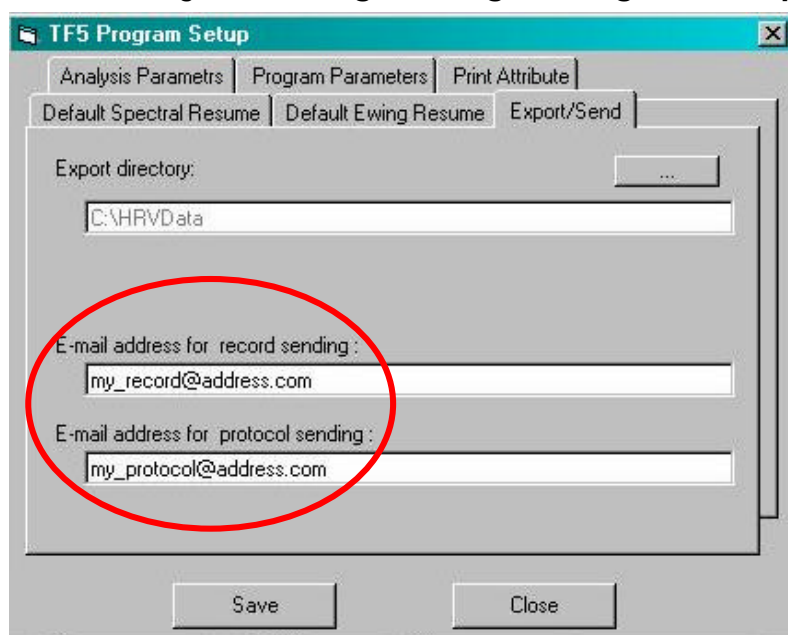## 5.11. License, Hardlock, Data Protection & Business Issues

In order to maximally protect your sensitive data and the know-how of the system, a special programmable, hi-tech hardlock is to be connected when using the system VariaCardio TF5. This hardlock is connected with the PC via standard printer port that can be found on the back of the computer. A "free" version of the TF5 program



– that does *not* require use of the hardlock -- allows browsing the pre-recorded demo data and its 3-D display & analysis only. All other practical steps in clinical use of TF5 require connection with the hardlock that includes license data specially pre-programmed for the individual user in order to allow her/him to make a maximum use of the system in accordance with her/his business model. Some relevant user-specific data (see below) are downloadable from the connected hardlock in the main menu section **Engineering → License**.

**Important notice:** Bear in mind, please, that programming the hardlock as well as adjustment of your TF5 system license conditions require – at least initially -- **presence of AMDG or its authorised representative**. Therefore, we **strongly suggest you to consult** any step regarding such license manipulations in advance. Otherwise, AMDG or its partners *can not* be held responsible for any direct in indirect damage potentially occurring in this respect.

## 5.12. How to Send Records and Protocols via E-mail

Separate HRV records and/or complete examination protocols with comments can be sent in encrypted form in order to enable consulting the data with the Remote Analysis Centre and/or to facilitate delivery of the complete examination protocols to related subjects. To do this, it is necessary first to adjust the e-mail addresses for data exchange in the **Engineering** -> **Program Setup** -> **Export/Send** option:
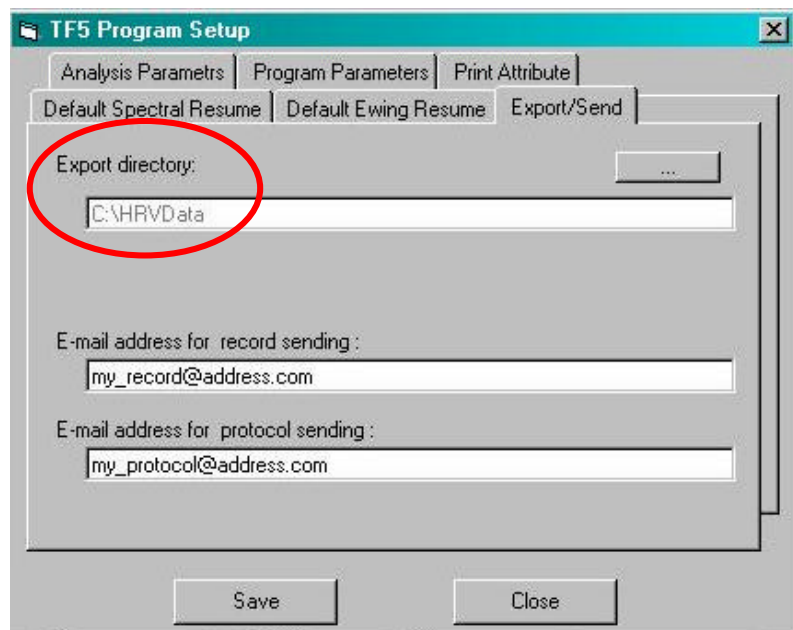
Then, select/mark the record to be sent - simply by moving the arrow at the left/hand side of the basic database screen (name of the subject in the upper part of the screen, individual record/s in the lower part). Afterwards, selected HRV data can be sent via a standard e-mail program (MS Outlook) by choosing option **Database** -> **Send Record**. Whenever connected to Internet, the data will be automatically sent to the address indicated in the Setup.

## 5.13. How to Export and Import HRV Records

Using **Database**->**Export Record** or **Import Record** option it is possible to manipulate the selected record of chosen subject. This is typically done e.g. when the HRV record is to be further processed separately (export) or a record from a different database is to be imported into another one (import). The newly generated file can be found in the export directory as adjusted in the **Engineering** -> **Program Setup** -> **Export/Send** option.
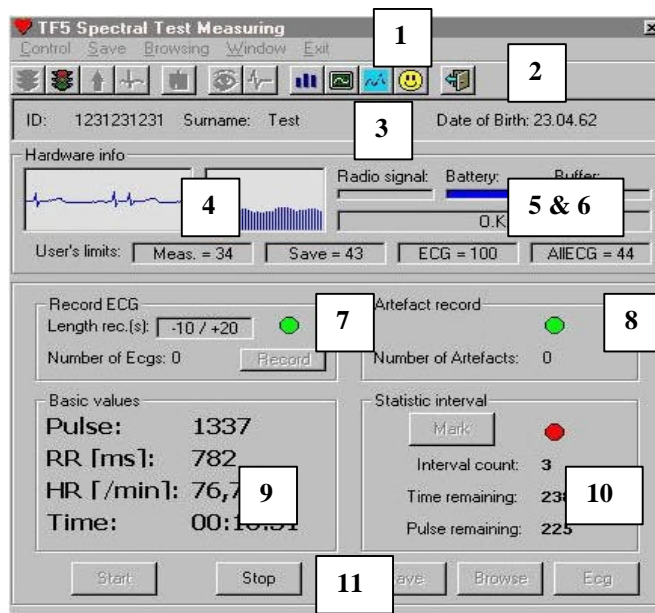
# 6. Clinical Use of the System: Measurements

## 6.1. Measurements: Spectral Test Measuring Screen

In the basic operation screen, click on icon Measuring ![heart icon] (**or** press CTRL + S **or** open Measuring option in the main program menu and select 'Spectral test').
New screen **Spectral test measuring** is displayed with following main sessions:

(1) **Commands menu** including submenu items Control, Save, Browse, Window and Exit.

(2) **Icons menu** corresponding with the above, including additionally Start and Stop, Interval marking, Record ECG icons etc., for details see below.

(3) **Subject identification** with ID, Surname and Date of birth items.

(4) **Hardware info** shows the current quality of data transfer/ECG in *left* window and progress of heart rate over recent time in the *right* window.

(5) **Radio signal** quality indicator, and **Battery** status show current state of these items.

(6) **Alert window** below the radio signal and battery status indicators informs you of system configuration and of possible errors (e.g., alert 'Receiver switched off...'). A strip with information "OK" shows normal setting, strip blinking in orange warns of errors and possible cause of the problem encountered is displayed. Furthermore, pre-defined user's limits – in accordance with pre-set/prepaid service – and currently available number of TF5 test actions are shown.

(7) **Record ECG** section contains data on ECG record length from pressing the CTRL + E hot keys **or** clicking on ECG record icon **or** pressing Record button, and information on total number of ECG records in this measuring session. The default setting '–10 / +20' shows that from the event the previous 10 seconds and following 20 seconds are recorded (=30 seconds for each ECG record). The red button in this section shows ECG strip recording.

(8) **Artefact record** section displays the number of artefacts and automatic artefact recognition state. The button when green indicates normal heart rate data, when red informs of automatically recognised and corrected artefacts (cardiac arrhythmia, movement artefacts e.g., while changing position from supine to standing).

(9) **Basic values** window delivers exact numeric information on instantaneous R-R data: Pulse number, Length of R-R interval in [ms], Heart rate in [beats per minute] and Time elapsed since pressing Start button in [hrs:min:sec] (Note, please, that this total time differs from the "Time remaining" information in the section 10).

(10) **Statistic interval** section is only active during recording the data for HRV analysis. Once Mark button is pressed, analysis interval count number is shown (normally 1 – 3, corresponding with examination procedure in 1-supine/2-standing/3-supine). Paralelly, countdown for Time and number of Pulses remaining starts from 300 downwards.

(11) **Measuring control buttons** at the bottom of the window control program functions such as Start, Stop, Save, Browse (R-R data) and (Browse) ECG.

## 6.2. Measurements: How to Perform Measurement

### 6.2.1. Measurements: What to Do *Before* the Examination

**Examined subject:**

It should be noted that autonomic nervous system response depends on numerous factors that influence the result of the examination:

- It is recommended to refrain from smoking or drinking coffee, tea, alcohol and/or other sympathomimetic substances for 8-12 hours prior to examination.
- In patients with chronic medication, it is recommended to continue with their usual medication and nutrition, with the exception of those using beta-blockers, which have been shown to substantially increase the vagal tone (diagnostic purposes!). In such case, consider an interim exchange with other pharmaceuticals.
- Subjects with insulin treated diabetes should avoid hypoglycaemia within the last 12 hours.

**Medical personnel:**

Be sure that examination conditions meet the standards necessary to obtain reliable and reproducible data:

- The examination should be performed in a quiet, gently illuminated room of a constant temperature and optimally between 8:00 AM and 2:00 PM.
- Patients should be requested to lie down quietly for a preparatory phase of 10-15 min to exclude relevant emotional or external influences on the autonomic regulation.
- In general, during the examination, speaking or physical activities that are not related to the testing procedure should be avoided.
- It is recommended not to make any telephone calls or undertake any other activities that may influence the steady state of autonomic regulations during the examination period.
- Ideally the examiner instructs the subject on the measurement procedure, enters personal and other relevant data and leaves the examination room leaving the examined subject alone.
- Check there is no conflict with the chapter 1.1. Cautionary Information in the Manual.

### 6.2.2.Measurements: What to Do *During* the Examination

(a)    Start the program, Select / Add the new subject in **Database**

(b)    Adjust the **chest belt** and **switch** the transmitter **on**.

(c)    Check if the yellow **LED diode** on transmitter is regularly blinking. Switch on the receiver and check if its both **LED diodes** are on.

(d)     Click on **Spectrum Measuring** section icon  (**or** press CTRL + P **or** open   Measuring option in the main program menu and select Spectrum).

(e)     **Spectral test measuring** screen is displayed. **Hardware info** section (object No 4, see chapter 6.1. Spectral test measuring screen) is activated immediately. Check quality of transmitted & displayed signals (ECG and heart rate course) in separated windows. Change the position or adjust the length of the chest belt if necessary.

(f)     If OK, Start the examination by clicking on **Start icon** (**or** open Control submenu and select Start **or** press CTRL + S **or** click the Start control button at the bottom).
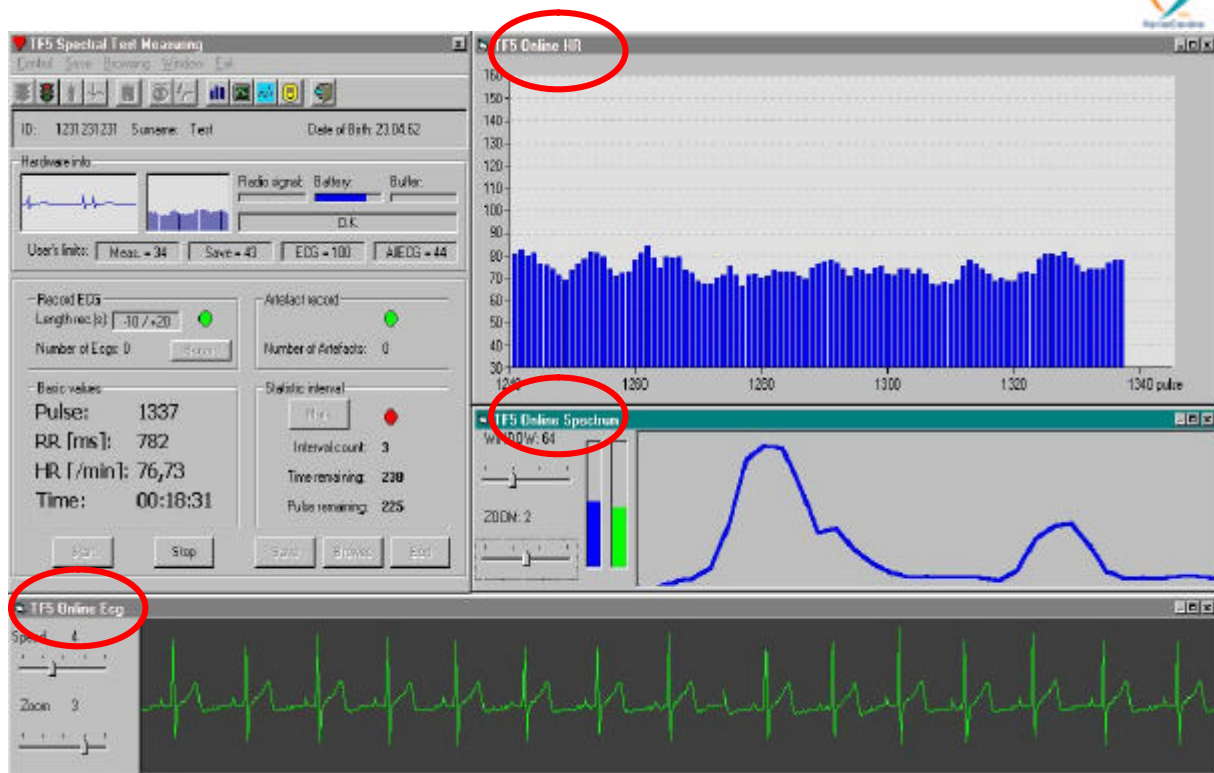


   **Important notice:** If for any reason it is necessary to record full-time ECG record throughout the whole examination, please choose this special option in the **Control** submenu -> **Start with whole ECG**, instead of clicking the Start icon shown above.

(g)     Note that -- when properly started -- **Icons setting** changes consistently, i.e., Start icon is disabled and Stop icon along with   other icons related to current program



step are enabled. The same is valid for **Measuring Control buttons** at the window bottom (Start, Stop, Save, Browse and ECG).

(h)     Additionally, in **Basic values** section (object No 9, see chapter 6.1. Spectral test measuring screen) information is displayed on: instantaneous Pulse number, Length of R-R interval, Heart rate and Time elapsed since pressing the Start button.

(i)     Also, information on the **transmitter battery status** and on **system functions** are displayed (objects No 5 & 6). Automatic artefact recognition and data correction procedure starts now, as well, showing continuously updated number of processed artefacts in **Artefact record** session. If possible, leave the examination room now and perform the further examination control / program steps from a separate room.

(j)  At the right-hand side & bottom of the screen, 3 new 'on-line' windows display:

- Window '**TF5 Online HR**' displays the course of heart rate against time within the recent approx 100 pulses (accordingly to the currently adjusted window size)

- Window '**TF5 Online ECG**' displays single-channel ECG (time resolution 500 Hz). It is possible to adjust the signal displaying speed and zooming by 'drag-and-drop' with PC mouse (like in most other windows in the program).

- Window '**TF5 Online Spectrum**' displays the instantaneous spectral curve based on recent 32 / 64 / 128 or 256 heart beats. This option has no influence on the performance of the statistics after the examination is finished and serves only for displaying the spectral curve *during* the measurement. Also here, it is possible to adjust the spectral curve window and zooming by 'drag-and-drop' with PC mouse. Additionally, two - blue and green - columns showing the instantaneous **'sympathovagal' balance** / spectral power distribution between low (0.05-0.15 Hz) and high (0.15-0.40 Hz) frequency bands can be found here.

- *Note: The first on-line spectral curve and sympathovagal balance graphics appear on the monitor only after the chosen number of pulses is reached (32 pulses being the minimum). In the case above a 64 pulses-window is chosen.*

All these 'online windows' can be switched off/on (see the icons) and are fully resizable to allow the user full flexibility to adjust the screen



accordingly to her/his needs. Default positions can be quickly adjusted by clicking the icon **Default** windows display or pressing CTRL + D.

(k)  When the subject's preparatory phase is finished, **Mark** beginning of the first examination interval (**or** press CTRL + M **or** open submenu

Control -> Mark **or** click the Mark button in the Statistic interval session). Only at this point +300 seconds/+300 pulses -- whichever takes longer -- the data will be included in the final statistical analysis (see also Statistic interval session No 10). Data obtained *before* and *after* this examination interval are displayed in the 3-D graphics but *not included* in the statistical analysis.

(l) **Statistic interval** section (No 10, for details see chapter 6.1. Spectrum measuring screen) is now activated, additionally: examination interval number is shown (normally 1 – 3, corresponding with examination procedure in 1-supine /2-standing /3-supine), and countdown for Time and number of Pulses remaining -- both starting from 300 downwards -- run.

(m) It is possible to record single-channel **ECG** strips as necessary, within the whole examination process. By pressing ECG record icon (**or** clicking



the Record button within the session /Record ECG session No 7/ **or** pressing CTRL + E **or** through program submenu Control -> ECG Record) a 30 second strip is recorded (–10 sec / +20 sec from the event). Red button in this section shows ECG strip recording, green button ECG recording not operating at present. In case of choosing the whole examination ECG record (see step /f/ in this chapter) this option is disabled.

(n) Once the 1st interval countdown is finished by reaching 0, **Interval count '1'** appears in the Statistic interval session and time/pulse countdowns disappear. In this moment you can request subject for active change of position – from supine to standing. Be aware that some seniors might need a help at this moment.

(o) Once subject is stable and his heart rate does not display artefacts or extreme changes related to the position change, **Mark** the beginning of the second examination interval (return to step /j/ and follow the above listed procedure). Please be aware that one of the most relevant conditions for successful HRV data analysis is its stability (data 'stationarity'). Therefore, wait for a while after position change before you mark the next interval.

(p) Once the 2nd interval countdown is finished by reaching 0, **Interval count '2'** appears in the Statistic interval section and time/pulse countdowns disappear. Again the subject can be requested to change position – from standing back to supine again. Afterwards, **mark** the third examination interval.

(r) After successful data collection **Stop** the measuring phase by clicking on Stop icon **or** open submenu Control -> Stop **or** press CTRL + P **or** click



the Stop control button at the window bottom.

(p) Remember, please, to **immediately save the collected data** (click Save icon **or** Save control button **or** Save command in main menu).

## 6.2.3. Measurements: What to Do *After* the Examination

Ensure that you have finished the recording correctly, i.e., after the 3$^{rd}$ examination interval (Statistic interval count = 3), by clicking Stop icon **or** via submenu Control - -> Stop **or** pressing CTRL + P **or** clicking the Stop control button at the bottom.

**Save** the record immediately (click Save icon **or** Save control button **or** Save command in main menu)! Further steps lead to browsing the record and to analysis.

## 6.3. How to Browse/Edit the Data

Before considering the results, check the integrity of the recorded data and remove any artefacts as necessary (by accepting/rejecting automatic recognition procedures and/or manually). Records that contain non-processable artefacts should be deemed as invalid and in these cases, the examination should be repeated. The same pertains in the final statistics table if excessive non-stationary parameters are found (i.e., statistical relative deviation exceeds approx. 20-30% in older population or approx. 30-40% in younger subjects).

Click the Browse icon **or** open Browse option -> select Browse spectrum **or** press CTRL+B keys together. A new window (**Browser**) opens that consists of several sections:
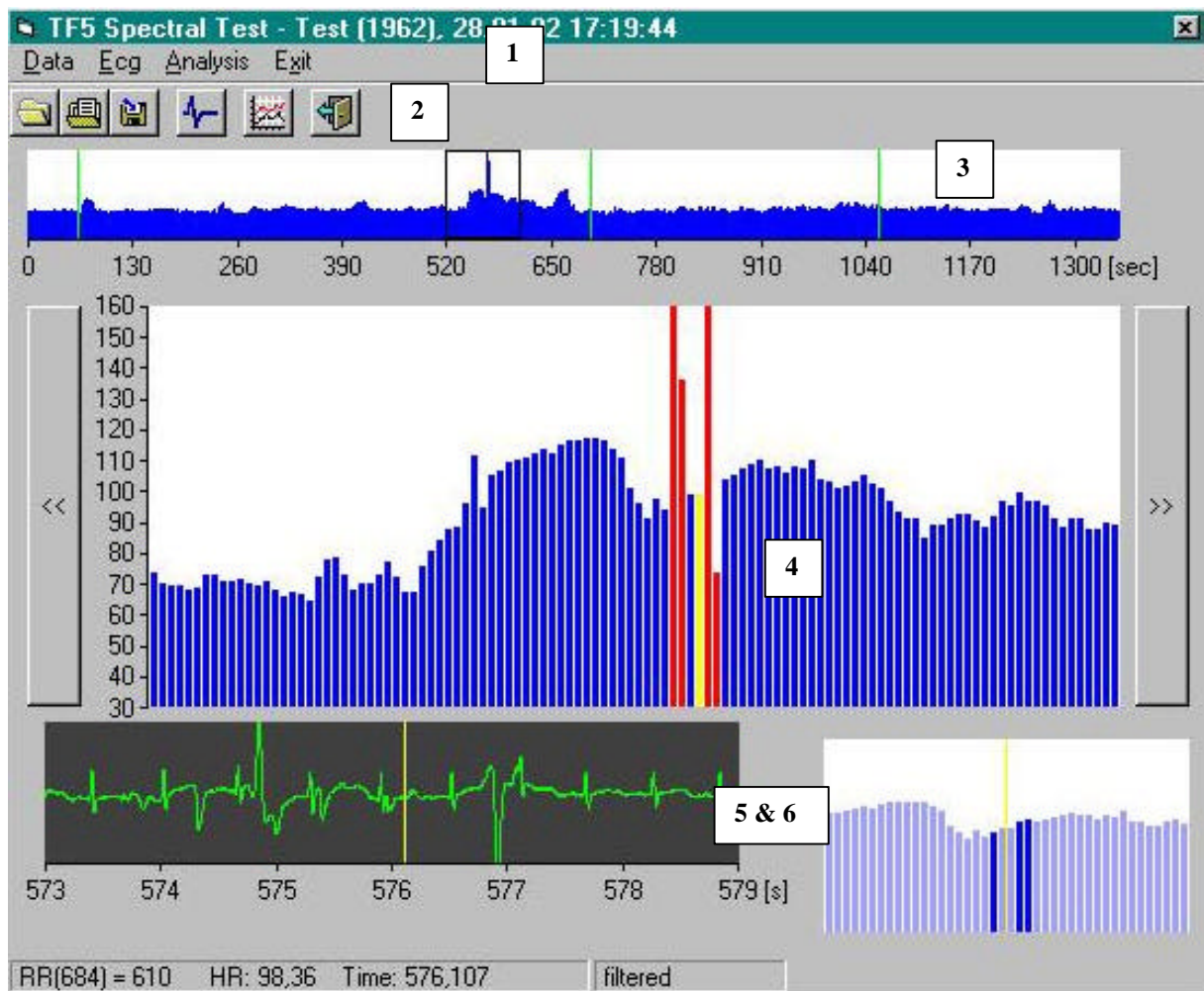
## 6.3.1. Browser Structure

(1) Browser commands **menu**
(2) Browser commands **icons**
(3) **Overview** display of whole examination **heart rate time course**
(4) **Heart rate detailed window** corresponding with the selection as in above window. Clicking on a selected bar in the HR detail window shows at the bottom information on the instantaneous pulse number, pulse rate and time relapsed since the beginning of examination.
(5) Optional window displays **ECG strip** related to the event (artefact). This window displays the short ECG strip only if it is automatically recorded. A standard ECG browser can be activated in other program sessions.
(6) **Artefacts processing** optional window
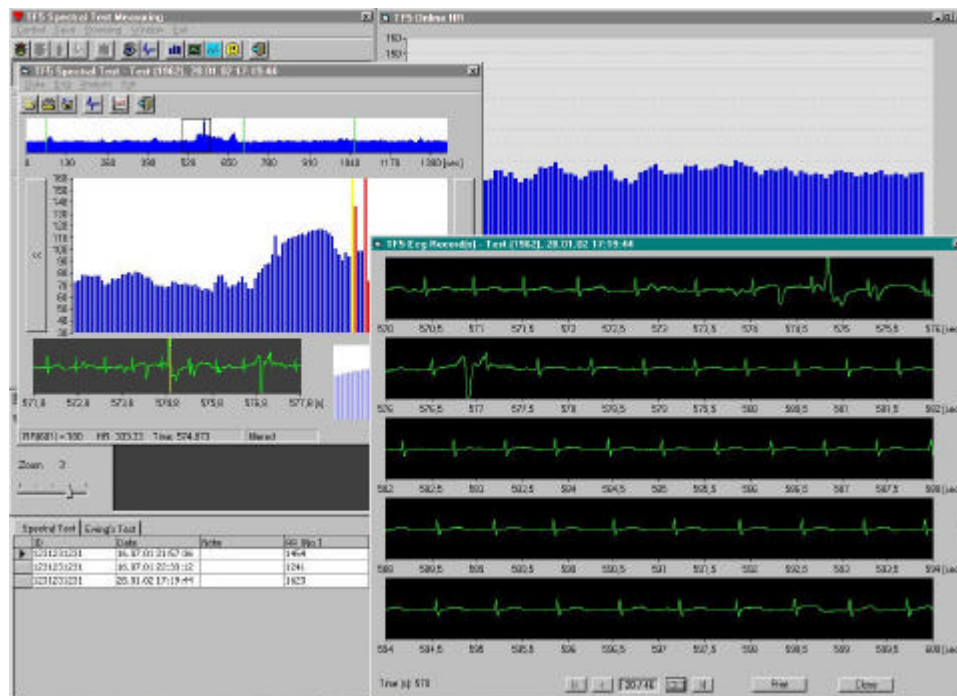
When **browsing** the heart rate record you can

- either move the selection window within the examination overview – using left mouse button and 'drag-and-drop' method in the window examination overview (section 3), whilst the selected heart rate part displays "zoomed" in more detail in the window below (section 4)
- or click on the sliders at the left or right-hand side of the detailed window (section 4) to scroll the HR data. This enables one to check the record thoroughly, however, it takes slightly more time.



Additionally, in the heart rate **overview** (section 3) or **detailed** (section 4) **windows** the following markers of various colours can be found:
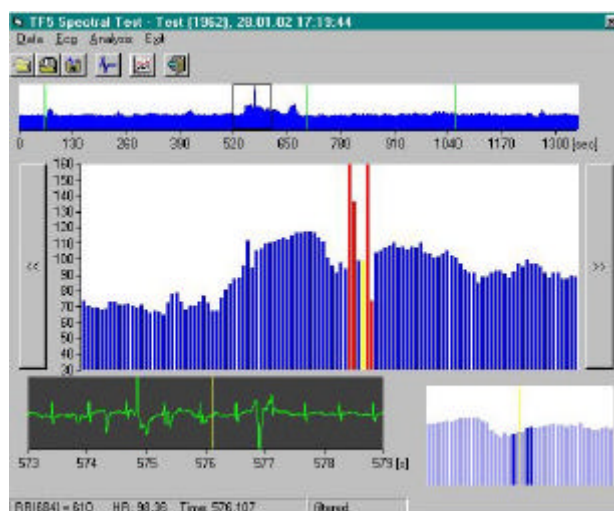
- **Green marker** – shows the beginning of each examination interval that is included into the final statistical analysis
- **Red marker** – indicates artefacts automatically recognised and recorded with corresponding 6-second ECG strip during the data collection. Artefact in form of red heart beat vertical bar(s) is displayed in the HR detailed window (section 4) and corresponding ECG strip -- as stored *automatically* during the examination -- in the window below (section 5).
- **Violet marker** – corresponds with 30-seconds ECG record as obtained during the examination. This data can be browsed simultaneously in a separate standard ECG Browser, for example see below:

*Practical example: HR browser showing automatically recorded artefact caused by ectopic beat (check section 5), proposed data correction (section 6) and ECG browser located over the HR browser window showing the long ECG strip (whole examination). You can switch between both browsers to view details, as well.*



### 6.3.2. How to Find and Process Artefacts

- Window HR **overview** (section 3): Find the automatically recorded artefact (red marker) in the HR overview. Move the selection window onto the red marker ('drag-and-drop' the window with left mouse button).

- Window HR **detail** (section 4): Selected HR course is displayed. Click the *left* mouse button and/or 'drag' over the artefacts to the right or left to mark them if necessary = if not completely detected/marked by program yet (red colour bar). The same procedure with *right* mouse button unmarks them (blue colour, again).

- Window **ECG strip** (section 5) shows corresponding ECG data while

- Window **Artefacts processing** (section 6) shows generated corrections in heart rate in dark blue colour based on calculations algorithm over surrounding normal heart beats. Check the proposed artefact correction and mark/unmark the artefact portion in the section 4 if necessary. In general, the heart rate course should be smooth (we suggest the exclusion of ectopic beats, as well, see the figure).

- Progress to other artefacts and use the same procedure. Once satisfied with artefacts processing, press the **Save** icon **or** Save command in the menu. For the final analysis, **only 'edited/filtered' data** can be used. Be aware, please, that even *one single artefact* can totally destroy the quality of the results.

- However, it is still possible to view the **original file**, as well. Click the 'Load original data' icon (**or** open 'Load' command and select Original data or press CTRL+O together). Similarly, you can return to the 'filtered' file – click on icon 'Load filtered data' (**or** open 'Load' command and select Filtered data or press CTRL+F together). The computer stores separately the latest processed file as a 'filtered' one while the 'original' file remains unchanged. Date (time point) of current file editing/filtering along with the date of original record are stored, and this data is available in the Report.

## 6.3.1. ECG Browser

It is possible to view either the 30-seconds long single-channel ECG strip(s) or the whole examination ECG record as recorded during the examination session, in a separate window. You can **open it** in

(a) **Spectral test measuring** session: click the ECG browse icon that is available immediately after the HR record has been saved (**or** open the Browse menu and select Browse ECG command **or** press CTRL + C together), or

(b) **HR Browser** session: click the ECG browse icon (**or** command), or

(c) **Basic operation screen:** select the subject and record (small arrow at the left-hand side), click the ECG browse icon (**or** Browsing main menu, command ECG **or** CTRL + E together)

**Structure** of the ECG browser is simple:

- **Window heading** shows personal data, date & time of ECG recording
- **Five strips** displaying ECG course from –10 until +20 seconds from pressing the ECG record button (time 0, violet marker)
- **Bottom line** includes information on number of R-R interval, marker time location on the heart rate course axis, present number and total number of recorded ECG files, and 'Close' button.

Its **main function** is to enable viewing the ECG record and to support decision making processes while browsing the heart rate course record and considering possible artefacts.
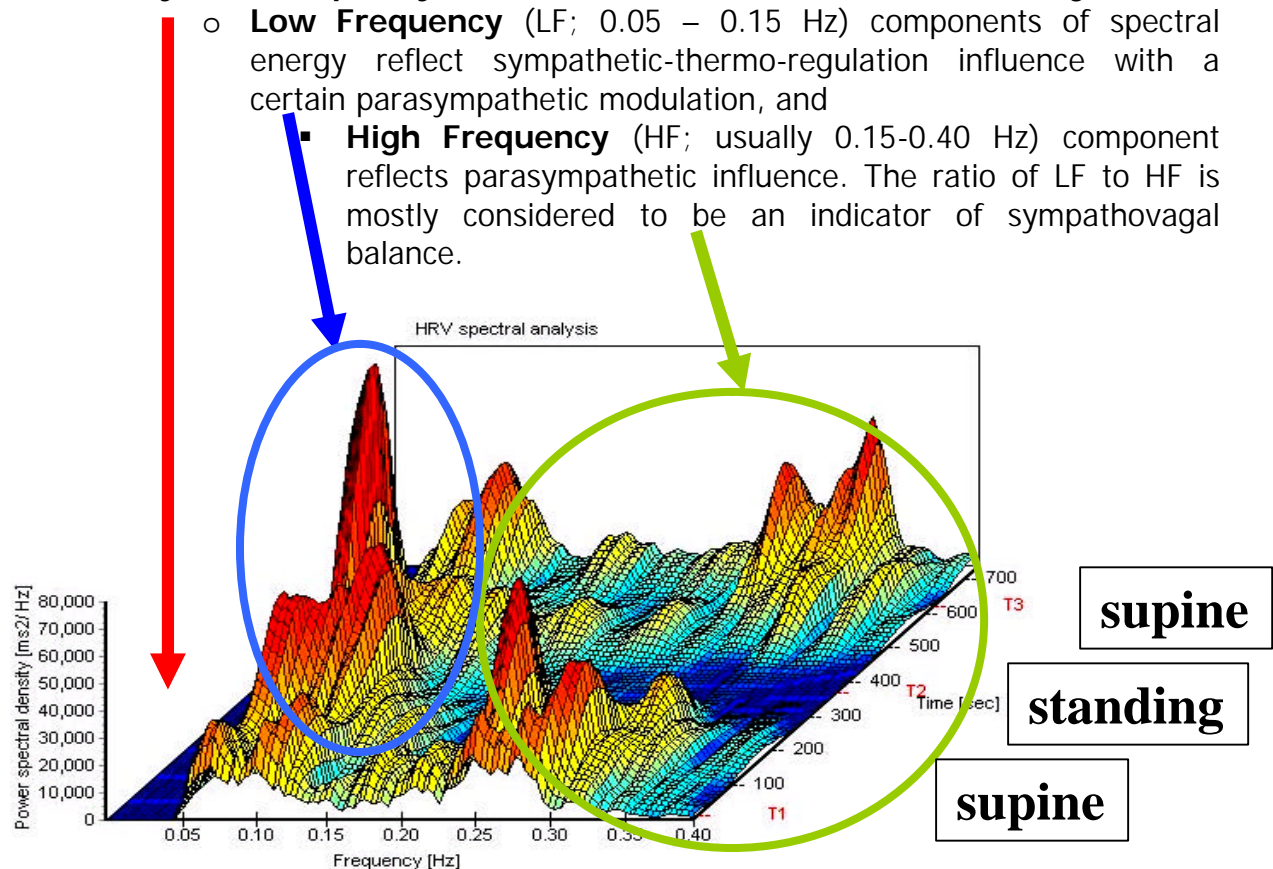
# 7. Clinical Use of the System: Analysis

## 7.1. HRV Basics. How to Understand the Principles of Analysis

In general, it is recommended to perform (and to understand) the examination as a view on **cardiovascular autonomic regulations during a modified orthostatic load**. This scheme allows assessment not only of the energy contents of the **autonomic control** during well-defined examination positions, but also disturbances in its **dynamics**. Therefore, both the absolute numbers in the statistics table and the changes/behaviour in autonomic control as displayed in the three-dimensional graphics are relevant for diagnostic resumes.

Spontaneous beat-to-beat fluctuations in heart rate reflect ongoing modulation of sinus node activity through several cardiovascular control mechanisms. In addition to the respiratory sinus arrhythmia (0.2 – 0.3 Hz), the heart rate typically oscillates at specific lower frequencies, most commonly at about 0.05 - 0.15 Hz and lower, as well. All these heart rate fluctuations can be quantified by the technique of **power spectrum analysis**, which calculates the frequency content of time-varying signals. Power spectra are quantified by measuring the area under the spectral curve (*Spectral Power*) and its density/amplitude (*Power Spectrum Density*) in two/three frequency bands (see the figure below; frequency axis 0.00 - 0.40 Hz, displayed spectrum range 0.05 - 0.40 Hz):

- **Very-Low Frequency** (VLF; 0.02 – 0.05 Hz) /*not included in this fig.*/ and/or
  - **Low Frequency** (LF; 0.05 – 0.15 Hz) components of spectral energy reflect sympathetic-thermo-regulation influence with a certain parasympathetic modulation, and
    - **High Frequency** (HF; usually 0.15-0.40 Hz) component reflects parasympathetic influence. The ratio of LF to HF is mostly considered to be an indicator of sympathovagal balance.
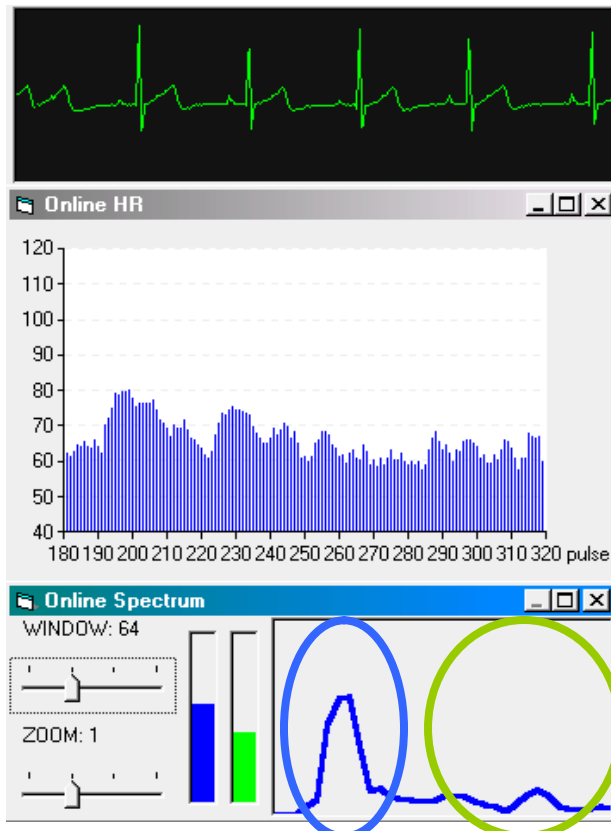


HRV spectral analysis

In the VariaCardio TF5, power spectra are calculated by computing the magnitude squared of the **fast Fourier transform** based on data points obtained from **300 seconds' tachometer** signal. As in any biological process, the data contain both harmonic and non-harmonic information, therefore no filtration of specific ('chaotic') parts of the information is used. The total power is then obtained by integrating the power spectrum from 0.02 to 0.40 Hz, the respective components of spectrum (VLF, LF & HF) represent then in the above mentioned frequency bands. Power at frequencies below 0.02 Hz should be probably not considered because it may not be reliably measured within data records 300 seconds long. (e.g., in case of less than 0.01 Hz the wave length is then more than 100 sec., i.e. energy of only a couple of cycles during one position recording is quantified).

Based on the length of record analysed, this kind of spectral analysis is also called a **"short--term" analysis**; the spectral power can be viewed as the variance in heart rate during the 300 seconds periods. The "long--term" spectral analyses are represented by analyses using 24h Holter recordings. However, to our current knowledge, none of the standard 24-hour Holter monitors does have a sampling frequency high enough to offer adequate analysis.

Short-term spectral analysis of HRV is **practical and easily applied** in the clinic. It was found that the immediate variability of short-term spectral measures of HRV was low, and short, 2- to 15-minute samples were found to be excellent predictors of mortality and correlated with prognostically important data from sustained recording periods. Due to this simplification, patients could accept more consecutive measurement series during longitudinal studies, as well. The method takes only a short time and is quite independent of the patient's compliance during the examination. In contrast to the less sensitive total Ewing standard score of cardiovascular reflex battery, the selected cumulative indices over more than one time segments (e.g., in positions supine-standing-supine) proved to be able to assess even small changes in cardiac autonomic supply.

The current methods most commonly used for analysis of HRV in frequency domain are based either on fast Fourier transform or on auto-regressive model. Under various conditions, both analytical approaches deliver similar results. As the examinations are commonly performed under routine clinical conditions requiring immediate results, system using **fast Fourier transform** analysis has the **advantage** of sufficient simplicity of well defined algorithms, high processing speed and on-line graphic display modality. Although the information given by the spectral indices corresponds to that given by indices of time-domain analysis, it was shown that **cumulative index** is more representative of the actual global state of autonomic regulation and reflects the total instantaneous sympathetic and parasympathetic effects.

## 7.2. HRV Basics. How the R-R Intervals Measurement Works



Surface **ECG** is continuously monitored and R-R intervals are measured with a time resolution of 1 ms and further processed by microprocessor in the transmitter unit. The ECG and R-R data are telemetrically transferred to a receiver connected to a PC-compatible computer.
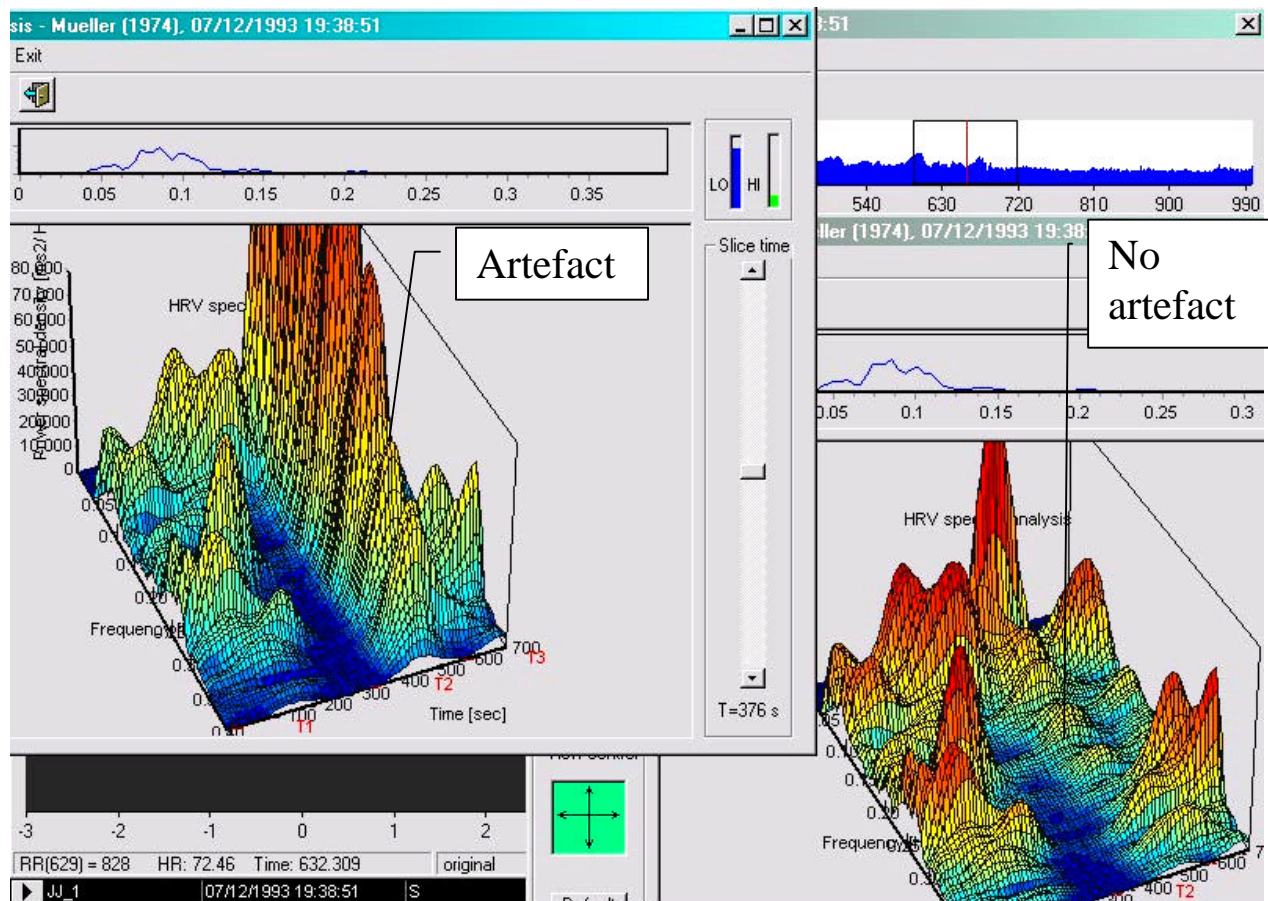
The ECG signal and computed **heart rate** is displayed after each heart beat on the monitor in form of a vertical bar graph with numerical information on current heart rate, R-R interval length and time elapsed since the beginning of measurement in a separate window.

**Instantaneous** (online) **spectral curve** based on the last 32, *64 (see the figure)*, 128 or 256 beats is displayed as well. The figure shows two typical peaks of LF and HF bands.

The automatic **artefact recognition** of the received data is processed on a **real-time basis** and displayed on the monitor. When recording has finished, the original data set is stored and then automatically filtered, excluding the recorded artefacts using a special recognition algorithm. Finally, there is a possibility to filter the file manually as well. Therefore, there are two files stored (**'original'** and **'filtered'** ones) related to one data set.

For better understanding **why the artefact processing is that important**, see the figures below:

- The *left* figure shows the spectrum created on data including one single artefact around the time point 640 seconds (see the Browser -- upper right window).
- The *right* figure shows spectrum based on the same dataset, however, with the artefact rejected and substituted by a computed data hat is consistent with the current data time series.

## 7.3. HRV Basics. How to Understand the 3D Results

The computational method of spectral analysis is based on a fast Fourier transform. The final results are immediately displayed on the monitor as a three-dimensional running spectrum, permitting a **general overview of the dynamics and of the absolute energy** content of the system. All parameters are computed for each time segment: within the high frequency band (0,15-0,40 Hz, attributed exclusively to parasympathetic tone), the low-frequency band (0,05-0,15 Hz) and very-low frequency band (0,02-0,05 Hz, shown to represent a combination of sympathetic and parasympathetic effects and others like thermoregulation etc. on cardiac autonomic tone). The autonomic control varies under different physiological states, typically during a modified orthostatic load: the *parasympathetic* component is predominant in supine position, while the *sympathetic* one during active standing.

The main outcome variables in *frequency domain* are:
- Absolute **spectral power** (units [$ms^2$]) and
- **Power spectral density** (units [$ms^2$/Hz]) in two or three frequency bands and their
- **Ratios** VLF/LF and LF/HF bands
- **Mean frequency** (units [mHz]) for each frequency band
- **Cumulative spectral power:** to increase the reliability of the short-term measurements and to assess even small intra-individual differences in global autonomic tone, the **cumulative index** (spectral power of the total