The effect of different stressors on the QT interval and the T wave

Doctoral Thesis

Gábor Andrássy, M.D.

Semmelweis University
Doctoral School of Basic Medicine

Supervisor: Prof. László Rosivall M.D., D.Sc.

Reviewers: Endre Zima M.D., Ph.D.
Prof. Aladár Rónaszéki M.D., Ph.D.

Head of Committee of Final Exam: Prof. Mátyás Keltai, M.D., D.Sc.
Members of Committee of Final Exam: Prof. József Borobola, M.D., candidate
Hajnalka Vágó, M.D., Ph.D.

Budapest
2007.

1. INTRODUCTION

1.1. Correction of the QT interval duration

Electrical surface recordings made during the electrocardiogram (ECG) correspond to the electrophysiological events occurring during impulse generation and conduction in the heart. At a given moment the primary factor that controls the duration of the QT interval is the heart rate, more exactly, the duration of the preceding cycle length, so heart rate correction is required in the analysis of repolarization duration. Various heart rate correction formulae have been developed in order to determine whether the QT interval is prolonged in comparison to its predicted value at a reference heart rate of 60 beats per minute (bpm), i.e., an RR interval of 1.0 second.

Theoretically, the task of describing the QT/RR relationship does not appear to be too complicated. In principle, it seems sufficient to accumulate enough data points of corresponding QT/RR intervals, subject these data to a curve-fitting procedure, and use known mathematical tools that should provide not only the mathematical form of the relationship but also the corresponding numerical parameters. Unfortunately, the problem is far from this simple. Although regression analysis of QT/RR data has been performed many times, the reported results are highly variable. The most known study by *Bazett*, involved 72 subjects including ECGs from both genders as well as children. Compared with other investigations, *Bazett*'s study was a methodological exception because it was purely observational and did not involve any regression modeling. Therefore it is not surprising that amongst all, the *Bazett* formula performs the worst: because of its inherent heart rate dependency, corrected QT (QTc) values incorporate an excess distortion that increases with divergence from the reference 60 bpm heart rate. Consequently, though the *Bazett* formula may remain useful in everyday practice, its use in research requires great caution. Considering that QT interval prolongation may be arrhythmogenic, a physiologic (or drug) effect on the QT duration is of outmost importance. Several clinical circumstances have been reported to be associated with QTc prolongation, but the use of the *Bazett* method questions their relevance. Amongst others, for example, such conditions with confounding reports are smoking, mental stress and being over weighted: significant differences were found between smokers and non-smokers, between subjects under and free from mental stress, and between normal- and over-weighted individuals.

In these reports the limitations of the *Bazett* method were often ignored that we have addressed in some Letters to the Editor. We stated that comparing QTc values measured at different heart rates using the *Bazett* method has no

sense because of the profound heart rate dependence inherent in this method. In other words, the *Bazett* method almost always yields an artificial though statistically significant difference between QTc-s measured at different heart rates.
Recently, it has been recognized that any meaningful precision of heart rate correction of the QT interval cannot be achieved with previously published "general" correction formulae. This is because the QT/RR pattern is highly individual and thus the QT/RR relationship is not reproducible between studies investigating different populations. Consequently, it has also been recognized that to improve the precision of heart rate correction, the data of the study/subject in hand need to be used to derive specific correction approach suitable for the given investigation or subject. To describe the baseline QT/RR relationship different regression models can be tested by the means of curve fitting, so that the mathematical model that leads to the lowest regression residual (best fit) may be selected for the purpose of heart rate correction. Practically, because the association between QT/RR in the HR range of 50-100 is near linear, the regression analysis regularly yields very straight (near linear) curves. Consequently, it was shown that the added value of non-linear mathematical modeling is limited, therefore the use of an optimized linear model (the slope of the straight line is defined for the given sample or subject) is practically appropriate.

1.2. **The effect of mental stress on the QT interval duration**

The balance of the sympathetic and parasympathetic effect is another important source of QT changes. Though the relationship has not been entirely clarified, in most studies QT interval shortening was found upon sympathetic stimulus, while the parasympathetic influence was less important. However, despite numerous observations and experiments, the relationship between mental stress and QT duration has not been elucidated. Using Holter monitors, upon mental stress QT interval prolongation was reported by *Toivonen* (1997) and *Merz* and *Pardo* (2000). Conversely, laboratory experiments by *Hedman* and *Nordlander* (1988), *Huang* (1989), *Haapalahti* (2000), *Paavonen* (2001) and *Insulander* (2003) revealed QT interval shortening as an effect of mental stress.
Reports on the effect of smoking on the QT interval are similarly confusing, *Karjalainen* (1996) reported QT interval shortening, *Romero Mestre* (1996) found neutral effect, *Fauchier* (2000), *Ileri* (2001) and *Dilaveris* (2001) disclosed QT prolongation. About the effect of acute smoking on the QT duration only one published report could be retrieved, *Canale* (1978) reported the prolongation of the *Bazett* corrected QT interval. Since both

smoking and mental stress have been reported to induce arrhythmias and increased cardiac morbidity and mortality, the better understanding of smoking and stress elicited QT changes is of great importance.

2. OBJECTIVES

The background of the present research was the perception of some erroneously interpreted data on QT duration changes due to the distortion of *Bazett*'s equation. Further, I supposed that the inappropriate QT adjustment might have lead to the disagreement between a number of studies in QT research, more specifically the divergent data on smoking and mental stress induced QT changes. Therefore, beyond theoretical considerations I attempted to prove in laboratory experiments that in case of heart rate differences, the *Bazett* approach is inappropriate to compare groups for QT duration. In addition, I undertook the effort to elucidate the effect of smoking and mental stress on the QT interval. In this research, mental stress was applied in the form of mental arithmetic (MA) and video game (VG) playing, also active and passive mental stresses (AMS and PMS) were discriminated. My thesis is based on the results of six subsequent trials that incorporate the experience of the preceding and comprise novel results on QT interval correction.

2.1. Shortcomings of the Bazett method

The effect of acute smoking (Study #I) and treadmill exercise (Study #II) on the QT interval was examined. Apart from the *Bazett* method QTc values were also calculated by other formulae deemed more accurate and by the study-specific, optimized method. In addition, I wanted to clarify the effect of smoking on the QT interval in Study #I.

2.2. The effect of mental stress on the QT interval

In Study #III I wanted to elucidate the effect of metal stress on the QT interval duration.

2.3. The role of cardiovascular reactivity in mental stress induced QT response

The results of Study III suggested that the mental stress induced QT response is not generic, marked inter-individual differences exist. Though

the cardiovascular response upon mental stress depends on numerous individual psychophysiological features, it was shown, that individual differences in cardiovascular reactivity (CVR) to mental stress may be characterized by a stable, two-dimensional pattern of response: cardiac vs. vascular reactors and reactors vs. non-reactors. This way, for example, according to heart rate or blood pressure response subjects may be easily classified into similar groups in terms of CVR. In Studies #IV and #V I wanted to see how CVR influenced mental stress induced QT response?

2.4. The effect of active and passive mental stress on the QT interval

One possible explanation of the confounding results on mental stress induced QT response may be the use of different stressors. In order to see the difference, in Study #VI an attempt was made to separately assess QT response to distinct episodes of AMS (the subject is required to actively cope or perform in a challenging situation) and PMS (the subject is unable to actively cope or do something about an unpleasant or distressing situation).

2.5. QT interval changes at the launch of mental stress

During Studies #III, #IV and #V I observed that brief stress protocols were more effective, also cardiovascular reactions (heart rate and blood pressure increases, QT changes) were most pronounced at the beginning of mental stress. Therefore in Study #VI a brief protocol was applied and data collection included the first 10 seconds of the stress.

3. METHODS

3.1. Experimental protocol in general

The six studies were completed in 2001 – 2005 in Budapest (Saint Francis Hospital=SFH) and in Nottingham, UK (Human Performance Laboratory, School of Biomedical Sciences, the Nottingham Trent University=NTU). Healthy subjects with normal baseline ECG-s were enrolled (except for Study #III, 3.2.3). The study protocols were approved by the local Ethics Committees and participants signed a written consent form. No drugs or medication were taken by any of the participants for at least 2 weeks before the experiments. Participants were instructed not to smoke or consume any

alcohol or caffeine, or to engage in strenuous physical activities for at least 12 hours prior to testing. Statistical analysis was performed using GraphPad Prism version 4.00 for Windows, GraphPad Software, San Diego, California, USA. All continuous variables are reported as mean±SD. A p value<0.05 was regarded as statistically significant. A summary of Studies #1-6 is presented in Table 1.

Table 1. Overview of Studies # 1-6 conducted at SFH and NTU in 2001 – 2005

	N (m/f/ age)	Loc	Stressor	QT meas.	QT corr.
I.	19 (8/12, 32±13)	SFH	Smoking	OSM	B, F, S
II.	20 (14/6, 44±15)	SFH	Treadmill	OSM	B, F, S, H, K, SP
III.	31 (3118/13, 74±9)	SFH	MA	OSM	B, S
IV.	20 (10/10, 35±12)	SFH	MA	OSM	SP
V.	46 (46/0, 21±1)	NTU	VG	EBP	B, SP
VI.	30 (30/0, 21±2)	NTU	MA, stressing images	EBP	IND

m=male, f=female. SFH=Saint Francis Hospital, NTU=Nottingham Trent University; MA=mental arithmetic; OSM= On-Screen Manual, EBP= Electrocardiograph Built-in Program; B=Bazett, F= Fridericia, S= Sagie, H= Hodges, K= Karjalainen, SP= Study Specific, IND= Individualized.

3.1.1. Mental arithmetic

In psychophysiology, because of its simplicity and effectiveness MA is one of the most frequently used active mental stressors. The effect of MA is characterized by a mixed alpha and beta-adrenergic effect, although most subjects respond with a more beta pattern. In our studies participants were asked to perform a 1-3 minute MA task that involved fast and correct serial subtractions from a three digit number.

3.1.2. ECG data acquisition and processing

ECGs were prepared in the supine (SFH) or sitting position (NTU). The simultaneous 12-lead ECGs were recorded at a paper speed of 25 mm/s and amplifier gain of 10 mm/mV. The paper recordings were than scanned to a JPG image file at high resolution (300 dpi) that could be interactively analyzed by means of the built in calipers of the commercially available Adobe Photoshop program. QT and RR intervals of 3-5 consecutive sinus beats in lead II (Study #1) or V3 (Studies #2, #3 and #4) were measured and averaged by me at three fold enlargement in a blinded manner. In Studies run at NTU, I used the QT and RR data provided by the built-in program of the electrocardiograph.

3.1.3. Correction of the QT interval for heart rate

In the studies the following previously published formulae were used: Bazett: $QTBc=QT/RR^{1/2}$; Fridericia: $QTFc=QT/RR^{1/3}$; Hodges: QTHc=QT+1.75(heart rate–60); Sagie: QTLc=QT+0.154(1-RR) and the nomogram method of Karjalainen (QTNc). Besides previously published methods, the study- and subject-specific QT correction methods were also used. In general, specific correction means that by regression analysis, a mathematical model that best fits a given QT/RR data set should be selected, and this equation should be used further to correct QT intervals for heart rate in the particular study group or individual. Because of the limited added value of non-linear mathematical modeling and relatively low number of QT/RR data, curve fitting was not performed in these studies; instead I used models that were shown best by others. According to *Malik* optimized linear [$QTcopt\text{-}lin=QT+\alpha(1-RR)$], parabolic [$QTcopt\text{-}par=QT/RR^{\alpha}$], and shifted-logarithmic equations [$QTcopt\text{-}shlog=\ln(eQT+\alpha(1-RR)$] were used, that means, the coefficients of these equations were determined so that the correlation between heart rate and corrected QT were near zero (*Pearson* $r\approx0.0$).

3.2. Experimental protocol in detail

3.2.1. Study #I

The study group consisted of healthy volunteers who smoked more than 10 cigarettes/day for at least 5 years (Table I). The study was placebo controlled with 2 experimental sessions in a random order that consisted of sham smoking (simulated smoking with a tobacco void cigarette) and smoking. This study was designed to examine directly the effect of the first morning cigarette on the QT interval duration after an overnight cessation of smoking; therefore exhaled carbon monoxide (CO) levels were determined before the experiments to rule out prior smoking. In the sham smoking condition, the subjects imitated smoking behavior with unlit cigarettes void of tobacco similar to the method used by *Grassi*. After 12 minutes of rest, electrocardiograms were obtained and blood pressure was measured in every 4 minutes. Between the third and fourth electrocardiogram and blood pressure measurement, the subjects smoked (or sham-smoked) 4 cm of a filter cigarette containing 0.9 mg of nicotine in 2 minutes. Data were analyzed with repeated measurements analysis of variance (ANOVA).

3.2.2. Study #II

From the 30 healthy volunteers enrolled in the study, 20 had exercise ECGs suitable for quality analysis (Table I). All subjects underwent a standard 6-minutes Bruce protocol treadmill stress test. Besides baseline resting standing ECGs, exercise ECGs obtained at 2-, 4-, and 6-minutes were selected for further analysis. Mean QT values were adjusted for heart rate using preformed formulae as well as the study-specific method. Data were assessed by ANOVA, post hoc intragroup comparisons were performed using the Bonferroni test.

3.2.3. Study #III

Participants were recruited from cardiac patients referred to the Department of Cardiology at SFH. Patients with ECG signs of left ventricular (LV) hypertrophy, bundle brunch block or ST segment deviation were not excluded, but patients with frequent ectopy, atrial fibrillation and ECGs where the end of T wave could not be exactly defined were not enrolled. Participants could keep on taking their concurrent medication. Before the study, all participants went through a complete echocardiographic examination where left ventricular dimensions (left ventricular hypertrophy: wall thickness $\geq$11 mm) and ejection fraction (impaired systolic function: EF $\leq$50%) were measured. Participants went through a 3-minute MA, ECGs were recorded at baseline and at the end of third minute. Baseline and third minute variables were compared with paired *t*-test.

3.2.4. Study #IV

Subjects' data are given in Table I. ECGs were recorded at baseline (PRE), at the 30. second during (DUR), and immediately at the end (POST) of a 1-minute MA. A cut off value of 5/min of heart rate increase during MA was used to classify subjects as stress responders and non-responders. Pooled baseline HR and QT values were used to optimize the linear and parabolic regression models separately for both groups. The mean differences were assessed by ANOVA.

3.2.5. Study #V

Healthy volunteers were enrolled in this study (Table I). Subjects played a VG (Noah's Ark, Astraware Ltd., Newcastle-u-Lyme, UK): the player needs to save pairs of animals as quickly as possible against a timer graphically

represented by continuous elevation of flood. Three lead ECGs were recorded in the first 10s of the minute for 6 consecutive minutes representing three 2-minute study periods: 1) before (PRE), during (DUR), and after the game (POST). Using a cut-off value of 5/min for HR increase during video game subjects were classified as stress-responders and as non-responders. Data on heart rate and QT interval duration yielded by the built-in software of the electrocardiograph were visually verified by me. QT correction was performed by preformed formulae as well as separately optimized (responders and non-responders) study-specific linear, parabolic and shifted-logarithmic equations. Data were analyzed with ANOVA.

3.2.6. Study#VI

Participants' data are shown in Table I. In Study #VI the effect of a 1-minute AMS and PMS was separately studied in a cross-over design. A simple MA was used for AMS, distressing audio-visual effect were applied for PMS. Between AMS and PMS subjects had 5 minute rest. Participants were asked to rate the perceived level of stress on a 7-point *Likert* scale. A total of 15 ECGs (*Mason-Likar* torso leads) were obtained from each participant: 2 resting (before the experiment and between AMS and PMS), 2-2 during AMS and PMS in the first and last 10 seconds, and further 9 ECGs in the last 10 seconds of various 3-minute isometric exercises. The purpose of these exercises was to obtain further QT/RR data pairs at different heart rates for the subject-specific QT correction (Table II).

Table II. Protocol for ECG trace collection

1	Rest 1
2	AMS I
3	AMS II
4	PMS I
5	PMS II
6	Rest 2
7	Sitting, arms above head (180°)
8	Sitting, 2 Kg weights held at 90°
9	Standing, arms by side
10	Standing, arms above head (180°)
11	Standing, 2 Kg weights held at 90°
12	Skier's squat
13	Skier's squat, 2 Kg weights held at 90°
14	Standing, balanced on tip-toes
15	Standing, balanced on one leg, other leg raised to waist

MA = mental arithmetic, AMS = active mental stress, PMS = passive mental stress

ECG data were visually validated by me. ANOVA was used to compare means of heart rate and QTc among the six study periods. The *Likert* scores were evaluated by using non-parametric *Mann-Whitney U* test.

4. RESULTS

4.1. The immediate effect of smoking on the QT interval

In Study #I as an effect of the first morning cigarette heart rate, blood pressure and QTBc significantly increased, QTFc and QTLc did not change. Sham smoking had no effect on these variables (Table III).

Table III. Five dependent measures in smoking and sham smoking condition over six periods, three before and three after smoking and sham smoking. Smoking/sham-smoking was performed between 12. and 16. minutes

	Condit.	4-min (pre)	8-min (pre)	12-min (pre)	16-min (post)	20-min (post)	24-min (post)
HR (bpm)	SS	67±6†	62±9†	67±10†	67±10†	67±10†	67±8†
	S	72±9	69±9	71±8	90±13*	81±9*	78±10
BP (mmHg)	SS	119±14	118±12	118±12	118±11†	117±11†	117±12†
	S	119±15	118±16	119±14	127±18*	124±20*	123±19
QTBc (ms)	SS	413±29	414±25	411±30†	406±26†	414±31†	414±27
	S	416±31	412±26	417±27	428±27*	426±25*	423±25
QTFc (ms)	SS	406±26	406±23	404±26	399±24	407±27	407±25
	S	404±24	402±20	406±22	401±20	405±21	405±20
QTLc (ms)	SS	406±26	407±22	404±25	400±24	407±26	408±25
	S	405±24	403±20	407±22	400±17	406±19	406±18

HR=heart rate; BP=systolic blood pressure. QTBc=*Bazett*, QTFc=*Fridericia*, QTLc=*Sagie* QT interval correction. SS=sham smoking, S=smoking. *= Significant vs. pre- (smoking) values in the same condition ($p<0.05$), †Significance between sham and smoking conditions ($p< 0.05$).

4.2. The effect of treadmill exercise on the QT interval

With exercise heart rate and QTBc significantly increased, the uncorrected QT and QTcopt-par significantly shortened. The other four previously published methods yielded nonsignificant changes (Table IV). The value of α in the optimized formula was 0.299.

Table IV. Comparison of heart rate and QT interval values of 20 subjects at rest and at exercise

	PRE	2-min	4-min	6-min	p
HR (bpm)	66±10	80±14	90±17	99±14	<0.0001*
QT (ms)	381±44	362±43	345±44	327±40	<0.0001*
QTBc (ms)	398±46	414±49	419±51	418±56	0.0007†
QTFc (ms)	392±43	396±44	393±45	385±48	ns
QTLc (ms)	393±43	397±41	393±40	385±40	ns
QTHc (ms)	392±42	396±42	397±41	397±44	ns
QTNc (ms)	394±42	393±41	397±39	393±43	ns
QTcopt-par (ms)	391±43	392±44	387±45	378±47	0.013#

PRE=baseline. QTBc=*Bazett*; QTFc=*Fridericia*; QTLc=*Sagie*; QTHc=*Hodges*; QTNc=*Karjalainen*-nomogram corrected QT. QTcopt-par=QTc yielded by the optimized parabolic equation. Significance: *all, †rest vs. other 3 periods, #rest vs. 6-min and 2-min vs. 6-min.

4.3. The effect of 3-minute MA on the QT interval in cardiac patients

From the 31 participants, 9 presented depressed LV function, 5 LV hypertrophy, 3 left bundle branch block and 2 right bundle branch block. A medical history of ischemic heart disease and previous MI was present in 12 and 9 patients, respectively. Fourteen patients were on amiodarone, 2 on propafenone and one was taking flecainide. At the end of the 3-minute MA, heart rate (70±14 vs. 73±15 bpm, $p<0.05$), systolic and diastolic blood pressure (132±19 vs. 137±17 and 79±11 vs. 84±11, mmHg, $p<0.05$) significantly increased. QTBc and QTLc did not change significantly (460±53 vs. 462±50 and 449±52 vs. 448±50, ms). In detail, QTBc and QTLc increased in 14 patients (17±10 and 12±8, ms) and decreased in 17 patients (10±10 and 12±9, ms).

4.4. The effect of 1-minute MA on the QT interval in healthy subjects

The value of α parameter was computed as 0.1691 and 0.2195 for the linear, and 0.3774 and 0.4340 for the parabolic model, in stress responders and non-responders, respectively. During MA, heart rate and QTc intervals yielded by both methods increased significantly in stress responders, whereas neither variable changed in non-responders (Table V).

Table V. Heart rate and optimized corrected QT data of 20 healthy subjects at baseline (PRE), during (DUR) and after (POST) a 1-minute mental arithmetic

	Stress Responders (n=12)			Non-Responders (n=8)		
	PRE	**MA**	**POST**	**PRE**	**MA**	**POST**
HR	75±13	90±12*	84±15	89±11	85±14	86±10
QTcopt-lin	401±17	412±19†	405±22	430±15	424±15	425±15
QTcopt-par	401±18	415±22†	406±26	426±18	419±17	420±18

HR=Heart rate. QTcopt-lin and QTcopt-par are optimized QTc values yielded by linear and parabolic equations, respectively. *=p<0.0001, †=p<0.05.

4.5. The effect of video game on the QT interval

The cut-off value of 5/min increase in heart rate classified 13 subjects as stress-responders and 33 subjects as non-responders. Table VI shows that in stress-responders, the mean QTc values obtained by all correction methods were significantly higher during VG than in the PRE and POST periods, whereas QTc did not change in non-responders. The increase in heart rate during VG was significant in stress-responders (65±12/min, 69±11/min, and 70±14/min in PRE, DUR and POST periods, respectively; p<0.0001), whereas heart rate did not change in non-responders (69±12/min, 69±11/min, and 70±14/min in PRE, DUR and POST periods respectively; ns).

Table VI. Corrected QT values before (PRE), during (DUR) and after (POST) video game playing yielded by six different correction methods.

	QTc	**α**	**PRE**	**DUR**	**POST**	**P**
Non-responders (n=33)	QTBc	0.5	395±24	399±14	400±20	0,2085
	QTFc	0.3333	385±23	388±22	390±22	0,1006
	QTLc	0.154	386±22	390±20	391±20	0,0927
	QTcopt-lin	0.1754	389±22	393±19	393±20	0.1165
	QTcopt-par	0.4335	390±23	394±20	395±23	0.1527
	QTcopt-shlog	0.2554	389±22	393±18	394±20	0.1075
Stress-responders (n=13)	QTBc	0.5	396±23	416±18	401±19	0.0001
	QTFc	0.3333	389±19	399±16	391±15	0.0001
	QTLc	0.154	390±20	401±15	392±15	0.0003
	QTcopt-lin	0.1130	387±19	393±15	387±15	0.0086
	QTcopt-par	0.2931	388±19	396±16	389±15	0.0012
	QTcopt-shlog	0.1652	387±15	393±15	388±15	0.0088

α=coefficient in correction formulae. *=significance. QTBc=Bazett corrected QT time; QTFc=Fridericia corrected QT time; QTLc=Sagie corrected QT time. QTcopt-lin, QTcopt-par and QTcopt-shlog are optimized QTc values yielded by linear, parabolic and shifted-logarithmic equations, respectively.

4.6. AMS and PMS induced QT interval and T wave changes

From the total 450 ECGs 37 exercise ECGs had to be discarded because of poor quality. Consequently, the participant-specific QT/RR relationship could be evaluated using 11.0±1.9 (minimum=7) ECGs per subject. Heart rate changes were sufficient for optimalization in each subject (44.1±12.0 bpm, range 23.3-71.1 bpm). The linear regression model was a good fit for the QT/RR data (r^2=0.63±0.18), and the slope was highly subject-specific (α=0.1136±0.0584, range=0.0229-0.1879). Heart rate was significantly increased at both measurements during AMS, QTc was prolonged only in AMS I. PMS elicited neither heart rate nor QTc changes (Table VII).

Table VII. The effect of active and passive mental stress in 30 volunteers. Heart rate (bpm) and individually corrected QT intervals (ms) in six study periods

	Nyug. I	AMS I	AMS II	PMS I	PMS II	Nyug. II
HR	67±12	88±16*	80±11*	67±12	67±12	68±12
QTc	380±26	390±24†	386±25	383±22	384±21	382±22

HR=heart rate. AMS=active mental stress, PMS=passive mental stress *= p<0.0001; †p=0.0004.

Each participant presented normal contour T waves at rest; however, 14 subjects developed bifid (or notched) and 8 subjects inverted T waves during AMS and during one or more exercise conditions (Figure 1).

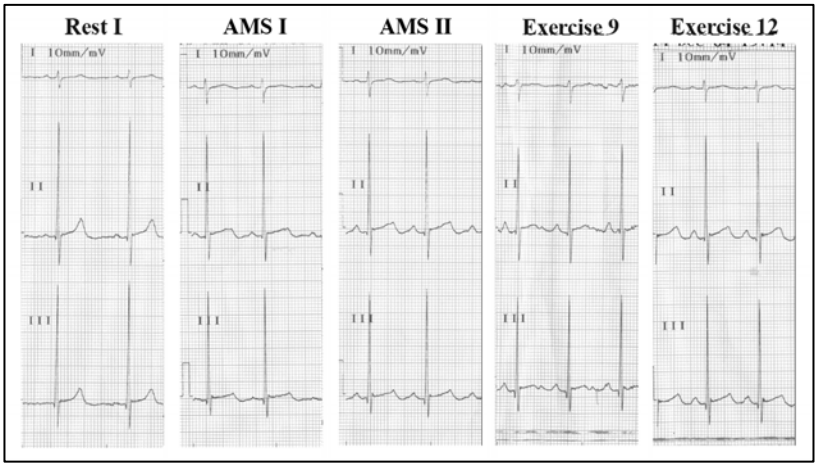

Figure 1. Subject No. 21 presents a substantial QT interval prolongation in AMS I that persists through AMS II. QT prolongation is also present in exercises 9 and 12. The incipient T wave notching in AMS becomes clearly visible in exercise 9.

Subjects found the perceived level of stress during AMS higher than during PMS, as indicated by the difference in *Likert* scale scores that showed marginal significance (3.7±1.1 vs. 3.1±1.2, p=0.06).

5. CONCLUSION

Most important new findings

It was successfully demonstrated in laboratory experiments that different QT correction methods yield significantly different results. From this aspect, the Bazett formula was inferior to all the other methods tested.

Confounding previous data on the effect of acute smoking on the QTc duration got clarified. We first reported that smoking has no effect on the QTc interval. The Bazett method yields artificial prolongation.

I have observed and experimentally confirmed that the QT response to mental stress is not generic; the response depends on cardiovascular reactivity.

I have first demonstrated under laboratory circumstances that mental stress may prolong the QTc interval in stress-responders. This effect is most pronounced at stress initiation.

I have observed, and we have first reported that mental stress and isometric exercises may induce T wave notching, a sign of nonhomogenous repolarization, that may link emotional stress with arrhythmia.

6. PUBLICATIONS

Publications directly related to the thesis

1. Andrássy G, Dunai A, Simon E, Nagy T, Trummer Zs, Tahy Á. (2002) A dohányzás hatása a QT intervallumra. Magy Belorv Arch, 55: 65-72.

2. Andrássy G, Simon E, Tahy Á. (2002) A QT intervallum és a szívfrekvencia kapcsolata: a Bazett formula kritikája. Orvostudományi Értesítő, 75(2-3): 176-179.

3. Andrassy G, Biliczky P, Lengyel C, Szabo A. (2002) Duration and dispersion of QT interval in smokers. Am J Cardiol, 89: 249-250. Letter.

4. Andrassy G, Szabo A, Dunai A, Simon E, Nagy T, Trummer Zs, Tahy A, Varro A. (2003) Acute effects of cigarette smoking on the QT interval in healthy smokers. Am J Cardiol, 92: 489-492.

5. Andrássy G, Szabó A, Dunai A, Simon E, Tahy Á. (2005) Heart rate correction of the QT interval during exercise. Cardiol Hung, 35: 17-20.

6. Andrassy G. (2005) Gender differences in electrophysiologic effects of mental stress and autonomic tone inhibition: a study in healthy individuals. J Cardiovasc Electrophysiol, 16: 679. Letter.

7. Andrassy G, Trummer Z, Ferencz G, Szabo A. (2006) Is neuroticism really associated with increased arrhythmia risk? J Psychosom Res, 61: 847. Letter.

8. Andrassy G, Szabo A. (2007) What is the cause of QTc prolongation in patients with alcohol withdrawal syndromes? Swiss Med Wkly, 137: 34. Letter.

9. Andrássy G, Szabo A, Ferencz G, Trummer Z, Simon E, Tahy Á. (2007) Mental Stress May Induce QT-interval Prolongation and T-wave Notching. Ann Noninvasive Electrocardiol, 12: 251-259.

Abstracts related to the thesis

1. Simon E, Andrássy G, Dunai A, Tahy Á. (2002) A QT intervallum változása elektromos kardoverzió után. Cardiol Hung, 31/1(Abstr Suppl): 94.

2. Andrássy G, Dunai A, Simon E, Nagy T, Trummer Zs, Tahy Á. (2002) A dohányzás hatása a QT intervallumra. Magy Belorv Arch, 55/1(Abstr Suppl): 66.

3. Andrassy G, Dunai A, Simon E, Nagy T, Trummer Z, Tahy A, Varro A, Szabo A. (2002) Immediate effect of cigarette smoking on the QT-interval in habitual smokers. Eur Heart J, 23/4(Abstr Suppl): 700.

4. Andrássy G, Dunai A, Simon E, Pászthory E, Tahy Á, Varró A. (2002) A clarithromycin hatása a QT időre. Magy Belorv Arch, 55/2(Abstr Suppl): 54-55.

5. Andrássy G, Dunai A, Simon E, Trummer Zs, Tóth L,Tahy Á. (2002) A QT-idő frekvencia-korrekciójának problémája. Magy Belorv Arch, 55/3(Abstr Suppl): 38.

6. Andrássy G, Dunai A, Simon E, Tahy Á. (2003) A terhelés hatása a korrigált QT-időre. Cardiol Hung, 33: A1.

7. Ferencz Gy, Andrássy G, Trummer Zs, Győző V, Tahy Á. (2003) A habituáció vizsgálata ismételt mentális stressz-teszt esetén. Magy Belorv Arch, 56/2(Abstr Suppl): 50.

8. Andrassy G, Szabo A, Trummer Z, Gyozo V, Tahy A, Varro A. (2003) The application of mental stress to detect impaired myocardial repolarization reserve. Eur Heart J, 24/4(Abstr Suppl): 283.

9. Ferencz Gy, Andrássy G, Trummer Zs, Győző V., Tahy Á. (2004) Az életkor, a korrigált QT-idő és egyes balkamra funkciós paraméterek összefüggése. Cardiol Hung, 34: C63.

10. Andrássy G, Szabo A, Dunai A, Simon E, Tahy Á, Karsai I. (2004) Measurement of the QT interval during exercise. Which correction formula to use? 9th Annual Congress, European College of Sports Science, July 3-6, 2004, Clermont-Ferrand, France. Book of Abstracts: p311.
11. Andrássy G, Szabo A, Buckenham C. (2004) A videojáték hatása a QT időre. Magy Belorv Arch, 57/2(Abstr Suppl): 36.

12. Simon E, Andrássy G, Trummer Z, Kőhalmi Z, Ferencz G, Tahy Á, Szabó A. (2004) A pszichofiziológiai reaktivitás szerepe a mentális stresszre adott QT intervallum változásban. Magy Belorv Arch, 57/2(Abstr Suppl): 118.

13. Andrássy G, Szabó A, Buckenham C. (2005) Videojáték alatti QT-idő változások vizsgálata. Cardiol Hung, 35: A1.

14. Simon E, Andrássy G, Trummer Z, Ferencz G, Tahy Á, Szabó A. (2005) A pszichofiziológiai reaktivitás szerepe a mentális stresszre adott QT-intervallum változásban. A QT-idő „optimalizált" frekvencia korrekciója. Cardiol Hung, 35: A80.

15. Andrassy G, Szabo A, Buckenham C. (2005) The effect of video game on the QT interval. Folia Cardiol, 12(Abstr Suppl)C: 56.

16. Ferencz G, Andrássy G, Trummer Zs, Tahy Á, Takács I. (2005) Hypoparathyreosis, hypokalaemia, hoszú QT-szindróma együttes előfordulása - esetbemutatás. Cardiol Hung, 35: B1.

17. Andrássy G, Szabó A, Spooner R. QT-idő megnyúlás aktív mentál streszben. A QT- idő individualizált frekvencia kontrollja. Cardiol Hung 2006;36: A1

18. Ferencz G, Szabó A, Spooner R, Andrássy G. (2006) A QT-idő változása aktív és paszív mentál streszre. Cardiol Hung, 36: A36.

19. Andrassy G, Szabo A, Spooner R, Ferencz G. (2006) Different types of mental stress elicit different QT responses. Eur Heart J, 27(Abstract Suppl), 321.

Other publications

1. Varga Zs, Papp L, Andrássy G. (1995) Hemochron Versus HemoTec Activated Coagulation Time Target Values During Percutaneous Transluminal Coronary Angioplasty. J Am Coll Cardiol, 25: 803-804. Letter.

2. Andrássy G, Kerkovits Gy, Varga Zs. (1996) Asymptomatic Cardiac Ischemia Pilot (ACIP) Study: What Clinical Implications Does It Have? J Am Coll Cardiol, 27: 1316-1318. Letter.

3. Tarr F, Somogyi A, Kiss R, Major L, Andrássy G. (1998) Postinfarctusos, instabil angina pectoris kezelése egymás után végzett thrombolysis, PTCA és coronaria bypass graftok segítségével. Cardiol Hung, 28: 232-241.

4. Andrássy G. (1999) Lipidcsökkentés és ACE-gátlás – Kapcsolat a prevenció és a terápia között. Az iszkémiás szívbetegség modern szemlélete. Kórház, 11: 24-28.
5. Andrássy G. (2000) Endothel diszfunkció és ACE-gátlás. A BAANF vizsgálat eredményei a klinikum szempontjából. Orvostovábbképző Szemle, 7/3: 53-56.

6. Andrássy G. (2002) Koszorúér betegség időskorban. Praxis, 11: 29-33.

7. Gellér L, Szilágyi Sz, Róka A, Gajdácsi J, Andrássy G, Merkely B. (2007) Pitvari flattern lineáris isthmus ablációja vena cava superior persistens esetén. Cardiol Hung, 37: 38-42.

Abstracts

1. Andrássy G. (2000) Endothelial dysfunction and cardiovascular disease: potential mechanisms and interventions. Cardiol, 9(1): K/C2A.

2. Andrássy G, Dunai A, Gábos L, Kerkovits Gy, Tahy Á. (2000) A kis dózisú amiodaron kezelés hatásossága és biztonságossága a sinus ritmus fenntartására pitvarremegésben és pitvarlebegésben. Cardiol Hung, 29/3(Abstr Suppl.): 12.

3. Andrássy G, Dunai A, Tóth L, Gábos L, Kerkovits Gy, Tahy Á. (2001) Propafenon alkalmazása perzisztáló pitvarremegés megszüntetésére. Cardiol Hung, 30/3(Abstr Suppl): 98.

4. Tóth L, Andrássy G, Dunai A, Simon E, Gábos L, Tahy Á. (2002) Flecainid alkalmazásával szerzett tapasztalataink visszatérő pitvarremegésben. Cardiol Hung, 31/1(Abstr Suppl): 15.

5. Toldy-Schedel E, Tomcsányi J, Andrássy G, Bezzeg P. (2002) A SVES és VES szívfrekvencia turbulenciára gyakorolt hatásának összehasonlítása postinfarktusos betegeknél. Cardiol Hung, 31/1(Abstr Suppl): 40.

6. Tóth L, Andrássy G, Gábos L, Trummer Zs, Simor T, Tahy Á. (2002) Az echokardiográfus szerepének fontossága konstriktív pericarditis esetén. Magy Belorv Arch 2002, 55/1(Abstr Suppl): 46.

7. Simon E, Andrássy G, Stangl E, Kerkovits Gy, Kerkovits G, Tahy Á. (2002) Extenzív anterior infarktust utánzó szokatlan lokalizációjú hypertrófiás cardiomyopathia. Magy Belorv Arch, 55/1(Abstr Suppl): 54.

8. Tóth L, Andrássy G, Tahy Á. (2002) Az emelkedett szérumfibrinogén-szint és az ischaemiás szívbetegség gyakoriságának összefüggése intézetünk antikoagulált betegei esetében. Magy Belorv Arch 2002, 55/2(Abstr Suppl): 56-57.

9. Simon E, Andrássy G, Tóth L, Dunai A, Tahy Á, Merkely B. (2002) Biventricularis pacemaker implantációval szerzett tapasztalataink végstádiumú szívelégtelenségben. Magy Belorv Arch, 55/2(Abstr Suppl): 57.

10. Dunai A, Andrássy G, Simon E, Trummer Zs, Tahy Á. (2002) Amiodaron kezelés hatása a pajzsmirigy-funkcióra. Magy Belorv Arch, 55/3(Abstr Suppl): 49.

11. Tóth L, Andrássy G, Trummer Zs, Simon E, Tahy Á. (2002) A szérum normális káliumszintje melletti halmozott kamrai extrasystolék esetei. Magy Belorv Arch 2002, 55/3(Abstr Suppl): 133.

12. Trummer Zs, Andrássy G, Tóth L, Simon E, Tahy Á, Markóczy Zs. (2002) Amiodaron indukálta pulmonális toxicitás három esete. Magy Belorv Arch 2002, 55/3(Abstr Suppl): 134.

13. Andrássy G, Trummer Zs, Győző V, Tahy Á. (2003) A Tei-index vizsgálata jó balkamra szisztolés funkció és balkamra hipertrófia esetében. Magy Belorv Arch, 56/2(Abstr Suppl): 32.

14. Trummer Zs, Andrássy G, Nagy E, Tahy Á. (2003) Aszpirin-rezisztencia és nonreszponzió előfordulása magas kardiovaszkuláris kockázatú betegeink szekunder prevenciója során. Magy Belorv Arch, 56/2(Abstr Suppl): 114.

15. Kőhalmi Z, Andrássy G, Tahy Á.(2004) Balkamrai aszinkróniára utaló EKG és ultrahang markerek. Cardiol Hung, 34: C63.

16. Andrássy G, Győző V, Gábos L, Mohay S, Tóth L, Kerkovits Gy, Tahy Á. (2004) A ciklushossz, a verőtérfogat és a kontraktilitás

összefüggésének vizsgálata pitvarremegésben. Cardiol Hung, 34: C36.

17. Ferencz G, Andrássy G, Trummer Z, Tahy Á. (2004) A ciklushossz és a jobb kamrai relaxáció közötti összefüggés vizsgálata pitvarremegésben. Magy Belorv Arch, 57/2(Abstr Suppl): 55.

18. Gábos L, Ferencz G, Andrássy G, Tahy Á. (2004) Carvedilol hosszú távú hatása súlyosan károsodott szisztolés balkamra-funkciójú betegek echokardiográfiás paramétereire. Magy Belorv Arch, 57/2(Abstr Suppl): 60.

19. Győző V, Andrássy G, Tahy Á. (2004) Kis dózisú amiodaron hatásosságának vizsgálata színuszritmus fenntartására. Magy Belorv Arch, 57/2(Abstr Suppl): 65.

20. Kőhalmi Z, Andrássy G, Tahy Á. (2004) Bal kamrai aszinkróniára utaló EKG- és ultrahang markerek. Magy Belorv Arch, 57/2(Abstr Suppl): 86.

21. Trummer Z, Andrássy G, Kőhalmi Z, Tahy Á. (2004) Az ismételt levosimendan-kezelés hatása dilatatív cardiomyopathiához társuló akut szívizominfarktus okozta kardiogén sokkban. Magy Belorv Arch, 57/2(Abstr Suppl): 137.

22. Gábos L, Ferencz G, Andrássy G, Tahy Á, Zámolyi K. (2005) Gender differences in enzyme dynamics in patients with acute myocardial infarction treated with thrombolytic therapy. Circulation, 111/4: E-70.

23. Ferencz G, Andrássy G, Trummer Z, Tahy Á. (2005) A ciklushossz és a jobb kamrai kontraktilitás közötti összefüggés vizsgálata pitvarremegésben. Cardiol Hung, 35: A40.

24. Gábos L, Ferencz G, Andrássy G, Tahy Á. (2005) Tartós carvedilol kezelés szignifikáns módon csökkenti a súlyosan károsodott systolés balkamra-funkciójú betegek balkamrai végdiastolés és végsystolés volumeneit. Cardiol Hung, 35: A85.

25. Andrassy G, Ferencz G, Trummer Z, Simon E, Gabos L, Tahy A. (2005) Evidence for an influence of interval-strength relationship on beat-to-beat variations in active relaxation in atrial fibrillation. Eur J Echocariography, 6:S157.