

# Repolarization Parameters in Heart Transplant Subjects

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## Abstract

*Heart transplant (HT) patients were analyzed to see whether the QTc depends more on sex of donor or recipient Subjects: 20 male/male (recipient/donor); 21 female/male; 17 female/female; 15 male/female; 23 healthy male; 20 healthy female. Continuous measurement was used over five postural changes: supine, sitting, supine, standing and supine.*

*Results: Significant QTc dependency on the sex of the recipient exists; no dependency on the sex of the donor was found. Heart transplant patients have lower coupling between heart intervals (RR) and QT intervals, lower RR reaction on postural changes and longer QTc than healthy subjects. The only dependency on the sex of the donor was found in heart rate in group of males with female hearts.*

## 1. Introduction

Cardiac repolarization has been analyzed since 1920 when Bazett's formula was originated. QTc as 60-bpm equivalent QT duration is used as a basic clinical marker and in drug tests [1], though doubts exist as to whether QTc is the best repolarization marker for pro-arrhythmias caused by delayed cardiac repolarization. Very little is known about the physiological background of repolarization and QT/RR coupling. It is well known that women have longer QTc and a steeper QT/RR slope compared to men [2-4], though the physiological explanation for such differences is not clear. These differences may be the result of genetic differences in the myocardium (heart properties, the distribution of action potentials) or genetic differences not originating in the heart (hormones, different concentration or distribution of ions). We analyzed measurements of heart transplant patients (HT) [5] with the aim, whether repolarization parameters are more dependent on the sex of the donor or the sex of the recipient.

## 2. Methods

Six groups of subjects were measured:

- A) HT male/male (recipient/donor), N=20, age  $59 \pm 11$ , 90/41 (mean  $\pm$  STD, max/min years);
- B) HT, female/male, N=21, age  $54 \pm 14$ , 73/25;
- C) HT female/female, N=17, age  $54 \pm 16$ , 68/22;
- D) HT male/female, N=15, age  $48 \pm 17$ , 68/22;
- E) Healthy male, N=23, age  $53 \pm 15$ , 71/24;
- F) Healthy female, N=20, age  $59 \pm 7$ , 70/40.

Continuous, 12-lead ECG was measured with the high dynamic system (sampling frequency 5 kHz, ADC 24 bits) from M&I Prague, CZ. Measurements were performed in an electromagnetically shielded room (Faraday cabin, MR-Schutztechnik, Dieburg, Germany) located at the International Clinical Research Center at St. Anne's University Hospital, Brno, Czech Republic. Data was measured over five postural changes: supine, sitting, supine, standing and supine, each of 8-minutes duration. Continuous analysis over 40 minutes was used.

### 2.1. QT detection

As the first step, QRS complexes were detected by a QRS detection algorithm [6]. The T wave shape in heart transplant patients was significantly distorted and we tried various preprocessing algorithms to obtain a course that best describes the duration of repolarization: recommended lead II; standard deviation over 12 leads; power over 12 leads and singular value decomposition [7]. Comparing the results of detection over a number of subjects, the singular value decomposition was selected as the best preprocessing method. End of T wave was defined by Philips QT interval measurement algorithms [8]. QT detection was done consecutively on a beat per beat basis; no averaging over multiple beats was used. Debatable beats were marked as non-detectable.

### 2.2. Heart rate variability and QT variability

QT depends significantly on heart rate and precise analysis of QTc and QT/RR coupling should be based on measurement with substantial changes of heart rate. The RR changes should be slow in order to analyze QTc, QT/RR slope and QT memory and fast to analyze QT

restitution. Missing slow RR variability substantially limits the analysis, and QTc assessment may be given by general corrections, as Bazett's or Fridericia's. We analyzed RR variability as the STD of RR intervals (varRR) and as power in two frequency bands – pass band (0.15, 2) Hz (RR\_HF\_PW) and pass band (0, 0.01) Hz (RR\_ULF\_PW). These bands correspond to QT/RR frequency response in healthy subjects [9]. Poincare plot was used to analyze the regularity of RR changes. The main axis of Poincare plot (a0) and the area of Poincare plot (PL2) are presented. The Pearson correlation coefficient (Cor\_RR/QT) was used to analyze the strength of coupling between RR and QT intervals and a linear fit represents a certain gain, i.e. QT/RR slope (Gain\_QT/RR).

QT hysteresis elimination was based on filter [10] or on exponential weighting [5] if the assessment of TRF model was noisy. Three QTc are presented: Fridericia's correction ( $QTcF=QT/RR^{1/3}$ ), linear Framingham correction ( $QTc0.154=QT+0.154(1-RR)$ ), and QTcL that correspond to minimal correlation between QT and RR.

### 3. Results

Mean levels over subjects for groups A to F are

Table 1. Mean levels and STD over groups. A: HT male/male (recipient/donor), B: HT female/male, C: HT female/female, D HT male/female. varRR and varQT are STD of RR and QT intervals. QTcF, QTc0.154 and QTcL are QTc given by Fridericia's, Framingham's and linear regression. RR and QT\_ULF\_PW is power in ULF band (0, 0.01) Hz. Parameters of Poincare plot a0, b0, PL2 are main axis, secondary axis and area. Gain QT/RR is given by linear regression between QT and RR. Cor\_QT\*RR is Pearson correlation coefficient, median and percentile, 10 and 90%.

Groups	A	B	C	D	E	F
RR [ms]	765±98	752±113	783±93	706±69	912±130	889±95
varRR [ms]	33±16	44±30	46±39	38±28	110±43	85±25
QT [ms]	317±24	342±33	345±29	314±25	321±23	335±18
varQT [ms]	20±12	34±25	29±22	21±18	17±6	27±17
QTcF [ms]	347±17	377±35	374±24	354±30	331±14	348±14
QTc0.154 [ms]	354±15	380±30	378±22	360±27	333±13	351±14
QTcL [ms]	404±124	463±208	399±45	596±300	337±19	357±18
RR_HF_PW [ms <sup>2</sup> ]	62±74	670±2600	181±260	99±172	1830±3600	515±400
RR_ULF_PW [1000 ms <sup>2</sup> ]	1.04±1.2	1.25±0.9	1.40±2.4	1.7±3.7	5.9±4.2	5.2±3.7
a0 [ms]	45±23	58±35	50±34	51±39	143±50	115±37
b0 [ms]	10±6	17±27	19±12	12±7	49±47	27±13
PL2 [1000 ms <sup>2</sup> ]	9±6	34±100	19±21	14±15	166±210	63±33
QT_ULF_PW [ms <sup>2</sup> ]	237±214	808±1300	405±544	398±700	159±134	173±130
Cor_QT*RR	0.68 -0.6/0.9	0.10 -0.6/0.9	0.47 -0.4/0.9	0.67 -0.6/0.9	0.92 0.47/0.95	0.90 0.59/0.94
Gain_QT/RR	0.11±0.4	0.04±0.6	0.23±1	-0.12±0.8	0.14±0.06	0.16±0.08

presented in Tab. 1. The distribution of selected parameters is given in Fig. 1. Statistically significant differences exist between healthy and HT with the following parameters: RR; varRR; RR\_HF\_PW; RR\_ULF\_PW; a0; PL2 and Cor\_RR/QT. In these cases, the P coefficient was lower than 0.05 with Bonferoni correction. Healthy men have a QTc statistically significantly shorter than all other groups (A, B, C, D and F) for all QT corrections (QTcF, QTc0.154, QTcL). Healthy women have a QTc statistically significantly shorter than group B and C only. Statistically significant differences in QTc among HT patients exist with QTcF and QTc0.154 only and exist between A vs. B or C and between D vs. B or C.

### 4. Discussion

Heart rate and heart rate variability are significantly different in healthy subjects and HT patients. The highest heart rate is in group D, i.e. men with a women's heart. The heart rate variability, including the reaction to postural changes is significantly lower in HT patients than in healthy subjects. The QT variability is comparable between HT and healthy, though a significant part of QT variability is random in HT, not corresponding to RR

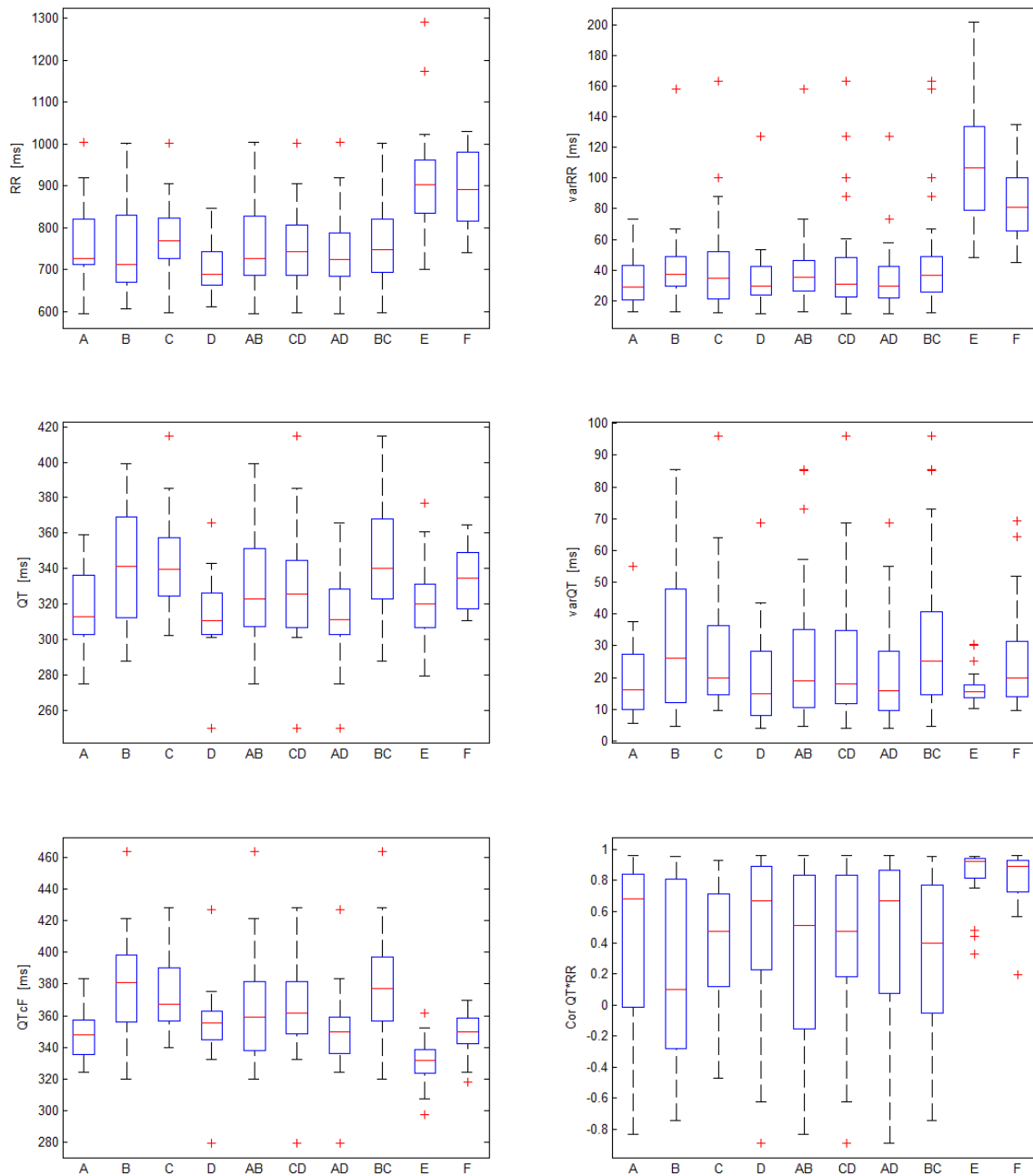


Figure 1. Distribution of parameters over groups. AB, CD are connected groups according to the sex of the donor, AD, BC are connected groups according to the sex of the recipient.

changes. The coupling between RR and QT changes is mostly low in HT patients, only a small number of patients have similar correlation as healthy subjects. A future study may focus on more detailed analysis, clustering the groups not only according to recipient and donor, but also according to level of reaction to postural changes or according to the level of coupling between RR and QT. The clustering used in this study is sufficient to

analyze QTc sex differences in HT patients.

The sex differences of QTc in HT patients should be based on general corrections, as presented QTcF or QTc0.154. We are aware of the limitations of such corrections, but both corrections give similar results and subject specific correction is impossible owing to low RR changes and irregular QT behavior in HT patients. Significant differences exist in QTc according to the sex

of the recipient. Recipient males have significantly shorter QTc than females (A vs. B or C,  $P < 0.01$ ; D vs. B or C,  $P < 0.05$ ), in connected groups, according to recipient (A+D vs. B+C) is  $P < 0.001$ . No dependency in QTc on sex of donor was found; the connected groups AB\*CD have nearly equal QTc.

Summary on QTc: As expected, the healthy females had longer QTc than healthy males. In heart transplant patients, the QTc depends on the sex of the recipient, not on the sex of the donor. A new question arises as to why HT patients have longer QT than healthy subjects. According to the study by More [11], heart donor candidates have severe neurological injuries that have been associated with significant prolongation of QTc. The post-transplant QTc was significantly shorter compared to pre-transplant QTc [11]. Some residual QTc elongation in transplanted hearts may however, remain. The prolonged QTc in HT may be the result of injury to the transplanted heart, drugs used or other, as yet unknown reasons.

A dependency on the sex of the donor exists in heart rate and heart rate variability. Males with female hearts have maximal heart rate. This probably corresponds to heart size; male recipients/females donors are mostly undersized in heart size and have the shortest survival [12, 13].

#### 4.1. Limitation

The presented analysis is limited by:

A) QT detection. We used automatic detection to be able to analyze large data. Various pre-processing, algorithms to detect QT interval, detection beat per beat or using median beat and definition of non-detectable beats; all these differences may had a significant impact on the results [14].

B) Limited number of HT subjects. More detailed clustering of HT should be used according to RR reaction to excitation and level of coupling between RR and QT.

#### 5. Conclusion

A significant dependency of QTc on the sex of the recipient exists, no dependency on the sex of the donor was found. Heart transplant patients have lower coupling between RR and QT, lower RR reaction to postural changes and longer QTc than healthy subjects. The only dependency on the sex of the donor was found in the heart rate of males with female hearts and this dependency is probably result of heart size.

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