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High Resolution Electrocardiography in Healthy Dogs: Time Domain Parameters and Comparison of the Non-Stationary (Wigner Distribution) Versus Standard Stationary Frequency Domain Analysis Methods

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Summary

Fractionated heart activation can be detected as late potentials from surface recordings of signal-averaged electrocardiograms (SA ECG) which are considered as a marker of sustained ventricular tachycardia. For animal studies, reference values in time and frequency domain analyses are essentially missing. In the present study, we have established reference values in SA ECG time domain analysis and time-frequency representation of heart activation in healthy dogs. A group of 25 healthy mongrel dogs (body weight 12-15 kg) was investigated. Wigner distribution and our modification of Fast Fourier transform (FFT), gliding window FFT, was applied in SA ECG frequency domain analysis. Reference values in time domain SA ECG were established. Time and voltage criteria were adapted to short duration of heart cycle and fast voltage decrement of the QRS complex in dogs. Wigner distribution and gliding window FFT were applied in order to describe mean heart activation in the frequency domain. Contribution of higher frequencies (30-80 Hz) was detected by both frequency analysis methods in the second third of ventricular activation in healthy animals. Presented results could offer a basis for further experimental arrhythmologic studies.

Key words

Signal-averaged ECG • Spectral analysis • Reference values • Late potentials

Introduction

High-resolution ECG is used for identification of electrical instability in patients after myocardial infarction (MI) (Haberl *et al.* 1988, Breithardt *et al.* 1991). Prolonged fractionated electrocardiograms are detectable after MI and they are considered as signs of an arrhythmia-prone state. The ventricular late potentials (LP) detected on the body surface by signal-averaged electrocardiography are thought to arise from injured tissue generating prolonged ventricular activation and they are also considered as a marker of sustained tachycardia (Freedman *et al.* 1991, Hatala *et al.* 1995). Late ventricular potentials are the most important factor for stratification of patients with risk of sustained ventricular tachycardia. This method is often used in experimental arrhythmologic studies for its high specificity and sensitivity (Simson *et al.* 1981, Spear *et*

al. 1985, DeLangen *et al.* 1988, Hanich *et al.* 1988, Yoh *et al.* 1990). Contribution of high frequency components in ECG signal is studied as a marker of fractionated heart activation (Gomes *et al.* 1987, Caref *et al.* 1989, Steinbeck *et al.* 1991, Yakubo *et al.* 1995).

The aim of our investigations was to create reference values for SA ECG in healthy dogs. Description of the onset and offset of heart activation was the next aim of our study. Our own method (Hulín *et al.* 1992) (cumulative amplitudes) was used for monitoring of speed in voltage changes during ventricular activation. Heart signal frequency content was evaluated using Wigner distribution (WD). This method allows us to construct spectro-temporal maps in order to monitor changes of single frequencies during heart activation (Jones *et al.* 1992, Khadra *et al.* 1993, Novák *et al.* 1994). Our modification of Fast Fourier transform (FFT) analysis (Hulín *et al.* 1993) was used to acquire an image of changes in contribution of higher and lower frequency bands during ventricular activation. We suppose that our investigations would provide basic information of the time domain and frequency domain analysis, information about the onset and offset of ventricular activation as well as information about changes in the frequency spectrum during ventricular activation in healthy dogs.

We consider detailed studies of heart activation very important especially in dogs because dogs are often used as an experimental model for arrhythmias and myocardial infarction. It is very important to have exact information of heart frequency activation spectrum because antiarrhythmic agents do not have an identical effect on all frequency components in the ECG. Many nonarhythmogenic drugs (e.g. antidepressants), which are used in the clinical practice might cause a fatal complication in some patients (Mladosievičová *et al.* 1996). Experiments in dogs with myocardial infarction have shown that antiarrhythmic drugs had different effect on terminal and earlier high-energy portion of the signal averaged ECG (DeLangen *et al.* 1988).

In human medicine, standards were specified for using high-resolution electrocardiography (Breithardt *et al.* 1991). Similar standards are missing for experimental animals. The principal arrhythmologic studies are, however, realized in experimental animals not in humans.

Methods

A group of 25 healthy mongrel dogs (body weight 12-15 kg) was investigated to determine reference averaged values in time domain analysis of the ECG signal. The ethical norms for experimental studies in animals were respected during the whole monitoring according to the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes. The experimental procedure was approved by the Ethical Commission of the School of Medicine, Comenius University, Bratislava, Slovak republic. Animals were under the supervision of a veterinarian during the whole period of the experiment.

ECG recording

ECG recording were performed in dogs in light total anesthesia induced by pentobarbital administration (Pentobarbital Spofa) in dose of 25 mg/kg body weight.

High-resolution electrocardiography

During the recording, dogs were lying on their right side (Hulin and Rippa 1970). Subcutaneous needle electrodes were used. Horizontal lead (X) was placed in the 4th intercostal space on the left and right side. The vertical lead (Y) was placed on the proximal part of the sternum and above the sacral bone. Sagital lead (Z) was placed in 4th intercostal space parasternally and on the corresponding position paravertebrally on the left.

Arrhythmia Research Technology Model 1200 EPX device was used to record simultaneous orthogonal X, Y and Z lead. The signal from each lead was analog-to-digitally converted at 16 bit accuracy with sampling rate of 1000 Hz. Ectopic or noisy beats were rejected. At least 100 beats were averaged with a mean noise level 1.0 μV.

Time domain analysis

The data were filtered using a bi-directional Butterworth filtering (25 to 250 Hz, 40 to 250 Hz and 80 to 250 Hz). Three orthogonal leads were combined together in a so called ‘composite’ lead. The earliest onset and the latest offset of the QRS complex were determined from unfiltered leads by a computer algorithm. The studied parameters included: 1) duration of the QRS complex, 2) duration of the terminal part of the QRS under 30 μV, and 3) root-mean-square amplitude of the terminal 20 ms. These parameters were determined at frequency bands 25-250 Hz, 40-250 Hz and 80-250 Hz.

Cumulative amplitudes

Curves of cumulative amplitudes were

constructed for each filtration of the QRS complex signal. This method was described in our previous work (Hulín *et al.* 1992) Curves of cumulative amplitudes depict the increment of potentials from the very beginning of QRS complex. Similarly, in the terminal part of QRS complex these curves depict the speed of voltage decrement. Cumulative amplitudes were constructed particularly for each frequency range.

Frequency domain analysis

Frequency spectrum was determined by two methods: Wigner distribution and Gliding window fast Fourier transform analysis.

Non-stationary method (Wigner distribution, WD) was used in order to obtain spectro-temporal representation of the QRS complex signal (Claasen and Mecklenbraeuker 1980, Martin and Flandrin 1985). Cross-terms in WD were partially eliminated by smoothing (Choi-Williams filtering was used in our study (Choi and Williams 1989).

The gliding window fast Fourier transform analysis (GWFFT) was described in detail in our previous article (Hulín *et al.* 1993). The area ratio was evaluated in a similar way as was evaluated by Cain and coworkers (Lindsay *et al.* 1988, 1990, Cain *et al.* 1989). We used window length of 40 ms. Curves of area ratios were constructed for each individual lead. This method of gliding window fast Fourier transform analysis eliminates the problem of the QRS segment choice with a relatively small signal region (Kelen *et al.* 1987).

Table 1. Averaged values of time domain analysis of HR ECG in dogs (±S.E.M.)

Frequency bands	25-250 Hz	40-250 Hz	80-250 Hz
RMS VOLTAGES			
Standard QRS, μV	726±64	463±36	167±15
Filtered QRS, μV	695±40	442±36	157±14
Last 20 ms, μV	40.4±10.8	40.6±10.9	23.3±6.8
DURATION			
Total QRS, ms	63.4±1.3	60.9±1.5	57.9±1.7
Under 30 mV, ms	15.3±1.1	17.9±0.9	20.2±1.1

Results

Time domain analysis

Averaged values of parameters in the group of healthy dogs are listed in Table 1. The shorter duration of the canine QRS complex in comparison with that in humans was taken into account by the time domain criteria suggestion.

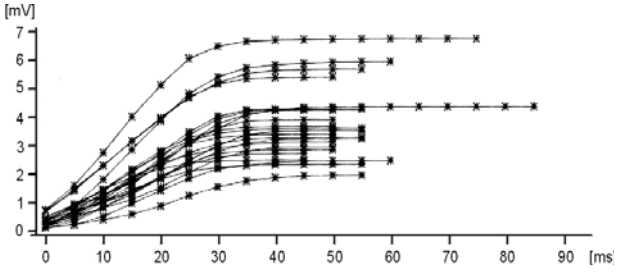

Fig. 1. The curves of cumulative amplitudes computed from the beginning to the end of QRS complex for all healthy dogs (frequency range 25-250 Hz).

Cumulative amplitudes

The first step was the root-mean-square (RMS) computing of the filtered QRS complex. In this way, the series of partial cumulative amplitudes were obtained. The cumulation of its values yields a curve of cumulative amplitudes representing the gradual voltage increase. Curves of the group of healthy dogs (frequency range 25-250 Hz) are shown on a single figure (Fig. 1). It is apparent that all curves have almost the same shape.

Frequency domain analysis

Spectro-temporal representation of the dog ventricular activation was acquired by Wigner distribution. The spectro-temporal maps (STM) of all 25 healthy dogs were centered on the R wave and then averaged to acquire an averaged STM (Fig. 2). An example of typical STM of a single healthy dog is shown in Figure 3. The contribution of higher frequencies is apparently higher in the second third of the ventricular activation. The averaged STM showed two typical,

partially smoothed peaks in higher frequency band (30-80 Hz) as shown in an example. Smoothing is caused by little time shifts of peaks in individual animals.

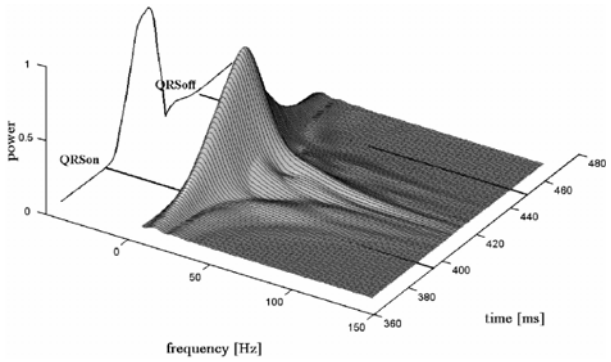

Fig. 2. Averaged STM of all healthy dogs as a result of WD - vector magnitude. 'QRS on' indicates the beginning of ventricular activation and 'QRS off', the end of ventricular activation. Amplitude is normalized to its maximal value.

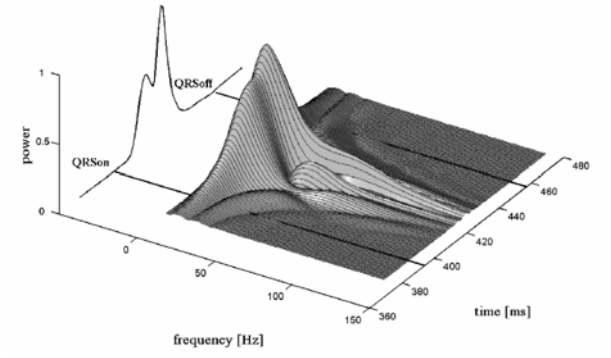

Fig. 3. A typical example of STM of single healthy dog resulting from WD - vector magnitude. 'QRS on' indicates the beginning of ventricular activation and 'QRS off', the end of ventricular activation. Amplitude is normalized to its maximal value.

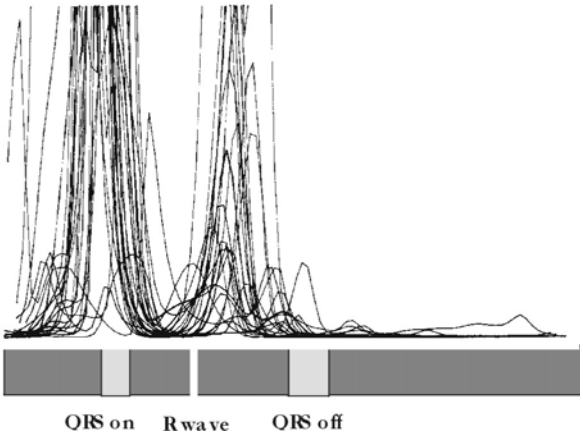

Fig. 4. Curves of gliding window FFT for all healthy dogs (composite lead) centered to R wave. 'QRS on' bar indicates the beginning of ventricular activation ± standard deviation; 'QRS off' bar, the end of ventricular activation ± standard deviation.

The gliding window fast Fourier transform analysis was applied to whole ventricular activation. In the Figure 4, there are curves constructed from area ratios of frequency bands 0-50 Hz and 0-120 Hz. Peak on the curve expresses either an increment of lower frequency bands or a decrement in the higher frequency band.

Discussion

Studies dealing with the analysis of late ventricular potentials in dogs with experimental myocardial infarction are aimed to compare parameters before and after MI had been induced. The general agreement in determining the time domain analysis parameters is still missing in dogs. Normal reference values for healthy dogs determined in this study are in good correspondence with the results of Spear and Moore (1985). The voltage sum of the terminal 20 ms of QRS complex and duration of terminal part of QRS complex under 30 μV were used as parameters for determination of late ventricular potentials in dogs after acute MI. Spear *et al.* (1985) considered the voltage sum at the terminal 20 ms of the QRS complex 13.5 μV or less, and duration of the terminal part of QRS complex under 30 μV more than 18.2 ms as a limit for presence of LPs in dogs with experimental MI. Almost identical limits were used in study of Kuchár *et al.* (1990). QRS duration more than 58 ms or 63 ms (Jiang 1990) was considered to be another limit for presence of late potential (LP). In our study the average was 57.91±1.67 ms for frequency band of 80-250 Hz and 62.41±1.32 ms for frequency band 25-250 Hz. In some studies criteria for humans are used for LP identification (Jiang 1990). In human medicine, one of the criteria of LP identification is the voltage of terminal 40 ms of QRS complex (adjustment of this criteria was made for sex, age, and myocardial location) (Savard *et al.* 1997). It is difficult to consider the 40 ms of the QRS complex duration as its terminal part in dogs. The duration of 40 ms represents the two thirds of the whole QRS complex duration (total 58-62 ms) in dogs.

Cumulative amplitudes are suitable for comparative studies for their ability to assess the onset of ventricular activation as well as its offset. The slower offset of QRS complex can be evaluated as LP. Cumulative amplitudes of the initial part are considered to be pathological if changes in ventricular activation onset (very slow bursting of ventricular activation) are present. When the activation front reaches a necrotic focus, it could be divided into two or more directions. In

such case the steepness of cumulative amplitude curve is apparently smaller. We suppose the steepness of cumulative amplitude curve is a parameter for detecting fractionated activation on the onset of QRS complex. These facts were described in our previous study (Hulín *et al.* 1992).

Gliding window FFT is based on area ratios expressing the contribution of particular frequency bands. Area ratios values were calculated using gliding window during the whole ventricular activation. By connecting all area ratio values together we obtained a continuous curve providing information about ratio amount in connection with its localization in QRS complex. This method eliminates the problem of window localization in ventricular activation. In addition, this method also provides information about exact value of area ratio peaks. The contribution of high frequency components in the whole QRS complex (not only at its end) has been the subject of many studies (Abbout 1987, 1989, Akselrod *et al.* 1988, Kubota 1995, Romberg *et al.* 1995a,b, Yakubo *et al.* 1995). It encounters the problem of window set up because a minimal shift of the window could cause considerable change in area ratio value. The GWFFT method provides information about ratios of higher and lower frequency bands during the whole ventricular activation. We suppose it might be generally useful in experimental arrhythmologic studies in dogs. On the other hand, the main drawback of the GWFFT method is that it uses area ratios.

Wigner distribution was designed for frequency domain analysis of signal with a time-dependent frequency content (non-stationary signals). The ECG signal belongs to this group of signals. In these consequences WD as non-stationary method could be considered superior to FFT or short-time FFT (ST FFT). Spectro-temporal maps give us an opportunity to have a complex overview of the dynamics of changes in a contribution of particular frequencies during heart activation. Frequency resolution of STM as a result of WD is more precise in both domains (time and frequency) in comparison with STM resulting from a short-time FFT. Time and frequency resolution of the ST FFT depends on the used window function. WD offers an algorithm for computing the frequency spectrum without a need of using any window function. Furthermore, FFT suffers from smearing and side-lobe leakage despite of WD. WD and GWFFT (as a modification of ST FFT) methods were compared in this study. The second peak in curves of area ratios was in agreement with the high frequency peak in STM as a result of WD. On the other hand, the first higher peak in area ratio curves (just before QRS onset) was not accompanied by an increment in STM resulting from WD.

Development of pathological fractionated activation and subsequent higher contribution of high frequencies in ECG signal is probably based not only on morphological substrate changes but also on myocardial electrical properties (Mor-Avi *et al.* 1987, Block *et al.* 1990, Freedman *et al.* 1991). Higher frequencies could be the consequence of changes in the myocardium without existence of any arrhythmogenic substrate. Anatomical arrhythmogenic substrate in heart 'generates' by itself the late ventricular potentials detectable by SA ECG. Arrhythmogenic substrate as a consequence of MI can be monitored by imaging methods (ECHO, radionuclid imaging), but the electrical activation of the heart is of crucial importance for the possible development of sustained ventricular tachycardia. Under these circumstances, principal interest is focused on methods for acquiring the most precise information about long-term changes in heart electric activation (Hanich *et al.* 1988, Ceral *et al.* 1999).

Structural arrhythmogenic substrate undergoes development even after certain stabilization, because the remodeling reaches healthy myocardium. It is manifested as fractionated activation in endocardial or epicardial recordings and as LPs in SA ECG. In experimental MI, late ventricular potentials are regarded as a consequence of the delayed epicardial activation after the end of QRS complex (Yoh *et al.* 1990, Goedel-Meinen *et al.* 1991). Presence of LPs corresponds with ventricular arrhythmias induced by programmed electrical stimulation (Zha *1*991, Jiang *et al.* 1990). It is assumed that beat-to-beat analysis could be more useful for the detection of the arrhythmogenic substrate (El-Sherif *et al.* 1985, 1990).

Berbari *et al.* (1994) have studied the relations between SA ECG recordings and epicardial recordings very precisely. They have suggested criteria for better LP identification. SA ECG was used in most studies for LPs identification. Frequency domain (FFT) analysis was rarely used in studies with experimental MI in dogs (Kubota 1995). No definite results were achieved in these studies. Thus, the Wigner distribution was applied in our study for frequency domain analysis. We have found that frequency spectrum is almost uniform in all healthy dogs. Increment in high frequency components was found in the second third of the ventricular activation. This peak corresponds to the presence of the peak in area

ratio curves.

The origin of the increment at higher frequencies in the second third of dog ventricular activation has to be explained. We suppose that activation in the second third of the QRS complex could be a consequence of the transition of activation progression from cell to cell. Transition of activation from one cell to another through a gap junction could be considered the origin of higher frequency contribution in ventricular activation signal. In the second third of ventricular activation most gap junctions are activated. This might be, as we suppose, the reason of higher frequency contribution in this phase of heart activation. The effect of myocardial fiber direction has also to be mentioned in this connection (Taccardi *et al.* 1994). Thus, there may be different sources of high frequencies within the QRS complex. Two most probable mechanisms of their generation concern: a) cell-to-cell conduction within the normal working myocardium manifested mainly during the terminal part of the QRS complex, and b) the activation of abnormal tissue within surviving fibers embedded within scar tissue. According to the location of the substrate relative to the time when it is activated, such high frequencies could be manifested during any portion of the QRS complex. However, in its most pronounced form, they will exceed the QRS complex, producing a late ventricular potential. Such late high frequencies correspond to delayed and fractionated terminal ventricular activation.

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