Alexander Riftine, Ph.D.

Quantitative Assessment of the Autonomic Nervous System based on Heart Rate Variability Analysis

Theoretical Review and Clinical Use

Intellewave, LLC.
1090 King Georges Post Road, Suite 1004
Edison, NJ 08837
Tel. (732) 738-8800
Fax: (732) 738-8877
www.intellewave.net

Email: info@intellewave.net

CONTENTS

1. Introduction: the Intellewave method 1-1
2. Heart Rate Variability Analysis in Intellewave assessment . 2-1
3. Clusterization of ANS states 3-1
4. Physiological interpretation of ANS states . . . 4-1
5. Test modalities for evaluating the ANS function . . 5-1
   - 5.1 Orthotest as a method of ANS assessmemt . . 5-1
     - Sample cases 5-3
   - 5.2 Valsalva maneuver combined with deep breathing . 5-6
     - Sample cases 5-11
   - 5.3 Combining Results of Orthotest and Valsalva Test for Overall Patient Assessment: Sample case . . 5-14
   - 5.4 Real-time ANS assessment 5-18
     - Sample cases 5-18
     - Hourly monitor 5-21
6. Bibliography 6-1

HRV testing provided by Intellewave allows physicians to monitor the activity of both sympathetic and parasympathetic branches of the autonomic nervous system (ANS) in order to assess the state of a patient's autonomic function. On the one hand, testing with Intellewave can detect different specific types of autonomic dysfunction, which can be linked to a multitude of clinical diagnoses. On the other hand, Intellwave is a tool for overall, general assessment of a patient's physiology, and, as a physiologic monitor, it provides a comprehensive, in-depth patient evaluation, often missing in standard medical practice. This feature determines the wide range of clinical applications of the Intellewave system and makes it principally different from all other classes of diagnostic devices.

Heart rate variability (HRV), or variations of beat-to-beat intervals length, is regulated by both sympathetic and parasympathetic branches of the autonomic nervous system.

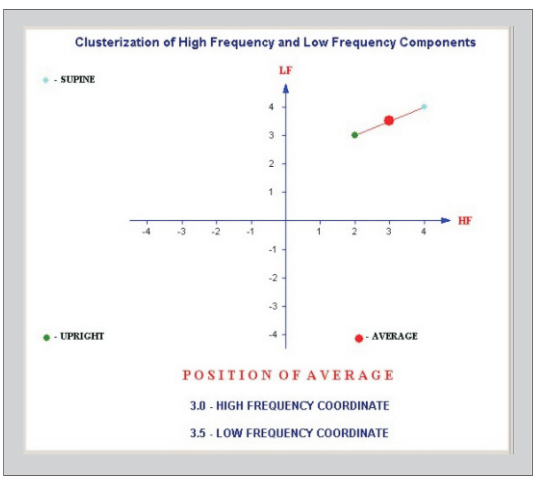


Figure 1. Clusterization Chart

Intellewave uses power spectral analysis for quantitative assessment of Heart Rate Variability and presents the results in the chart shown on the right, called ***Clusterization Chart.*** The system measures interrelation of the two most significant components of HRV analysis - power of high frequency (HF) variations and power of low frequency (LF) variations and displays them on the Cartesian system of coordinates. Numerous research studies demonstrated high correlation of HF intensity with activity of parasympathetic system, and the LF intensity with a mixture of various regulatory inputs, including sympathetic and partial parasympathetic inputs as well as activity of baroreceptors, mechanisms of termoregulation, hormonal control and other neurohumoral mechanisms. In HRV testing, the LF intensity parameter serves primarily as a tool for assessing sympathetic nervous system (SNS) activity while the HF parameter serves for assessing parasympathetic (PSNS) activity. The graph displays the LF intensity (reference – sympathetic activity) on the vertical axis while the HF intensity (reference – Parasympathetic activity) is on the horizontal axis.

Traditionally the ANS is regarded in terms of its structure and its function. The structural components are the sympathetic and parasympathetic branches while the functional aspect is illustrated by a list of disorders, collectively known as dysautonomia. The HRV analysis provided by the Intellewave system rises on a higher level by treating structure and function simultaneously – it detects up to 81 distinctive relationships between sympathetic and parasympathetic systems that correspond to 81 states of physiological functioning.

The Intellewave system can be used for patient testing during initial assessment or at any stage of the treatment. Any medical intervention immediately triggers a reaction of the ANS, and with HRV testing a physician can monitor this reaction. Functioning of both branches of the ANS is regulated by input from all internal structures and mechanisms of the body, which broadens the scope of application of HRV testing: it can be used for a wide range of conditions starting from psychiatric disorders to pathologies of internal organs. The testing thus provides the physician with a highly reliable feedback for any treatment, and helps to optimize the treatment strategy in virtually all areas of medicine.

The system allows the physician to investigate 3 modalities:

1. Assessment of reaction of the ANS on orthostatic intervention (lying-to-standing test).
2. Assessment of autonomic reaction on Valsalva maneuver followed by deep breathing.
3. Real-time autonomic assessment, where results are updated with selected frequency (which can range from several minutes to several seconds).

NOTE

The Intellewave system is not a diagnostic device: it is an instrument for physiological assessment based on Heart Rate Variability – the parameter that helps physicians to monitor the Autonomic Nervous System status. The results provided by Intellewave should be combined with standard clinical data in order to optimize treatment strategy.

The significance of the Intellewave method in the development of HRV assessment

Prior to the application of HRV to ANS assessment, the Autonomic function could only be approximately assessed by the following three parameters:

- Autonomic Balance (Vegetative Homeostasis),
- Sympathetic Prevalence,
- Parasympathetic Prevalence.

Traditionally, the criteria used for evaluating these three parameters were clinical and laboratory findings. Assessment of the Autonomic function was thus labor intensive and not always feasible.

The introduction of HRV analysis - especially, the identification of the power of low-frequency band of HRV spectral function with the activity of Sympathetic Nervous System (SNS) and the power of its high-frequency band with the activity of Parasympathetic Nervous System (PSNS) - opened up new theoretical opportunities for ANS assessment. But to make practical use of this important scientific discovery one had to solve the problem of deriving some form of quantitative relationship between SNS and PSNS from the spectral function.

HRV analysis is based on measuring variability in heart rate; specifically, variability in intervals between R waves - “RR intervals” (cf. Fig. 2). These RR intervals are then analyzed by spectral (as in Intellewave) or some other form of mathematical analysis (e.g., chaos, wavelet theories). Such mathematical analysis generates multiple parameters; typically 20-30. The problem of SNS-PSNS quantification, which has remained for many years the principal dilemma of HRV analysis, is specifically in reducing all possible variations of these multiple parameters to a quantitative relationship between only two parameters: SNS and PSNS.

Intellewave is **the first and only system to solve the problem of SNS-PSNS quantification**. This technological breakthrough is achieved by using proprietary algorithms and a new approach based on one of the leading theories of Artificial Intelligence - Marvin Minsky's Theory[3]. Intellewave objectively and reliably evaluates the state of ANS during rest (up to 24 hours) as well as during Orthostatic (lying-to-standing) test and Valsalva maneuver combined with deep breathing. Due to its highly sophisticated HRV analysis, Intellewave is the only method that enables precise recognition and classification of up 81 ANS states with a corresponding quantitative description of each one.

The algorithms used by Intellewave have been developed and tested for over twenty years in studies involving more than twenty thousand patients. The goal of the Intellewave system designers is to provide the physician with a reliable office device with a wide range of clinical applications: assessment of risk in cardiovascular diseases, objective assessment of benefit for cardiac and orthopedic intervention, and quantification of drug effect on the autonomic function.

Until the development of the Intellewave method there was no practical way to use ANS assessment technology outside of a research laboratory as automatic reproducibility proved to be unattainable by any other HRV analysis system available to date. In addition to delivering HRV analysis to the physician's office, Intellewave became the first and the only system to provide a quantitative interpretation of HRV spectral function as well as qualitative analysis of the resulting parameters.

[1] M. Minsky. *Structures for Knowledge Representation. Machine Vision Psychology*. Mir, 1978.

The Intellewave advantage and applications

The advantage of the Intellewave system stems from the following distinctive features that determine the domains of its application:

1. High degree of sophistication and reliability in detecting the early signs of pathological developments of functional disorders, which may not be revealed in the course of ordinary physical examination. This makes Intellewave an **objective probing tool for early detection and early intervention** by a physician regardless of the patient's complaints.

2. High degree of flexibility and robustness in effective assessment for any type of therapy, medication or activity. Thus, Intellewave becomes an **objective assessment and research tool.**

3. High degree of versatility and customization in identifying and refining the optimal protocols for medical assessment, which makes Intellewave a **perfect health management tool.**

It is well known that autonomic response is the first human response to any intervention or to any physical, physiological, or psycho-emotional activity. Likewise, any pathological process will immediately provoke an ANS response. And the main regulatory mechanism in Heart Rate Variability (HRV) is autonomic regulation. Therefore, HRV method is unique in its ability to assess the impact of any intervention or activity and to detect the early signs of pathological developments or functional disorders, which may not be revealed by routine physical examination.

To perform Heart Rate Variability analysis, Intellewave uses an effective and transparent visual representation, known as the **Method of Rhythmography**[1], which reflects HRV wave structure and serves as a "fingerprint" of autonomic regulatory mechanisms. The method is based on drawing the time intervals between consecutive heartbeats as straight vertical lines. The longer the interval between two heartbeats (RR), the longer the corresponding vertical line (Figure 2).

When these lines are graphed sequentially, they form a **Rhythmographic strip** - a curve-specific wave portrait of RR Intervals Variability (Fig. 3a). Rhythmographic representation allows a great deal of information to be compressed in a simple picture. The wave portrait in Fig. 3a is composed of 448 RR intervals of the ECG. A spectral analysis of this wave "portrait" allows Intellewave to identify two main spectral components (Fig. 3b):

- Low frequency: 0.033 - 0.15Hz
- High frequency: 0.15 - 0.5Hz

In HRV testing it has been widely accepted that HF parameter serves primarily as a tool for assessing parasympathetic (PSNS) activity while the LF parameter serves primarily as a tool for assessing sympathetic (SNS) activity. Numerous research studies referenced below demonstrated high correlation of power of HF band with activity of parasympathetic system, and the power of LF band

[1] developed in 1967 by Dr. Zhemaitite of Lithuania, one of the leading Soviet authorities on cardiology automation; cf. D. I. Zhemaitite. *The methodology for automatic analysis of rhythmograms and its clinical applications*. The Doctoral Dissertation (Doctor of Medical Science). Kaunas, Lithuania, 1972.

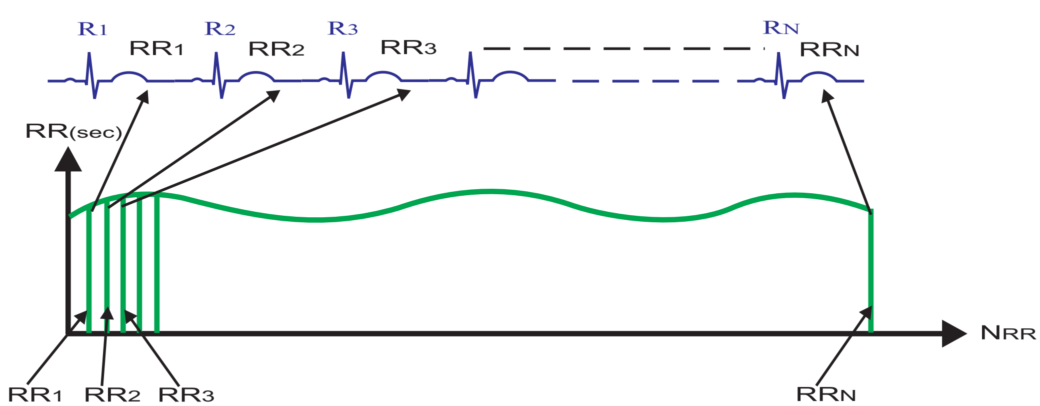


Figure 2. Method of Rhythmography.

Figure 3a. Rhythmographic strip.

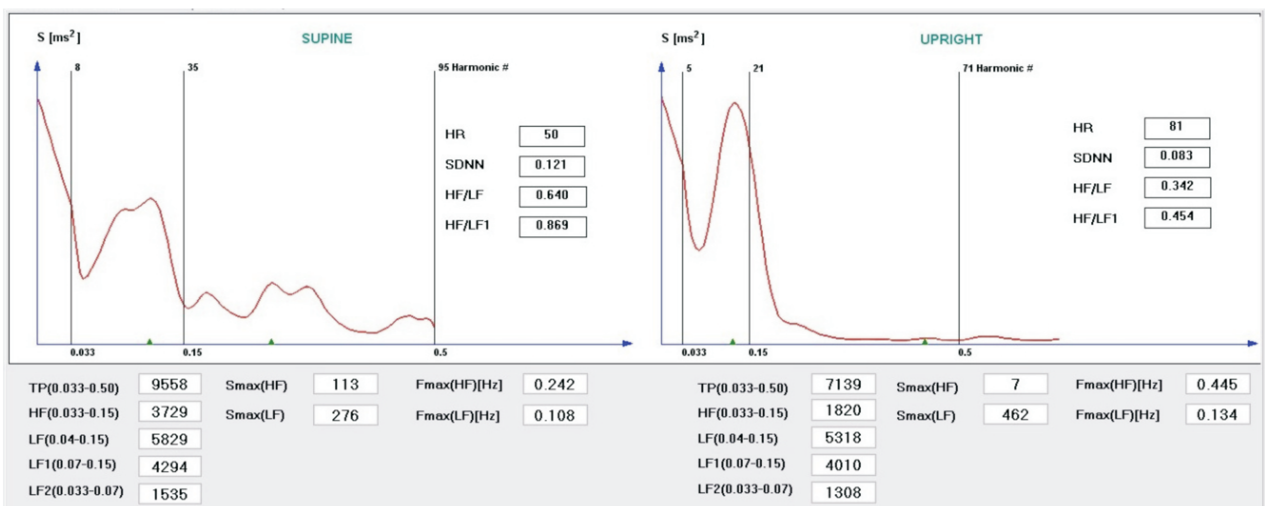


Figure 3b. Spectral chart.

with a mixture of various regulatory inputs, including sympathetic and partial parasympathetic inputs as well as activity of baroreceptors, mechanisms of termoregulation, hormonal control and other neurohumoral mechanisms. These findings have been well documented in a number of medical and scientific publications and in conference reports from the American College of Cardiology, The American Heart Association, and others (please refer to the Bibliography section of this review). For convenience, we reference the horizontal, or HF axis values of the Clusterization chart, with PSNS activity: **HF (R_{PSNS}).** In accordance with the established practice in HRV testing to treat LF parameter as an indicator of SNS activity, we reference the vertical, or LF axis, with SNS activity: **LF (R_{SNS}),** while keeping in mind that the latter is influenced by a range of different determinants in addition to parasympathetic input.

Intellewave's proprietary algorithm analyzes the power of both high and low-frequency bands as well as their peak amplitudes and pre-and-post autonomic intervention shifting. It then automatically clusterizes ANS states into 74 types, which represent different relationships between SNS and PSNS activities, and displays them on the graph – Clusterization Chart.

Intellewave performs ***Cluster Analysis of the ANS States***: it recognizes different types of relationships between SNS and PSNS activities and assigns these types into ***clusters***. It recognizes 81 ANS states, or clusters, and groups them into 9 categories of ANS conditions.

NOTE

Here and further, we will discuss Sympathetic Nervous System (SNS) and Parasympathetic Nervous System (PSNS), keeping in mind a well established in scientific publications correlation between High Frequency (HF) with PSNS activity and Low Frequency (LF) with SNS activity.

Intellewave then graphs the HF(PSNS) on the horizontal or X-axis and the LF(SNS) on the vertical or Y-axis (Fig. 4a). The intersection point of the LF(SNS) and HF(PSNS) axes is the point of Autonomic Balance. To the right of and above this balance point, Intellewave displays an area of increased PSNS and SNS activities in 4 gradations. Decreases in HF(PSNS) and LF(SNS) activities are shown to the left and below the balance point.

81 ANS states are subdivided into nine categories (circled in red in Fig. 4a, with corresponding numbers marking each category - e.g., 1, 2):

Category 1 PSNS prevalence with the average level of SNS activity is illustrated by 4 points:

Point 1 represents a slight PSNS prevalence.
Point 2 represents a moderate PSNS prevalence.
Point 3 represents a significant PSNS prevalence.
Point 4 represents a sharp PSNS prevalence.

Category 2 A simultaneous increase in both PSNS and SNS activities, with different variations, is illustrated by 16 points

Category 3 SNS prevalence is illustrated by 4 points (slight, moderate, significant, and sharp)

Category 4 PSNS decrease with an SNS increase is illustrated by 16 points

Category 5 PSNS decrease with the average level of SNS activity is illustrated by 4 points (slight, moderate, significant, and sharp)

Category 6 A general decrease in both SNS and PSNS activities is illustrated by 16 points

Category 7 A point at zero value on the coordinate system indicates ANS balance

Category 8 SNS decrease with average level of PSNS is illustrated by 4 points (slight, moderate, significant, and sharp)

Category 9 Increase in PSNS with a decrease in SNS is illustrated by 16 points

Clusterization of the Autonomic Nervous System's states

by Alexander Riftine, Ph.D

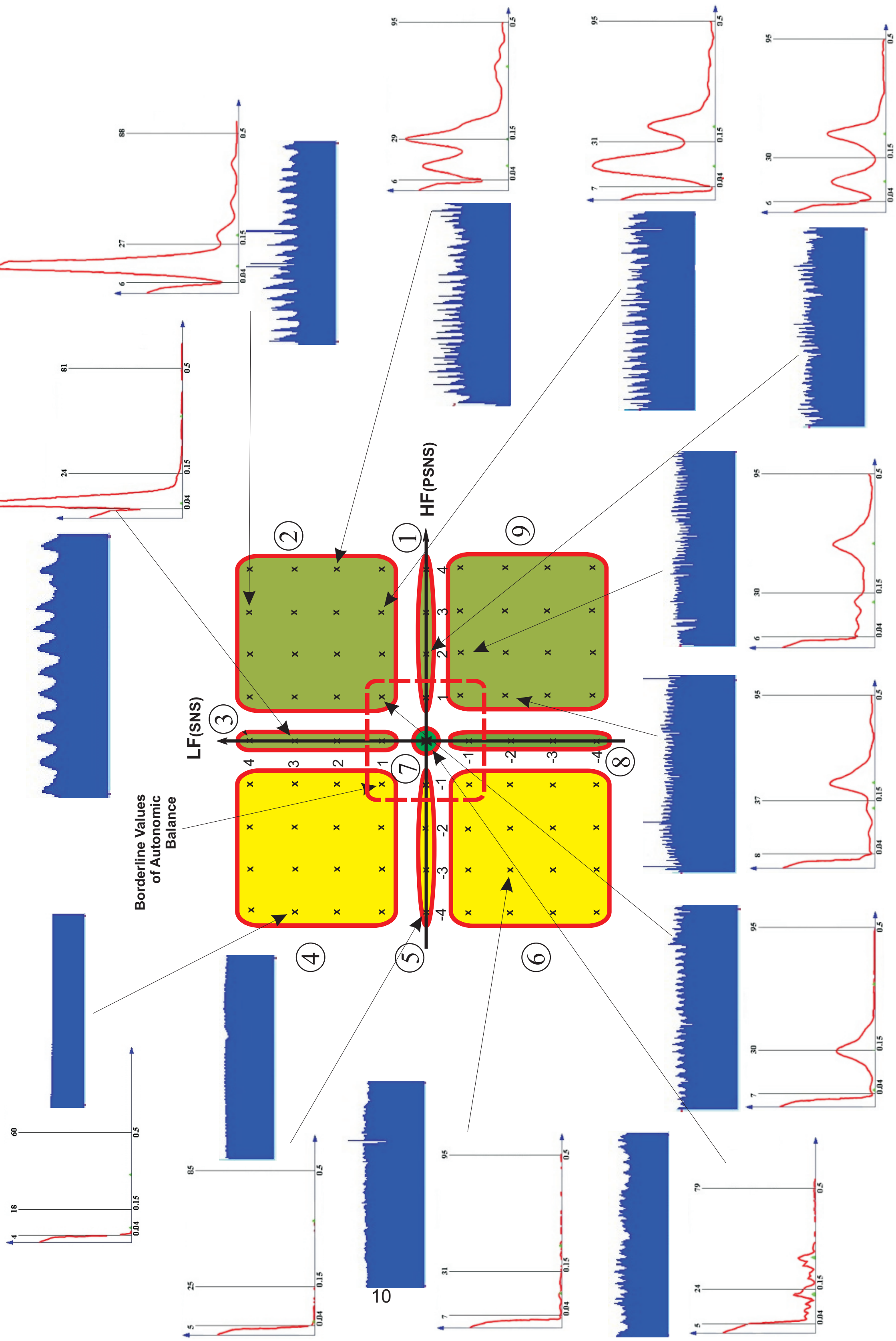


Figure 4a. Nine categories of the Autonomic Nervous System's conditions

10

The main physiological meaning of the ***Sympathetic Nervous System (SNS)*** is that it could be viewed as a “mobilizing” or “energy-boosting” division of ANS. SNS is concerned primarily with preparing the body for energy-expending, stressful or emergency situations. It controls the “fight or flight” reaction, increasing blood pressure, heart rate, and blood flow to the muscles. SNS is also a biological marker of age. Conversely, the main physiological meaning of the ***Parasympathetic Nervous System (PSNS)*** is that it could be viewed as a “restful” or “energy-conserving” division of ANS. PSNS is most active under ordinary, restful conditions. It also counterbalances the effects of the sympathetic division, and restores the body to a resting state following a stressful experience.

In response to various internal and external processes and stimuli, an individual experiences a continuous interplay of these two main ANS forces, constantly trying to balance each other. For example, during an emergency, the sympathetic division will cause the heart and breathing rates to increase; following the emergency, the parasympathetic division will decrease these activities.

In the Cartesian system of SNS/PSNS axes, the basic guiding principle is that parameters displayed at or to the right of the point of Autonomic Balance (PSNS > or = 0) represent basically healthy people (area colored green in Fig. 4b), while those to the left (PSNS < 0) mostly represent temporarily dysfunctional or chronically sick people (area colored yellow in Fig. 4). Notice the difference between Rhythmograms and Spectral Function Graphs corresponding to different ANS categories and their segments. Specifically, notice the sharply fluctuating and regular Rhythmogram patterns of the green ("healthy") areas (PSNS > or = 0) vs. the flat and chaotic patterns of the yellow ("problem") areas (PSNS < 0). The basic principle in reading a Rhythmogram is: the sharper and more regular the fluctuation pattern, the healthier the person it belongs to.

The nine ANS categories are now considered in more detail (Fig. 4b).

1 PSNS prevalence with the average level of SNS activity:

This category represents PSNS dominance. It is usually observed when a patient is resting or during the first stage of sleep (specifically, dreamless sleep). In the second stage of sleep, SNS activity is generally increased, at times markedly so. This category is further subdivided into four subcategories, depending on the state of PSNS (slight, moderate, significant, sharp prevalence - cf. Category 1 on p. 3-1). This category is somewhat limited, since it can only be observed in patients with strictly median values of SNS activity.

2 Increase in PSNS and SNS activities:

This category is subdivided into sixteen different combinations of PSNS/SNS activity. It is characteristic of mostly healthy subjects. One distinctive area in this category represents what might be called the “high sympatho-adrenergic” state corresponding to a significant increase in SNS (points [3.3], [3.4], [4.3], [4.4]. A person reaches this state when he/she experiences a major energy boost (i.e., a sharp SNS increase). The “high sympatho-adrenergic” state is characterized by a sudden adrenalin surge similar to what an athlete feels before a competition or a tiger before a jump.

Physiological Interpretation of ANS States

by Alexander Riftine, Ph.D

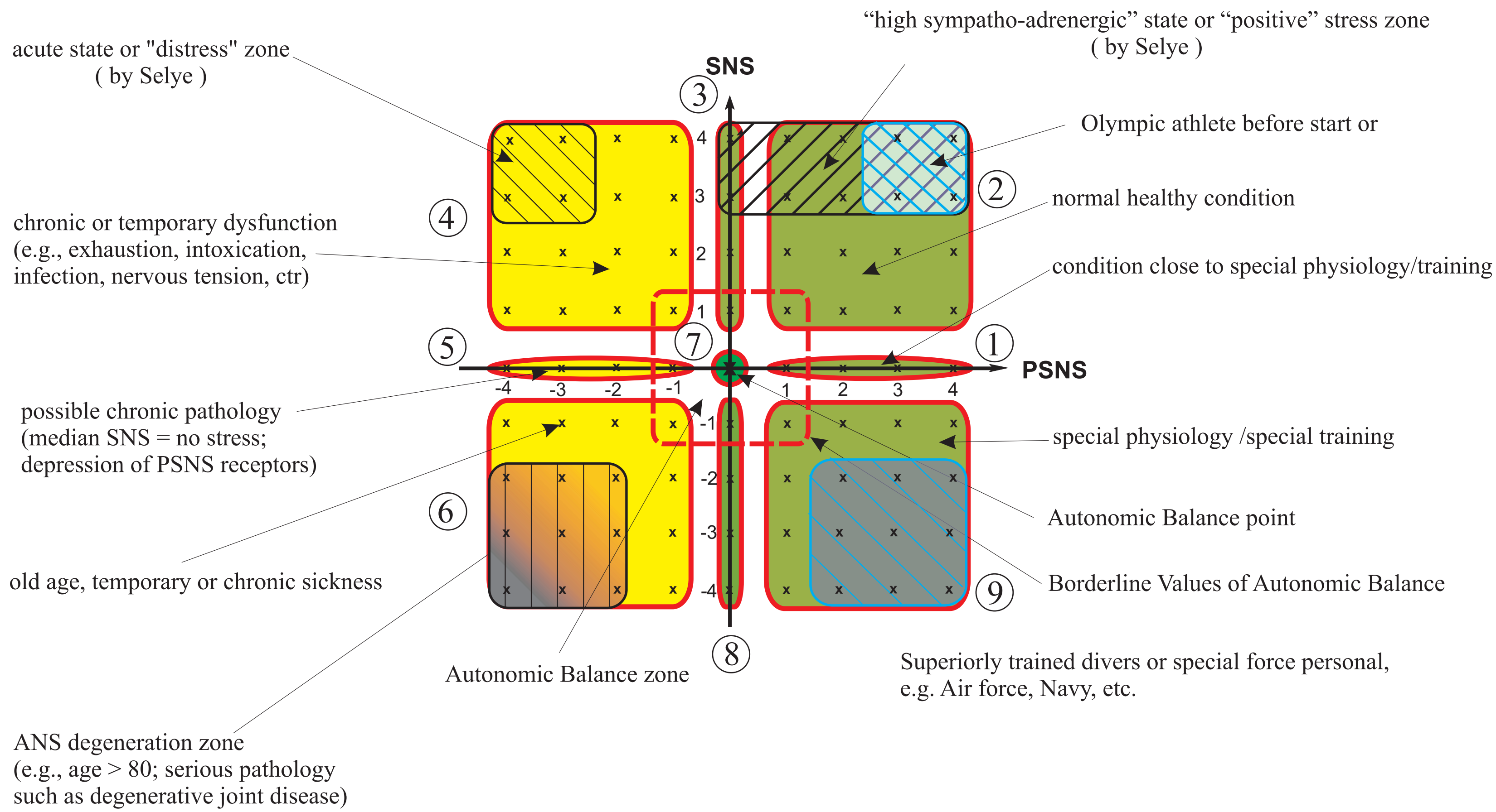


Fig. 4b Nine categories of the Autonomic Nervous System's conditions

NOTE

There is an interesting correlation between our results and the popular "Theory of Stress" by Selye. According to this theory, stress could be subdivided into 2 categories: 1) stress as a positive idea, and 2) distress as a negative idea.

Categories 1 through 3 represent basically healthy persons, but we have to keep in mind that healthy people may have two different physiological states. One state has a low level of sympathetic activity and the other has a significant increase in sympathetic activity. Both states are distinguished by an increase in parasympathetic activity. In Selye's stress theory, an increase in PSNS and a significant increase in SNS reflect “positive” stress while a decrease in PSNS and a significant increase in SNS reflect distress. Condition of a healthy person with a significant increase in SNS and an increase in PSNS (our “high sympatho-adrenergic” state) thus corresponds to Selye's idea of “positive” stress.

3 SNS Prevalence:
This category represents an increase in SNS combined with a median value of PSNS. From the physiological standpoint, this category represents a transitional stage between the second and fourth categories.

4 PSNS decrease with SNS increase:
This category can apply to both clinically sick and clinically healthy individuals (defined as those not requiring medical intervention). However, the use of the term "healthy" is not always appropriate since functional imbalance from stress, physical exhaustion, nervous tension, infection, intoxication (including drugs and alcohol), exacerbation of chronic conditions, and many other causes may still be present. In such cases a decrease in PSNS due to depressed PSNS nerve centers can be observed, along with a simultaneous Sympathetic activation, which is triggered by the struggle of the nervous system to balance itself. When Sympathetic activation is high (points: [-3.3], [-3.4], [-4.3] [-4.4]), a person reaches an "acute" state characteristic of an acute illness or extreme stress/dysfunction.

NOTE

✔ The "acute" section of Category 4 with a decrease in PSNS and a significant increase in SNS clearly corresponds to Selye's idea of distress as a “negative stress” (see NOTE to Category 2 above).

5 PSNS decrease with average level of SNS:
This category, like the third, is transitional. Everything that pertains to the fourth category can be related to it, but here, SNS activity is within median values. This means that stress, or nervous overload is unlikely. This category may often reflect a depression in the receptor system of PSNS, indicating the possibility of chronic pathology.

6 SNS and PSNS decrease:
The sixth category, especially beyond the point -3 on either axis, reflects a general involuntary degeneration of both SNS and PSNS nervous centers. The majority of cases found in this category are either very old patients or those with diseases causing a significant decrease in the sensitivity of the entire receptor system along with partial degeneration of nervous centers. Examples are the elderly people, patients suffering from cancer or any other disease causing similar depression of ANS centers.

☑ NOTES

- ✔ Point [-1.-1] of this category is an exception to this. It represents an insignificant, general decrease in ANS and approximates the point of Autonomic Balance. It can be interpreted as a border line value of Autonomic Balance.
- ✔ Points [-1.-2], [-1.-3], [-1.-4] are usually, though not exclusively, found in patients with hyperkalemia or excessive levels of potassium ions, which alter the usual polarized state of the cardiac muscle fibers leading to a decrease in the rate and force of contractions.

7 Autonomic Balance:
It is a category, even though formally it is only a point, and all other points in its vicinity that belong to the other eight categories can be interpreted as borderline values of the Autonomic Balance. The central point is circled in red; the extended “Autonomic Balance” area is marked with a red dotted line in Fig. 4.

8 SNS decrease with average level of PSNS:
This category, like the third and fifth, is transitional. Everything that pertains to the sixth and nineth categories can be related to it, but here, PSNS activity is within median values.

9 Increase in PSNS with decrease in SNS:
The ninth category is rather unusual because normally an increase in PSNS is accompanied by an increase in SNS. This rare condition is found in water polo athletes, long-distance runners, navy seals and persons with special heart training for deep-sea diving.

Intellewave implements a battery of three tests as the most comprehensive and informative combination of tests for ANS purposes:

1. Orthostatic, or lying-to-standing, test as the initial method for ANS provocation.

2. Valsalva maneuver combined with Deep Breathing as the optimal method for revealing the hidden abilities of the Autonomic function and distinguishing between chronic and temporary abnormalities.

3. Real-time Intellewave test as the ultimate method for ANS assessment in long-term therapy, continuous monitoring (especially, under anesthesia/intensive care), research and experimentation.

All three tests may be conducted on a single patient as well as on two patients simultaneously for comparative purposes (with a special cable).

Orthotest as a Method of ANS Assessment

A proper evaluation requires measurements of a patient under at least two different conditions. The method used here is to examine a patient both at rest and during physical activity. This can be accomplished by having a patient engage in some activity where the general response of a healthy person is known. Based on the patient's reaction, a more accurate assessment of ANS is possible.

Intellewave uses a very popular method of ANS provocation - the Orthostatic Test, which is simply a transition from a supine to a standing position. Any physical or mental dysfunction will be exhibited as an inadequate ANS response during this test.

Intellewave graphs the ANS State and its reaction using SNS and PSNS activities as, respectively, the vertical or "Y" and the horizontal or "X" axis.

☑ NOTE

☑ The most important group of points among the 81 recognizable possibilities is the group along the line bisecting the [0,0] coordinates as shown in Fig. 5. This line contains 9 points (including [0,0]) with numerically equal coordinates. Formally these points may be considered points of Autonomic Balance due to their characteristic parity of PSNS and SNS activity. Thus the point [0,0] may be interpreted as a point of balance in the general activity of PSNS and SNS which correlates with the accepted notion of "vegetative homeostasis". It is important to realize that a slight increase [1, 1] or a slight decrease [-1.-1] still reflects a normal average level of the traditional notion of "vegetative homeostasis", but any deviation outside of these parameters, though mathematically still balanced, must not be interpreted as a clinical homeostasis. Children, however, will typically show a moderately to sharply increased balance.

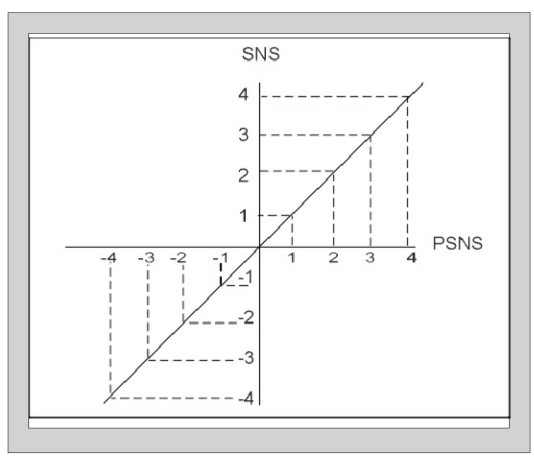
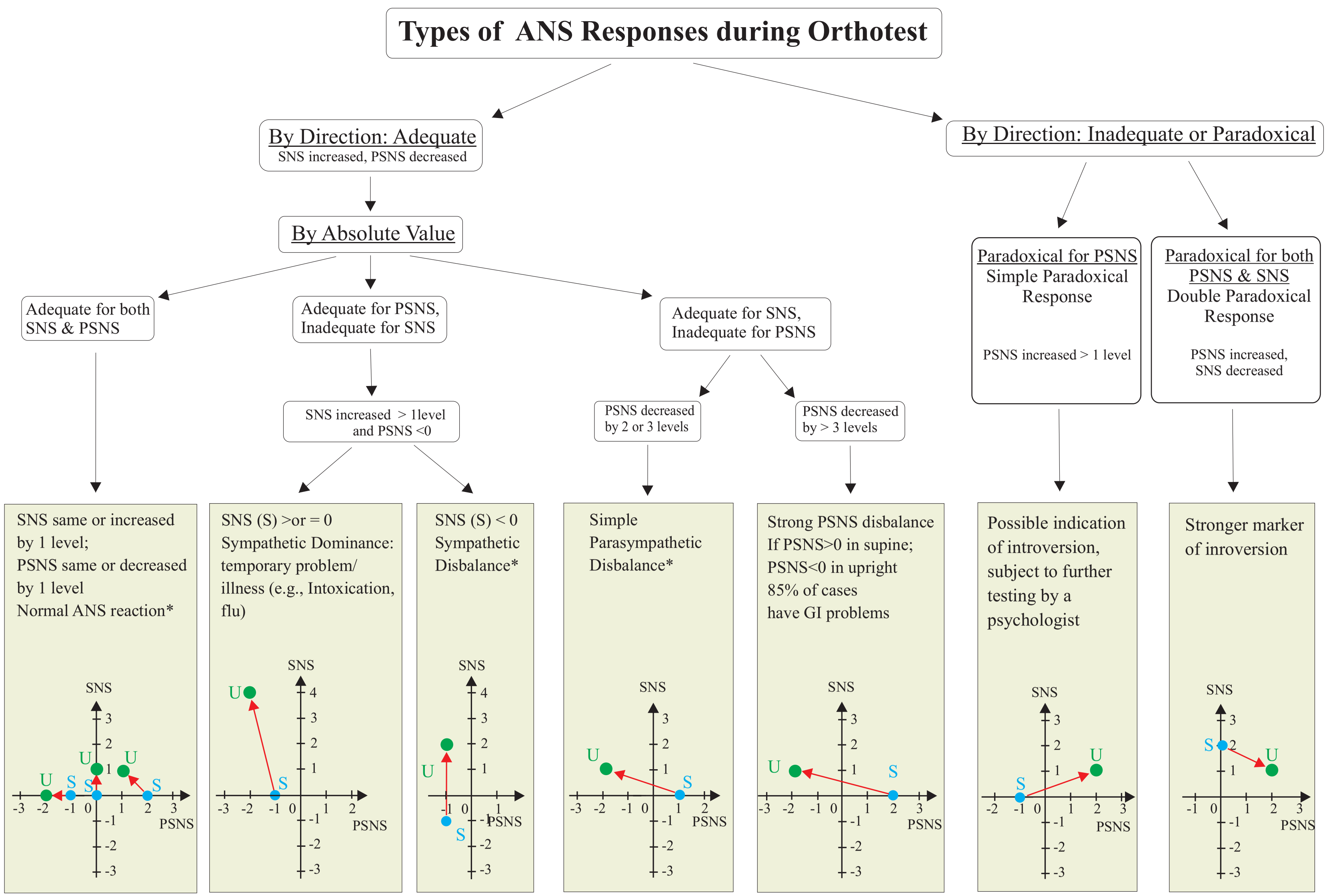


Fig. 5

Diagram 1. ANS RESPONSES during ORTHOTEST with ILLUSTRATIONS and PHYSIOLOGICAL IMPLICATIONS



* Healthy or unhealthy condition depends on the zone (cf. Fig. 4)

The general approach is to balance ANS or restore it to homeostasis. However, you can and should develop your own methods, based on the needs of specific cases. Evaluating a patient's ANS State using Intellewave's Orthotest before and after any treatment can provide an accurate and reliable evaluation of treatment effectiveness. For example, in cardiology, it is very important to optimize the therapeutic strategy for the assessment of beta-blockers' effectiveness. Or, in clinical pharmacology, one of the important tasks is to assess the influence of some particular medicine on Autonomic function.

HOW TO INTERPRET ORTHOTEST

The classification of types of ANS responses during Orthotest and sample cases are given on Diagram 1. Types of ANS Responses during Orthotest.
Diagram 1 provides classification of patient reaction to lying-to-standing test along with illustrations – chart diagrams and physiologic implications. The chart diagrams illustrating each type of response are provided as one of all the possible cases within this type and serve as examples of such reactions to Orthotest.

SAMPLE CASES

Evaluating a patient's ANS state by Intellewave's Orthotest before and after any treatment can provide an accurate and reliable evaluation of treatment effectiveness. Figures 6 - 7 provide some examples. The measurements in Figure 6 are typical for a healthy, fit person.

Another example can be seen in Figure 7. It represents test results of a patient previously diagnosed with Ischemic heart disease.

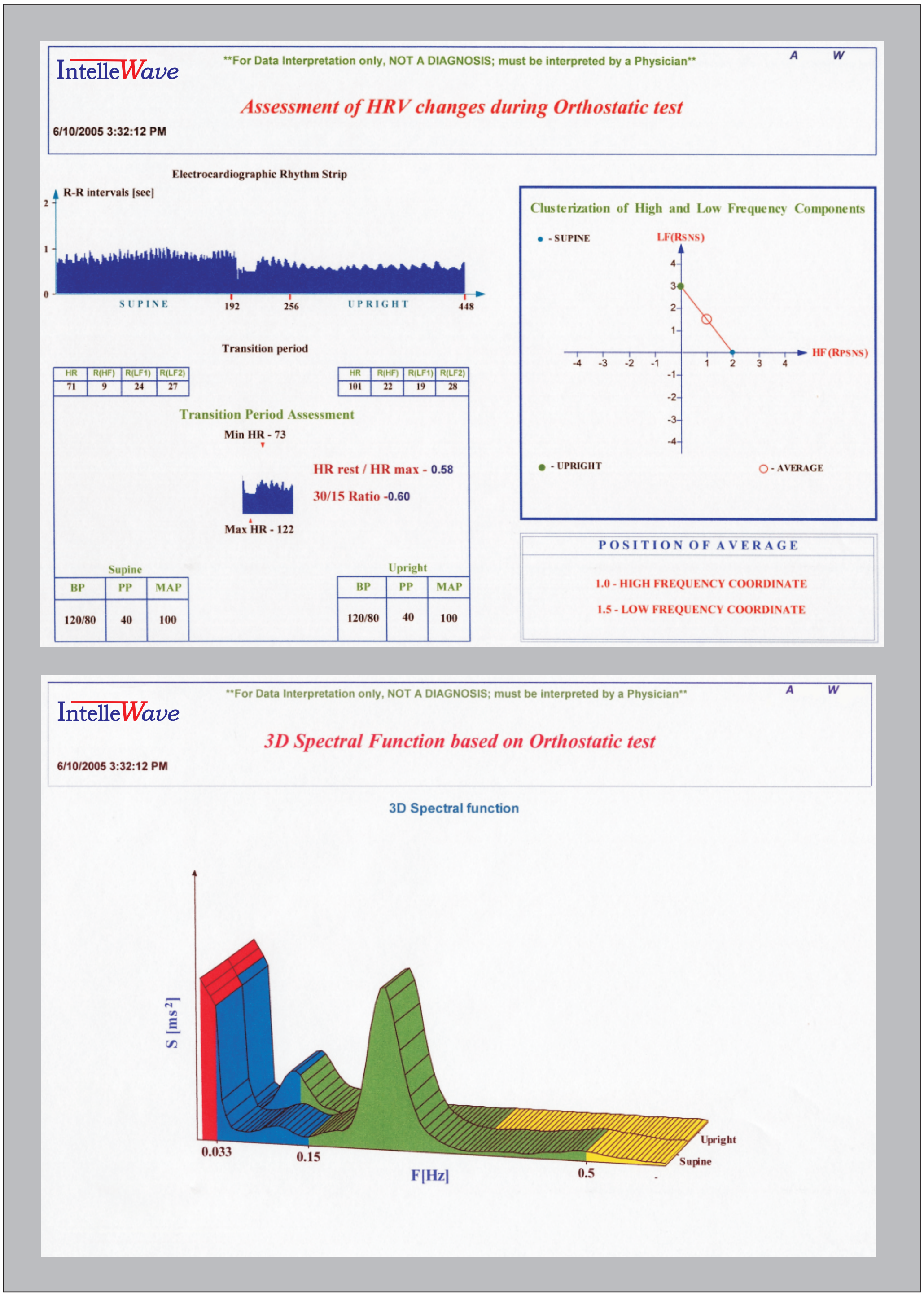


Figure 6. Orthostatic test results for healthy person.

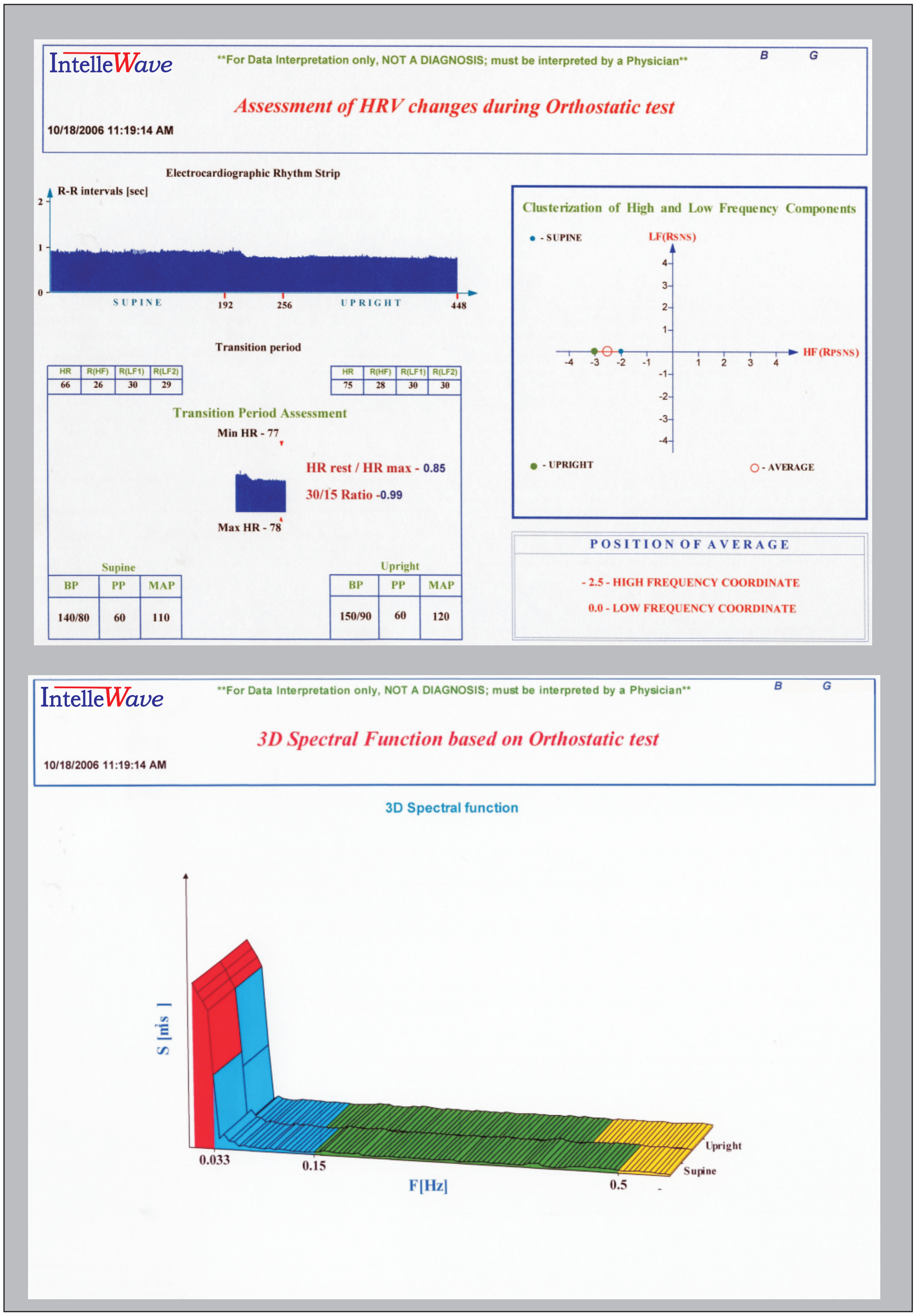


Figure 7. Orthostatic test results for patient previously diagnosed with Ischemic heart disease

Valsalva maneuvre combined with Deep Breathing as a method of ANS assessment

While Orthostatic Test is used for initial ANS assessment, the Valsalva maneuver combined with Deep Breathing is the second-tier, more in-depth test, which primary purpose is threefold:

1. Revealing the hidden abilities of the Autonomic function
2. Indirect assessment of the sensitivity of baroreceptors
3. Distinguishing between chronic and temporary abnormalities.

We recommend the Valsalva maneuver only as a follow-up to Orthotest and only if it shows negative parasympathetic results, i.e., if the midpoint between the Supine and Upright positions, marked by a red dot, has a negative PSNS value. Valsalva maneuver is explicitly NOT recommended if the stress level is too high, i.e., SNS = 3 or 4.

Orthostatic test (Orthotest) and Valsalva maneuver combined with deep breathing test (for convenience further referred to as Valsalva test) together form an overall picture of the patient's physiological functioning. While Orthotest reflects current status of the organism, the Valsalva test shows functional reserves of the ANS.

HOW TO INTERPRET TEST "VALSALVA MANEUVER COMBINED WITH DEEP BREATHING"

☑ NOTE

☑ Valsalva maneuver combined with deep breathing is further referred for convenience as "the Valsalva test."

The test provides two types of results:

1. Valsalva Index,
2. Comparative Analysis of the ANS status of Normal vs Deep Breathing (reflected on the ANS chart).

The latter result is by far more reliable and informative. The test "Valsalva maneuver combined with deep breathing" targets to reveal changes from normal to deep breathing and compare these two stages. Valsalva maneuver itself is auxiliary in this test and is used as a stimulus to induce these changes by activating baroreceptors and receptors of the ANS.

1 HOW TO INTERPRET VALSALVA INDEX

Calculated Valsalva Index falls into one of the three zones:

>1.7	- High level,
1.3-1.7	- Average level,
<1.3	- Low level.

Based on our long-termed research, we have established that the Transitional Process in Valsalva is practically impossible to standardize since Valsalva maneuver is the act of will, and, therefore, is determined by many subjective factors due to variations in individual physiology and psycho-emotional makeup (e.g. persons with special training such as Air Force or Navy personnel are more adaptable to Valsalva maneuver). A classical Transition Process during Valsalva, which serves as a basis for calculating the Valsalva Index, does exist, but in real life, it is observed in only a small percent (about 10-15%) of population. Therefore, while a good Valsalva Index is significant, a poor Valsalva Index may have no clinical significance: it may result from a poor control by the patient or a lack of training. In case of a low Valsalva Index, the test results should be interpreted in terms of comparison of HRV response during normal and deep breathing.

On Figure 8 you can see an example of a test report showing a classical transitional process in Valsalva maneuver .

2 HOW TO INTERPRET ANS CHART (CLUSTERIZATION CHART OF HF (PSNS) VERSUS LF (SNS) COMPONENTS) IN THE VALSALVA TEST

The test Valsalva maneuver combined with deep breathing targets to assess functional reserves of both sympathetic and parasympathetic branches of the ANS.

In interpretation of results on the Clusterization chart both the position of the points and the dynamics of the test should be taken into the consideration. The types of ANS responses to Valsalva test are described below.

In order to understand how to interpret a patient's reaction to the test, let us first look at the reaction of the parasympathetic nervous system (PSNS) and then at the reaction of the sympathetic nervous system (SNS).

1-1 How to assess response of Parasympathetic Nervous System (PSNS) during the Valsalva test

In order to separately consider response of the PSNS we will look at trends when SNS remains unchanged while the PSNS system response varies.

GENERAL TREND: Independently on the position and dynamics of SNS, increase in PSNS activity from normal breathing to end of test usually indicates that functional reserves of the PSNS come into action; the larger the increase, the greater the reserves of the PSNS.

Different types of responses of PSNS are shown on Diagram 2. Please note that each type has a range of values that fall into that type, and a specific example is given below to represent one of all possible cases of this type. The range of values for the final position of PSNS is shown by shaded area of the graph.

1-2 How to assess response of Sympathetic Nervous System (SNS) during Valsalva test

Reaction of SNS should be evaluated depending on the position of PSNS. First, determine which of the two zones

PSNS reaction falls into, shown by the shaded areas, then follow the scheme to trace the dynamics of SNS.

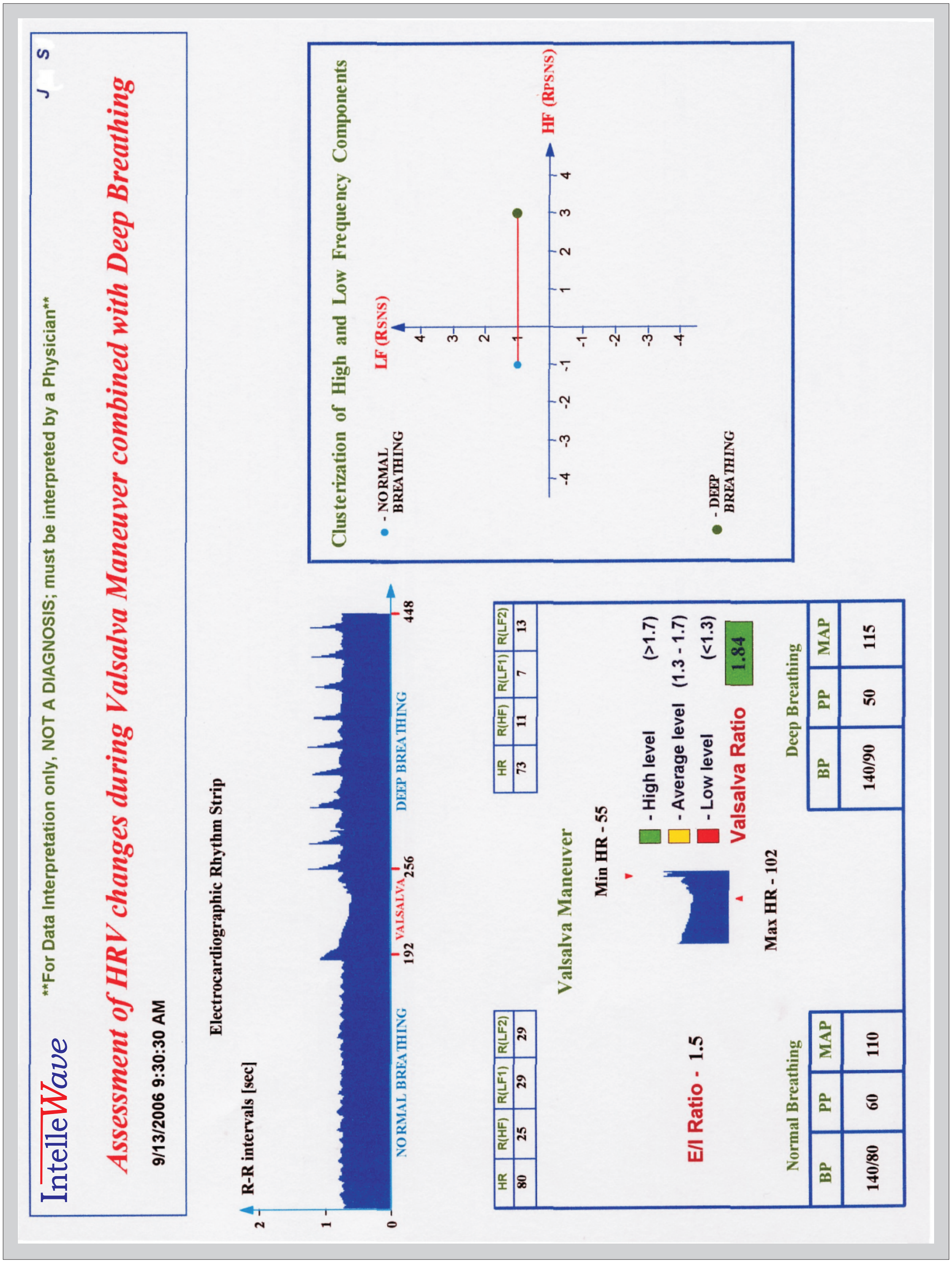
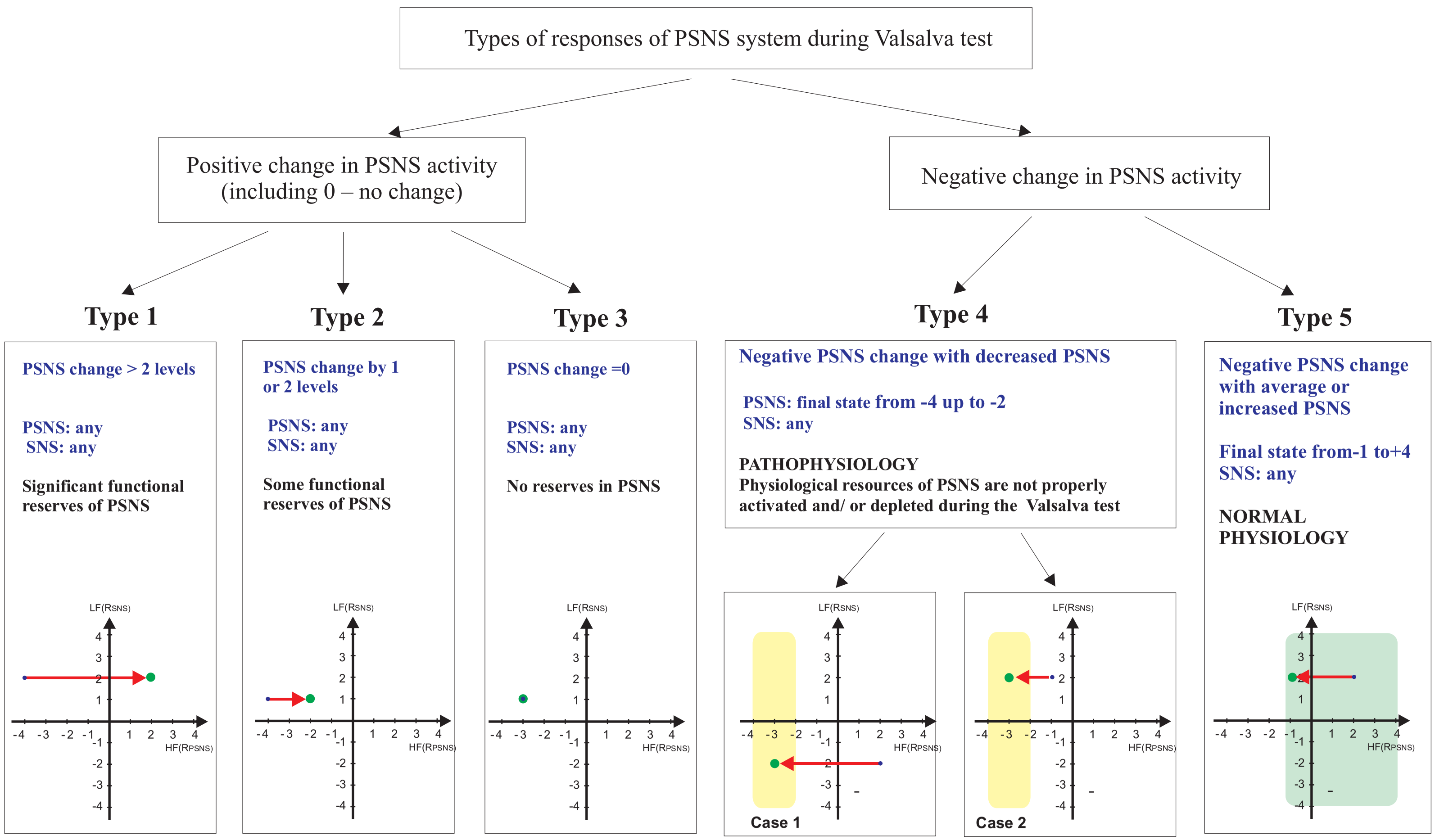

IntelleWave
For Data Interpretation only, NOT A DIAGNOSIS; must be interpreted by a Physician
Assessment of HRV changes during Valsalva Maneuver combined with Deep Breathing
9/13/2006 9:30:30 AM
Electrocardiographic Rhythm Strip
R-R intervals [sec]
2
1
0
NORMAL BREATHING
VALSALVA
DEEP BREATHING
192
256
448
HR R(HF) R(LF1) R(LF2)
80 25 29 29
HR R(HF) R(LF1) R(LF2)
73 11 7 13
Valsalva Maneuver
Min HR - 55
Max HR - 102
E/I Ratio - 1.5
- High level (>1.7)
- Average level (1.3 - 1.7)
- Low level (<1.3)
Valsalva Ratio 1.84
Normal Breathing
BP PP MAP
140/80 60 110
Deep Breathing
BP PP MAP
140/90 50 115
Clusterization of High and Low Frequency Components
- NORMAL BREATHING
- DEEP BREATHING
LF (RSNS)
HF (RPSNS)
4 3 2 1 -1 -2 -3 -4
-4 -3 -2 -1 1 2 3 4

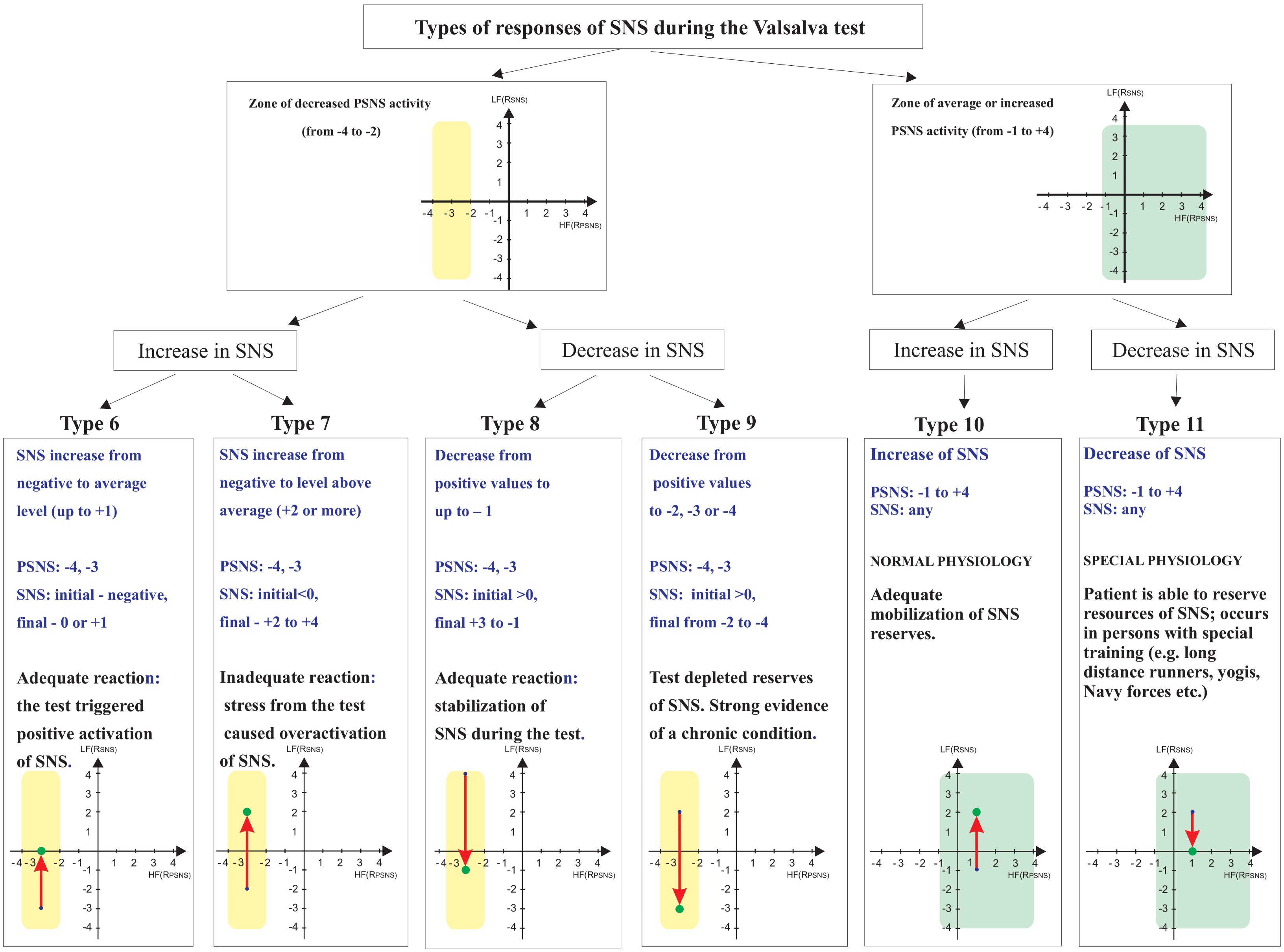
Figure 8.

Diagram 2. Types of responses of PSNS during Valsalva test



NOTE:
-Shaded area – range of all possible values of final position of PSNS.
-Charts below each type represent only one specific example of all possible cases of this type.

Diagram 3. Types of responses of SNS during the Valsalva test*



*NOTE: Position of -1 of PSNS activity can be considered a borderline value. If the initial position of SNS is 0, any SNS decrease indicates stabilization of the sympathetic branch. If SNS from positive values decreases to 0, this characterizes borderline condition and can indicate either normal or inadequate reaction depending

1-3 HOW TO INTERPRET MIXED RESPONSES WHEN BOTH SNS AND PSNS CHANGE

In most cases, the test demonstrates a mixed response when both SNS and PSNS change after performing the Valsalva maneuver and deep breathing. To interpret the result, you should treat the arrow representing the ANS response as a vector and break it down into the vertical (SNS) and horizontal (PSNS) components as shown on Figure 9 below.

Step 1 Draw the horizontal component of the vector and assess the change in PSNS according to the scheme discussed above,

Step 2 From the end of the PSNS vector component, draw the vector corresponding to the SNS change and assess it according to the scheme discussed above.

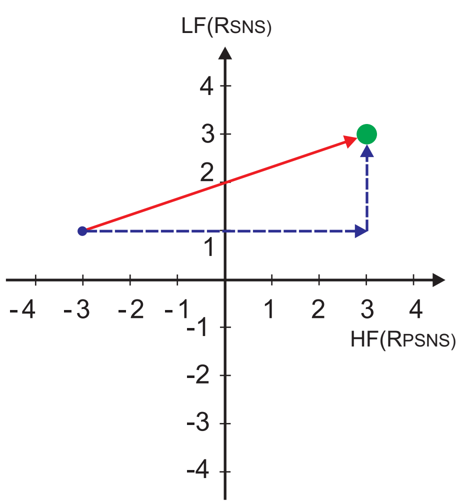


Figure 9

EXAMPLE OF INTERPRETATION OF MIXED RESPONSE

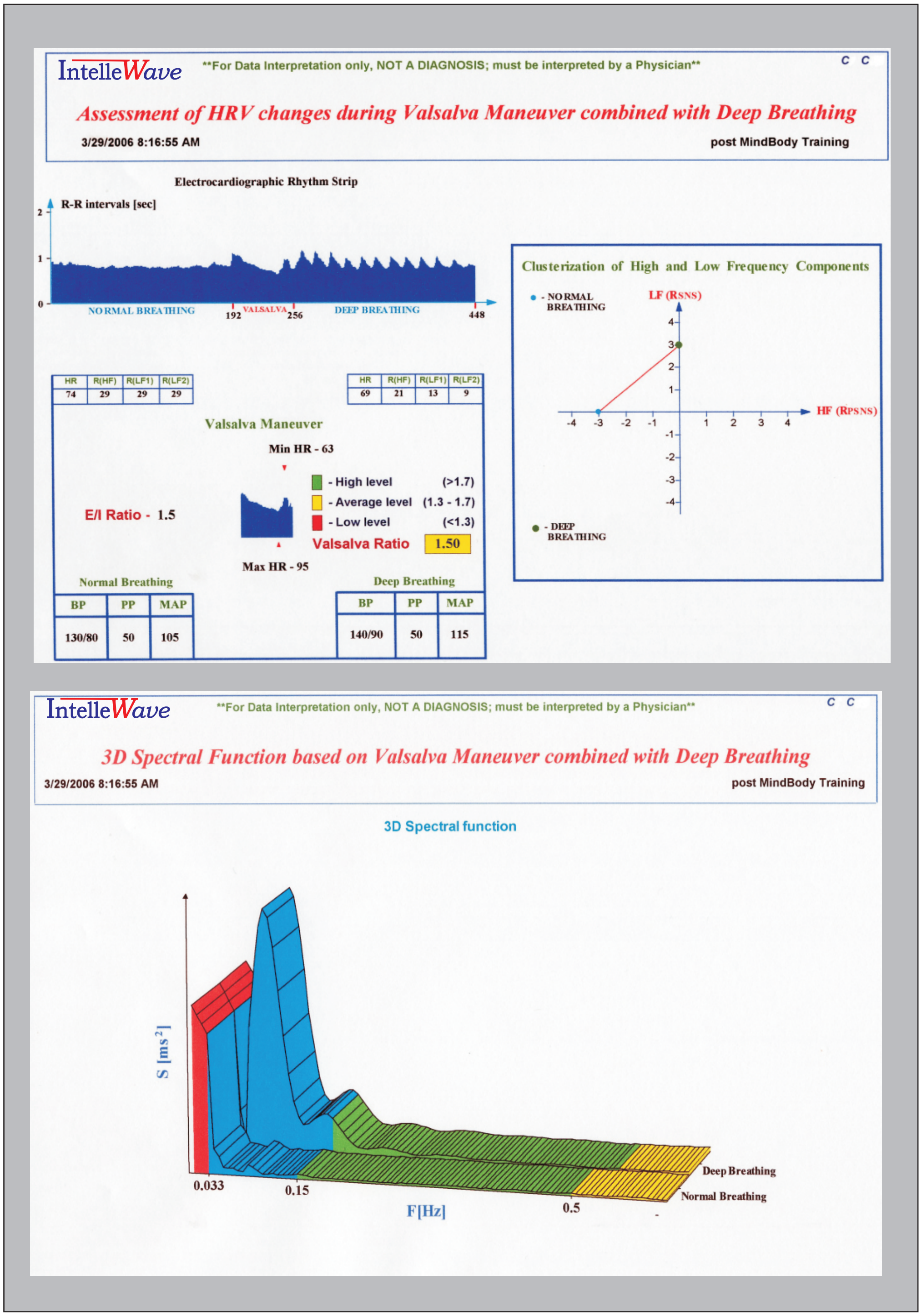
Step 1 PSNS component: change from -3 to +3, significant functional reserves of PSNS,

Step 2 SNS component: zone 2 (positive PSNS): Increase of SNS activity - Normal physiologic response, indicating adequate mobilization of SNS reserve.

SAMPLE CASES

Figures 10 - 11 provide some examples. The measurements in Figure 10 are typical for a healthy, fit person.

Another example can be seen in Figure 11. It represents test results of a patient previously diagnosed with Ischemic heart disease.



HR	R(HF)	R(LF1)	R(LF2)
74	29	29	29

HR	R(HF)	R(LF1)	R(LF2)
69	21	13	9

BP	PP	MAP
130/80	50	105

BP	PP	MAP
140/90	50	115

Figure 10. Valsalva maneuver combined with Deep Breathing test results for healthy person

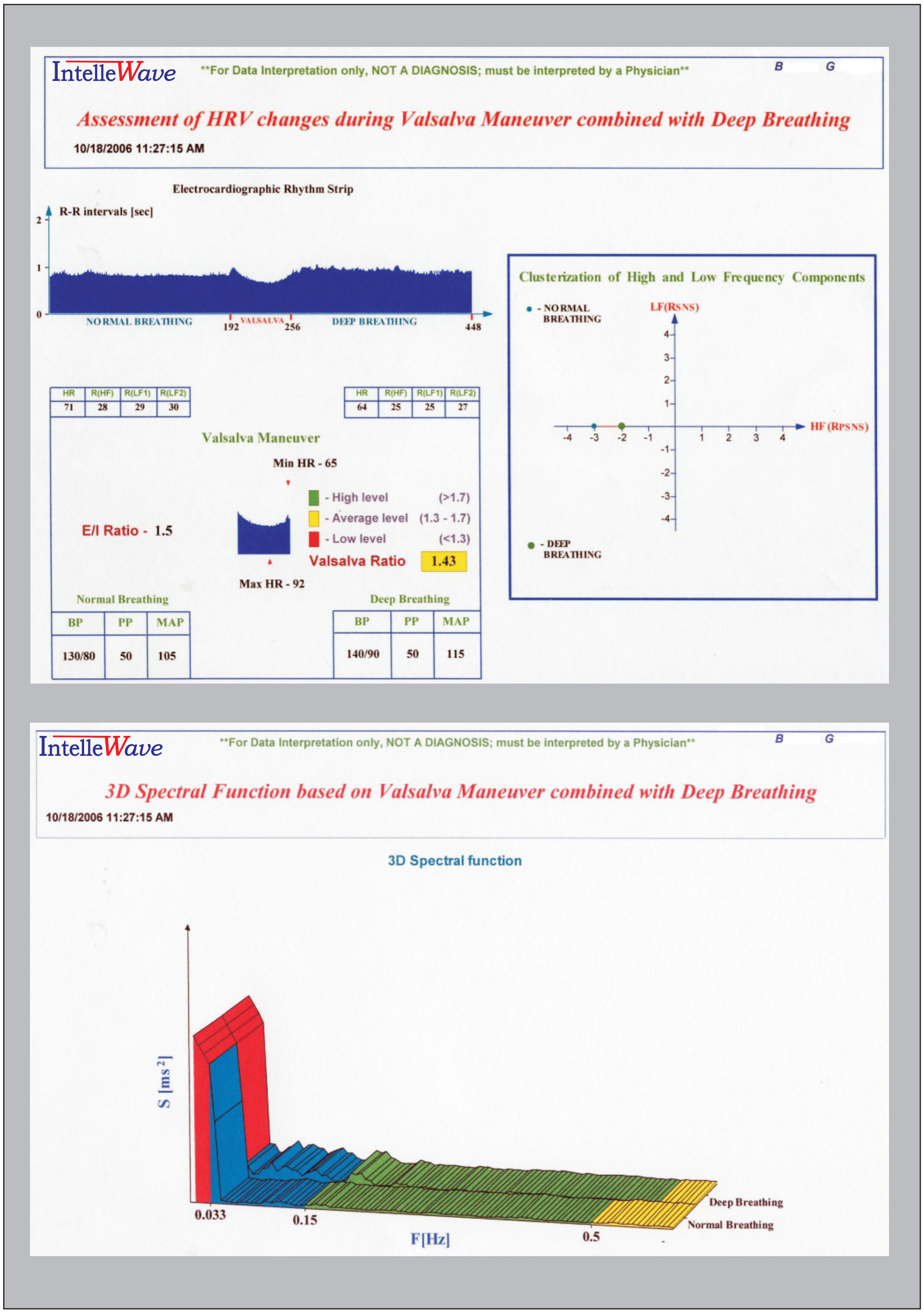


Figure 11. Valsalva maneuver combined with Deep Breathing test results for patient previously diagnosed with Ischemic heart disease

COMBINING RESULTS OF ORTHOTEST AND VALSALVA TEST FOR OVERALL PATIENT ASSESSMENT: Sample case

A diagram for suggested steps for overall patient assessment is shown on Figure 12.

Let us go through the steps of assessment and evaluate results of an actual patient. As recommended in the diagram, Orthotest was administered first, and produced the results shown on Figure 13. As you can see from the Clusterization chart, Parasympathetic level was decreased from -2 to -3, while Sympathetic level was increased from +1 to +2, which indicates an adequate overall response with lower than average performance of PSNS during the test, which is typical for most clinical cases and may indicate some health abnormality. The results and other clinical data available to the physician from standard assessment methods suggested that there are no contraindications for Valsalva maneuver. The Valsalva test was thus performed according to the standard protocol and produced results shown on Figure 14. An excellent Valsalva ratio was obtained; PSNS increased by 6 levels from – 3 to + 3 while SNS increased by 2 levels: the test revealed excellent reserves of PSNS and adequate mobilization of SNS reserve.

Conclusion

Orthotest has detected a health problem, while Valsalva test has demonstrated excellent functional reserves of the ANS. The combination of results of both tests suggest that the problem revealed during Orthotest is most likely a temporary, acute condition in a person with good overall health.

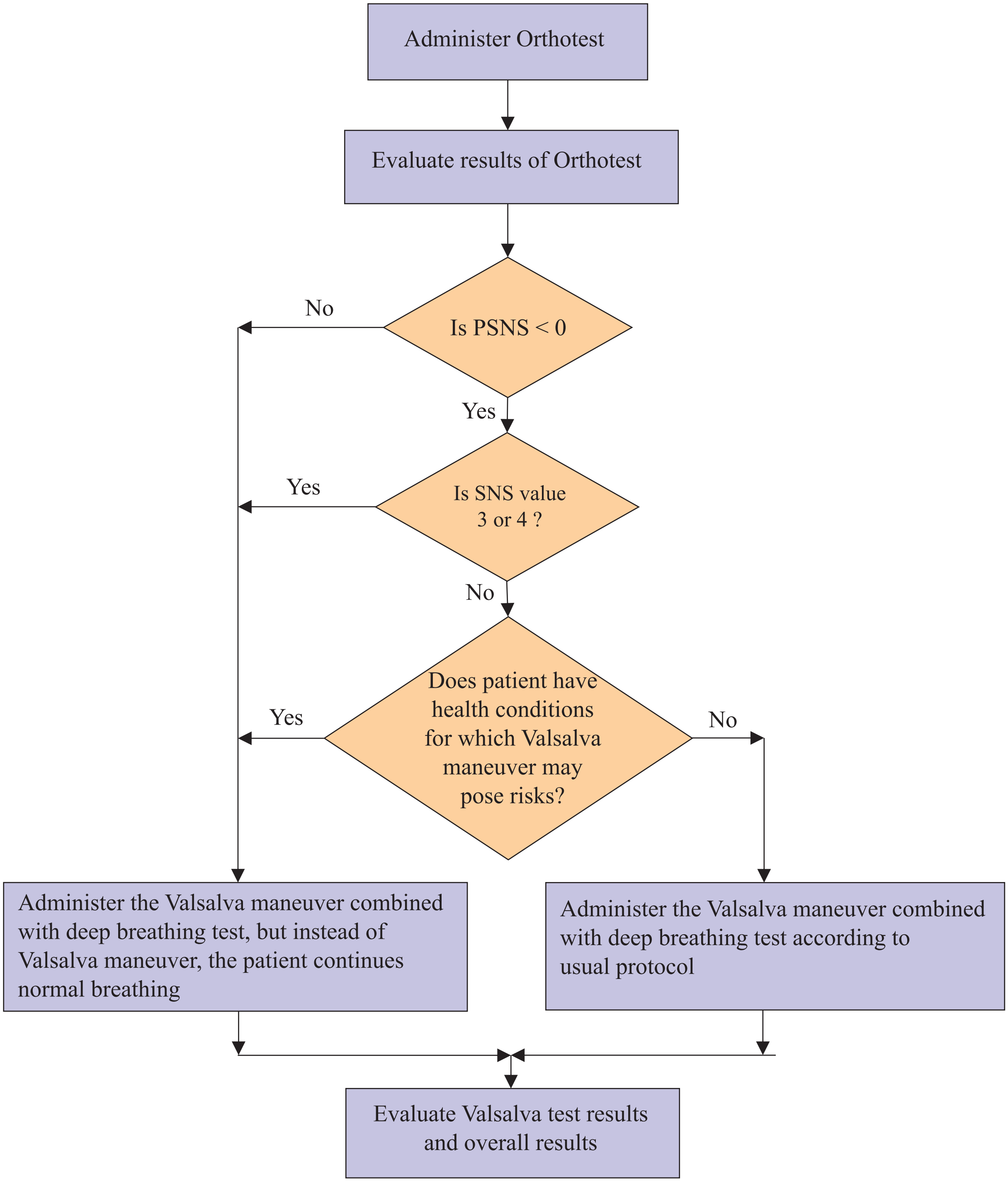


Figure 12. Recommended sequence for Overall Patient Assessment by Intellewave system

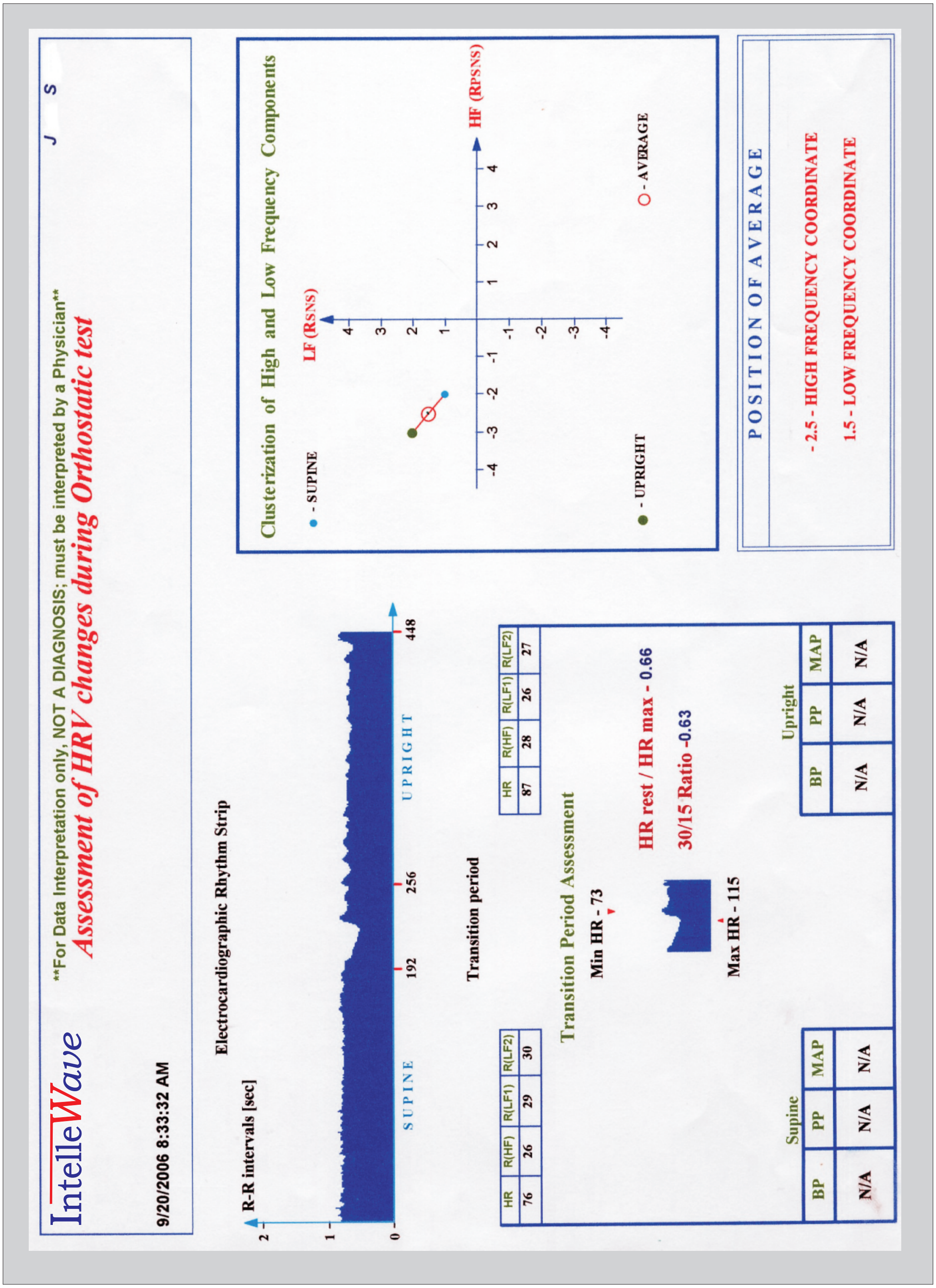

IntelleWave
9/20/2006 8:33:32 AM
For Data Interpretation only, NOT A DIAGNOSIS; must be interpreted by a Physician
Assessment of HRV changes during Orthostatic test
J S
Electrocardiographic Rhythm Strip
R-R intervals [sec]
SUPINE
UPRIGHT
192
256
448
Transition period
HR R(HF) R(LF1) R(LF2)
76 26 29 30
87 28 26 27
Transition Period Assessment
Min HR - 73
Max HR - 115
HR rest / HR max - 0.66
30/15 Ratio -0.63
Supine
Upright
BP PP MAP
N/A N/A N/A
Clusterization of High and Low Frequency Components
- SUPINE
- UPRIGHT
- AVERAGE
LF (RSNS)
HF (RPSNS)
POSITION OF AVERAGE
-2.5 - HIGH FREQUENCY COORDINATE
1.5 - LOW FREQUENCY COORDINATE

Figure 13

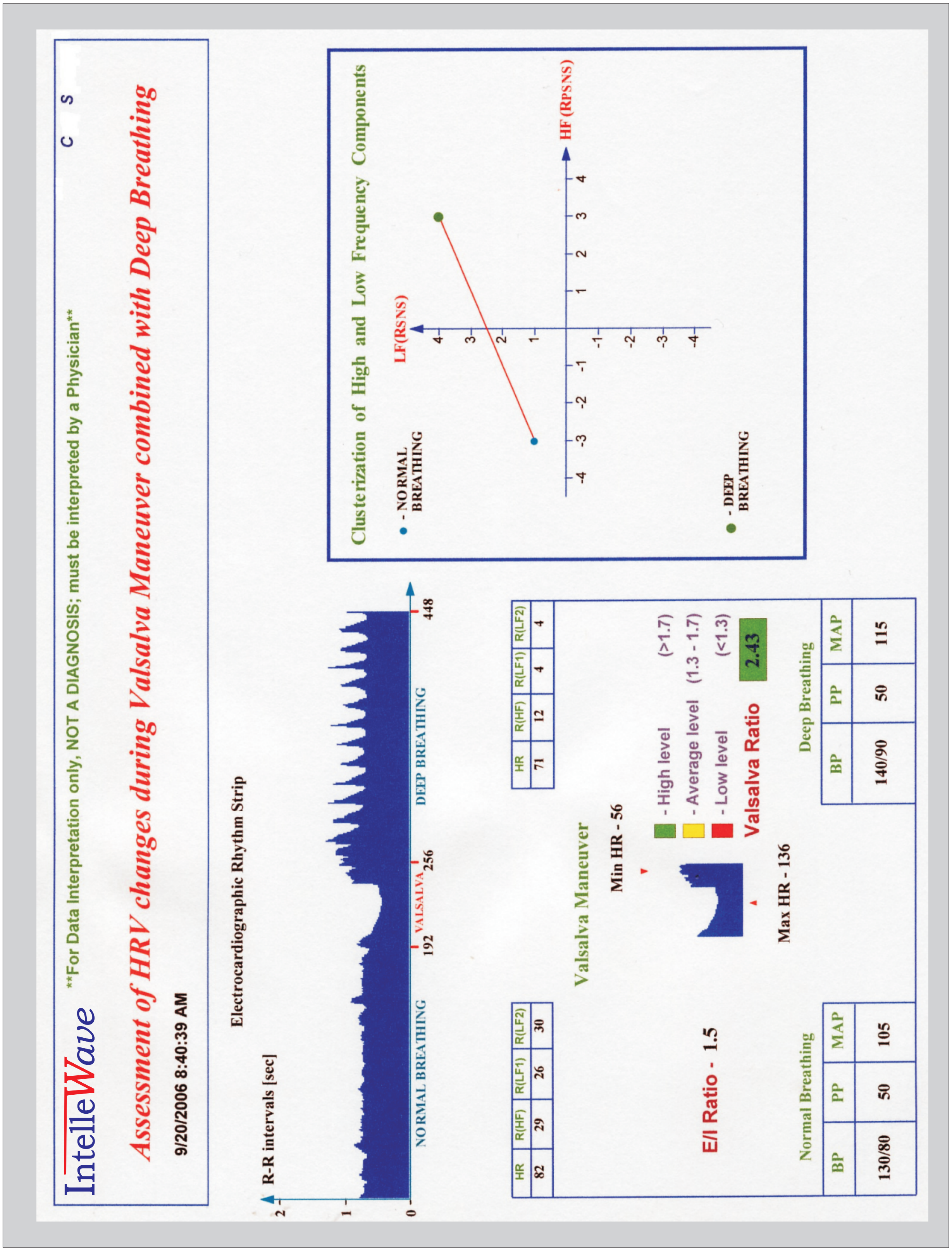

IntelleWave
For Data Interpretation only, NOT A DIAGNOSIS; must be interpreted by a Physician
Assessment of HRV changes during Valsalva Maneuver combined with Deep Breathing
9/20/2006 8:40:39 AM
Electrocardiographic Rhythm Strip
R-R intervals [sec]
NORMAL BREATHING
VALSALVA
DEEP BREATHING
192
256
448
HR R(HF) R(LF1) R(LF2)
82 29 26 30
71 12 4 4
E/I Ratio - 1.5
Valsalva Maneuver
Min HR - 56
Max HR - 136
- High level (>1.7)
- Average level (1.3 - 1.7)
- Low level (<1.3)
Valsalva Ratio
2.43
Normal Breathing
BP PP MAP
130/80 50 105
Deep Breathing
BP PP MAP
140/90 50 115
Clusterization of High and Low Frequency Components
- NORMAL BREATHING
- DEEP BREATHING
LF(RSNS)
HF(RPSNS)

Figure 14

Real-time ANS Assessment

☑ NOTE

☑ Here and further when referring to ANS assessment we mean assessment of the Autonomic Nervous System based on Heart Rate Variability.

This type of assessment is used for long-term testing in research and clinical practice. Intellwave enables ANS assessment in a "real-time" mode, which means that data is analyzed as it is put in. In this mode, the maximum test length is 24 hours; the minimum test length is determined by the time it takes to collect data on 192 consecutive heart beat intervals, which can correspond to 2-4 minutes depending on the patient's heart rate.

Results can be produced and updated with certain periodicity – the physician can choose the result update frequency: from every 192 heart beats to as little as every 6 heart beats.

In spite of simplicity of the "real-time" mode, it is essentially universal, and can be used in both clinical practice and research since it enables the autonomic response assessment during different kinds of long-term therapy or any controlled exercises (cf. Figures 12, 13) aimed at therapeutic strategy optimization. The system represents a powerful tool for investigational use in both basic and clinical research studies. The "real-time" mode allows the investigators to assess the patient's physiological response to various factors during any treatment. Of particular interest are experiments with allergic agents identification, as in the case of asthma. The list of practical applications can be extended, and practitioners and researchers in all areas of medicine can find their own uses of the system.

The system was specifically designed to include the possibility of interrupting data input during therapeutic intervention, using the "Pause" option. For example, clicking on "Pause" at the time of injection eliminates irrelevant ANS response to pain and leaves only ANS response to treatment.

SAMPLE CASE

Figures 12 and 13 show a sample printout during a controlled exercise. The results screen in this test represents the dynamics of LF power and the dynamics of HF power separately, so the upper chart is indicative of the dynamics of the sympathetic tone while the lower chart is representative of the dynamics of the parasympathetic tone. Each stage here lasts 192 heart beat intervals; the dots on this graph correspond to consecutive stages of the test. Here ANS reaction is typical of most cases. At the onset of the exercise, the Parasympathetic response decreases and the Sympathetic response increases. With the increase of the workout the process is intensified. At the end of the exercise (recovery period) we can observe the restoration of the autonomic tone to its initial level.

Fig. 12 shows separate responses of Sympathetic and Parasympathetic Tone, stage by stage. Figure 13 depicts the 3D spectral analysis for all stages.

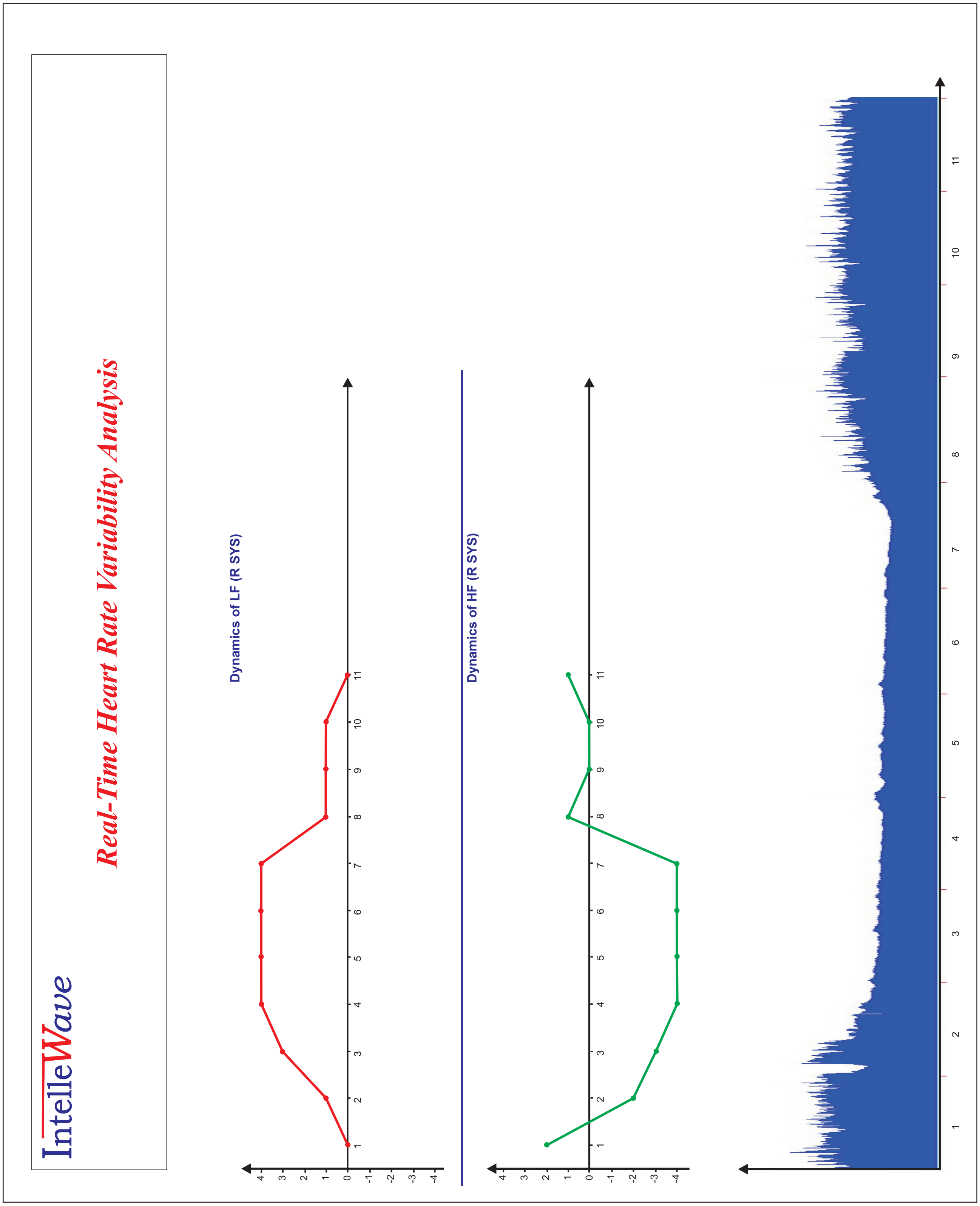

IntelleWave
Real-Time Heart Rate Variability Analysis
Dynamics of LF (R SYS)
Dynamics of HF (R SYS)

Figure 15

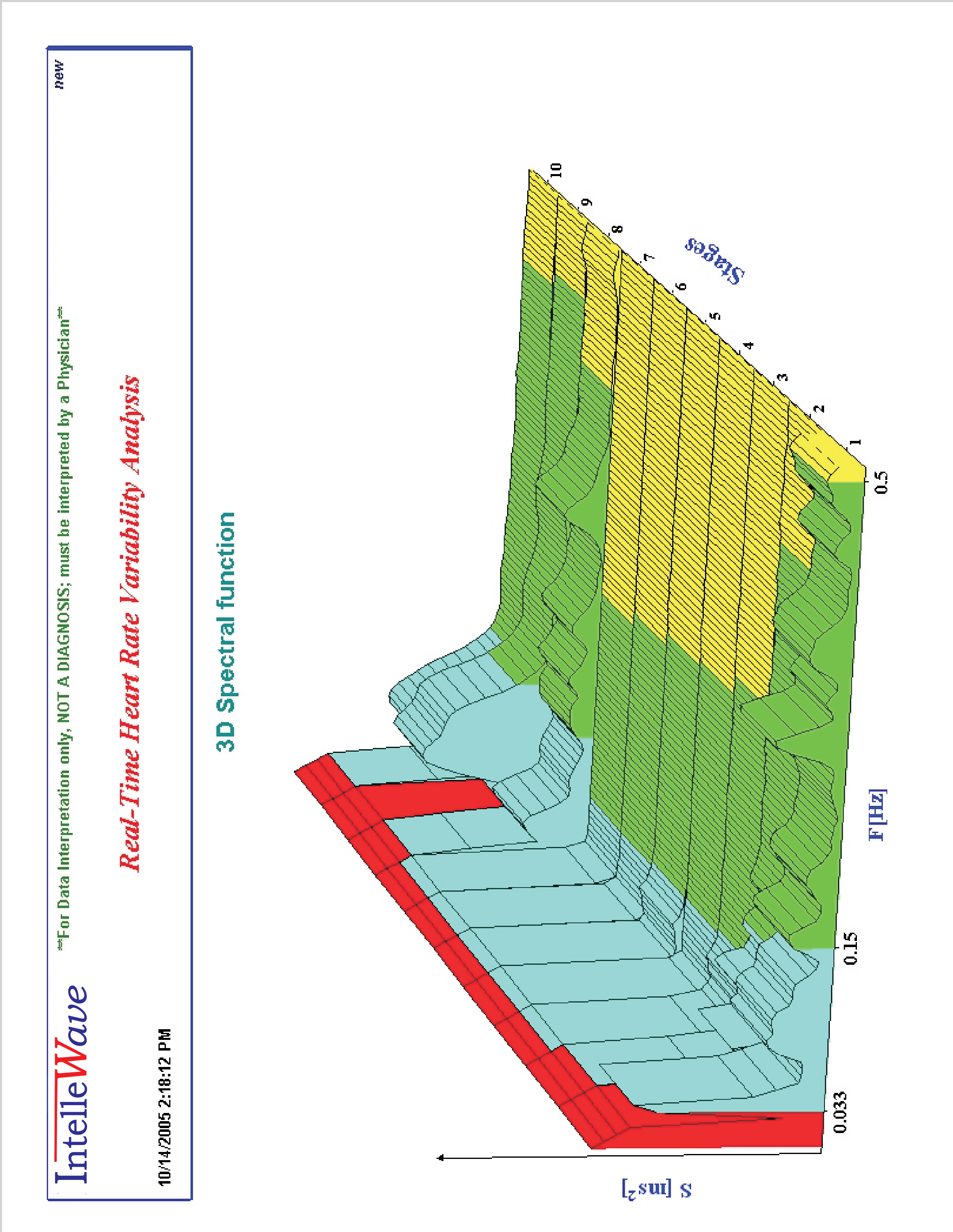

IntelleWave
10/14/2005 2:18:12 PM
For Data Interpretation only, NOT A DIAGNOSIS; must be interpreted by a Physician
new
Real-Time Heart Rate Variability Analysis
3D Spectral function
S [ms²]
0.033
0.15
F [Hz]
0.5
Stages
1
2
3
4
5
6
7
8
9
10

Fig. 16

Hourly Monitor

Intellewave presents a unique, pioneering method of ANS assessment with our new Hourly Monitor of autonomic function based on Heart Rate Variability. This method marks another step in ANS diagnostics, making Intellewave a more powerful device for detecting serious health impairments and sleep disorders.

With this new feature, you can monitor ANS activity continuously AND see the dynamics of autonomic function during up to 24 hours on one graph!

The Hourly Monitor allows you to compare ANS activity during daytime and nighttime, which is a key to detecting health abnormalities of two kinds:

1. **Detecting serious health impairments.** Seeing the difference between daytime and nighttime activity of ANS system is critical for distinguishing between a temporary health problem and a serious disorder. Normally ANS system balance should improve during sleep, if it does not, this indicates a serious, chronic health problem.

2. **Detecting sleep disorders**. Instability of parasympathetic nervous system activity during sleep beyond the normal range is a marker of a sleep disorder.

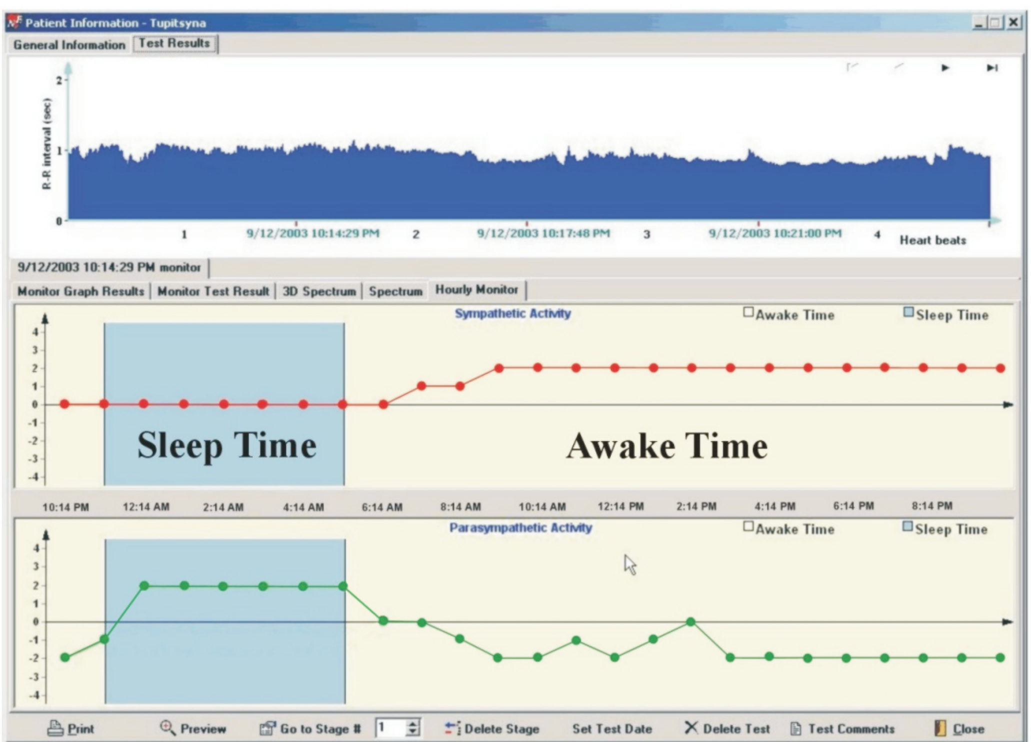


Fig. 17

1. Bigger JT Jr, Rottman JN. Spectral Analysis of RR Variability. Chapter 19 in Cardiac Arrhythmia – Mechanisms, Diagnosis, and Management, Podrid PJ, Kowey PR editors. Baltimore: William & Wilkins, 1995, pp.280-298.

2. Chireikin, L. V. Shurygin D. Ya., and Labutin V. K., Automatic Analysis of Electrocardiograms [in Russian], Nauka,. Leningrad (1977).

3. D. I. Zhemaitite. The methodology for automatic analysis of rhythmograms and its clinical applications. The Doctoral Dissertation (Doctor of Medical Science). Kaunas, Lithuania, 1972.

4. M. Minsky. Structures for Knowledge Representation. Machine Vision Psychology. Mir, 1978.

5. Riftine, Alexander. Recognition of physiological states of an individual based on mathematical analysis of heart rate variability. PhD thesis.Glushkov's Institut of Cybernetics. Scientific council of biomedical cybernetics. 1987. Kiev

6. Riftine, Alexander. Clusterization of the Relationship between SNS and PSNS activity by Heart Rate Variability Analysis. 33rd International Congress of Electrocardiology. July 2006. Cologne, Germany. Poster Presentation

7. Rottman JN, Steinman RC, Albrecht P, Bigger JT Jr, Rolnitzky LM, Fleiss JL. Efficient estimation of the heart period power spectrum suitable for physiologic or pharmacologic studies. Am J Cardiol 1990; 66:1522-1524.

8. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiologic interpretation, and clinical use. Circulation 1996; 93:1043-1065.

NOTES

Additional information on Heart Rate Variability and Blood Pressure Analysis for Autonomic Nervous System testing and related problems

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. With the remaining 30-35% of low-frequency activity relating to other regulatory mechanisms such as neuro-humoral, hormonal, thermoregulatory and baroreceptor mechanisms. Thus, from a scientific point of view, we cannot fully assess ANS activiy 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. We realize that 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, besides IntelleWave, the only two other devices using 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. 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 such as the theory of Production, which 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.

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

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 great 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].
This problem is the key problem because in medical practice, a doctor usually has no time to manually analyze some mathematical numbers. The representation of the Autonomic Nervous System status should be absolutely clear and understandable without special training.
IntelleWave has solved this problem by developing a proprietary algorithm based on Artificial Intelligence methods, in particular the Marvin Minsky's Frame Theory.

Additional Advantages of Intellewave

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 the 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).

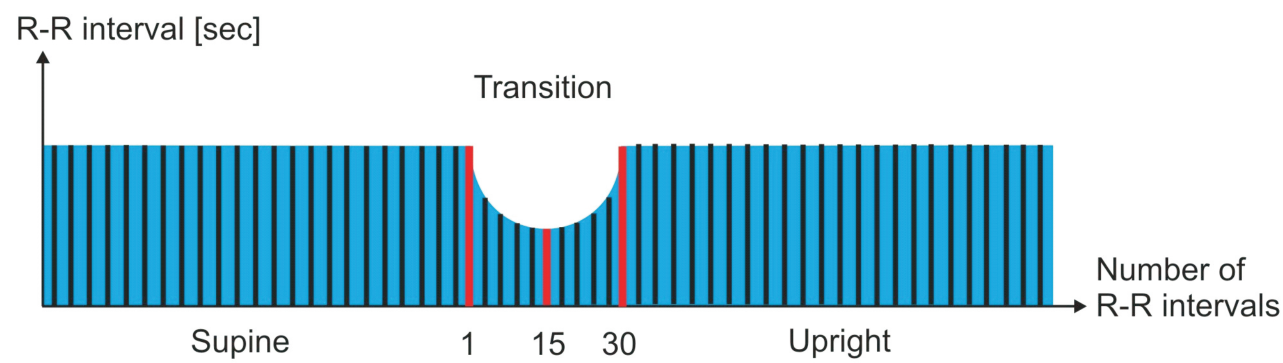


FIG. 1

NOTE: Each vertical line on this figure is corresponding with 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 fig. 2 below

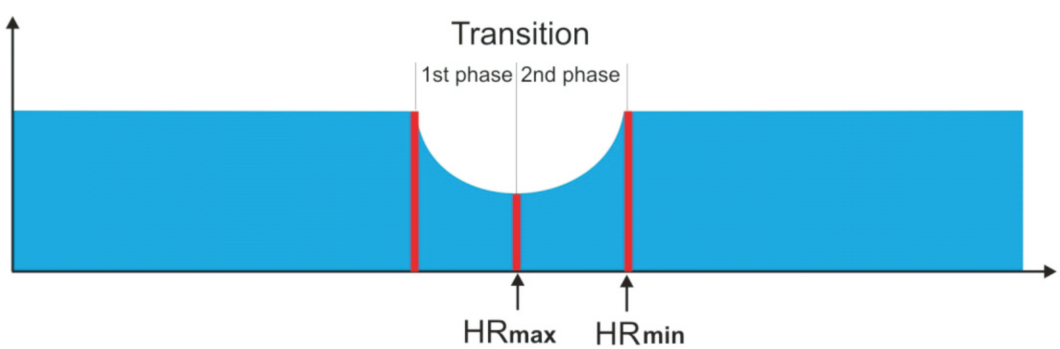


FIG. 2

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 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 we realized that possibility to match Heart Beat #15 with HR (max) and #30 with HR (min) can be just one from a thousands cases. Therefore, if somebody still calculated 30/15 Ratio exactly as HR on beat 30 by HR on beat 15 they 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 fig. 3 below).

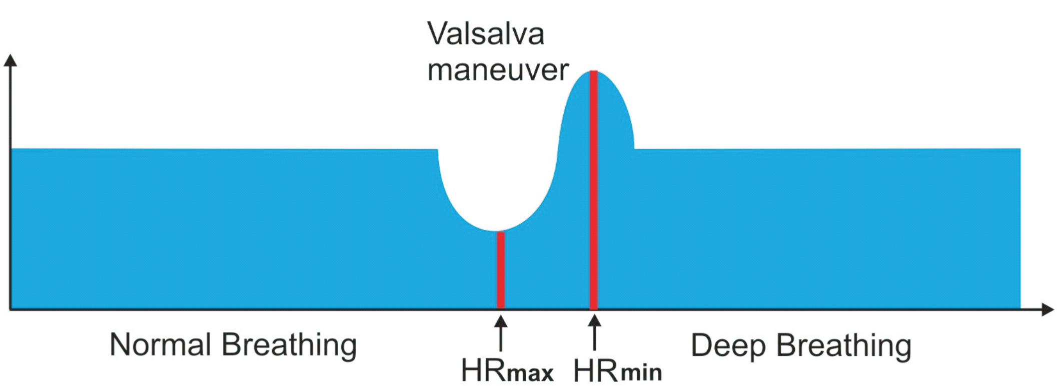


FIG. 3

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 fig. 4 below).

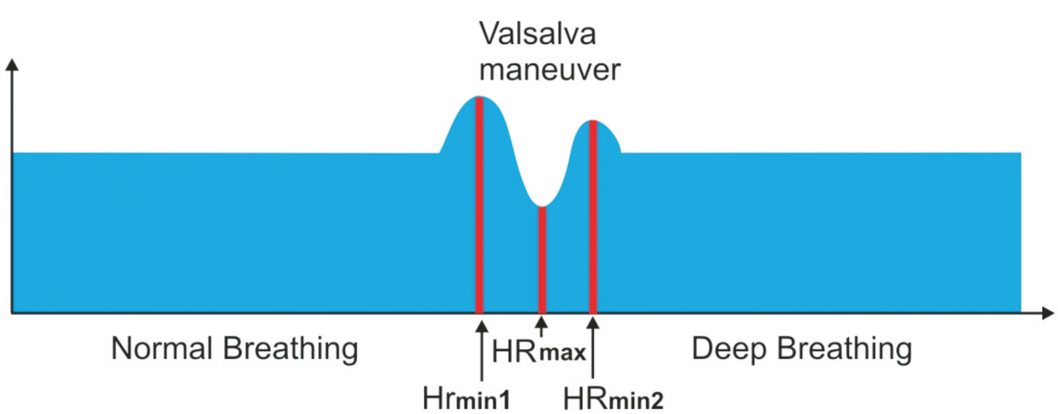


FIG. 4

In such cases the correct calculation will be HR (max)/HRmin1), 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.

References:

1. Malik M, Bigger JT, Camm AJ, et al. Heart Rate Variability. Standards of measurements, Physiologic interpretation, and clinical use. European Heart Journal 1996; 17: 354-81.
2. A. Malliani, Milan, Italy. The Pattern of Sympathovagal Balance Explored in the frequency Domain. News Physiol. Sci.: 1999
3. F. Lombardi, Milan, Italy. Clinical applications of Present Physiological Understanding of HRV Components. Cardiac Electrophysiology Reiew, 2002.
4. Pagani M, Lombardi F, Guzzetti S et al. Power spectral analysis of heart rate and arterial Pressure variabilities as a marker of sympatho-vagal interaction in man and conscious. Circ. Res. 1986; 59: 178-193
5. Benhur Aysin, Elif Aysin "Effect of Respiration in Heart Rate Variability (HRV) analysis.
6. Riftine, Alexander. Clusterization of the relationship between SNS and PSNS activity by heart rate variability analysis. In proceedings of the 33rd International Congress of Electrocardiology. Cologne, Germany, July, 2006.
7. Riftine, Alexander. New quantification of the relationship between SNS and PSNS activity by Heart rate variability analysis. In proceedings of General assembly of Polish Cardiac Society – 1st Appointment. Warsaw, Poland, 2005.
8. L. I. Osadchy, "Body position and blood circulation", Medicine, 1982, Moscow.