Analysis of Hemodynamic Related Changes in High Frequency Content of QRS Complex in Working Isolated Rabbit Heart

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Abstract

Aim: High frequency content of QRS complex (HF-QRS) is thought to be related to local conduction velocity (CV). There also exists the evidence suggesting the coupling between CV and mechanical stretch via so-called mechano-electric feedback. The aim of this study was to investigate possible relationship between left ventricular (LV) load and the most common HF-QRS parameters.

Methods: Six isolated rabbit hearts in working mode underwent an experimental protocol consisting of upward and downward steps in preload (8-11 cmH_2O). Eight unipolar pseudo-ECGs, left atrial pressure, and flow rate were recorded at f_s=10 kHz and 16-bit resolution. QRS complexes from hemodynamically stable experiment phase were clustered, aligned, and decomposed into 3 HF-QRS bands followed by the assessment of power envelope RMS, the tallest peak value and its position.

Results: No statistically significant changes associated with LV load alteration were observed in HF-QRS parameter.

Conclusion: No evidence of load dependent changes in conduction velocity was found in the study. However, HF signal may represent a complex spatial depolarization behavior. Low sensitivity of used metrics should also be taken into consideration.

1. Introduction

The relationship between the change of heart hemodynamic conditions and action potential conduction velocity (CV) was previously investigated in isolated rabbit heart [1], isolated rabbit papillary muscle [1] and canine heart *in vivo* [2]. The results vary in the statement of clear relationship's existence. One of possible reasons for these ambiguous results may be a lacking reliability of the measurement methodology.

Another technique, originating from high frequency content of QRS complex (HF-QRS) is thought to be related with local changes in CV under some pathophysiological conditions. The relationship between HF-QRS components and local CV was observed in isolated canine hearts [5], and in patients with left and right branch bundle block [3]. In silico experiment with three-dimensional model showed that changes seen in HF-QRS might result from slowing the CV in patients with myocardial ischemia [4].

Therefore, the aim of this study was to verify whether or not an invoked physiological stretch of the LV affects local CV to such an extent that it becomes observable in the HF-QRS signal of the isolated rabbit heart.

2. Material and methods

All animal experiments were carried out with respect to recommendations of the European Community Guide for the Care and Use of Laboratory Animals. The experimental protocol was approved by local Committee for Ensuring the Welfare of Laboratory Animals.

2.1. Experimental setting

Six adult New Zealand white rabbits (both sexes) were medicated by diazepam (2.5 mg), xylazin (4 mg/kg), ketamin (60 mg/kg) and heparin (1000 IU/kg). The heart was excised and fixed to a modified Working Heart System (Radnoti, USA) and perfused with Krebs-Henseleit solution (2.5 mM $CaCl_2$, 37 °C, pH 7.4) aerated by pneumoxyd (95% O_2; 5% CO_2).

For 15 minutes, heart was perfused in Langendorff mode at a constant pressure (80 mmHg). System was then switched to working heart mode (preload, 8 cmH_2O; afterload, 60 cmH_2O) and the heart was left to stabilize for next 15 min [6].

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During the protocol the heart rate was controlled by pacing the right atrium to inhibit the influence of QT-RR relationship. Baseline of the pacing rate was set to 10% above natural heart rate. Single upward and downward step in the heart rate was performed to verify correct dynamic response of QT-RR. Preload and afterload were adjusted by appropriate height of the water column. The magnitude of preload and afterload step change was chosen in order to induce sufficient change in PV parameters and to maintain physiological function of the heart (i.e. satisfactory cardiac output, avoiding EG abnormalities, etc.) [9]. The experimental protocol and analyzed parts of waveforms related to the LV hemodynamics are depicted in Figure 1.

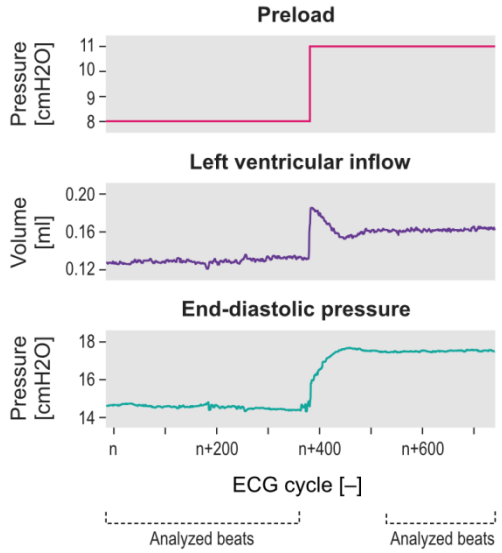

Figure 1 Experimental phase consisting of the upward step in preload and the response of analyzed hemodynamic parameters.

2.2. Data recording

Unipolar pseudo-ECGs were measured by eight non-contact Ag-AgCl electrodes placed on an interior wall of buffer-filled chamber. Electrodes were uniformly spaced along the LV wall [6][7].

Measurement of left atrial (LA) volumetric flow rate was performed by inline ultrasonic flow meter (Transonic Systems, USA). LA pressure was measured in the LA cannula by the TruWave blood pressure transducer (Edwards Lifesciences, USA). Signals were amplified by DAM50 Bio-Amplifiers (World Precision Instruments, USA), and acquired by NI USB-6259 measuring card (National Instruments, USA) with sampling frequency of 10 kHz and 16-bit resolution. Direct measurement of the LV hemodynamics via catheter was not performed in order to avoid any mechanical interference with valves and the LV wall.

2.3. Signal processing

LV inflow (LVI) was calculated for each ECG cycle as the integral of LA flow rate within duration of the cycle. End-diastolic pressure (EDP) was estimated from LA pressure waveform as the pressure at a sample just before start of the LV contraction.

Only data from experimental phases with stable end-diastolic pressure and volume were selected for further analysis (separate areas for the phase before and after the sudden change of preload, see Figure 1).

Pseudo-ECGs were preprocessed by removing a baseline wandering using the high-pass FIR filter (cut-off frequency of 0.32 Hz). R wave positions, QRS onsets and offsets were detected by custom made algorithm [7] and visually revised.

Extraction of the HF-QRS consisted of following steps: 1) QRS complexes with correlation coefficient > 0.985 were aligned with respect to the position of the R wave and the maximum of cross-correlation; 2) averaging the aligned QRS complexes; 3) filtering the averaged QRS complex using the 6th order IIR band-pass filter with cut-off frequencies at 300–500, 500–700, and 700–900 Hz, respectively; 4) computation of HF-QRS envelope; 5) smoothing of the envelope by low-pass FIR filter [10][11]. The example of averaged QRS complex and HF-QRS envelopes for each band are depicted in Figure 2.

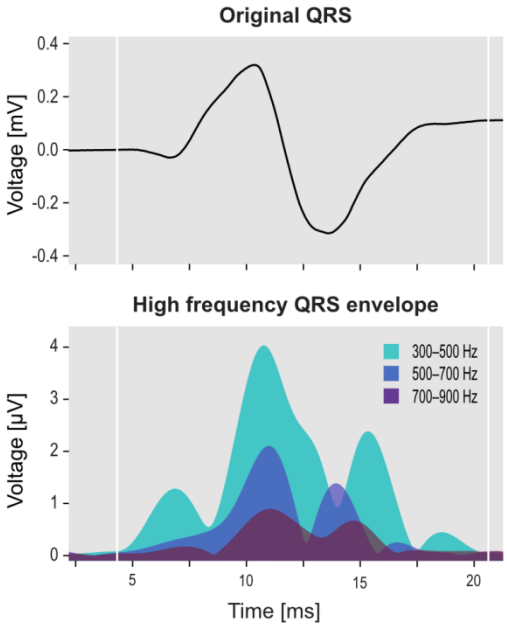

Figure 2 The example of the signal-averaged QRS complex (upper box) and related power envelopes of particular high frequency bands (lower box).

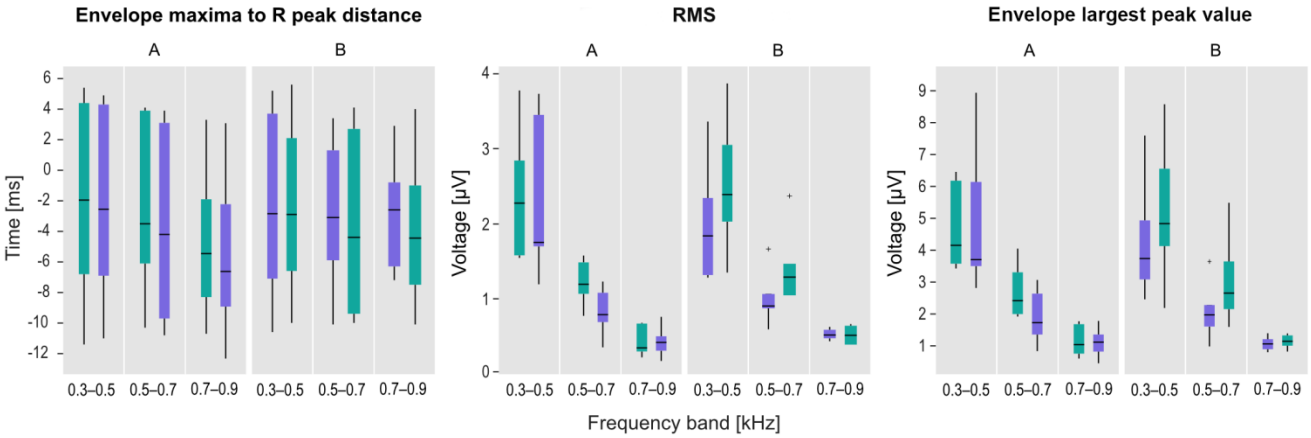

Figure 3 Overall results of HF-QRS parameters for single pseudo-ECG lead. From left to right: envelope maxima relative position with respect to a position of R peak (0 on y axis); envelope RMS voltage; envelope largest peak value. Green boxes: preload 8 cmH_2O; purple boxes: preload 11 cmH_2O; A: upward step in preload; B: downward step in preload.

2.3. HF-QRS parameters

The effect of changes in LV hemodynamics on HF-QRS was investigated using following parameters measured from HF-QRS power envelope:

- Envelope largest peak value (EPV) [10][11]
- Envelope maxima to R peak distance (ERPD) [10][11]
- Root mean square (RMS) of the HF-QRS [3] area calculated as:

$$x_{rms} = \sqrt{\frac{1}{n}(x_1^2 + x_2^2 + \cdots + x_n^2)}, \qquad \text{Eq.1}$$

where x_{rms} is the value of RMS and $x_1^2 \ldots x_n^2$ are the values of n HF signal power envelope within the QRS area. Parameters were calculated for each of three frequency bands mentioned above.

3. Results

Due to a limited space, only results for single pseudo-ECG lead are presented. The lead sensing the electrical activity of the lateral LV wall was chosen as it showed the highest sensitivity to electrical changes in the LV of isolated rabbit hearts in our previous experiments [8]. Identical results were observed within all remaining channels.

Table 1 Behavior of hemodynamic parameters in reaction to preload upward (↑) and downward (↓) step change

Parameter	**↑Preload (mean ±SD)**	**↓Preload (mean ±SD)**
ΔEDP [cmH_2O]	-2.43±1.48	2.48±1.19
ΔLVI [µl]	-48±20	47±20

Table 1 provides an insight into LV behavior during analyzed experimental phases. Differences in hemodynamic parameters before and after a step change in preload level are statistically significant (Wilcoxon rank sum test, p=0.031) and are in an agreement with physiological function of the LV.

Overall results of EPV, ERPD and RMS for all frequency bands are depicted in Figure 3. Consecutive green and purple boxplot represents the distribution of evaluated HF-QRS parameter before and after the induced change in the preload, respectively. Gray boxes divide the data according to the analyzed frequency band. Statistically significant differences were not observed in EPV, ERPD or RMS considering particular hemodynamic states of LV.

The relationship between electric HF-QRS parameters (EPV, ERPD and RMS) and hemodynamic parameters (EDP and LVI) appears not to be uniform. According to Figure 3, the only the RMS is visually different in frequency band 500-700 Hz. The rest of parameters was not affected significantly in any of the analyzed bands.

Table 2 Spearman correlation coefficients of correlation between HF-QRS parameters and hemodynamic parameters

Parameter	**EDP [cmH_2O]**	**LVI** [ml]	**EDP/LVI [cmH_2O]/** [ml]
EPV [µV]	0.242	0.715	-0.235
ERDP [ms]	-0.049	0.182	-0.077
RMS [µV]	-0.182	0.308	-0.294

Table 2 shows nonparametric correlation coefficients describing the relationship between HF-QRS and hemodynamic parameters, respectively. For the purpose of clarity, only results for frequency band 500-700 Hz are

presented. However, none of the correlation coefficients was statistically significant across all three frequency bands.

4. Discussion

Previous studies mostly measured the conduction velocity delay as an absolute time difference gained from the area between two electrodes. However, such measurement may be affected by prolongation of the trajectory related to LV enlargement. More importantly, the activation path should not always be considered straightforward between the measured points due to the tissue heterogeneity.

In our study, the changes induced in hemodynamic parameters (EDP and LVI) were not accompanied by any significant manifestation in investigated HF-QRS parameters (EPV, ERPD and RMS). We can hypothesize that changes in LV pressure and volume, carried out within physiological levels, resulting in only minor changes in conduction velocity that are not detectable by commonly used HF-QRS parameters. However, elementary principles and the interpretation of the HF-ECG have not been fully investigated yet. This ambiguity could lead to false expectations towards the reaction of HF-QRS parameters.

Further credible and verifiable studies are needed to adequately evaluate the relationship between mechanical stress of myocardium and the action potential conduction velocity.

5. Conclusion

This study did not confirm any connection and relationship between the LV load and HF-QRS components of EG signal gained from isolated working rabbit heart.

Acknowledgements

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