PhD Theses

TECHNICAL PITFALLS OF HEART RATE VARIABILITY ANALYSIS

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1. Introduction

Recent developments in computer sciences and digital signal processing have facilitated the expansion of heart rate variability (HRV) analysis both in research and clinical fields. Before this time (and in most cases even today) the physiological parameters were specified by a single measurement or by averaging some measurements, and the information carried by their fluctuation was lost. In normal conditions the beat-to-beat variation of the heart rate comes from the momentary summing of sympathetic and parasympathetic effects on the sinus node. Due to the extensive associations of the autonomic nervous system, vegetative, somatic and psychical influences are integrated in the heart rate and its variability. Several factors affect HRV such as posture, respiration frequency, age, gender, physical or mental load, pain, numerous disease conditions, and different drugs. The altered HRV has prognostic value in various diseases: acute myocardial infarction, coronary artery disease, congestive heart failure, diabetic neuropathy, hypertension, dilatative cardiomyopathy, etc.; it can predict acute cardiovascular events like ventricular tachyarrhythmias; and it may be applied in stress assessment: e.g. quantifying the operative strain of the surgeon. HRV measurement also has consequences in the investigation of physiological and pathological autonomic regulation.

Besides methodical and biological pitfalls, there are many technical hitches in data acquisition, signal conditioning, processing and presentation; those can be resulted in inaccurate HRV analysis. Additionally, environmental or intrinsic noises/interferences may be present, further impairing the measures of HRV. Eliminating or minimizing above traps can assure the reliable evaluation of HRV, and may contribute to the liquidation of present misunderstanding in the area of HRV analysis.

The latest comprehensive methodical recommendation for HRV analysis was published in 1996 (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, Circulation, 1996, 93: 1043-1065). Currently this article is respected as one of the most frequently cited paper in Circulation (http://circ.ahajournals.org/reports/mfc1.dtl), however, it should be verified in the light of recent technical improvements and the existing ambivalent results in this field. The Task Force precisely covers the duration of the ECG recording, the upper corner frequency of the ECG amplifier, the sampling rate (digitization), validating the equipment with fully reproducible signal with exactly known HRV parameters, standardization of several time and

frequency domain measures, and interpretation of the results, besides the underlying physiopathology and possible clinical implications. According to the recommendation, the upper-band frequency cutoff lower than about 200 Hz may create a jitter in the recognition of the QRS fiducial point, causing a measuring error of RR-intervals. However, higher corner frequency may retain more noise in the ECG record also resulting in erroneous RR-interval detection. The ubiquitous power line interference itself or its intended suppression by notch-filters also can flutter the ECG fiducial point. Poor quality digital records due to low sampling rate also may yield inaccurate measurements, on the other hand, unnecessarily fast sampling results in extreme memory usage, processing time and elevated production costs. There is an inconsistency in the cited Task Force suggesting about 200 Hz analog upper cutoff and 250-500 Hz sampling frequency without interpolation. According to Nyquist's sampling theorem the sampling frequency must be at least twice the highest frequency component of interest in the analog signal.

Present investigation examines the actions of different upper and lower corner frequencies of the amplifier, analog power line notch filtering and various sampling rates on the accuracy and precision of RR-interval detection and HRV parameters in uncorrupted and contaminated ECG signals via computer simulation.

2. Aims

2.1. Construct an accurate system for ECG recording and HRV analysis including hardware and software

2.2. Develop a precisional ECG signal generator and analyzer for RR-interval measurement

2.3. Build analog low pass, high pass and notch filters to be evaluated

2.4. Develop special software for the simulation and evaluation of sampling error at different rates

2.5. Analyze the exactness of RR-interval detection in uncorrupted and noise-contaminated artificial ECG records before and subsequent to high and low pass filtering at different corner frequencies

2.6. Analyze the exactness of RR-interval detection in uncorrupted and AC interference-contaminated artificial ECG records before and subsequent to notch filtering

2.7. Investigate the effects of various sampling rates on the accuracy and precision of RR-interval recognition in ECG samples with different variability

3. Methods

3. 1. The system for HRV analysis

The author's first computer-interfaced, μA741-based ECG amplifier was constructed in 1998. The signal was digitized at 500 Hz with a SoundBlaster-16 sound card programmed in Borland Pascal and Assembly. The need of an easy-going system was recognized during the initial HRV-measurements, however it was achieved in 2002: a good-quality single-channel amplifier with the INA114 integrated circuit (Burr-Brown Corporation, Tucson, AZ) was born with a frequency transfer of 0.5 to 300 Hz. Digitization occurs at 1 kHz and 12 bit resolution by the ADC-42 analog to digital converter (Pico Technology Ltd., St. Neots, UK) with a notebook computer assuring a portable system. The fully Windows-based ECG-recorder (ECGRec 1.0), interactive RR-interval detector (ECGRdet 2.0) and HRV-analyzer (Varian 1.1) software were written in Delphi by the author. The equipment showed 1 ms maximal error of RR-interval detection during the test performed with the ECG signal generator (see at **3. 2.**), which is comparable to the sampling error at 1 kHz. Besides acquiring human ECG-samples for further simulation and investigation, there are numerous projects in preliminary stage with the recent ECG-system.

The intelligent RR-interval detector assures digital filtering (moving average, 50 Hz notch, derivative, and 15-40 Hz band pass); direct ECG-peak recognition, detection of the first zero-crossing after the positive peak, the positive peak, negative peak, or their midpoint in the filtered signal; setting the trigger limits of amplitude or RR-interval (±30, 25, 20, and 15% of the latest accepted interval); visual check and cutting of the tachogram.

The HRV-analyzer gives the mean, minimum and maximum RR-interval, the standard deviation (SDNN), relative mean or coefficient of variation (CV=SDNN/mean), root mean square of successive RR-interval differences (RMSSD), and the percentage of RR-interval differences greater than 50 ms (pNN50) in the time domain; fast Fourier transformation (FFT) and its derived standard parameters; Lorentz-plot and its derivated parameters; and an RR-interval histogram with its numeric parameters.

3. 2. The ECG signal generator and the analyzer

The signal generator (ECGSim 1.0) was built on the DaqBoard2000 factory-calibrated data acquisition card (IOTech Inc., Cleveland, OH). The artificial ECG record is synthesized off-line from a single heart cycle template and a tachogram; both of them can be loaded from

existing files or defined in the software considering the recommendations of the Association of the Advancement of Medical Instrumentation (AAMI). Adding a given amplitude of Gaussian (electromyography) noise, 50/60 Hz sine wave (AC interference), sine wave of 5 Hz (motion artefact), and 0.5 Hz sine wave (breathing artefact) or their arbitrary combination is also possible. The generated signal is stored on hard disk and played back with a gain of 1000 using DMA (Direct Memory Access) for continuous high-speed data transfer at 10 kHz digital to analog conversion and 16 bit resolution. The signal before and subsequent to the actual analog filter circuit was digitized at 1 kHz per channel, 16 bit and stored on hard disk by DMA. These latest files containing both channels were further investigated.

The analyzer software (ECGAn 1.0) works simultaneously on the two channels: automatically detects the peaks (local maxima), and finds the 2/3, 1/2 and 1/3 height of the peak amplitude on both the ascending and descending slopes of the ventricular complexes. The distance between these 7 reference points (RR-intervals, see *Fig. 1*) or their position relative to the equivalent points of the original signal were allocated and visually checked.

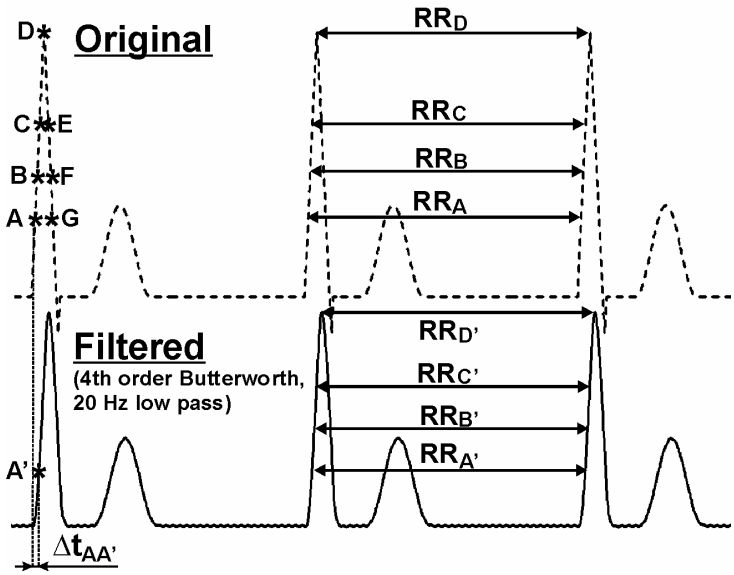

Fig. 1. Detecting the 7 reference points by the analyzer software: the peak (D) and the 1/3, 1/2, and 2/3 amplitude on both the ascending (A, B, C) and descending (E, F, G) slopes of the ventricular complexes. The RR-intervals given by the distance of the pairs of these 7 points or their timing difference were analyzed.

3. 3. The analog filters

Analog high pass, low pass and notch filters were assembled using the UAF42 monolithic universal active filter block (Burr-Brown Corporation, Tucson, AZ) tuned by external components calculated by the Filter42 software provided by the manufacturer. The circuit was built on a solderless breadboard (Type 4, Conrad Electronic, Germany). It was shielded by a grounded metal box and powered from the ±15 V outputs of the DaqBoard2000 card. See frequency responses on *Fig. 2.* Filter characteristics are specified in **3. 5.** and **3. 6.**

A) ***B)***

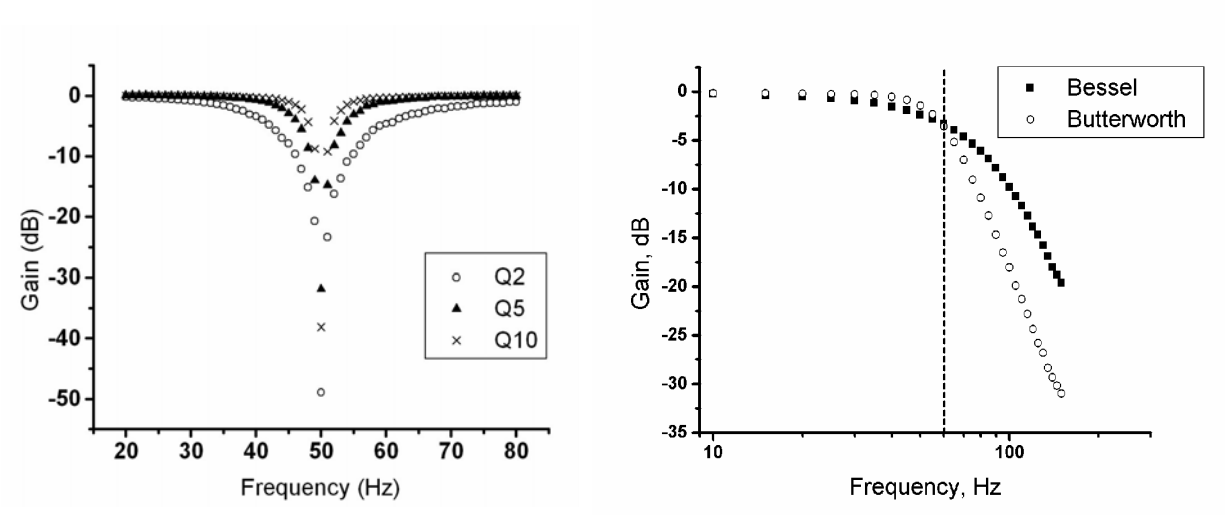

Fig. 2. A) Frequency response of the 50 Hz notch filters with Q=2, 5 and 10. B) Frequency response of the 4th order Bessel and Butterworth low pass filters at 60 Hz (logarithmic scale)

3. 4. Software for the simulation and evaluation of digitization error

The sampling error (SE) comes from the discretization at finite time resolution (sampling interval – SI) in the digitized signal. This software – Samplerr 1.0, also developed by the author – models the SE by adding a uniformly distributed random series in the range of $-0.5*SI \leq SE \leq 0.5*SI$ to the supposed R-fiducial point of the "original" tachogram. The original tachogram can be loaded from a .dat file (e.g. real human tachogram) or synthesized in the program (Gaussian random, uniformly distributed random, sinusoid at a given frequency, logistic or any of them mixed with a given frequency sine wave at a certain phase shift and amplitude). The original tachogram shifted to a known mean (e.g. 800 ms), skewed (shrink or stretch) to standard deviations of a given range (e.g. 5-30 ms in steps of 5 ms) are

the adjusted tachograms (n=6), those are “resampled” at SI in the chosen range (e.g. 1-10 ms in 1 ms steps). The resampling may be repeated several times (e.g. 15) resulting in 6*10*15=900 resampled-adjusted tachograms in our example. Separately for all repetitively resampled group (from each 15-element set), the mean, standard deviation, relative accuracy error ($RAE=(X_{mean}-X_{true})/X_{true}$) and relative precision error ($RPE=SD/X_{mean}$), are computed automatically from the mean RR-interval, SDNN, RMSSD and the pNN50 of the resampled-adjusted tachograms and compared to the same parameters of the original, nominally uncorrupted tachograms. The output of the program can be checked in a text box or saved as .dat file for further processes.

3. 5. Testing the effects of different high and low pass filtering

The ECGSim 1.0 (**3. 2.**) generated the augmented ECG signal consisting of 21 cycles (giving 20 RR-intervals) with the following parameters: Rs-amplitude=4 V, T-amplitude=1.2 V, RT=350 ms, Rs=65, 85 or 115 ms (ventricular complex duration, VCD), T=180 ms. The T-wave was formed by a sine wave instead of a semicircle in order to avoid uncharacteristic abrupt changes at the T-wave boundaries and consecutive spike formation after high pass filtering. The RR-interval was set to 803 ms, in order to prevent synchronization of the ECG signal and AC interference (20 ms period) in the corrupted series. Besides sterile records, power line interference- (added 50 Hz sine wave with 25% or 50% peak-to-peak amplitude of ventricular complex amplitude) and Gaussian noise- (electromyography artefact, 10%, 25%, and 50% rms amplitude of ventricular complex amplitude) corrupted records were investigated.

Filtering was performed by 2^{nd} order Butterworth high pass at 0.1, 0.5, 1.0, 2.0, 5.0 and 10 Hz; and 4^{th} order Bessel and Butterworth at 20, 40, 60, 80 and 100 Hz low pass frequencies. The Bessel filter has excellent pulse response due to its inherent flat group delay in the pass band, while the Butterworth filter has the flattest pass band magnitude response and steeper attenuation beyond the cutoff frequency. (Technical details in **3. 3.**)

The mean±SD and maxima were calculated individually from the (1) absolute phase shift of the 7 predefined pints of the ventricular complexes, and (2) from the reduction in peak amplitude. The mean±SD of the measured RR-intervals and the maximum deviation from the nominal 803 ms were computed also by the analyzer software (**3. 2.**).

3. 6. Testing the effects of AC notch filtering

Predefined ECG templates (Rs-amplitude=4 V, T-amplitude=1.2 V, RT=350 ms, Rs=65, 85 or 115 ms, T=180 ms) were repeated ten times at 803 ms. AC interference was represented by adding 5%, 10%, 25% and 50% peak-to-peak amplitude 50 Hz sine wave (**3. 2.**). The above mentioned 7 points of the ventricular complexes were found and manually checked. The mean, SD and maximal deviation from the corresponding point of the uncorrupted ECG were computed before and subsequent to notch filtering (**3. 2.**). The 50 Hz band rejection was tuned with filter Q=2, 5 and 10 (**3. 3.**).

3. 7. Effects of the sampling rate on the time domain parameters

Two 375-element high-quality ECG tracings derived from a healthy volunteer and a cardiovascular high-risk, diabetic patient with significantly reduced HRV were shifted to a mean of 800 ms and stretched (or shrunken) to standard deviations of 5-120 ms in 5 ms steps with the **3. 4.** software. All adjusted tachograms were "resampled" at 1-10 ms in 1 ms steps, ten times repetitively at each sampling rate. The mean, standard deviation, RAE and RPE were calculated from the mean RR-interval, SDNN, RMSSD and the pNN50.

4. Results

4. 1. Testing the effects of different high and low pass filtering

High pass filtering up to 0.5 Hz of the uncorrupted signal does not result in significant changes in the ECG morphology. At 1 Hz and 2 Hz corner frequency, considerable alterations befall present, at 5 Hz and 10 Hz cutoff the ECG signal is unrecognizable, however, the error of RR-interval detection remains within 1 ms with the applied algorithm.

Low pass filtering of the uncorrupted ECG signal (*Fig. 3 A*) causes a slight amplitude reduction. The phase delay depends on the cutoff frequency (20 Hz: 12-19 ms, 100 Hz: 4-5 ms), the reference point of the ventricular complex (ascending slope: 4-14 ms, peak: 5-15 ms, descending slope: 4-20 ms), the type of the filter (on the peak, at 20 Hz, Bessel: 17 ms, Butterworth: 14-15 ms), and in a lesser amount on the VCD (65 ms: 4-19 ms, 115 ms: 4-20 ms). The RR-interval detection remains within 1 ms accuracy error due to the constant phase shift of the ventricular complex within a tachogram at both types of filters.

Power line interference corruption proportionally alters the reliability of heart rate detection. At 25% or 50% interference, the peak is the most sensitive point (maximum divergence from the nominal 803 ms: 13 ms and 16 ms, respectively), the slopes are somewhat more resistant (maximum difference: 10 ms and 14 ms, respectively).

Bessel or Butterworth filtering at 40 Hz does not considerably recover the accuracy of rate detection. Bessel filtering of the 50% interference series at 20 Hz reduces the maximum error to 7 ms at the peak, whereas down to 2 ms on the slopes. Butterworth filtering at 20 Hz cutoff decreases the maximum difference to 12 ms at the peak, and 7 ms on the slopes.

Bessel filtering of the 25% interference series at 20 Hz low pass results in a maximum deviation of 3 ms on the peak, and 1 ms on the slopes. Applying a 20 Hz Butterworth filter reduces the error to 8 ms at the peak and 3 ms on the slopes.

Gaussian noise contamination causes unpredictable rate detection error independently of the chosen reference point. The 10% noise results in 3-10 ms maximum RR-interval differences from the nominal 803 ms. After passing through the low pass filter, this is reduced to 0-1 ms at every corner frequencies and both type of filters. The 25% rms amplitude noise causes 6-26 ms error that is reduced to 1-2 ms at 20-40 Hz low pass (see *Fig. 3 B*), while 1-3 ms at 60-100 Hz cutoff. The 50% Gaussian noise gives 10-34 ms deviations. 20-40 Hz low pass is associated with 1-4 ms error, while it is 2-6 ms at 60-100 Hz corner frequency.

The Bessel filter shows superior performance in the suppression of AC interference related errors at either 25 or 50% amplitude of the interference (probably due to its smoother impulse response), whilst there is no significant difference between the Bessel and Butterworth filters in reducing heart rate detection errors due to Gaussian noise.

A) Uncorrupted ***B) 25% rms amplitude Gaussian noise***

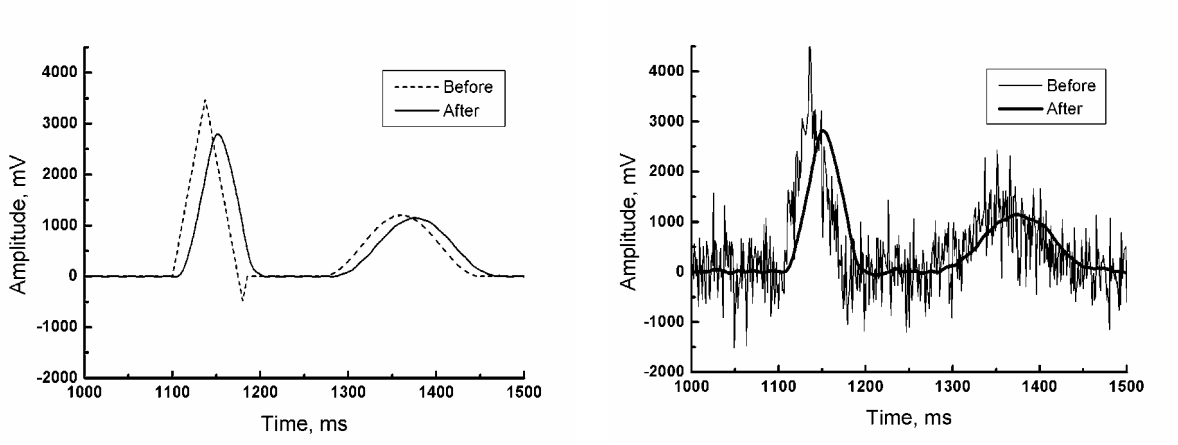

Fig. 3. Filtering uncorrupted (A, dashed line) and 25% rms amplitude Gaussian noise contaminated (B) ECG signal with 4th order 20 Hz low pass Butterworth response.

4. 2. Testing the effects of AC notch filtering

The notch filtering of uncorrupted ECG records does not result in RR-interval detection error greater than 1 ms, which is comparable to the theoretical sampling error at 1 kHz. AC interference contamination proportionally to its amplitude distorts the ECG and alters the accuracy of reference point localization: 5% interference amplitude: 2 ms, 10%: 4 ms, 25%: 8 ms, and 50%: 14 ms, which is consistently restored by notch filtering at any filter Q with a minimal error (≤1 ms on the ascending slope and peak, see *Fig. 4.*). The accuracy of peak detection without filtering is maintained up to 10% interference within 1 ms error. The wider the VCD, the more sensitive the RR-interval detection to mains interference, however this difference is not remarkable.

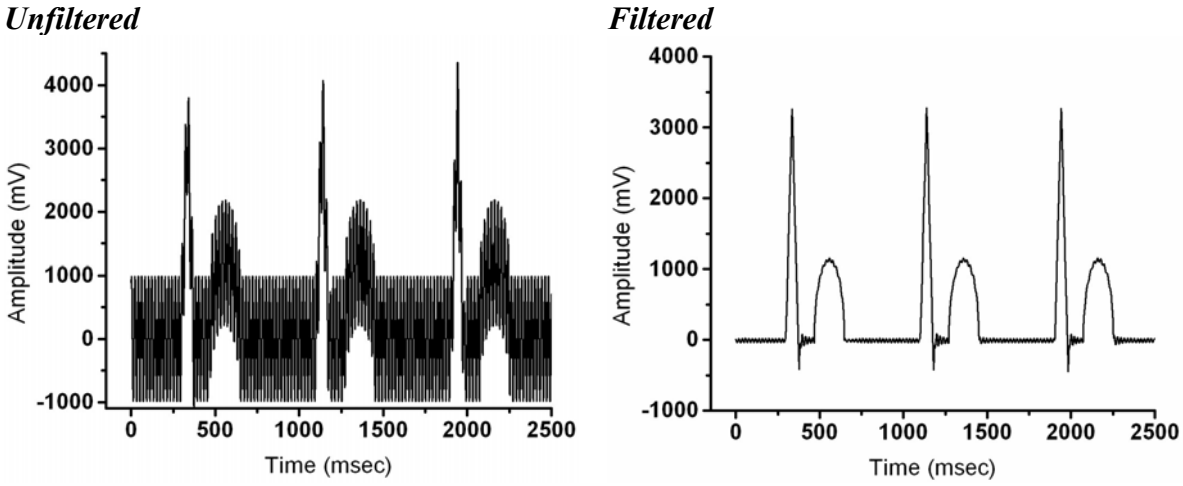

Fig. 4. Notch filtering (Q=5) the power line interference corrupted (50% of ventricular complex amplitude) ECG record.

4. 3. Effects of the sampling rate on the time domain parameters

The RAE and RPE of the mean RR-interval were below 0.1% at every sampling interval and in both healthy and high-risk series.

The RAE of the SDNN for the healthy and high-risk group showed identical trends due to the equal adjustment of this parameter. The smaller is the nominal SD, the higher are the RAE and RPE of SDNN. The RAE exceeded 1% at 2 ms SI, 5% at 4 ms SI, and 30% at 10 ms SI in the series with nominal SD=5 ms. Over 35 ms nominal SD, the RAE remained below 1% even at 10 ms SI. The RPE of SDNN exceeded 1% at SI of 7 ms, and 2% was not reached in the examined range.

The RAE of RMSSD was as high as 225.2% in the lowest variability tachograms at SI=10 ms. In the 5 ms nominal SD tachogram from the high-risk patient, SI of 1, 2 or 4 ms

resulted in RAE of 4.8%, 18.1% and 54.3%, respectively. Resampling the 15 ms adjusted SD series from the high risk patient at 1, 2, 4 or 10 ms SI, the RAE of RMSSD equalled 0.7%, 2.5%, 7.8% and 45.1%, respectively. The RPE of RMSSD was below 5% in the entire observation. The different trend in the RMSSD in spite of the same nominal SD reflects a more decreased beat-to-beat variability relative to the overall variability in the tachograms based on the high-risk patient.

The RAE of pNN50 was 16% for the healthy group, and nearly 50% for the high-risk group even at SI of 1 ms. The RPE showed poor precision: it was above 200%. The pNN50 has worse statistical properties, as the threshold of 50 ms gives pNN50 a discrete nature, which makes it extremely sensitive to noises.

5. Conclusions

A frequency band pass of 0.5-20 Hz may be sufficient in the ECG amplifier used for exclusively HRV analysis, which preserves ECG morphology, and improves the accuracy and precision of heart rate detection by reducing AC interference and electromyography noise.

Suppression of the ubiquitous power line interference is recommended in the ECG equipment for HRV analysis, since notch filtering itself does not deteriorate the accuracy of RR-interval detection, rather improves it in cases where significant AC corruption is present.

The mean heart rate interval is extremely resistant to the sampling error. For accurate measurement of SDNN and RMSSD even in patients with seriously reduced variability, 1 ms SI is recommended. However, lower sampling rate may be satisfactory in cases where higher variability or its changes are expected. The pNN50 is not a reliable measure even at 1 ms SI; therefore its use is not suggested in HRV analysis.

The above investigations expectantly call attention and demand to avoid some ignored technical pitfalls of HRV analysis, which may contribute to elucidate present unclear results persisting in this escalating field of cardiology.

6. Novel findings

In the available literature there is no similar meticulous investigation on the corner frequencies, AC notch filtering and sampling rate of the ECG for HRV analysis related to the accuracy and precision of heart rate interval detection and the time domain HRV indices. Our examination clearly demonstrates the adverse effects of some inappropriate technical conditions on the accuracy and reliability of HRV measurements. The sampling rate and upper band frequency cutoff suggested by the most comprehensive Task Force for HRV analysis has been obviously refuted by our empirical studies. On the contrary, the 200 Hz upper corner frequency recommended by that paper may retain more high-frequency noise, which can result in considerable errors of RR-interval detection, and consequently false HRV measures.

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