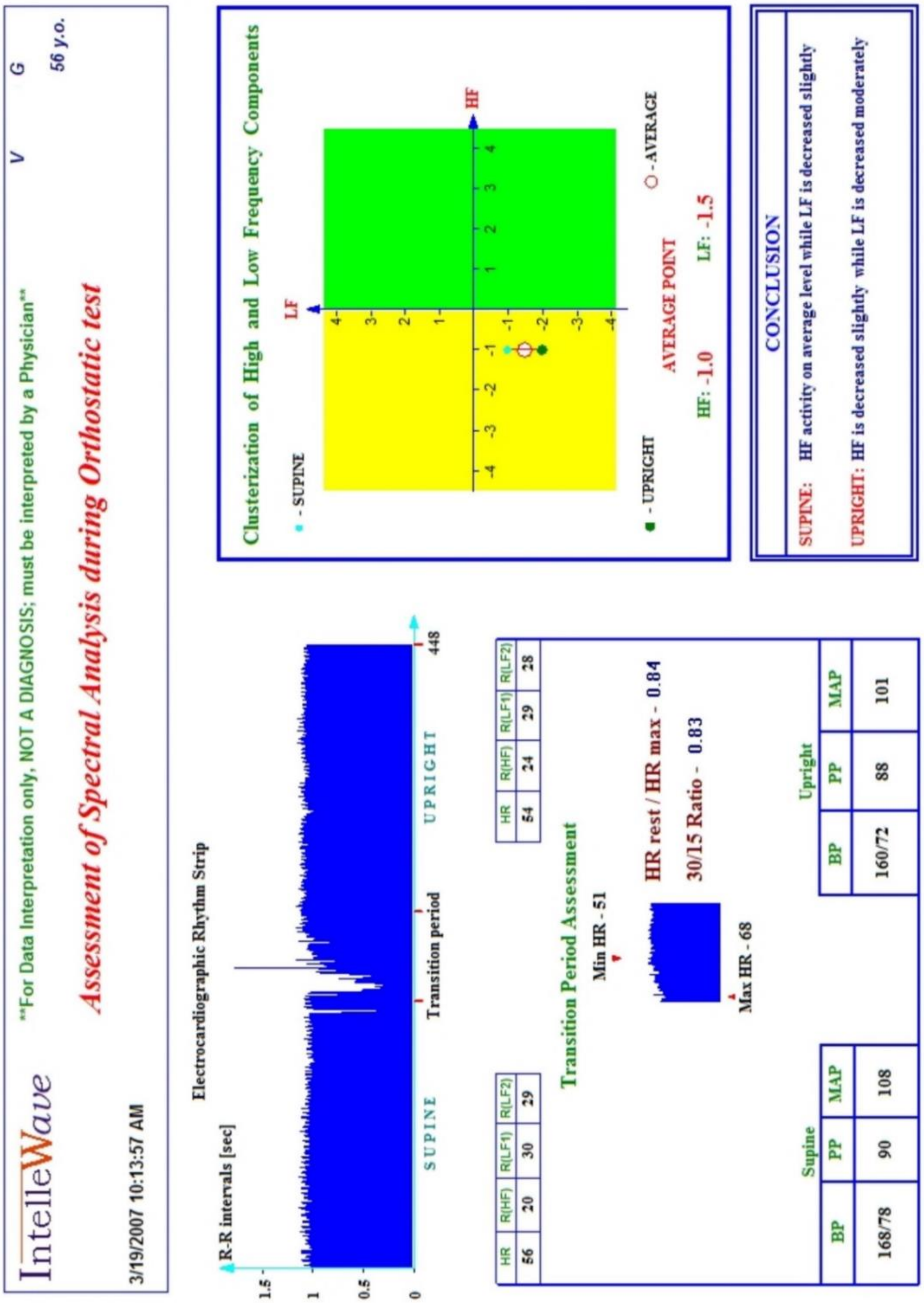
Total Power -2

-4	-3	-2	-1	0	1	2	3	4

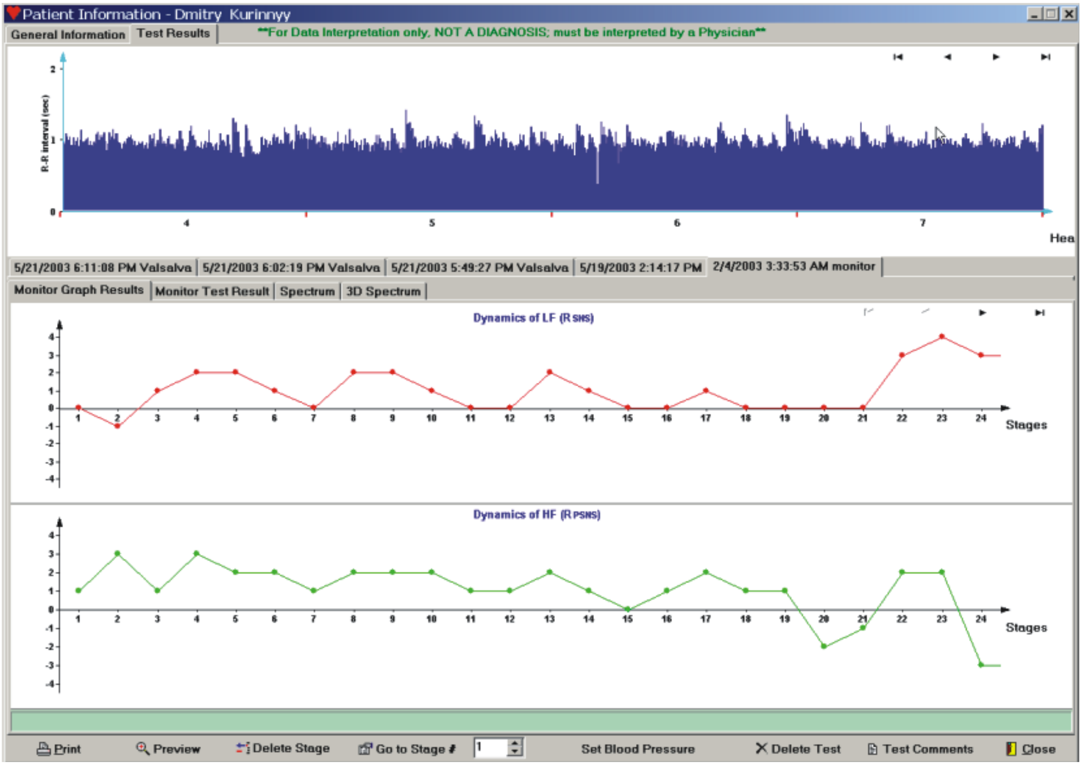
Case of Chronic stage of CAN with a number of PVC's and SVT – Valsalva maneuver combined with Deep Breathing

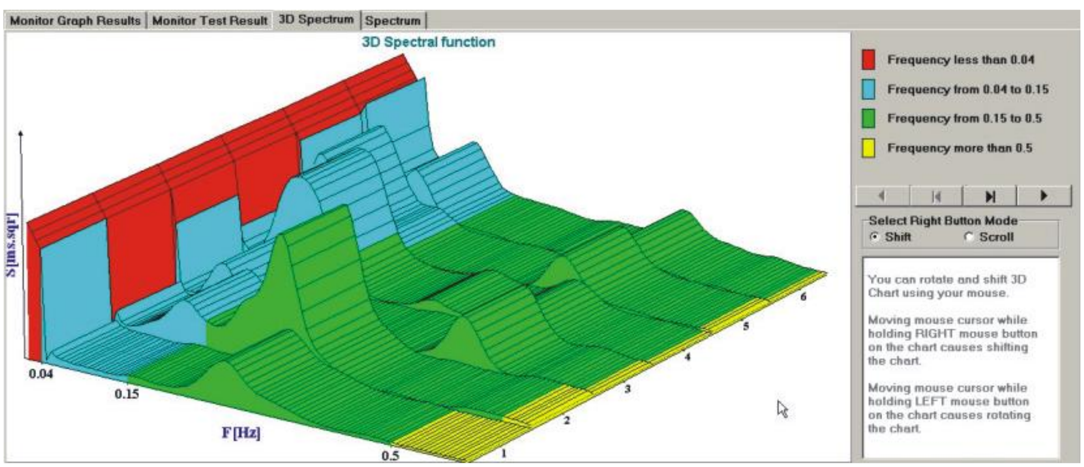
Chronotropic Incompetence case

Orthostatic test

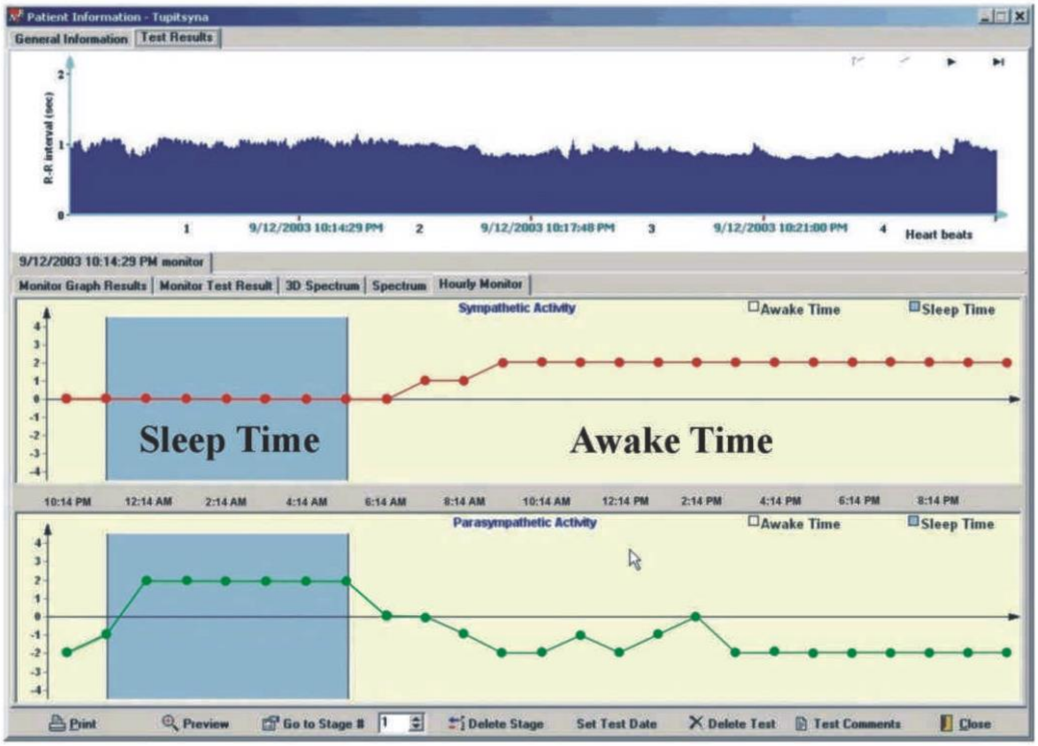


Real-time Heart Rate Variability Analysis (every 2 -4 minutes)

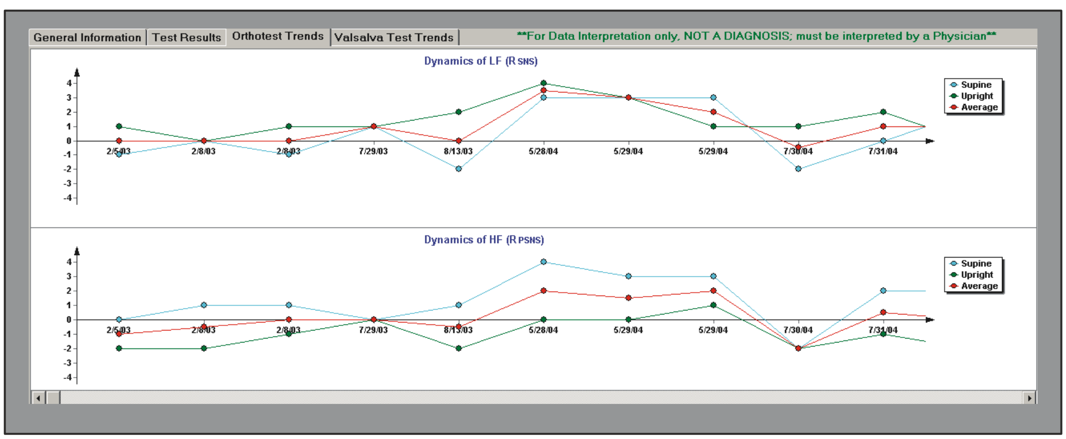




Hourly monitor (calculation each hour)



Orthostatic Test-to-test Trends of HRV components

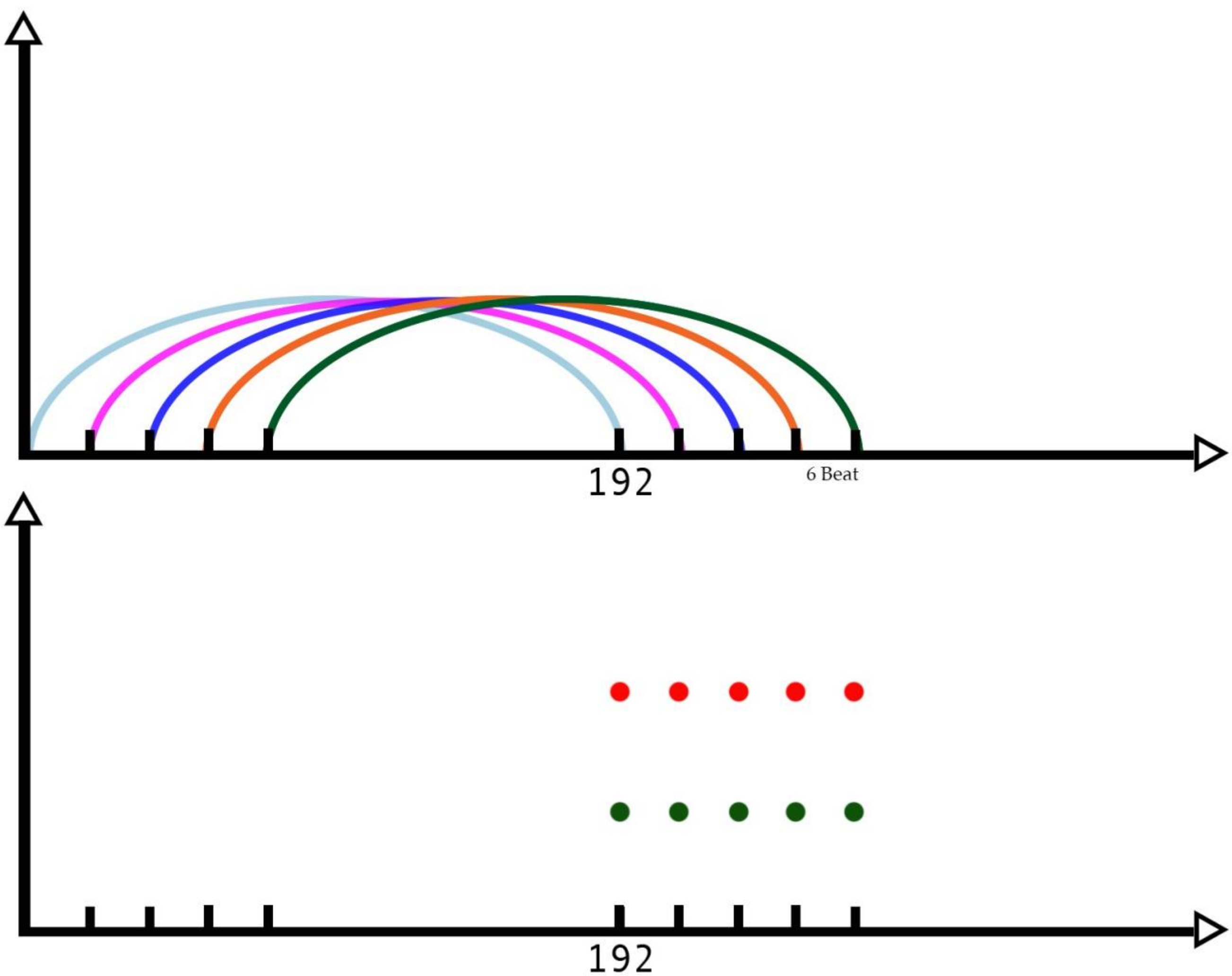


Syncope – pathophysiological development, during Tilt-table testing

The main benefit of Real-Time HRV analysis during Tilt-Table testing is to see changes of Spectral function components immediately after tilt, because this information can help physician to see how developed pathophysiological process, or how created pathophysiological mechanisms.

Tilt-Table testing started with collection of 192 R-R intervals as base line data, after that immediately calculated first HF and LF components (displayed on a screen) and automatically started fast method of calculation HF and LF components after collections each next 6 R-R intervals. Calculation provided only by analysis of 192 R-R intervals each time shifted to the right after collection next 6 R-R intervals as

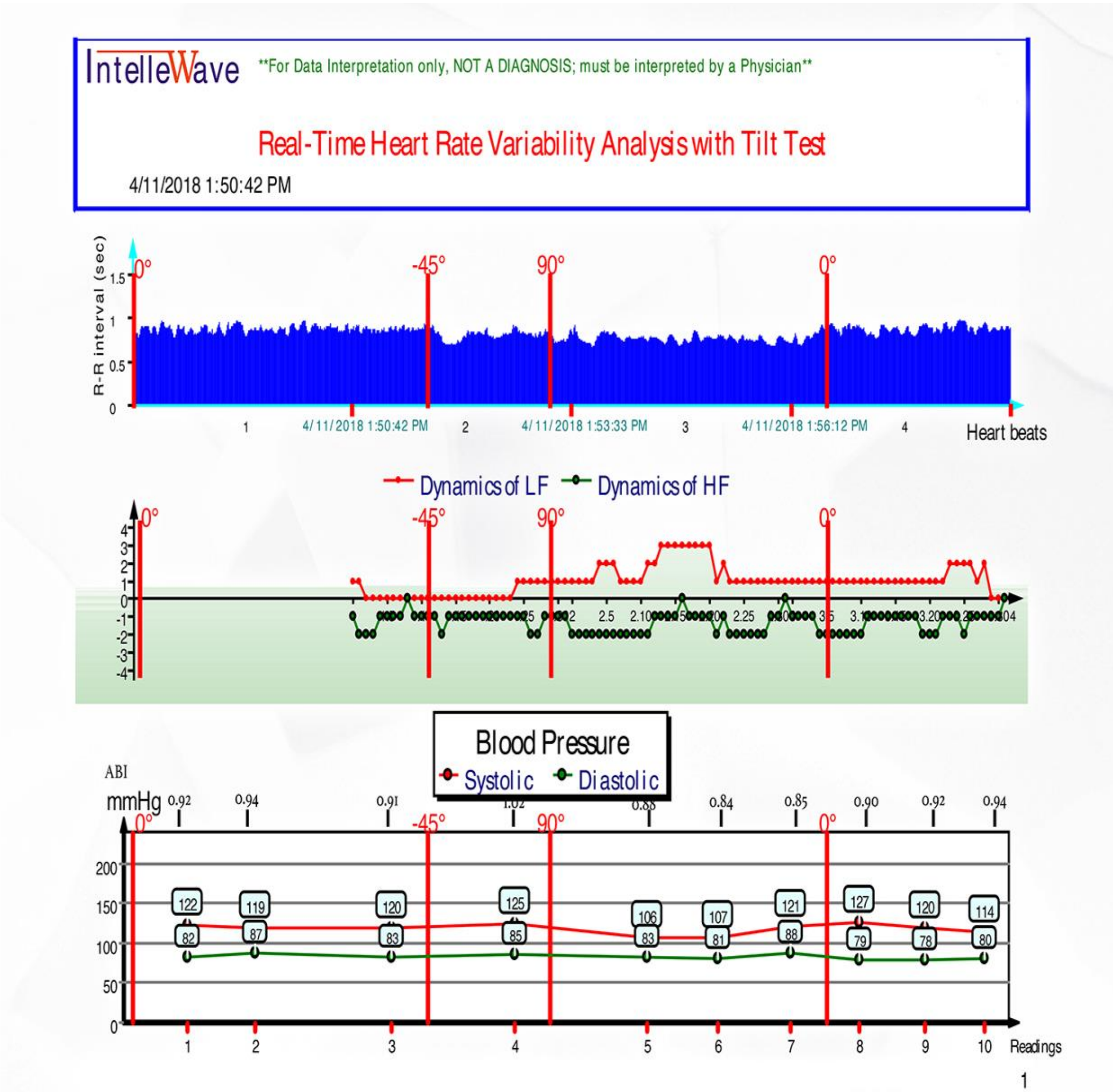
shown on picture below.



Red dot shown on a bottom graph is related with LF (SNS) changes, but Green dot is HF (PSNS) changes displayed after collection of each next 6 R-R intervals

On a final printout page, we can see 3 parts of information:

- Rhythmographic strip
- Changes of LF(SNS) AND HF(PSNS)
- Approximately each 1 min changes of Systolic and Diastolic Blood Pressure, see picture below



Tilt-Table testing to recognize Syncope development.

Additional information on Heart Rate Variability 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 PSNS activity and other regulatory mechanisms such as neuro-humoral, hormonal, thermoregulatory and baroreceptor mechanisms.

Thus, to recognize SNS and PSNS activity separately is very difficult and 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, cannot 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 R-R 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 (former name is the 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 Integrated High-Frequency (HF) and Integrated 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.

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).

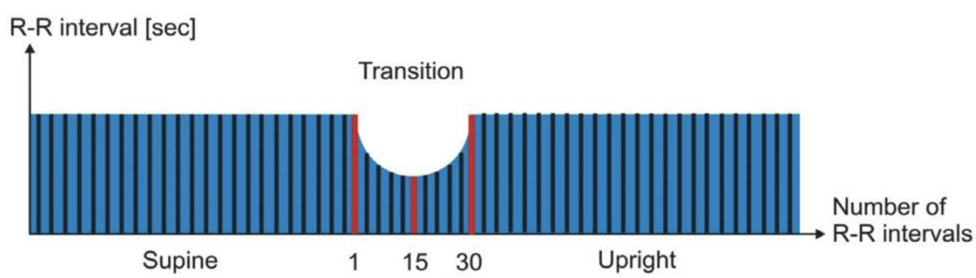


Figure 1

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.

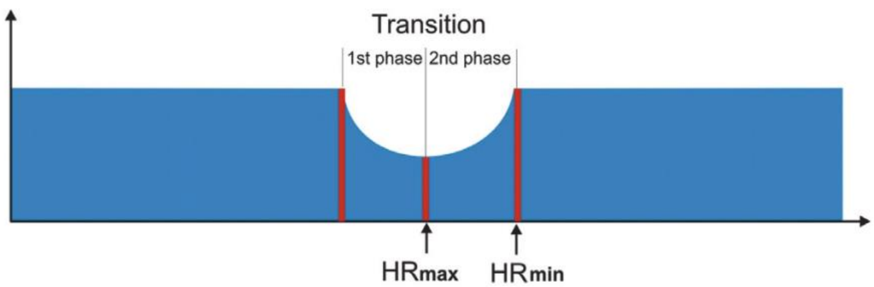


Figure 2.

Figure 2

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 Rhythmographic strip begins to curve downward (see Figure 3 below).

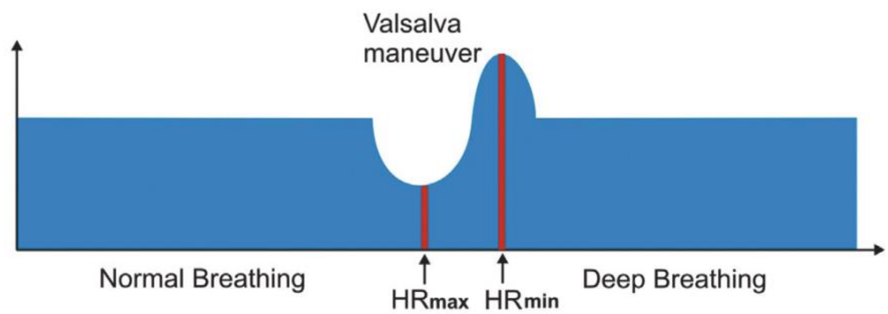


Figure 3

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).

In such cases the correct calculation will be HR (max)/HR (min1), and the wrong calculation--HR (max)/HR (min2).

This is just a short description of the most important problems related to the ANS testing based on Heart Rate Variability and Blood pressure analysis.

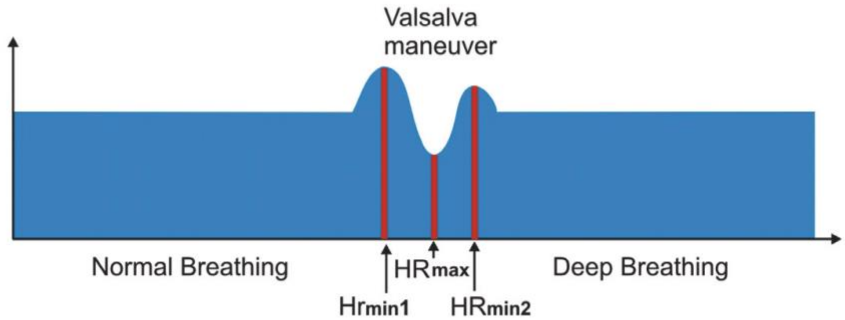


Figure 4

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