Can Functional Cardiac Age be Predicted from the ECG in a Normal Healthy Population?

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Abstract

We hypothesized that in a normal healthy population changes in several ECG parameters together might reliably characterize the functional age of the heart.

Data from 377 healthy subjects (209 men, 168 women, aged 4 to 75 years) were included in the study. In all subjects, ECG recordings (resting 5-minute 12-lead high fidelity ECG) were evaluated via custom software programs to calculate up to 120 different conventional and advanced ECG parameters. Using factor analysis, those 5 parameters that exhibited the highest linear correlations with age and that were mutually the least correlated were evaluated by multiple linear regression analysis to predict the functional electrical age of the heart. Ignoring small differences between males and females, functional electrical age was best predicted (R^2 of 0.76, P < 0.001) by multiple linear regression analysis incorporating the RR-interval normalized high frequency variability of RRV; the RR-interval normalized value of a QT variability parameter called QTcor; the mean high frequency QRS (150-250 Hz) amplitude; the mean ST segment level at the J point; and the body mass index.

In apparently healthy subjects, functional cardiac age can be estimated by multiple linear regression analysis of mostly advanced ECG parameters.

1. Introduction

It is known that changes in parameters such as the amplitude, duration and electrical axis of different ECG waves or variability of ECG intervals such as HRV and QTV reflect the effects of age and gender on the resting ECG [1-5]. We hypothesized that in a normal healthy population changes in several ECG parameters together might reliably characterize the functional age of the heart.

2. Methods

2.1. Participants

Our study population was recruited at four sites: in Slovenia from both rural areas (312) and urban Ljubljana (222); from Johnson Space Center (Houston, TX) (245); and from healthy pediatric controls at Lund University Hospital (138). The initial population of 917 subjects was ultimately reduced to 377 subjects (209 men, 168 women, ranging from 4 to 75 years of age) after exclusion criteria that included hypertension, diabetes, smoking, positive cardiac history, overt ECG abnormality, regular rigorous endurance exercise training and/or extreme BMI. All participants gave original informed consent, and the Institutional Review Boards of one or more of the institutions approved the studies.

2.2. Data collection

In all subjects, high-fidelity (1000 samples/sec/channel) ECG systems from Cardiax/CardioSoft (Budapest, Hungary/Houston, TX) [6] were utilized to acquire resting 5-minute ECG recordings in the supine position to get a minimum of 256 waveforms acceptable for both signal averaging and variability analyses which were evaluated via custom software programs to calculate up to 180 different conventional and advanced ECG parameters. Besides, body height and body weight were measured to calculate body mass index (BMI).

2.3. Analysis of ECG signals

A. Conventional ECG parameters. Signals from the conventional ECG were analyzed automatically in software with respect to the RR, PR, P-wave, QRS and uncorrected and corrected QT and JT intervals; P, QRS and T-wave amplitudes; frontal plane QRS and T-wave axes; and ST segment levels.

B. Advanced ECG parameters derived from signal averaging and from variability analyses. Signal averaging was performed using software developed by the authors [6-9] to generate results for parameters of:

1) 12-lead high frequency (HF, 150-250 Hz) QRS ECG from which principal vectors were determined by singular value decomposition (SVD) and the first three vectors used to calculate a root mean square (RMS) HF QRS amplitude defined as a square-root of the sum of the squared first three principal signals. Both the peak (HFQRS A) and mean (HFQRS M) HFQRS RMS signals were characterized;

2) derived 3-dimensional ECG, using the Frank-lead reconstruction technique of Kors et al [10] to derive several vectorcardiographic (VCG) parameters including e.g. the spatial mean QRS-T angle, the magnitude, azimuth /elevation [11] and the spatial ventricular gradient and its components;

3) QRS and T-waveform complexity via SVD, e.g. to derive parameters such as the principal component analysis (PCA) ratio, intradipolar ratio (IRD) [7,12,13] the "relative residuum" [7,14] and the dipolar and non-dipolar voltages [6,15] of the QRS and T waveforms, and

4) Several parameters of beat-to-beat RR and QT interval variability (RRV and QTV) were evaluated via custom software programs developed by the authors as described in previous publications [5,6,16-18]. These included different components of the frequency power spectra (VLFP, LFP, HP and TP: very low, low, high and total, respectively), obtained using the autoregressive model or Lomb periodogram [19]; the "QT variability index" (QTVI), but using the means and variances of the RR interval[5,20] rather than those of the heart rate [21] in the denominator of the QTVI equation, and the "unexplained" part of the QT variability [5,16] For the latter, the QTV signal was decomposed into two parts as previously described: one part that can be accounted for by the concomitant HRV and/or by the concomitant variability of the QRS-T angle and ECG voltages, and the other part representing the "unexplained" part of QTV [5,16]. The QT signals were fit by a linear combination of the RR interval, QRS-T angle and voltage signals, with the fitted part representing the "explained" QTV and the remaining "error" part representing the "unexplained" QTV. A modified "index of unexplained QTV" (UTVI) similar to QTVI was then calculated by replacing the variance of the total QTV by the variance of the unexplained QTV. In addition, the cross-correlation (QTcor) between the QT signal and its explained QT signal was determined for all ECG leads.

2.4. Statistical methods

The parameters thus obtained for each subject represented variables for further statistically analysis. First, correlations among each variable and age were determined using a median fit regression by minimizing absolute deviation (dev). From the latter, the t statistic parameter b1/dev, defined as slope of the regression line (b1) divided by absolute or standard deviation was determined. Parameters that satisfied the criteria abs(b1/dev) > 2 and the correlation coefficient $R^2 > 0.2$ were used in the multiple linear regression [22].

Variables were standardized by converting raw data to unitless standardized deviates by subtracting the mean of each variable and dividing by the standard deviation of the variable. For elimination of multicolinearities, the correlation matrix of the standardized variables was calculated and the matrix rotated to identify collinear variables [23]. Factor analysis was used to identify representative ECG parameters from the subset of 21 variables, with utilization of principal component analysis (PCA) for final extraction of the reduced factor model.

3. Results

An acceptable correlation with logarithm of age was found for 31 parameters that could be arranged into several groups based on the particular waveform characteristic (e.g., amplitude, duration, axis) or its beat-to-beat variability.

Best regression was obtained for the group of the variability parameters of either the RR or the QT interval, with the largest R^2 being obtained for the HF component of RRV from the Lomb periodogram as normalized by the RR interval (LoHF/RR). R^2 was only slightly lower for the QTcor/RR and certain other QT variability parameters (Table 1). We introduced the ratio of LoHF (and QTcor) to the RR interval (i.e., the parameters LoHF/RR and QTcor/RR) after noting that they become smaller with age but "saturate" below age 20, whereas the RR interval itself increases roughly up to age 20 and stabilizes thereafter. The use of the ratios reduced non-linearity over the whole range of log(Age) and improved correlations by roughly 50%.

For the QRS complex the largest R^2 was obtained for the HFQRS M, followed by that of the conventional QRS upslope (dVdt1QRS). The conventional QRS amplitude and frontal plane QRS electrical axis were not particularly contributory, nor were conventional characteristics of the T and P wave except for modest contributions of the P wave duration (Pd) and T wave amplitude.

A considerably good correlation with log(Age) was observed for the ST segment level evaluated at the J point (ST-J) as represented by the mean value for ECG leads I, II, V5 and V6. This value was also correlated with the derived-VCG transverse plane azimuth angle of the ST.

In the final model those 5 parameters that exhibited the highest linear correlations with age and that were mutually the least correlated by the factor analysis, were evaluated by multiple linear regression analysis.

Table 1. Linear median fit regression of log(Age) for different ECG parameters (377 healthy subjects).

Parameter	b_i/dev_i	r^2
RR_mean	1.96	0.14
LoHF	-3.69	0.39
LoHF/RR	-6.01	0.62
ARHF	-3.24	0.30
QTcorr	-3.44	0.39
QTcor/RR	-5.42	0.55
BMI	3.93	0.40
HFQRS_M	-2.96	0.29
dVdt QRS	-2.73	0.26
ST-J	-2.43	0.23
ST azi	1.91	0.20
dP	2.02	0.13
QRSdev	-0.89	0.04
Amp_QRS	-1.96	0.16
NDPVQRS	-1.96	0.16
UTVI II	2.55	0.23
QTVI II	1.21	0.12

b_i/dev_i:the slope of the regression line divided by the absolute deviation; R^2:squared value of the correlation coefficient; p: p value; RR mean: mean RR interval [ms]; LoHF, ARHF: logarithm of the HF component of the RR interval power spectrum for the Lomb periodogram and the autoregressive model, respectively [Ln ms^2/Hz]; QTcorr: the cross-correlation coefficient of the measured and fitted QT signal [unitless]; HFRR/RR, QTcor/RR: Lo HF and QTcorr divided by RR interval; BMI: body mass index [kg/m^2]; HFQRS M: mean value of the RMS HF QRS signal [µV]; ST-J: mean value of the J point level [µV];ST azi: azimuth angle of the ST segment in the transverse plane; Pd: P wave duration [ms]; QRSdev: deviation of the QRS axis in the frontal plane [deg]; Amp_QRS: RMS amplitude of the QRS complex as obtained from PCA; NDPVQRS: non dipolar value of the QRS complex; UTVI: index of QT variability similar to QTVI but with the variance of the unexplained part of QTV instead of the total QTV; QTVI II: QTVI index in the standard lead II; for all p<0.0001.

Ignoring small differences between males and females, functional cardiac age was predicted (R^2 of 0.76, $P < 0.001$) from a linear combination of the following best 5 univariate predictors (Figure 1, Table 2) that were the best surrogate variables for the five dimensional factor space: the variabililty parameter LoHF/RR of RRV, the repolarization parameter QTcor/RR, mean high frequency QRS amplitude (HFQRS M), the J point level (ST-J), and the anthropological parameter BMI (for all p<0.001).
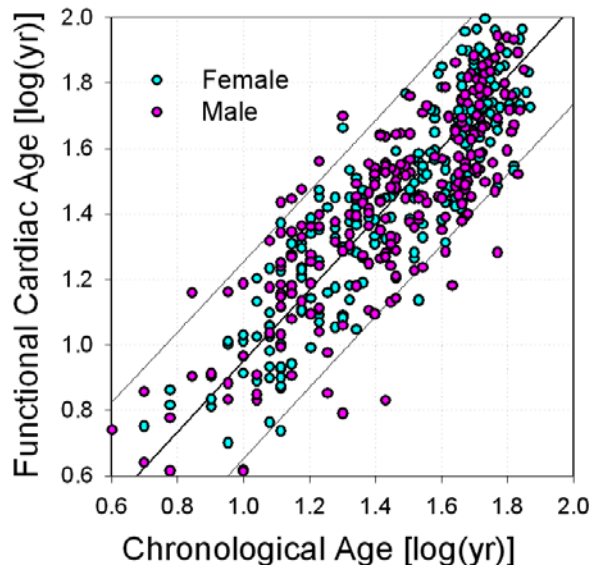

Figure 1. Functional cardiac age, as estimated by multiple linear regression analysis of the chronological age

When the group of subjects was increased to all outwardly healthy subjects (including smokers, athletes and those with extreme BMI and asymptomatic hypertensives and diabetics) the explained variance was decreased to R^2 of 0.73, i.e. only slightly, but with the regression line at slightly higher age.

Table 2. Multiple linear regression analysis for the selected ECG parameters (377 subjects).

Parameter	Coeff.	IncVar
LoHF/RR	-0.0628	0.62
QTcor/RR	-0.2536	0.66
BMI	0.0132	0.71
HFQRS_M	-0.0166	0.73
Jpt level	-0.0019	0.76
Const	1.85	0.76

Coeff.: coefficients of the linear regression equation; IncVar: explained variance increased by adding successive parameters from LoHF/RR to ST-J, for all p<0.0001. For explanation see Table 1.

4.   Discussion and conclusions

We found that in apparently healthy subjects, functional cardiac age can be estimated by multiple linear regression analysis of mostly advanced ECG parameters. More than 80% (=0.624/0.76) of the estimate was contributed by LoHF/RR, i.e. the HF parameter of RRV, as normalized to the mean RR interval. Although some of

our advanced ECG parameters of repolarization manifested good linear correlations with age, our study failed to reproduce those notable correlations to age previously reported for conventional electrocardiographic parameters such as the frontal plane QRS electrical axis [1], although modest correlations between age and this parameter were present our Slovenian rural population subgroup. A surprisingly good correlation was also found between age and the J-point ST segment level in the leftwardly-directed primary ECG channels I, II, V5 and V6, with reduction in this J-point level of approximately 50 µV over the span of a typical lifetime.

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