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

Doctoral Thesis

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Budapest
2007.

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ABBREVIATIONS

ACTH	: adrenocorticotrophic hormone
AMS	: active mental stress
ANOVA	: analysis of variance
ANS	: autonomic nervous system
AP	: action potential
bpm	: beats per minute
CAD	: coronary artery disease
CNS	: central nervous system
CO	: carbon monoxide
CRF	: corticotropin releasing factor
CV	: cardiovascular
CVR	: cardiovascular reactivity
ECG	: electrocardiogram
EPI	: epinephrine
ERC	: electrical restitution curve
ICD	: implantable cardioverter-defibrillators
IKr	: rapid component of the delayed rectifier current
IKs	: slow component of the delayed rectifier current
KATP	: ATP - channel
KATP	: adenosine triphosphate sensitive potassium current
LQTS	: long QT syndrome
LV	: left ventricular
MA	: mental arithmetic
MI	: myocardial infarction
NE	: norepinephrine
NTU	: The Nottingham Trent University
PMS	: passive mental stress
PTCA	: percutaneous transluminal angioplasty
QTBc	: corrected QT interval by the Bazett formula
QTc	: corrected QT interval

QTFc	: corrected QT interval by the Fridericia formula
QTLc	: corrected QT interval by the Sagie formula
RR	: R-R interval, cycle length
SFH	: Saint Francis Hospital
TCRT	: total cosine R to T
TdP	: torsade de pointes ventricular tachycardia
TWA	: T wave alternans
TWR	: T wave residua

SUMMARY

The effect of different stressors on the QT interval

The duration of the QT interval on the surface ECG is a global measure of the time the heart takes to depolarize and repolarize. Prolonged QT interval is associated with the generation of life-threatening rhythm disturbances and sudden cardiac death. The QT duration is principally influenced by heart rate (RR, cycle length), so heart rate correction is required in the analysis of repolarization duration. Based on mathematical modeling of the QT/RR relationship several correction equations have been published, including the most commonly used Bazett formula that was a methodological exception because it was purely observational and did not involve any regression modeling. Not surprising that amongst all, the Bazett formula performs the worst: because of its profound inherent heart rate dependency, QTc values incorporate excess distortion. Several clinical circumstances have been reported to be associated with QTc prolongation, but the use of the Bazett method questions their relevance. One such condition with confounding reports is smoking, that has been found both to prolong or either to shorten the QT interval. Consequently, we conducted a placebo controlled trial and clarified the effect of acute smoking on the QT interval: as an effect of smoking the Bazett corrected QT interval prolonged but corrected QT-s obtained by more reliable methods did not change. Further, in another model when exercise ECGs obtained at different heart rates were compared, we demonstrated that the study specific method of QT correction (fitting the correction method to the studied data set) is superior to any other preformed formula. In addition, Bazett method was inferior to all the other formulae. These findings underscore the importance using a reliable QT correction method when comparing QT-s measured at different heart rates: the Bazett method is clearly inappropriate, its use may lead to erroneous conclusions.

The autonomic nervous system, which can act directly at the cellular level or indirectly through modulation of heart rate, is another important source of QT changes. Both chronic and acute mental stresses induce cardiovascular and neuroendocrine responses including QT changes and lethal arrhythmias through alterations of the neural transmissions to the heart. Epidemiologic evidence also suggests that there is a relationship between stress and cardiac morbidity and mortality in susceptible

individuals. However, the effect of psychological stress on the QT interval is subject to speculation: previous reports provided conflicting data on the effect of mental stress on the QT interval duration. Therefore, we have accomplished four trials assessing the effect of various mental stressors on the QT interval. To overcome controversy about the use of fixed equations for QT correction, QT adjustment in these studies included the study and subject specific methods that were reported to perform best. These studies yielded important results and new findings. First, we found that the mental stress induced QT response is not generic, substantial individual differences exist. We have shown that these differences are linked to the individual's cardiovascular reactivity. Second, we have first demonstrated under laboratory circumstances that mental stress prolongs the corrected QT in stress-responders. This effect is most pronounced at stress initiation. Third, we have also first report that in otherwise healthy subjects mental stress and isometric exercises may induce T wave notching, a sign of nonhomogenous repolarization, that may link emotional stress with arrhythmia.

ÖSSZEFOGLALÁS

Különböző stresszorok hatása a QT időre és a T hullámra

A szív depolarizációjának és repolarizációjának az idejét a felszíni EKG-n a QT idő jelzi. A megnyúlt QT idő életveszélyes szívritmus zavarokhoz és hirtelen halálhoz is vezethet. A QT időt elsősorban a szívfrekvencia (RR, ciklushossz) határozza meg, ezért a repolarizáció értékeléséhez a QT időt a frekvencia szerint korrigálni kell. A QT/ RR összefüggés matematikai modellezése alapján számos korrekciós eljárást közöltek, köztük a leginkább elterjedt Bazett képletet, ami kivételt képez, mivel kidolgozása során nem történt matematikai analízis: pusztán megfigyelésen alapul. Nem meglepő, hogy az összes formula közül a Bazett működik a legrosszabbul, a képletben rejlő jelentős frekvenciafüggőség miatt a QTc érték torzít. Az irodalomban számos klinikai állapotot hoztak QTc megnyúlással összefüggésbe, de e közlések valódi értéke a Bazett módszer használata miatt megkérdőjelezhető. Jó példa erre a számos egymásnak ellentmondó publikáció melyben a dohányzás hatását vizsgálták a QT időre: mind a QT idő megnyúlását mind annak megrövidülését kimutatták. Magunk placebo kontrollos

vizsgálattal igazoltuk, hogy habár dohányzás hatására a Bazett korrigált QT idő megnyúlik, mégis, a megbízhatóbb egyenletek alapján történő korrekció szerint a QTc nem változik. Egy másik vizsgálatban pedig, ahol terhelés során különféle szívfrekvenciák mellett mért QT időket hasonlítottunk össze igazoltuk azt, hogy a vizsgálat specifikus QT korrekciós eljárás (a korrekciós módszernek az adott vizsgálati mintához történő illesztése) jobb eredményt ad, mint bármely fix formula. Továbbá, itt is megmutatkozott, hogy a fix képletek közül a Bazett módszer korrigál a legrosszabbul. Ezek az eredmények alátámasztják annak fontosságát, hogy különböző frekvenciákon mért QT idők összehasonlításakor elengedhetetlen a QT korrekció megbízható kivitelezése: a Bazett módszer erre egyértelműen alkalmatlan, használata téves következtetésekhez vezethet.

A QT idő az autonóm idegrendszer állapotától is függ, ez a hatás részben a szívfrekvencián keresztül, részben közvetlenül sejtszinten jön létre. Mind a krónikus mind az akut mentális stressz hat a cardiovaszkuláris és a neuro-endokrin rendszerre, befolyásolja a QT időt, és mentális stresszel összefüggésben letális ritmuszavarok is észlehetők. Epidemiológiai adatok arra utalnak, hogy fogékony egyedekben összefüggés van a stressz és a cardiális megbetegedések, illetve halálozás között. Mégis, a mentális stressz és QT idő közötti összefüggés ez idáig tisztázatlan, az irodalmi adatok ellentmondásosak. Ezt tisztázandó, négy vizsgálatot végeztünk, melyekben többféle mentális stresszor hatását vizsgáltuk a QT időre. Azért, hogy elkerüljük a Bazett formula használatában rejlő buktatókat, a jelenleg legjobbnak tartott vizsgálat- és személy-specifikus QT korrekciós eljárásokat is alkalmaztuk. Kutatásaink több fontos felismerést és új eredményt hoztak. Először: kimutattuk azt, hogy a mentális stresszre adott QT válasz nem generikus, jelentős, az egyéni cardiovaszkuláris reaktivitással kapcsolatos individuális különbségek vannak. Másodszor: elsőként igazoltuk laboratóriumi körülmények között, hogy a mentális stressz kiválthat QT idő megnyúlást, ami a stressz kezdetekor a legkifejezettebb. Harmadszor: elsőként közöljük, hogy a mentális stressz és bizonyos izometrikus gyakorlatok során egészségesekben is észlelhető a T hullámok hasadása, ami a repolarizáció inhomogenitására utalhat. Ez a jelenség fogékony egyénekben a mentális stressz és a ritmuszavarok közötti kapcsolatot is jelentheti.

1. INTRODUCTION

1.1. THE QT INTERVAL

1.1.1. The Cardiac Cycle

Electrical surface recordings made during the electrocardiogram (ECG) correspond to the electrophysiological events occurring during impulse generation and conduction in the heart. Each heartbeat starts as electrical excitation, is generated in the sinoatrial node and is rapidly conducted throughout the atria. On surface ECG measurements, the P wave represents the combined electrical activity of atrial depolarization. Impulse conduction to the ventricles occurs following conduction through the atrioventricular node and excitation is transmitted rapidly across both ventricles via the His–Purkinje system and by virtue of the tight electrical coupling between ventricular cells. The QRS complex of the ECG corresponds to the depolarization of the ventricles (and masks the electrical activity associated with repolarization in the atria); the T wave is associated with ventricular repolarization. Thus, the QT interval represents the duration of the ventricular action potential (AP). This is shown diagrammatically in Figure 1. in which AP corresponds to QT interval.

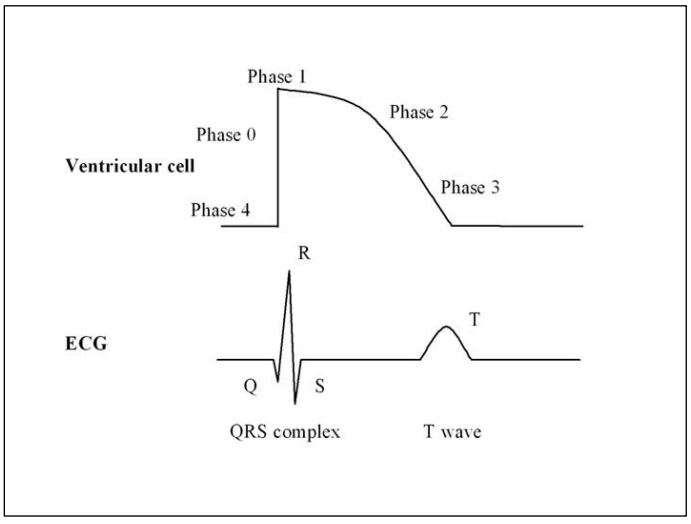

Figure 1. The length of the action potential of the myocardial cell (above) corresponds to the duration of the QT interval on the surface ECG (below).

Of note, the QT interval is a sum of the ventricular electrical activity; substantial differences in AP duration can be detected across different types of myocardial cells.

1.1.2. The Duration of the QT Interval

In a given individual 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. The electrical restitution curve (ERC) that was originally defined by Bass in 1975, describes the time course of recovery of AP duration as a function of the diastolic interval or cycle length between a steady-state response and an extrastimulus response – from the most premature past the steady-state response to postmature responses (1). As it was shown, the ERC in the human heart is a function of the diastolic interval, not the cycle length (2, 3). The AP duration is the net result of a number of electrogenic ion channels, each of which has individual onset and off-set recovery kinetics. Consequently, restitution of AP duration is governed by a multitude of different ion channel recovery kinetics.

1.1.3. QT Hyteresis

On the surface ECG, complete adaptation of the QT interval to a sudden change in heart rate is associated with a time delay (QT–lag) (4-7). This phenomenon is called 'QT delay' (hysteresis), which in humans may take approximately two to three minutes (8). The QT hysteresis may have an important impact on the QTc if the QTc is evaluated during significant changes in RR interval. For example, if heart rate changes quickly to a new sustained higher rate during sudden exertion, it may take several minutes before the QT interval adapts to the new steady-state heart rate. The converse is also true, such that as heart rate slows, the QT interval will require several minutes to fully prolong to its new steady-state value.

1.1.4. Measurement of the QT interval

The QT interval on the surface ECG is measured from the beginning of the Q wave (or R wave if there is no Q wave present) to the end of the T wave (Figure 2).

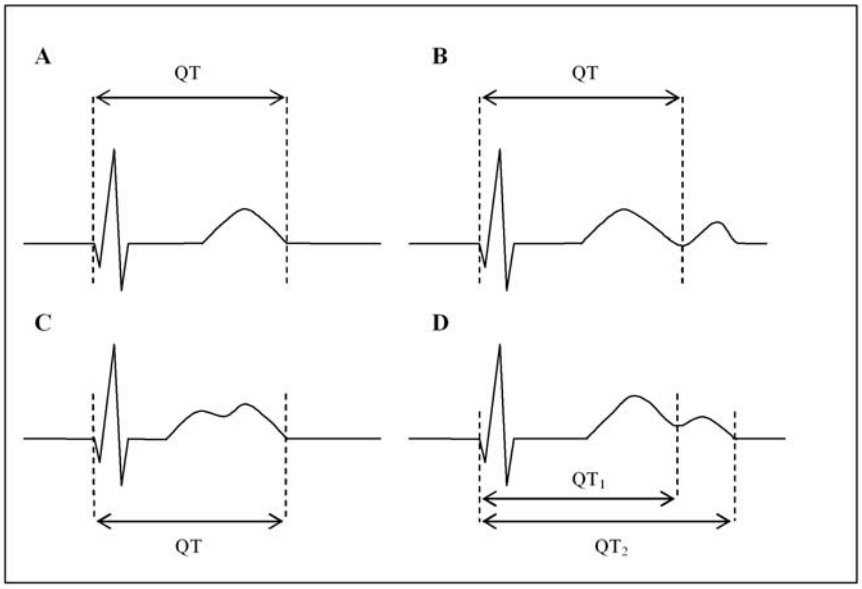

Figure 2. (A) When the T wave morphology is normal, the T wave offset is identified when the descending limb returns to the TP baseline; (B) when the T wave is followed by a distinct U wave, the T wave offset is identified when the descending limb of the T wave returns to the TP baseline before the onset of the U wave; (C) when the T wave is biphasic with T1 and T2 waves of similar amplitude, the T wave offset is identified at the time when T2 returns to baseline; and (D) when a second low-amplitude repolarization wave interrupts the terminal portion of the larger T wave (it should be categorized as T2 wave or a U wave?), the T wave offset should be measured both at the nadir of the two waves and at the final return to baseline (9).

Because U waves are typically less prominent in lead II, it has been suggested that lead II be used to measure QT (10). However, others suggest to use anteroseptal leads (V2 or V3) if measurements are confined to one or a few leads (11). Despite this, there is no standard means of lead selection for QT measurement, different studies use different criteria. Manual ECG readings may be performed using visual determinations ("eyeball"/caliper techniques), digitizing methods, and/or on-screen computerized methods. A technologically advanced option is to display digitally recorded ECGs on a computer screen, where they can be measured using computer-driven, on-screen

calipers. This latter approach is recommended at core laboratories performing centralized analyses of a large ECG database, because it provides high-quality ECG data with 5 ms accuracy of measurements (9). Scanned paper-recorded ECGs can also be subjected to on-screen measurements (9). The accuracy of the automatic measurements of the QT interval is questionable in many cases and should be supplemented by manual reading (9). A standard 12-lead ECG tracing at 25 mm/s paper speed at 10 mm/mV amplitude is generally adequate for accurate measurement of the QT interval duration and the QT interval should be determined as a mean value derived from at least 3–5 cardiac cycles (9).

1.2. THE CORRECTED QT INTERVAL

1.2.1. The Concept of QT Interval Correction

The QT duration is influenced by heart rate (RR, cycle length), so heart rate correction is required in the analysis of repolarization duration. In principle, every heart rate correction formula assumes that a mathematical form exists to describe the physiological QT/RR relation. 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. An example to calculate corrected QT (QTc) from RR and raw QT data gained from a given cohort is presented in Figure 3.

Application of the mathematical function that best fits these values to a straight line (a least-squares regression line [f(RR) = 0.1854(RR) + 0.2213] will produce a predicted QT (QT pred) for each observed QT. The difference between these 2 values (QT obs – QT pred) is equal to the difference between the derived QTc (QTc) and the reference QTc (QTc ref = QT pred at reference RR interval, here illustrated at 1.0 sec). Therefore, QTc = QTc ref + (QT obs - QT pred). For instance, a QT of 0.283 sec is observed at an RR of 0.475 sec (heart rate = 126 beats/min). The linear regression model predicts a QT of 0.309 sec [0.1854(0.475) + 0.2213].The difference of -0,026 sec (0.283 – 0.309) is added to the reference QTc = 0.407sec [0.1854(1.0) + 0.2213], yielding a QTc of 0.381 sec.

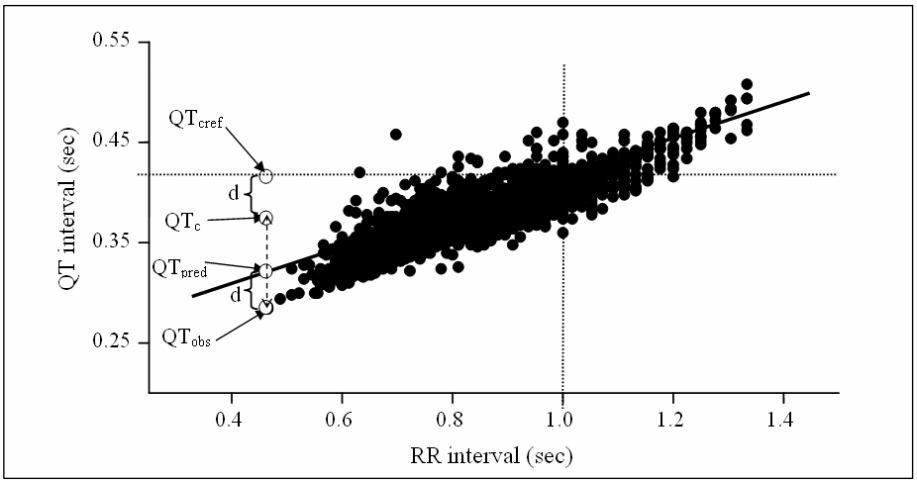

Figure 3. Baseline (preintervention) QT versus RR and derivation of QTc. A number of observed QT intervals (QT obs) at various heart rates (QT:RR pairs of 2477 subjects from both genders, mean age 50.6±16.1 yrs; Andrássy, unpublished data). See text for explanation.

1.2.2. The History of QT Correction

Investigations of the relationship between specific parts of the cardiac cycle and heart rate are not new. Well before the invention of electrocardiography, studies have reported the portion of the cardiac cycle taken by systole as measured from radial sphygmographic tracings and mechanical apexograms. It is interesting to read about what maneuvers were used more than one century ago to achieve different heart rates when recording the subjects with a rather complicated mechanical apparatus.

It was suggested that the duration of cardiac systole was almost constant and heart rate independent, whereas the duration of systole was concluded to change with the cube root of cardiac period (10, 11). Later, when using mechanical cardiograph rather than sphygmograph, it was proposed that the duration of systole is related to the square root of the cardiac cycle (12). After the introduction of electrocardiography, these investigations eventually turned to the proportion between the QT and RR intervals, and the disputes about the proper formula to describe the QT/RR relationship have continued ever since.

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 and RR intervals, subject these data to a curve-fitting regression 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. Frequently, perhaps because of the mathematical simplicity, QT interval has been related to different exponents of RR interval, i.e., it has been postulated that QT is a fixed proportion of RR^{α} (with RR interval measured in seconds).

The most known study by Bazett, which suggested a $\alpha = 0.5$, involved ECGs of 12 normal children aged 1 day to 11 years, 50 ECGs of 37 normal men aged from "boy" to 38 years, 32 ECGs of 20 normal women aged 20 to 53 years, and 16 ECGs of 3 healthy men who exercised (13). Compared with other investigations, Bazett's study was actually a methodological exception because it was purely observational and did not involve any regression modeling. A more detailed analysis of the data used by Bazett shows that had Bazett used regression analysis, he would have obtained the result of approximately $\alpha = 0.4$ (14).

Contemporary to Bazett's work, the study by Fridericia used a detailed mathematical evaluation of 50 ECGs of 28 men and boys and 22 women and girls and concluded that the optimum parameter of $\alpha = 0.3558$ may be approximated by a $\alpha = 1/3$ (15). However, in a study of 200 "quite healthy" Japanese subjects (135 men) aged 18 to 64 years, $\alpha = 0.604$ was found, whereas $\alpha = 0.31$ was suggested based on data from 12,543 ECGs of Japanese children and adolescents (16, 17). A series of ECGs of 649 men and 311 women was investigated and it was concluded that $\alpha = 0.32$, with an age-related increase of QT by about 3 ms every 10 years (18). In a study involving heart rate changes by atrial pacing, atropine, isoproterenol, exercise, and recovery, it was concluded that $\alpha = 0.25$, in addition by others $\alpha = 0.398$ was proposed in men and a $\alpha = 0.384$ in women; further $\alpha = 0.38$ was also reported (19-21). The inconsistencies among the individual findings are substantial. The differences between the smallest (0.25) and largest (0.604) values of previously reported α values lead to discrepancies around 25 ms when the heart rate changes only between 55 and 65 beats/min!

Similar inconsistencies also exist among studies investigating other types of QT/RR relationship. The slope β of linear relationship between QT and RR intervals was

investigated, β = 0.205 was reported based on data from 650 healthy soldiers aged 18 to 44 years (22). Others were reported a value for β = 0,14 and β = 0,125, whereas from the data of the Framingham study (2,239 men and 2,779 women), Sagie observed β = 0.154 applicable to both sexes (18, 23, 24).

1.2.3. Evaluation of the Fixed QT Correction Formulae

Besides exponential, logarithmic, and linear formulae several other mathematical equations have been derived mainly from resting ECGs of different subject cohorts, therefore these formulae require a stable sinus rhythm without sudden changes in the RR-interval. The goal of each heart rate correction formula is to provide QTc interval values that are independent of the corresponding RR interval values. Such independence may, for instance, be tested by computing correlation coefficients. For an "ideal" heart rate correction formula, the correlation between QTc and RR is zero. Practically this means, that the value of the α coefficient for a given equation should be computed when the correlation between QTc and RR is zero (for example, in the linear model: $QTc = QT + \alpha(1 - RR)$, or in the parabolic model: $QTc = QT/RR^{\alpha}$ (25). To assess the performance of a particular heart rate correction formula, the correlation between the QTc intervals calculated using the formula and the RR intervals can be assessed. If it differs from zero, as is the case with most of the above described formulae, the correction formula is not truly successful (26).

The most commonly used equation to correct the QT interval for heart rate is Bazett's square root formula: $QTBc = QT/RR^{1/2}$ (13). When heart rate is particularly fast or slow, the Bazett formula may overcorrect or undercorrect, respectively, but it remains the standard for clinical use. Because the terms "undercorrection" and "overcorrection" of the QT interval are frequently used without much insight, the following convention may be proposed: Uncorrected QT interval increases with increasing values of RR interval; thus, the correlation between uncorrected QT interval and RR interval is positive, as is the slope of the QT/RR regression. The goal of a correction formula is to produce QTc values that are uncorrelated with RR intervals and thus have the slope of QTc/RR regression zero. Hence, in essence, a correction formula should tilt (and "uncurve") the QT/RR pattern so that the QTc/RR pattern is straight and flat. Those formulas that tilt the QT/RR pattern too much (and thus lead to a negative correlation

between QTc and RR and to a negative QTc/RR slope) overcorrect, whereas those formulas that tilt the QT/RR pattern too little (and thus lead to a still positive correlation between QTc and RR and to a positive QTc/RR slope) undercorrect.

The cube root Fridericia formula ($QTFc = QT/RR^{1/3}$) has the same limitations at slow heart rates, but is considered to reflect a more accurate correction factor in subjects with tachycardia (15). Linear formulae may have more uniform correction over a wide range of heart rate. The most commonly used linear formula derives from the Framingham study, named Framingham or Sagie formula: $QTLc = QT + 0.154(1 - RR)$ (24). The "L" in the abbreviation QTLc comes from "linear", this formula is noted most frequently this way.

The latter formulae may give QT values that are too low at slow heart rates. There is no general consensus on the best formula to be utilized in clinical practice. Of note, in resting conditions with heart rates in the 60–90 beats/min range, most formulae provide almost equivalent results for the diagnosis of QT prolongation. Even if the rate dependence of the QT interval is probably best described by an exponential relation, in the normal heart rate range the QT/RR relation is approximately linear (9).

There is one major methodological problem with all of the studies that yielded these fixed formulae. The design of such a universal heart rate correction formula is based on the assumption that the investigated QT/RR data are representative of a "physiologic" QT/RR relationship that is the same in every healthy subject or at least in a same subject of a well-defined group (e.g., in healthy men) i.e., to establish a rule that allows conversion of a pair of QT and RR durations into a standardized QTc value corresponding to a "basal" RR interval of 1 second. Unfortunately, as reported recently, it appears that such a common "physiologic" QT/RR relationship does not exist because the QT/RR patterns exhibit remarkable interindividual differences (26, 27).

For instance, Figure 4 shows QT and RR interval data carefully measured on Electrocardiograms of two healthy male subjects at rest and also during different stress situations (28).

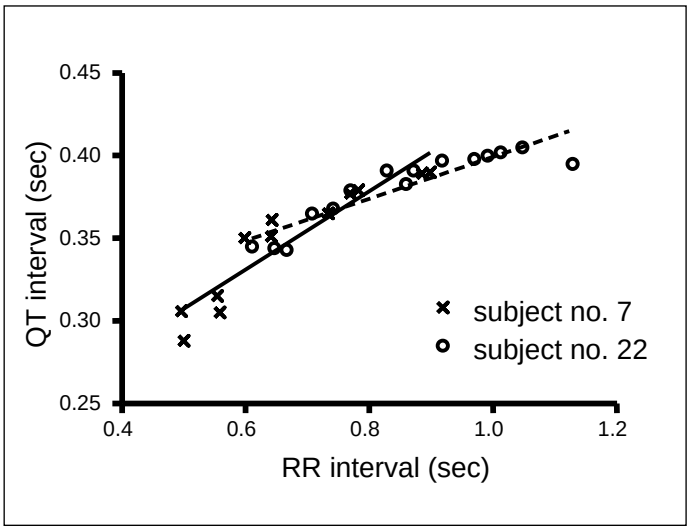

Figure 4. Scatter diagrams of QT and RR intervals measured on serial ECGs obtained at rest and during various stress conditions in two healthy male subjects. Linear regression analysis of the QT/RR data yielded equations QTc = 0.2773(RR) + 0.1887 and QTc = 0.1268(RR) + 0.2725 for subject no. 7 and subject no. 22, respectively (28).

It is obvious that the QT/RR pattern is somewhat flat in one subject but is much steeper in the other subject. Specifically, with identical changes of the RR interval in these individuals, different changes of the QT interval duration occur because of the different slopes of the regression lines. Thus, there simply cannot be a common correction formula or a common numerical QT/RR regression model that would fit the data of both these subjects. Attempts to find a "true" and universally applicable correction formula seem bound to be fruitless.

1.2.4. Study Specific and Subjects Specific QT Interval Correction

Investigations that require precise assessment of QTc interval are crucially dependent on the appropriateness of the correction method. 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 (29). This is because the QT/RR pattern is highly individual and thus the QT/RR relationship is not reproducible

between studies investigating different populations (26, 27). Consequently, it has also been recognized that to improve the precision of heart rate correction, the data of the study in hand need to be used to derive specific correction approach suitable for the given investigation (30). To derive a study specific correction formula, a reasonable number of baseline QT/RR data pairs pooled from all participants need to be available. Generally, these data cover a range of heart rates wide enough to allow accurate regression analysis. 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.

The subject specific (individualized) QT interval correction is even superior to the study specific method (31). The need for subject specific correction should always be considered when comparison of the QT interval at the same heart rate is not possible or is impractical to organize, for example; supine ECGs off and on treatment with a drug that changes heart rate (26). The philosophy is very similar to that of the study specific QT interval correction, just instead of pooled baseline QT/RR study data, a number of individual baseline QT/RR data with adequately broad range of heart rate should be collected from each participant. Curve fitting may be performed then for each individual's QT/RR data pairs to establish the mathematical model that best describes the QT/RR association for that subject. The curve fitting then yields the coefficients of the specific equation that could be used afterwards to adjust raw QT values for heart rate in the tested subject.

1.3. VARIABLES AFFECTING QT DURATION

QTc is affected by a broad set of influences, both internal (genetic, physiologic, and pathophysiologic) and external (food, drugs) for a given individual. In general, women have a longer (~ 10 to 20 ms) QTc than men (24, 32-36). Also, a positive correlation between QTc and age was found (34, 36). Additionally, QTc changes markedly during the day. A mean lengthtening of QTc by 13 ms has been observed during sleep, believed to be related to either increased vagal or reduced sympathetic tone (37).

Increased variability of QTc during sleep has also been described, with the longest values recorded during the hour of awakening (32).

Cardiac and non-cardiac drugs may prolong the QT interval either by directly influencing repolarization currents or due to drug interactions (38). Increased deposition of intra-abdominal fat assessed by computerized tomography was significantly associated with prolongation of the QTc interval independent of obesity and other cardiovascular risk factors (39). In one study, the heart rate and QTc interval correlated with the severity of obesity independent of age, sex and blood pressure (40). Obesity is also associated with longer QTc duration, moreover, the QTc interval was found to shorten with weight loss according to another report (41). However, avid dieters using the liquid-protein-modified-fast diet presented QT interval prolongation that was linked to sudden unexpected death among them (42).

Alcoholism and alcoholic liver disease were associated with longer QT interval duration compared to controls, importantly, the significant difference was also present when QT adjustment was performed using the cube-root formula that was shown largely heart rate independent (43, 44).

Electrolyte disturbances like hypokalemia, hypomagnesemia, and hypocalcemia lead to QT interval prolongation (45, 46). Hypoglycemia and diabetes mellitus, mainly when complicated with diabetic autonomic neuropathy leads to QTc prolongation (47-52). Some other factors and conditions that have been linked with QTc prolongation are: hypothyroidism, pituitary insufficiency, and central nervous system insults like stroke, subarachnoid hemorrhage, trauma, infection and tumor (45, 46, 53, 54).

1.4. QT PROLONGATION

1.4.1. Overview

Prolongation of ventricular repolarization results in an increase in the absolute refractory period. Although this is the mechanism by which some antiarrhythmic drugs (e.g., Vaughan Williams Class III agents) prevent or terminate ventricular tachyarrhythmias, prolonging repolarization may also cause arrhythmias. The QTc interval is considered prolonged when it exceeds 0.45 second (55). Although arbitrary, this value is often considered as a cut off point separating normal from abnormal values.

Some authorities established other cutoff points to discriminate normal from prolonged QTc, for example QTc is normal if <0.46 second in women and <0.45 second in men according to a recent guideline (56).

The most common type of drug-induced ventricular arrhythmia is a form of polymorphic ventricular tachycardia known as TdP (torsade de pointes, twisting of the points), so named because there is a progressive rotation of the QRS axis (57). This is frequently a self-limiting tachyarrhythmia that typically causes intermittent dizziness or syncope, but it can degenerate into ventricular fibrillation and sudden death. Although QTc is widely viewed as a surrogate marker of the arrhythmogenic potential of a drug, the precise relationship between the extent of QTc prolongation and the risk of sudden death is unknown. However, a QTC > 0.50 second in either sex has been shown to correlate with a higher risk for TdP (58-60). Reported cases of drug-induced torsades de pointes indicate that the vast majority occur in patients with QTC > 0.50 second (61). It is important to point out that this rule has exceptions. For example, amiodarone causes marked prolongation of the QT interval but is not associated with a high risk for proarrhythmia. Another problem in recommending a QT prolongation criterion for clinical practice is that no threshold has been established below which QT prolongation is considered free of proarrhythmic risk (62).

1.4.2. Population-Based Studies

Several epidemiologic databases have described QTc (mostly using the corrected Bazett formula) in populations of healthy volunteers, and reported on the usefulness of QTc as a predictor of clinical outcome (variously defined). In those studies reporting QTc measurement for the general population the means ranged from 394 to 405 ms, (63-65). QTc prolongation was defined as an interval greater than 440 ms in most of these reports.

In summary, most studies suggest that in the general population, a prolonged QTc is associated with increased risk for cardiac death (34, 36, 63, 65). However, other reports fail to support this association (65, 66). The lack of uniformity in these results could be caused by a number of factors, but the consistent observations that patients with a QTc greater than 440 ms have a greater risk for cardiovascular mortality than patients with a QTc less than 440 ms may reflect the role of QTc as a marker of underlying cardiac

disease. In support of this conclusion, all general population studies that performed additional analyses on healthy (noncardiac) subset failed to show a relationship between QTc and cardiac related mortality (65, 66).

1.4.3. Congenital Long QT Syndrome

The last decade brought a breakthrough in the understanding of genetic etiology and mechanisms underlying long QT syndromes (LQTS). LQTS research is continuously evolving, and currently 8 genetic forms of the disorder are identified with mutations in genes coding for sequences of aminoacids in cardiac potassium and sodium ion channels causing distinct forms of LQTS (67, 68). The first was described by Drs. Jervell and Lange-Nielsen (1957) in several families of Scandinavian origin and was associated with deafness at birth and the second form of the syndrome when the hearing was normal was described in 1963 by Romano in Italy and Ward in Ireland (69-71).

Syncope or sudden death are the most common symptoms, and are characteristically associated with sudden increases in sympathetic activity, such as during physical exertion (notably swimming) or emotional excitement like anger or fear. In a small percent of cases it may occur during sleep or increased arousal following sleep. Sudden awakening caused by alarm clock, telephone ring or thunder) seem to be specific triggers for some individuals. In a prospective follow up study, it was shown that three factors made significant independent contributions to the risk of subsequent syncope or sudden death before age 50 years, whichever occurred first: QTc (the largest the worst), history of cardiac event and heart rate (72).

Even in the pre-genetic era of the LQTS research, it was recognized that this disorder could have quite variable presentation regarding ECG findings and clinical symptoms, what implied different mechanisms leading to the disorder (72, 73). AP in cardiac cells is governed by a complex interplay of ion currents, and disruption of the system by abnormal function of one or more channels causes changes in AP duration and shape with subsequent manifestation of these changes on ECG. The most frequent genetic types of LQTS (LQT1, LQT2, and LQT3) have distinct patterns of repolarization that require attention by clinicians. Morphological changes of T wave help in identifying patients suspected of having the disease and indicate the possible genetic form of the disease, which should be confirmed using genetic testing. Spontaneous and drug-

induced dynamics of repolarization also differs among LQTS genotypes and could improve identification of LQTS patients.

1.4.4. Acquired Long QT Syndrome

The most common form of acquired LQTS results from exposure to drugs that extend the duration the QT interval. An example from our research for drug interaction leading to substantial QT interval prolongation is presented in Figure 5 (74). Bazett corrected QTc was 416 ms at baseline and 466 ms during treatment representing 50 ms QTc prolongation (QT values were measured on-screen under 3x magnification in a blinded manner in lead II and averaged from 3 cycles). QT interval correction by Fridericia and Sagie also revealed 31 and 27 ms prolongation, respectively. Eventually it turned out, that this patient besides chlarithromycine was also taking cisapride.

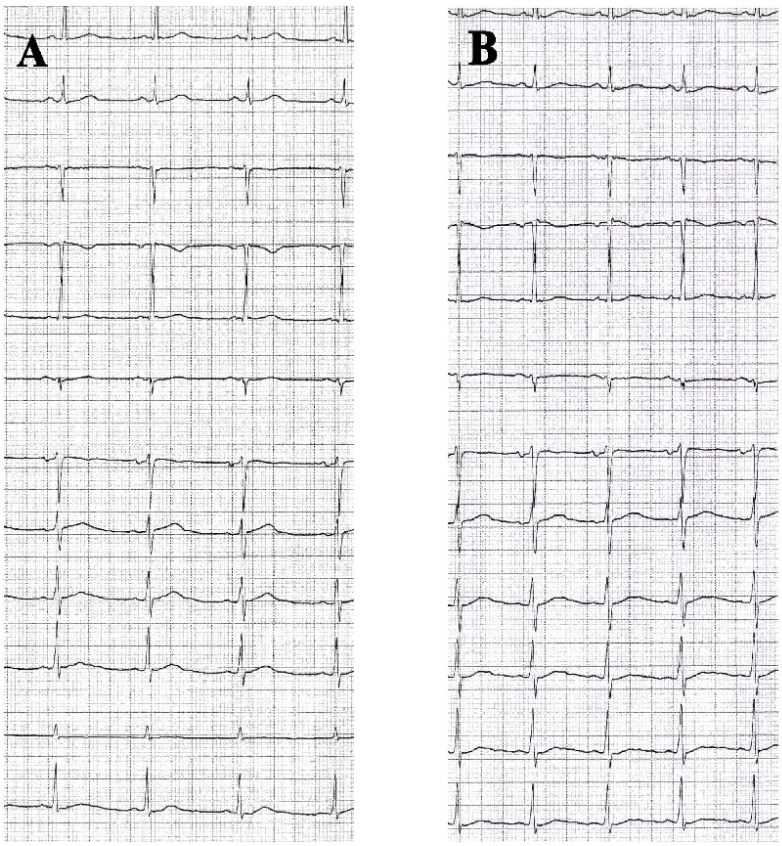

Figure 5. An example from our research for drug interaction leading to substantial QT interval prolongation (74). Baseline (inset A) and on-treatment ECGs (inset B) from a patient who underwent chlarithromycine treatment to eradicate Helicobacter Pylori.

Macrolid-antibiotics, such as clarithromycine may prolong repolarization by inhibiting the rapid component of the delayed rectifier current (I_{Kr}), also, inhibit CYP3A4 and should not be used in conjunction with cisapride (75). Cisapride because of its torsadogenic potency has been withdrawn from most drug-markets.

Such prolongation may be the primary pharmacodynamic action of the drug (cardiac drugs like antiarrhythmics, particularly procainamide, quinidine, amiodarone, sotalol, etc), on the other hand several drugs (non-cardiac drugs) developed for other purposes have the unwanted effect of provoking QT interval prolongation. Internet sites that continuously update the list of drugs that may cause TdP or the drugs that may lead to adverse interactions can be easily accessed (http://www.torsades.org/). A review of reports of TdP-s caused by non-cardiac drugs to determine how many of those patients had easily identifiable risk factors found that easily identifiable risk factors included the following: female gender, underlying heart disease, hypokalemia, toxic drug levels, drug interactions, a history of familial LQTS or a previous history of drug-induced torsade or a prolonged QT interval (QTc $\geq$ 0.45 sec) in the baseline electrocardiogram (76). In brief, it was found that 96% of affected individuals had at least one easily identified risk factor, in fact, 72% of cases of TdP from non-cardiac drugs had at least 2 risk factors.

Among others, non-cardiac drugs that most commonly induce QT prolongation and TdP typically come out from antihistamines (astemizole, terfenadine etc.), antimicrobial/antifungal agents (thiomethoprim-sulfa, erythromycin, ketoconazole etc.), and psychotropics (haloperidol, risperidone, thioridazine, tricyclics, etc.).

1.4.5. Ischemic Heart Disease

The behavior of the QT interval in ischemic heart disease cannot be defined straightforwardly, which is clearly reflected by the numerous reports on this topic with contradictory findings. This controversy is probably mainly caused by the heterogeneity of clinical conditions that represent different stages of this disease (i.e. coronary sclerosis without previous myocardial infarction (MI), acute angina, and different stages of the acute MI, healing of the infarction, and also left ventricular remodeling with dilatation of the left ventricule). Study design and the use of Bazett correction also appear as further reasons of the diverse results.

It is generally believed that the QT interval is determined by the AP duration of the ventricular myocytes (77). Acute myocardial ischemia opens the K_{ATP} channel and shortens AP duration in mammalian ventricles (78, 79). However, in experimental animal model, acute regional ischemia is typically associated with QT interval lengthening in spite of AP duration shortening in the ischemic zone (80). Why QT interval lengthening should occur early in acute myocardial ischemia has not been clearly elucidated (81). It is known that regional ischemia in humans and in experimental animals creates QT prolongation (80, 81). One possible explanation is that the QT interval is determined by the longest AP duration in the ventricles. Because AP duration in the nonischemic region may lengthen after the creation of ischemia, the QT interval on surface ECG also lengthens. Therefore, the AP duration shortening in ischemic region is not associated with QT shortening (82).

Local alterations in sympathetic response to chronic ischemic heart disease are important and may enhance inhomogeneity of local cardiac electrical activity (83-87). In addition, development of myocardial hypertrophy prolongs ventricular repolarization by decreasing I_{Ks} expression and increasing risk for lethal arrhythmias (84, 88, 89). In experimental models, the post MI groups of animals that presented prolonged surface QT intervals were prone to develop ventricular fibrillation during treadmill stress test (90,91). Furthermore, when ischemic disease progressed to produce left ventricular disfunction, QT interval prolongation became more profound and was associated with spontaneous death (91). It was speculated, that increased sympathetic activity in susceptible animals resulted in regional hypertrophy and down-regulation of repolarization potassium channels in specific areas, which led to heterogeneity of repolarization.

It is important to note that in these animal studies, the same experimentally induced infarction elicited different subject-specific responses characterized by different level of tissue responses due to different amount of sympathetic activation.

Initially, ischemia-induced very tall upright or a deeply inverted T wave, and shortened QT interval were described in humans as transient phenomena followed by postischemic T wave abnormalities associated with QT lengthening (92). However, in one study, when Bazett corrected QTc intervals gained from 80 patients with unstable angina during ischemic pain and in the absence of pain were compared, the QTc interval

was not found to change during transient ischemia (93). Another research group studied surface and intracoronary ECG s during acute ischemic episodes in patients undergoing percutaneous transluminal angioplasty (PTCA) (94). Heart rate was maintained constant by 80/min frequency right atrial pacing; therefore no QT interval correction was necessary. They found that during the ischemia induced by PTCA the QT interval became shorter with the increase in the duration of ischemia. In case of acute MI those patients who underwent successful reperfusion therapy the QT interval was lengthened initially and later shortened, while in those who had unsuccessful reperfusion the QT interval was progressively lengthened (94). Others found that acute reversible myocardial ischemia induced by balloon inflation caused an increase in QT dispersion, and this increment was the result of a decrease in minimum QT values whereas maximum QT remained unchanged (95).

A number of studies have reported a direct correlation between ventricular tachyarrhythmia and QTc prolongation during the post-MI recovery period (96,97). QTc thresholds for increased risk for ventricular tachycardia and/or arrhythmias were variously reported in the range of 0.43 – 0.52 sec. All studies used the QTc interval by Bazett correction, except the nomogram QT-corrected interval of Karjalainen. (36, 63, 96-99). The association between QTc prolongation and mortality is much stronger for the post MI population than for the general population, thus QTc prolongation may identify patients at greater risk for mortality because of its association with more severe underlying ischemic heart disease (100).

1.5. STRESS AND THE CARDIOVASCULAR SYSTEM

1.5.1. The Evolution of Stress Concept

Hans Selye has a historic role in the development of the stress concept. Before his short article in Nature in 1936, the neuroendocrine response to nonspecific injury was thought to be restricted to the release of catecholamines, as recognized by Cannon (101). Selye was the first to appreciate the crucial role of the adrenal cortex/hypophysis axis in the stress response. He also insisted on the nonspecificity of this neuroendocrine response, and he named the stress-causing agent “stressors.”

In 1946, in a comprehensive theoretical outline of the stress concept Selye termed the response to stress as the "general adaptation syndrome" (102). According to this theory, the initial reaction to stress is shock, which is followed by a counter shock phase, and gradually resistance develops to the stressor. This resistance may go into exhaustion, however, if the stressor persists; and death may ensue. Biologic stress is the "nonspecific response of the body to any demand made upon it," according to the latest definition Hans Selye used in his last books (103, 104).

The wording of a definition for stress changed over the years, but the meaning remained the same: emphasis of the revolutionary recognition that agents very diverse in nature (e.g., excessive heat or cold; forced immobilization or exercise; chemical, biologic, and psychological agents) may elicit the same neuroendocrine (hence nonspecific) response, which consists of elevated secretion of adrenocorticotrophic hormone (ACTH) by the pituitary leading to enhanced release of glucocorticoids from the adrenal cortex (101, 104). However, it was shown that not all stress response is identical (105). It was shown that that passive stress (no control) elicits different autonomic response than active stress (where coping is possible).

Selye's model of the stress response presaged more modern conceptions of allostatic systems (those that respond to stressors through the dynamic regulation of physiological states). Allostatic load often involves frequent or prolonged responding. Such sustained arousal may be due to recurring stress, poor adaptation to repeated stressors, or the inability to inactivate allostatic responses after a stressor ends (106).

Mental stress applied to subjects in laboratory conditions was shown to induce cardiovascular response, thus it proved to be a valuable tool to study acute stress responses. However, cardiovascular reactivity (CVR) captures only the magnitude of the stress response and assesses only the response that occurs at the time the stressor is present; thus it is not suited to assessing prolonged cardiovascular arousal. This approach neglects assessment of the frequency of the response as well as its duration: the speed and degree of recovery in the period following the stressor and the extent to which the cardiovascular response occurs in anticipation of stressors that may yet occur. Thus, laboratory reactivity is inherently limited in its ability to model the multidimensional nature of real-life responding, also it is artificial because the subject

knows that he participates in an experiment that has an outcome which is neutral (no influence) on his personal life.

1.5.2. Stress, Reactivity, and Brain Processing Patterns

Associated with the individual's emotions and behaviors are a host of central and peripheral physiologic responses, or reactivity. Reactivity includes the activation of the cardiovascular system, sympathetic nervous system, and neuroendocrine/hypothalamic–pituitary–adrenal axis system. It is the reactivity of these systems by which the brain sets in motion the bodily processes to support the overt behaviors required for a successful response to environmental demands. Control over these systems is organized hierarchically, from cortical regions, where our thoughts and emotions are initiated, shaped, and stored, to the hypothalamus, where visceral output is integrated, to the brainstem, which informs our intrinsic respiratory, hemodynamic, and cardiac rhythm. To illustrate, a model in which activation of the cortical, neocortical (limbic system, memory), and hypothalamic central nervous system (CNS) regions results in one form of reactivity, altered peripheral sympathovagal balance, is shown in Figure 6.

The initial cognitive evaluative process that shapes our response to environmental demands occurs in the prefrontal and frontal cortices. The brain responds to stimulation with integration and evaluation of auditory, visual, and motor responses (107). Sensory input is filtered by the thalamus. The thalamus has functional anatomic projections to higher cortical regions and to the hypothalamus, a component of the limbic system, which amplifies emotions through the overlay of memory. The components of the limbic system are the hypothalamus, which controls various biological functions; the hippocampal complex, which provides memories and context; the amygdala, which integrates emotional information from other brain regions; and the cingulate gyrus, which helps form connections that create our awareness of emotions.

The hypothalamus is influenced not only by lower (brainstem) but also higher frontal cortical regions related to evaluation, as well as subcortical limbic areas related to memories that are explicit (hippocampus) and those that are implicit (amygdala) (108).

The physiologic response to the activation of the limbic system is an increase in heart rate and blood pressure, which defines hemodynamic reactivity. These biological reactions are largely a result of the physiologic effects of catecholamines. In this manner

the brain and the biological reactions are integrated and produce a response to environmental circumstances in the stress equation. Hence, several regional CNS centers are neuroanatomically and functionally interconnected to form a network, culminating in sympathoadrenal reactivity.

In summary, the response of the brain to psychosocial stress is a highly sophisticated and integrated process by which sensory input is evaluated and appraised for its importance in relation to previous experience and current goals. This is a hierarchical response that includes specific functional neuroanatomic regions working in concert and the coordination of peripheral responses (reactivity) that enable the individual to behave effectively.

1.5.3. Anatomical and functional autonomic nerve projections to the heart

Autonomic nerve projections into the heart promote understanding of how the ANS (ANS) regulates the heart. The anatomy of cardiac sympathetic nerve projections into the human heart was described by James (109). The right stellate cardiopulmonary nerve, from the right stellate ganglia, courses through the dorsal nerve plexus to the left lateral cardiopulmonary nerve and projects into the lateral wall of the left ventricle. The dorsal medial and lateral cardiopulmonary nerves, from the central cervical ganglia, form the left coronary nerve which runs alongside the main left coronary artery. The coronary artery, in turn, separates into two branches running alongside the circumflex and left anterior descending coronary arteries and on into the adjacent epicardium. The left ventral cardiopulmonary nerve, from the left cervical ganglia, connects solely to the right coronary cardiac nerve which runs adjacent to the right coronary artery and projects into the right ventricle and inferior posterior wall of the left ventricle. The left dorsal cardiopulmonary nerves join with the right dorsal cardiopulmonary nerves to form the dorsal plexus and the left coronary cardiac nerve: a connection also exists between the dorsal plexus and the right coronary cardiac nerve. None of the sympathetic nerve projections, however, influence an exclusive cardiac territory, although the anterior region of the left ventricle appears to be mainly regulated by nerve fibers from the right sympathetic ganglia.

The parasympathetic innervation of the heart is provided by efferent paraganglionic parasympathetic neurons in the medulla oblongata, which project axons onto the heart

where they synapse with efferent postganglionic parasympathetic neurons that innervate the heart. Despite the existence of an abundant parasympathetic innervation of the atria, intraventricular parasympathetic ganglion cells are sparsely distributed (108). Further, reduced contractility was observed more markedly in the left ventricular base than in the apex by stimulation of the cervical vagosympathetic trunk, indicating less innervation in the apex than in the base of the left ventricle (110).

In summary, sympathetic nerves distributed in the anterior region are most likely to be regulated by the right sympathetic basal ganglia whereas those in the inferioposterior region are most likely to be regulated by the left sympathetic basal ganglia. Furthermore, the inferioposterior region of the heart contains a greater number of ventricular receptors with parasympathetic vagal afferent nerves than the anterior region.

1.5.4. Stress Effector Systems

There are various neurological conduits that integrate the behavioral and neuronal stimuli and mediate the stress response, referred to as "stress effector systems". These include the sympathoneural system, the adrenomedullary hormonal system, the parasympathetic nervous system, and others, including the hypothalamic–pituitary–adrenal axis, renin-angiotensin-aldosterone, and vasopressin systems (111). Different stresses evoke different patterns and intensities of stress effector response. Whereas mental challenge results in physiologic responses mediated by the sympathoneural system, distress, which implies affective engagement, results in adrenomedullary hormonal system activation (111).). This makes the difference between active and passive stress, hence the stress response is quite specific, rather than nonspecific. It varies in amplitude and frequency and also in systemic (effectors) involvement.

Although a comprehensive pathophysiologic model acknowledges the influence of the hypothalamic–pituitary–adrenal axis, renin-angiotensin-aldosterone, and vasopressin stress effector systems, the catecholamine response is the most influential determinant of the cardiovascular response to acute stress. Most laboratory-induced mental stressors, which create both mental challenge and affective distress, increase both EPI and NE (112-114).

1.6. MENTAL STRESS

1.6.1. Mental Stress and Cardiovascular Innervation

The heart itself is richly innervated with sympathetic nerves, which project into the myocardium, coronary arteries, and conduction system. Although different types of nerve fibers are present in different organs, the predominant innervation of the cardiovascular system is via sympathetic vasoconstrictor fibers. These sympathetic fibers affect vasoconstriction through α_1-adrenergic receptors. It is through these nerves that cortical and subcortical regions of the brain influence systemic vascular resistance. In the heart (and in exercising muscle) the vasoconstrictor effects of these nerves are counterbalanced by local metabolic conditions that promote vasodilatation, thereby matching blood flow to work. Although the precise mechanisms involved in regulation of coronary flow are not fully understood, it is likely that this adrenergic innervation is involved in the various deleterious effects of mental stress on the heart. One potential mechanism may involve a reduction in coronary blood flow during mental stress, even in the presence of minimal epicardial stenosis (115, 116). In addition to this direct cardiac innervation, the myocardium itself contains adrenergic receptors that transduce the effects of mental stress. β_1- and β_2- adrenergic receptors are the predominant adrenergic receptors in the myocardium itself and are stimulated during stress as a result of endogenous (local) and exogenous catecholamine release. Given the prominent role of the CNS and peripheral sympathoadrenal effector systems in psychological stress, an understanding of cardiac innervation is the key to a comprehensive model of mental stress effects on the heart.

1.6.2. Active and Passive Mental Stress

Active mental stress is defined in the literature as stress in which the subject is required to actively cope (do something) or perform in a challenging situation (117). Passive mental stress is defined as stress in which the subject is unable to actively cope (do something) about an unpleasant or distressing situation. It is characterized by the lack of control over the source of stress (117).

1.6.3. Hemodynamic Effects

During active mental stress, the net result of this stimulation is an increase in contractility. In addition, the balance of parasympathetic and sympathetic systems is most important with regard to its effect on the conduction system, which shifts toward more sympathetic activation, leading to an increase in heart rate. Thus overall myocardial oxygen demand may increase during psychological stress in a manner similar to that which occurs during exercise, albeit at a lower magnitude. The augmentation of the ANS, resulting in neurohormonal release, has diverse effects on hemodynamic reactivity, vasoconstriction/vasoreactivity, platelet activation, endothelial injury, and proarrhythmogenicity, as discussed below.

The effects of mental stress on cardiovascular hemodynamics have been addressed in several studies. Overall, these studies suggest that variability in response to mental stress is common among healthy subjects and patients with coronary artery disease (CAD). Data from the PIMI study in healthy subjects indicated that mental stress tasks (Stroop color word task and public speaking) result in an increase in heart rate and blood pressure, with an overall increase in rate-pressure product of 30% to 45% (113). Younger subjects, however, did not show as robust an increase in rate-pressure product during mental stress. Furthermore, recent results suggest that there appear to be two typical major response patterns to mental stress in healthy subjects. Some healthy individuals primarily exhibit a rise in cardiac output during mental stress, whereas others mainly exhibit an increase in peripheral resistance (118). Likewise, in patients with CAD, increases in rate-pressure product during mental stress occur but vary from subject to subject (119). The hemodynamic effects of mental stress appear to be similar in both healthy subjects and CAD patients. Data suggest that the magnitude of hemodynamic response to mental stress may be associated with myocardial ischemia, as well as with indicators of autonomic arousal. In the PIMI study, for example, patients with mental stress ischemia showed a greater increase in systemic vascular resistance than those without ischemia (119). The hemodynamic increases were associated with increased plasma EPI levels during stress, presumably mediated via the cognitive stress and abovementioned effector systems. Other data indicate that increases in systemic vascular resistance are associated with left ventricular dysfunction during mental stress (120). An exaggerated hemodynamic response to mental stress also appears to be

associated with exercise-induced myocardial ischemia in subjects at high risk for CAD (121). This response was correlated with increased normalized low-frequency power on ambulatory measures of heart rate variability, indicating a shift to higher sympathetic arousal.

1.6.4. Alterations in Coronary Vasoreactivity

It is becoming clear that mental stress can induce heterogeneity of myocardial perfusion in some patients with CAD. Two studies provided initial evidence for mental stress–induced perfusion defects. In the earliest demonstration of this effect, it was found that 12 of 16 patients with CAD and positive exercise test results had regional perfusion abnormalities develop during mental stress testing (122). Subsequently, it was reported that 85% of patients with CAD had regional perfusion abnormalities by planar technetium 99m sestamibi perfusion. Several groups of investigators have used quantitative positron emission tomography to assess changes in absolute myocardial blood flow during mental stress. One research group compared myocardial blood flow responses during mental stress in patients with CAD and in healthy subjects (123). They found that despite similar increases in rate-pressure product, the magnitude of the flow increase during stress was smaller in patients than in healthy subjects. These studies suggest that an alteration in coronary vasoreactivity occurs during challenging mental tasks. Coronary angiography studies also have provided evidence that dynamic coronary obstruction is involved in the pathophysiology of mental stress–induced myocardial ischemia. Direct angiographic evidence of epicardial coronary artery vasoconstriction has been observed during mental stress (115, 124).

1.6.5. Platelet Activation

The importance of platelet physiology in acute and chronic CAD is well established. The influence of psychological stressors on platelet function is less known, but the evidence supporting a role is strong. Acute psychological stress, in the form of mental arithmetic (MA), public speaking, and the Stroop color conflict test, have been shown to activate platelets, as assessed by measurement of β-thromboglobulin, platelet factor 4, and/or adenosine diphosphate (125, 126). Although the mechanisms by which

psychological factors affect platelet function are unclear, several lines of evidence suggest that neurohumoral factors may be key components in the process (127-130).

1.6.6. Endothelial Injury

There is evidence that the vascular responses to mental stress are mediated through the endothelium and that endothelial-dependent vasodilatation is attenuated during or after periods of stress. Interestingly, the phenomenon of mental stress–induced endothelial dysfunction has been described in healthy subjects, as well as in patients with CAD and hypertension (115, 131-134). The effects of a brief period of stress on endothelial-dependent vasodilatation may last for several hours, suggesting that periodic stress as may be encountered during daily life may have more lasting effects (132). Also, the individual responses of the coronary or brachial arteries to mental stress are variable, suggesting that the endothelium in a particular vascular bed may be responding to differential neurohumoral "inputs" from one patient to the next (115, 131). Importantly, experimental data that used psychosocial stressors in monkeys indicate that stress can cause endothelial injury (135, 136). Thus the potential deleterious effects of mental stress are acute, as manifested by acute alterations in vascular tone and/or hemostatic milieu, and chronic, affecting the overall "health" of the endothelium.

1.6.7. Arrhythmias

Epidemiologic studies show an increase in sudden cardiac death in populations subjected to natural disasters such as earthquakes or war, unrelated to trauma or physical effort (137-139). The physiologic link between psychological stress and sudden cardiac death remains unknown. The effect of mental stress as a trigger of myocardial ischemia, as previously discussed, may represent one mechanism involved in the pathogenesis of arrhythmias in context of sudden cardiac death. There is additional evidence, however, directly connecting psychological stress with arrhythmogenicity. Experimental studies in animals exposed to social stress demonstrate an increased susceptibility to ventricular arrhythmias compared to control animals (140-142). These findings also suggest that this effect is mediated by a relative increase in sympathetic activation. Recent investigations with humans also suggest that acute psychological stress increases the propensity for arrhythmias in patients with CAD or

history of arrhythmias (112, 116). Finally, data obtained on circadian variability of arrhythmias, which indicate a predominance of sudden cardiac death and/or ventricular arrhythmias in the morning, support the concept of alterations in adrenergic state as a facilitator of arrhythmia in susceptible populations (143-148).

1.6.8. Behavioral state

The view that behavioral factors may trigger malignant arrhythmias has gained strong support in the recent years. Researchers have established such a connection on the basis of psychometric tests for various behavioral indices and measures of cardiac electrical instability including defibrillator discharge frequency and T wave amplitude (TWA). The linkage between emotional and physical stressors in provoking spontaneous ventricular arrhythmias in patients with implantable cardioverter-defibrillators (ICDs) was systematically examined recently (149). Detailed diaries of mood states and physical activity were obtained during two periods preceding spontaneous, appropriate ICD shocks and during control periods 1 week later. In the 15-minute period preceding shocks, there was a significant incidence of high levels of anger. Other mood states, notably anxiety, worry, sadness, and happiness, did not trigger ICD discharge. Physical activity was also associated with increased incidence of shocks. Similar findings were reported by others, who found seven fold increased risk of ICD shock with high levels of physical activity and nine fold increased risk of ICD shock with mental stress (150). These observations are consistent with recent experimental and clinical findings, demonstrating that anger may trigger significant increase in cardiac electrical instability (151, 152). In fact, there is an extensive literature indicating that anger is the affective state that is most commonly associated with sudden cardiac death (153). The dynamic influence of mental and physical activity on cardiac electrical function finds further support in a recent study of ambulatory ECG-based TWA analysis in post–MI patients (154). In the "Autonomic Tone and Reflexes After Myocardial Infarction" (ATRAMI) study, individuals at risk for arrhythmic death showed increased TWA levels at maximum heart rate and at 8 AM, suggesting that daily mental and physical stress can disclose clinically significant levels of electrical instability. Although the increase in TWA may be associated with maximum daily heart rate, elevated heart rate *per se* does not appear to be the sole factor, as TWA measured at peak heart rate did not correlate

with the magnitude of the heart rate change nor did the maximum heart rates differ between patients with and without events. These increases in TWA in some cases are likely to reflect the influence of enhanced sympathetic nerve activity, because β-adrenergic receptor blockade reduces TWA magnitude, an effect shown to be independent of heart rate, when this variable is controlled by pacing (155, 156). In a recent study, stored intracardiac electrocardiograms from patients with ICDs were retrieved and analyzed in relation to corresponding mood states, and ventricular arrhythmias occurring in the setting of anger were more likely pause dependent and polymorphic (157).

This finding suggests that in predisposed populations anger may create an arrhythmogenic substrate susceptible to more disorganized rhythms, a possible mechanism linking emotion and sudden death.

1.6.9. Effect on the QT Interval

Besides heart rate, the ANS, which can act directly at the cellular level or indirectly through modulation of heart rate, is another important source of QT changes (37). The role of the ANS was demonstrated by the prolongation of the QT interval during sleep, independent of heart rate. This observation was attributed to circadian changes in sympathovagal balance (158). The QT interval is prolonged in patients with diabetic autonomic neuropathy and in patients with familial dysautonomia (49, 159). Similarly, QT interval is increased in patients with primary autonomic failure due to pure autonomic failure or multiple system atrophy (160). Both chronic and acute mental stresses induce cardiovascular and neuroendocrine responses. Stress-induced ANS activation might also trigger lethal arrhythmias through alterations of the neural transmissions to the heart (161). Epidemiologic evidence suggests that there is a relationship between stress and cardiac morbidity and mortality in susceptible individuals (137-139, 162).

The prolonged QT interval is regarded as a marker of imbalanced distribution of sympathetic nervous system activity on the heart; also QT interval prolongation has been associated with a lowered ventricular fibrillation threshold and with the occurrence of sudden cardiac death (100). However, the effect of psychological stress on the QT interval is subject to speculation. Previous published reports provided conflicting data

on the effect of mental stress on the QT interval duration. For example, it was observed that the QT interval of physicians prolonged when they got alarm calls (163). This report has outmost merit, because the use of Holter monitors made it possible to evaluate QT interval changes without heart rate correction: the QT interval shortened only slightly and was on average 59 to 67 ms longer ($p < 0.001$) than that at similar heart rates during stable conditions. Also, a patient on Holter monitoring accidentally being awakened with bad news in the night presented marked QT prolongation (164). Conversely, other laboratory based studies reported QT interval shortening as an effect of mental stress (165-169). Huang (165) reported that during "stressful interviews" the QT intervals shortened.. Similarly, QT shortening was observed by Insulander (166) during Stroop color-word test and by Haapalahti (167) during MA. In these three studies QT intervals were not corrected for heart rate, so almost certainly the physiologic decrease of QT time was related to increases in heart rate. Furthermore, Paavonen (168) measured heart rate and QT interval duration at peak heart rate during a combination of Stroop color-word test and MA, and reported QTc interval shortening). However he used the Bazett and Fridericia methods to correct QT intervals for heart rate, but this approach has been severely criticized (26). It has been shown that no fixed correction formula is suitable to compare QT intervals at different heart rates because the QT/RR relation exhibits a substantial inter-subject variability. Finally, in one published study it was attempted to overcome the shortcomings inherent in the use of fixed correction formulae. Hedman and Nordlander (169) applied fixed rate ventricular pacing on 10 subjects with high degree atrioventricular block. Stroop color-word task was presented while the ventricular rate was kept constant by ventricular pacing. QT measurements were performed at "peak stress" defined as the maximal atrial rate. With this method a minor QT interval shortening was detected. But, since it has been shown that asynchronous VVI pacing triggers both sympathetic overactivity and vagal withdrawal, the net effect of mental stress on the QT interval remained still unclear (170).

One major problem in this area of research is the use of inconsistent test protocols to induce mental stress. Different methods have previously been used, with studies assuming that the mental stress response is generic. Conversely, it has been shown that different psychological stressors produce specific cardiovascular responses (105, 171). Further, it has been demonstrated that conditions of active mental stress (AMS) and

passive mental stress (PMS) promote different levels of sympathetic and parasympathetic stimulation to the heart, thereby producing different heart rate and blood pressure responses (117). Despite these known differences in the cardiovascular response to these two forms of mental stress, to date, no attempt was made to separately assess the QT responses to AMS and PMS. Therefore, to date it is unknown how the QT interval is affected by these two forms of mental stress.

2. OBJECTIVES

2.1. SHORTCOMINGS OF THE BAZETT METHOD

In the literature a large number of conditions are reported to be associated with QTc interval prolongation, moreover, QTc prolongation is frequently believed to be the reason of the related increased risk of mortality. Some of such reports have been addressed by us in Letters to the Editor (172-174). In these papers 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, without any provocation of the repolarization system, the Bazett method almost always yields a statistically significant difference between QTc-s measured at different heart rates even in the same study group. To support this contention of ours, I wanted to demonstrate these shortcomings of the Bazett method by designing studies using other QT correction methods besides Bazett's. Initially (Study #1), besides the Bazett equation we also used the Fridericia and Sagie-Framingham methods that were reported to be more reliable. (13, 15, 24). Later (Study #2), when the concept of study-specific (i.e. group-, data-specific) QT correction was introduced we included this in our methods (30).

In Study #1 acute cigarette smoking was used as stressor, because the known sympathetic effect elicited by smoking appeared to be suitable to induce heart rate changes, so that QT changes at different heart rates could be evaluated and compared by the means of different correction methods. In the literature, several papers are available with conflicting results on the effect of smoking on the QTc interval, so that as a

secondary objective, we supposed that a placebo-controlled (sham-smoking) design would be appropriate to elucidate real effects of smoking on the QT interval duration (175-178).

In study #2 we used exercise testing, because exercise testing assures a relatively clear condition of sympathetic preponderance with gradually increasing heart rate, yielding a condition where various QT correction methods can be assessed. Our contemplation was as follows: during exercise, a correction method that works well should indicate the shortening of the corrected QT interval, because QT shortening is the predicted physiologic response to sympathetic influence (37, 158, 169). Therefore, Study #2 was designed to test the appropriateness of some previously published and frequently used heart rate correction formulae to adjust QT intervals derived from exercise ECGs of healthy adults. These formulae included the Bazett, Fridericia, Sagie, Hodges and Karjalainen methods (13, 15, 24, 179, 180). In this model, we also wanted to gain experience with the recently published study specific QT correction method (30).

2.2. MENTAL STRESS INDUCED QT CHANGES

Mental stress has been reported to induce cardiovascular response including an increase in heart rate and blood pressure. Interestingly, conflicting results on the effect of mental stress on the QT interval could be retrieved from the literature, some reporting prolongation others shortening. Because both mental stress and QT interval prolongation may induce malignant rhythm disturbances and also sudden death, even causative relationship might have been suspected between them. Therefore we designed Study #3 to elucidate the effect of mental stress on the QT interval by enrolling different cardiac patients. In this study mental stress was applied in the form of a simple laboratory MA.

The results of Study #3 suggested that the QT response to mental stress is not generic, marked individual differences were shown (181). Consequently, the finding of individual variation of the QT response needed to be reinforced with results on healthy subjects. Further, we were curious, if it was possible to reproduce this result by using a different active mental stressor. Accordingly, we conducted two other studies (Study #4 and Study #5) on healthy volunteers using MA and video game playing as active mental

stressors. In Study #5 we also applied study specific equations for QT interval correction.

2.3. CARDIOVASCULAR REACTIVITY AND QT RESPONSE

It was shown that across individuals and between genders, differences in the magnitude of physiological responses to acute mental challenges exist, therefore study groups in this research field should be either homogenous, or controlled for the potential confounding factors such as personality traits and prior life stress (182). Both trait characteristics (extraversion, neuroticism, hostility, anger, over-commitment, anxiety etc.) and prior life stress influence the appraisal of acute stress situations and thereby modify the physiological reaction to the laboratory mental challenge. Of course, the scenario gets even more complicated when considering the potential moderating role of the locus of control (internal or external) and coping styles (183, 184).

However, 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 (185). For example, changes in heart rate, blood pressure, impedance-derived measurements of cardiac pre-ejection period, stroke index, and total peripheral resistance may classify study subjects into similar groups in terms of CVR that could be then compared for other features of interest (186).

The results of Study #4 and Study #5 were suitable for further analysis to test the hypothesis if subjects could be classified according to CVR that would also characterize these individuals in terms of the QT response elicited by mental stress.

2.4. EFFECT OF ACTIVE AND PASSIVE MENTAL STRESS ON THE QT INTERVAL

It has been identified that conditions of active mental stress (AMS) and passive mental stress (PMS) promote differing levels of sympathetic and parasympathetic stimulation to the heart, thereby producing different heart rate and blood pressure responses (117, 187). Despite the known differences in cardiovascular response to these two forms of

mental stress, to date, no attempt was made to separately assess QT response to distinct episodes of AMS and PMS. As such, no conclusions have so far been drawn as to the specific QT interval response to these two forms of stress-conditions. We supposed that further insight into QT changes related to these two distinct psychophysiologic entities would help us to explain the confounding reports on mental stress induced QT changes (163-169).

The purpose of Study #6 was to individually assess QT response to isolated conditions of AMS in the form of a simple MA and PMS (video clip of distressing images) in a laboratory setting. Further, in Study #6, to overcome the controversy about the use of fixed equations we used subject specific QT interval correction that was found even superior to the study specific method (26).

2.5. QT CHANGES EARLY UPON MENTAL STRESS

After completing Studies #1-5 (and some other trials not incorporated into the present work) an important experience related to the way of mental stress application was gained. It was remarkable that most of the cardiovascular response occurred early upon stress initiation. Despite such interventions like metronome use, urge to compute more rapidly etc, subjects' interest in maximum performance could not be maintained for minutes. We observed that subjects got accustomed to the stress rapidly, in a large number of cases after 30-60 seconds an "escape-like" phenomenon arose as subjects started to "cool-down", that was also reflected by heart rate and blood pressure drops. This cooling-down was also evident in younger participants, yet we found them more eager to sustain good performance than older participants.

Consequently, we conjectured that brief mental stress protocols would be more suitable, more specifically; we focused our interest on QT interval changes coming up just at the initiation of stress. Study #6 was designed according to this theory, using brief stress protocols allowing instant QT data sampling.

3. SUBJECTS AND METHODS

3.1. OVERVIEW

Between 2001 and 2005, we conducted six separate experiments under laboratory circumstances to assess the effect of mental stress on the QT interval. Four studies were performed in the Cardiac Laboratory of Saint Francis Hospital (SFH), Budapest, Hungary; the other two studies were run in collaboration with the Human Performance Laboratory of the School of Biomedical Sciences at the Nottingham Trent University (NTU), U.K. In Study #3 participants were enrolled from cardiac patients of the Department of Cardiology at Saint Francis Hospital, in the remaining 5 studies participants were volunteers recruited from hospital workers or university students. The study protocols were approved by the local Ethics Committees and participants signed a written consent form. Except for the Study #3, only healthy subjects were enrolled and based on self-reports, 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 in each study 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

Study	n	Loc.	Stressor	QT measur.	QT correction	Ref.
1.	19	SFH	Smoking	OSM	B, F, S	198
2.	20	SFH	Treadmill	OSM	B, F, S, H, K, SS	205
3.	31	SFH	MA	OSM	B, S	181
4.	20	SFH	MA	OSM	SS	223
5.	46	NTU	Videogame	EBP	B, SS	224
6.	30	NTU	MA (active	EBP	IND	28

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.

3.2. MENTAL ARITHMETIC

In psychophysiology, because of its simplicity and effectiveness MA is one of the most frequently used active mental stressors. MA was used in four out of the six studies. In our studies participants were asked to perform a 1-3 minute MA task, which has been shown to induce psychological stress: in most cases this results in parasympathetic withdrawal and a mixed alpha and beta-adrenergic effect, although most subjects respond with a more beta pattern (117). Accordingly, heart rate generally increases substantially but the blood pressure response is less prominent. The amount of reaction of the autonomic nervous system depends on commitment; therefore every effort should be done to motivate participants. In our protocols, the task involved fast and correct serial subtractions from a three or four digit number, for example by 7 from 700. In our studies, in order to increase the perceived importance and stressfulness of the task, participants were told to speak the results out loudly and that the number of correct answers would be recorded. Also, in experiments conducted at SFH, a metronome with 120 beats/min was used for distraction.

3.3. ECG DATA ACQUISITION AND PROCESSING

In studies performed at SFH (Studies #1, #2, #3, and #4) ECGs were prepared in the supine position. The standard 12-lead ECGs were recorded at a paper speed of 25 mm/s and amplifier gain of 10 mm/mV on a "Marquette MacVU" electrocardiograph (Marquette Electronics Inc., Milwaukee, Wisconsin, USA). The simultaneous 12-lead 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 at three fold enlargement in a blinded manner by a single experienced observer (GA). QT-interval was measured from the beginning of the QRS complex to the end of the T wave, defined as a return to the baseline. When T wave deflections of equal or near-equal amplitude result in a biphasic T wave, the QT interval was measured to the time of final return to baseline (9). Mean RR and mean QT values were calculated for each

electrocardiogram. In studies conducted at NTU a commercially available electrocardiograph (FUKUDA FX3010, Fukuda Denshi CO Ltd, Tokyo, Japan) was used according to the details described in the Methods part of Studies #5 and #6.

3.4. CORRECTION OF THE QT INTERVAL FOR HEART RATE

The traditional method of QT interval adjustment for heart rate is based on using previously published formulae. In Study #2, we used the nomogram method of Karjalainen that was elaborated using ECGs of 324 healthy young men tested for suitability for the Finnish Air Force. The nomogram provides the correction values in 1 beats/min steps that should be added to the measured QT times between heart rates 40-120/min. The value of the correction figures are negative below 60, positive above 60, and equals zero at 60/min heart rate. In this research four preformed QT correction formulae and the nomogram method were used (Table 2).

Table 2. QT Correction Methods Used in Studies #1 – 6

Author	Published	Formula	Reference
Bazett	1920	$QTBc = QT/RR^{1/2}$	13
Fridericia	1920	$QTFc = QT/RR^{1/3}$	15
Hodges	1983	QTHc = QT + 1.75 (rate – 60).	179
Sagie	1992	QTLc = QT+0.154(1-RR)	24
Karjalainen	1994	Nomogram	180

Besides previously published methods, the study-specific QT correction method was used in Studies #2, #4 and #5. In Study #6 we used only the subject specific QT correction. 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. 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 (188). Besides this point, in our studies the relatively low number of available QT/RR data also questioned the feasibility of curve fitting.

A successful heart rate correction should lead to corrected QT values that are independent of the original RR interval (or heart rate) values. In our research when using specific QT correction, the coefficients of the mathematical equations (linear or non-linear) were always determined so that the correlation between heart rate and corrected QT were near zero. For example, in Study #2 we optimized the parabolic equation $QTc = QT/RR^{\alpha}$, that is also the generic form of the Bazett and Fridericia formulae. First, we took an arbitrary value around 0.3 for α and computed corrected QT values from each QT/RR data pairs. Second, we calculated the correlation coefficient (Pearson r) between RR and QTc. Third, in a stepwise manner this process was repeated with some other α values yielding further r values. The r values could then be plotted against α showing a linear association between these variables (Figure 6).

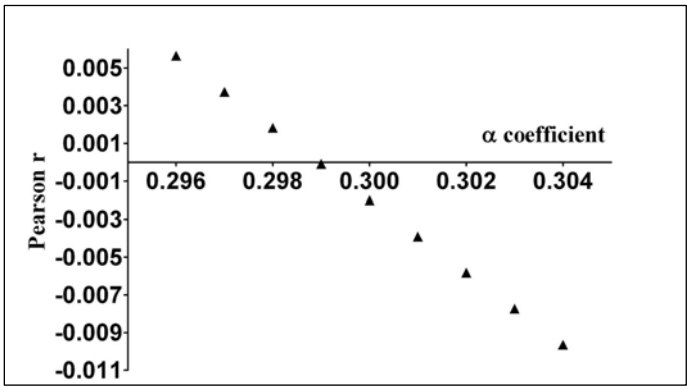

Figure 6. Study-specific QT correction in Study #3. Correlation (Pearson r) between QTc and RR in case of α values between 0.296 and 0.304 is depicted. QTc was computed by equation $QTc = QT/RR^{\alpha}$. At $\alpha = 0.299$ the correlation is near zero (r = -0.00009).

The intercept on the horizontal axis than provided the searched value for α that could be defined by either a linear regression analysis of the α/r plots or by multiple successive trials with further α values allowing to get closer and closer to r = 0.

3.5. STUDY #1

3.5.1. Subjects

The study group consisted of 19 healthy volunteers recruited from SFH staff. Subjects smoked more than 10 cigarettes/day for at least 5 years. Their ages ranged from 18 to 58 (32±13) years and 8 were men. All subjects had normal standard electrocardiogram and no structural heart disease as documented by medical history, physical examination, and echocardiography.

3.5.2. Methods

This study was designed to examine directly the effect of the first morning cigarette on the QT interval duration in habitual smokers after an overnight cessation of smoking; therefore exhaled carbon monoxide (CO) levels were determined before the experiments to rule out prior smoking. Subjects were studied in the supine position. The arm cuff of an automatic sphygmomanometer (Cardiotens, Meditech, Budapest, Hungary) was attached to the subject's dominant arm. The technique of ECG data acquisition and process was described under 3.3 in detail. The arrival of the participants was followed by a 5-min briefing session in which the nature and purpose of the study was fully explained. Volunteers were then put down to supine position, blood pressure was measured and ECG electrodes were attached to their body.

The study was placebo controlled with 2 experimental sessions in a random order that consisted of sham smoking and smoking. In the sham smoking condition, the subjects imitated smoking behavior with unlit cigarettes void of tobacco similar to the method used by Grassi (189). 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 were asked to smoke 4 cm of a filter cigarette containing 0.9 mg of nicotine in 2 minutes. Subjects underwent an identical experimental session on a separate day in which they simulated smoking with a tobacco void cigarette (sham smoking).

QT values were adjusted for heart rate according to Bazett's square root formula, the cubic root formula introduced by Fridericia and the linear formula proposed by Sagie (13, 15, 24).

Data were analyzed with a gender (male, female) by condition (smoking or sham) by period (pre- and post-smoking) mixed model multivariate repeated measurements analysis of variance (ANOVA), with QT interval, heart rate, diastolic / systolic blood pressure, and mean arterial pressure as the dependent measures. The analyses were repeated for the three methods of QT adjustment.

3.6. STUDY #2

3.6.1. Subjects

From the 30 healthy volunteers enrolled in the study, 20 (14 men and 6 women) had exercise ECGs suitable for quality analysis: 10 subject had to be discarded because of overwhelming muscle noise. The age of the studied participants ranged from 21 to 73 (mean: 44±15) years. All subjects had normal standard ECG and no structural heart disease as documented by medical history, physical examination, and echocardiography.

3.6.2. Methods

The arrival of the participants was followed by a 5-min briefing session in which the nature and purpose of the study was fully explained. Volunteers were then seated, blood pressure was measured and ECG electrodes were attached to their body. All subjects then 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. This fashion of ECG trace collection was supposed to account for the QT hysteresis, because by the second minute of the exercise stages heart rate stabilized, and previously it was described that 90% of QT interval adaptation to an abrupt change in heart rate takes approximately two minutes (190). The technique of ECG data acquisition and process was described under 3.3. Mean RR and mean QT were obtained for each ECG, and mean QT values were adjusted for heart rate using the methods of Bazett, Fridericia, Sagie, Hodges and Karjalainen (13, 15, 24, 179, 180).

A successful heart rate correction formula should lead to corrected QT values that are independent of the original RR interval (or heart rate) values. Such independence can be tested by calculating the correlation coefficient between the calculated corrected QT and original RR interval values. In this study, the correlation coefficient between the

corrected QT intervals and RR intervals was calculated for each heart rate correction formula. Further, we described the QT/RR relationship of our data by constructing a data-specific, optimized correction formula (OPT) that reflected the character of this study group. Using the approach described by Malik, in this study the coefficient α for OPT was defined from the generic parabolic form of QTcopt-par = QT/RR^{α}, such that the correlation coefficient between QTcopt and RR interval was zero (30). The means studied were assessed by ANOVA; post hoc intragroup comparisons were performed using the Bonferroni test.

3.7. STUDY #3

3.7.1. Subjects

31 patients (mean age 74±9 yrs, 18 males and 13 females) with regular sinus rhythm took part in this study. These 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.

3.7.2. Methods

All participants went through a complete two-dimensional and M-mode echocardiographic examination prior to the study (SONOS 1500; Hewlett-Packard Co., Medical Products Group Headquarters, Andover, MA, USA). LV dimensions and wall thickness were measured according to the recommendations of the American Society of Echocardiography by use of the leading edge convention (191). LV end-diastolic and end-systolic volumes were measured using the apical biplane Simpson's method (192). The percent fractional shortening was calculated from these measurements and the LV ejection fraction was estimated using Quinones' prediction formula (193). Depressed LV systolic function was defined as ejection fraction < 50%. LV hypertrophy was defined as a mean value of LV thickness (half of the sum of the thickness of

interventricular septum and posterior walls) ≥ 11 mm as wall thickness measured by M-mode from the standard parasternal long axis view.

The arrival of the participants was followed by a 5-min briefing session in which the nature and purpose of the study was fully explained. Volunteers were then asked to assume a supine position, following which blood pressure was measured by an automatic sphygmomanometer (Cardiotens, Meditech, Budapest, Hungary) and ECG electrodes were attached to their body. Afterwards participants went through a simple verbal MA, in the fashion described in 3.2. Simultaneous 12-lead ECGs were recorded and blood pressure was measured at baseline and at the end of third minute of the stress. The technique of ECG data acquisition and process was described under 3.3. The Bazett and Sagie methods were used to adjust the QT interval for heart rate. Variables measured at baseline and in the third minute were compared with paired *t*-test.

3.8. STUDY #4

3.8.1. Subjects

Twenty healthy volunteers (35±12 yrs, 10 men) deemed healthy based on medical history and normal ECG were enrolled. Subjects were recruited from SFH staff and from referred subjects proved to be healthy and volunteering to participate.

3.8.2. Methods

The arrival of the participants was followed by a 5-min briefing session in which the nature and purpose of the study was fully explained. Volunteers were then asked to assume a supine position, blood pressure was measured and ECG electrodes were attached to their body. Subjects went through a simple verbal MA as described in 3.2. Simultaneous twelve-lead ECGs were recorded at baseline (PRE), at the 30. second during (DUR), and immediately at the end (POST) of a 1-minute MA. The technique of ECG data acquisition and process was described under 3.3. We used a cut off value of 5/min of heart rate increase during MA to classify subjects as stress responders and non-responders. To remove all HR influence on the QT correction, we used the pooled baseline HR and QT values to optimize the linear (QTcopt-lin = QT + α x (1-RR) and

parabolic (QTcopt-par = QT /RR^{α}) regression models separately for both groups. The mean differences were assessed by repeated measurements ANOVA.

3.9. STUDY #5

3.9.1. Subjects

This study investigated 46 male, volunteers (mean age 21±1 yrs) with no history of cardiac disease, a normal physical examination, and a normal baseline 12-lead ECG. The participants were recruited from undergraduate students of Nottingham Trent University, Nottingham, UK.

3.9.2. Methods

The experiments were done during standard working days, in a quiet room, and started between 10.00 a.m. and 15.00 p.m. at least 2 hours after the subject's last meal. Subjects were studied in the sitting position. ECG electrodes were attached to the left and right shoulders, and to the left lateral side of the thorax in the fifth intercostal space. After a demonstration and brief practice period, participants were asked to play a video game under standard laboratory conditions (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.

Subjects were urged to try hard to save as many animals as possible in 2 minutes. Three lead electrocardiograms were recorded in the first 10s of the minute for 6 consecutive minutes representing three 2 minute study periods: 1) before the game (PRE - 2 min), during the game (DUR - 2 min), and after the game (POST - 2 min). As measure of cardiovascular reactivity, we used a cut-off value of 5/min for HR increase during video game, that classified subjects 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 (GA) and used for further analysis.

In each subject, the representative heart rate and QT values for the three study periods were obtained by calculating the means of the in-period data-pairs (RR, QT, and QTc). The Bazett, Fridericia, Sagie and the study specific correction methods were used as described in 3.4. (13, 15, 24). The limited number of QT/RR data-pairs in our study was

not optimal for a systematic curve fitting, so we selected some models that performed best in most comparisons: the parabolic regression model QTcopt-par = QT/RR^{α} because this is the generic form of the most widespread Bazett and Fridericia formulae, and the also frequently used generic linear model QTcopt-lin = QT + α x (1-RR) of the Sagie – Framingham equation, and the recently proposed shifted logarithmic model QTcopt-shlog = ln(eQT + α x (1-RR) (13, 15, 24, 27).

A successful heart rate correction formula should lead to corrected QT values that are independent of the original RR interval (or heart rate) values. Such independence can be tested by calculating the correlation coefficient between the calculated corrected QT and original RR interval values. To study the QT/RR relation, the pooled baseline (PRE) data of QT and RR intervals of responders and non-responders were studied separately. Using a method described by Malik, we defined the coefficients α for the optimized generic formulae in both responders and non-responders, such that the correlation coefficients between QTcopt-par, QTcopt-lin and QTcopt-shlog and RR intervals were near zero in each case (26). Data were analyzed with repeated measurements ANOVA.

3.10. STUDY #6

3.10.1. Subjects

Thirty non-smoking male university students at NTU (mean age 21.2±1.8 years), with no history of cardiac disease and normal resting 12-lead ECGs volunteered for the study.

3.10.2. Methods

3.10.2.1. Active psychological stress

As detailed in 3.3., in this study participants were asked to perform a 1-minute MA task as active mental stress (AMS) that involved fast and correct serial subtraction by 7 from 700. In order to increase the perceived importance and stressfulness of the task, as well as to assure active involvement, participants were told that the number of correct answers would be recorded.

3.10.2.2.Passive psychological stress

In this study as passive mental stress (PMS), participants watched the 1-min video clip of distressing images. Past research confirms that this form of stress triggers a stress response, which implies affective engagement and results in activation of the parasympathetic nervous system (171). Consequently, for a manipulation check purpose, immediately after exposure, participants were asked to rate the perceived level of stress on a 7-point Likert scale: 1 = not stressed at all, 7 = extremely stressed (194). Stress-exposure periods were followed by a 5-min recovery period.

3.10.2.3.Isometric exercises

The third stage of testing comprised of each participant performing a series of nine physical exercises in conditions free of psychological stress. Briefly, these exercises entailed sitting, skier's squat and standing (on one or two legs and balancing on tip-toes), with arms by side or raised above head at 180° or held at 90° with 2 Kg weights (Table 3).

Table 3. Protocol for ECG trace collection

1	Rest #1 (baseline 1)
2	MA #1 (AMS I)
3	MA #2 (AMS II)
4	Video #1 (PMS I)
5	Video #2 (PMS II)
6	Rest #2 (baseline 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

These physical exercises were designed to elicit different levels of sympathetic and vagal responses, so that conditions of gravitational and isometric stress, and a combination of both, were involved (195). The purpose of these exercises was to collect additional QT and RR interval data at different heart rates for the subject-specific QT interval correction. Each exercise was performed for 3 minutes to allow for QT hysteresis (190).

3.10.2.4.Experimental design

Trauma depicting photographs from various media resources were edited into a 1-min video clip at NTU Audiovisual Suite. This video clip, consisting of sixteen rotating shocking images accompanied by a soundtrack of loud weather noises was used for PMS. Based on two pilot studies, it was confirmed that the video clip was shocking and capable of inducing high subjective ratings of psychological stress. The stressor was presented to the participants on a combined television/VHS player (Philips, Model PV235/07, Koninklijke Philips Electronics Ltd., Eindhoven, Netherlands) while the accompanying soundtrack was presented via a cordless headphone (Goodmans, Model Pro-CD 9007, Goodmans Industries Ltd., Portsmouth, U.K.). Participants' blood pressure was measured with a Hem-405 C digital blood pressure monitor (OMRON Corporation Ltd.. Kyoto, Japan). The ECGs were recorded as described in 3.3., using Nutrode-P20M0 pre-gelled ECG electrodes (GE Medical Systems Accessories) and printed at a paper speed of 25 mm/s and amplifier gain of 10 mm/mV. Tests were conducted between 9:00 a.m. and 4.00 p.m. in the Human Performance Laboratory at NTU. The arrival of the participants was followed by a 5-min briefing session in which the nature and purpose of the study was fully explained. Volunteers were then seated, blood pressure was measured and ECG electrodes were attached to their body. To account for the “muscle noise”, the Mason-Likar method of electrode placement was used (196). After the leads have been connected and a good trace was observed, participants sat quietly until a steady heart rate was measured for more than three minutes. First, a 10-sec baseline ECG was recorded at rest. The participants were then exposed to isolated, 1-min conditions of AMS and PMS in a counterbalanced order. Between the two mental stress periods, the participants had a 5-min rest. Two 10-sec ECG measurements were recorded during each mental stress period; the first between 0

and 10 seconds, and the second between 30 and 40 seconds. After 5-min stress recovery a second resting ECG (a second baseline) was recorded. Subsequently, a series of nine 3-min isometric stretches were performed and a 10-sec ECG trace was obtained in the last 10 seconds of each period. This way, a total of 15 ECGs were obtained from each participant. The experimental design is shown in Figure 7.

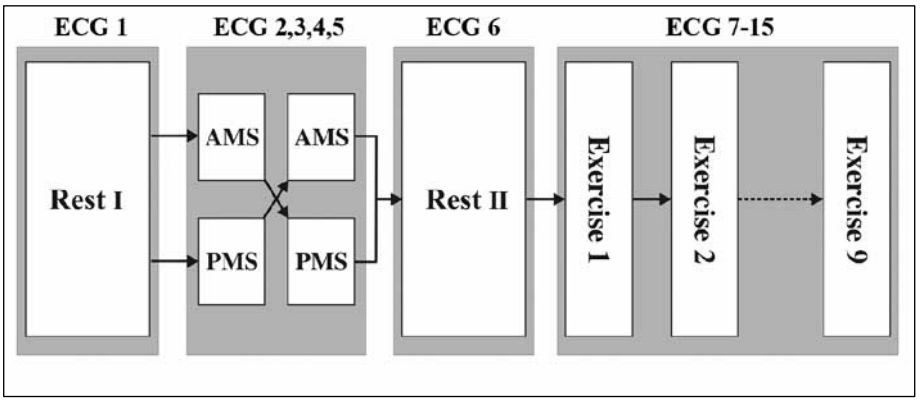

Figure 7. Experimental design. Participants were exposed to active and passive mental stress (AMS and PMS) in a counterbalanced order. A set of isometric exercises yielded 9 additional ECGs, so that a total of 15 ECGs were gained from each subject.

Visual checks verified the automatic QT interval and RR measurements in all records (GA). ECGs with poor quality data were excluded. To study the QT/RR relation, the data of QT and RR intervals of each participant were studied separately by subject specific method in order to minimize the correction error (26). This technique is based on multiple ECG samples at different heart rates obtained within the same individual that are further used to determine the QT/RR relationship for that person. QT values from the 15 ECG records obtained during the study were plotted against their corresponding RR values producing a QT/RR plot with a total of 15 data points for each person. Though the best fit mathematical form that describes the pattern of the QT/RR relation varies among individuals, the added value of non-linear mathematical modeling appears to be limited (188). Therefore, linear regression analysis of the QT/RR data pairs was used to determine the slope of the regression line in each participant, that is the value of the parameter α in the generic linear heart rate correction formula: QTcopt-

lin = QT + α x (1 – RR). Repeated measures 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. Correlations between heart rate and QT interval were calculated using Pearson Product Moment correlation.

4. RESULTS

4.1. STUDY #1. THE EFFECT OF ACUTE SMOKING ON THE QT INTERVAL

A significant multivariate condition by period interaction ($p < 0.001$) was found that pointed to increased sympathetic activation in the smoking, but not in the sham smoking condition (Table 4).

Table 4. Eight dependent measures in smoking and sham smoking condition over six periods, three before and three after smoking and sham smoking

	Condition	4-min	8-min	12-min	16-min	20-min	24-min
HR (bpm)	Sham	67±6†	62±9†	67±10†	67±10†	67±10†	67±8†
	Smoking	72±9	69±9	71±8	90±13*	81±9*	78±10
SBP (mmHg)	Sham	119±14	118±12	118±12	118±11†	117±11†	117±12†
	Smoking	119±15	118±16	119±14	127±18*	124±20*	123±19
DBP (mmHg)	Sham	72±8	72±9	73±8	73±8†	73±7†	72±8
	Smoking	72±10	71±9	73±10	82±10*	77±10*	74±10
MAP (mmHg)	Sham	88±9	87±9	88±8	88±8†	88±8†	87±9
	Smoking	87±11	87±11	88±11	97±12*	93±13*	90±12
QT	Sham	394±28	393±28	391±28	386±28	394±27	394±29
	Smoking	381±18	384±18	385±18	352±19	367±20	373±22
QTBc (ms)	Sham	413±29	414±25	411±30†	406±26†	414±31†	414±27
	Smoking	416±31	412±26	417±27	428±27*	426±25*	423±25
QTFc (ms)	Sham	406±26	406±23	404±26	399±24	407±27	407±25
	Smoking	404±24	402±20	406±22	401±20	405±21	405±20
QTLc (ms)	Sham	406±26	407±22	404±25	400±24	407±26	408±25
	Smoking	405±24	403±20	407±22	400±17	406±19	406±18

SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; MAP = Mean Arterial Pressure. * = Significant vs. pre- (smoking) values in the same condition ($p < 0.05$), † Significance between sham and smoking conditions ($p < 0.05$).

Follow up univariate tests confirmed a condition by period interaction, indicating a smoking-induced increase in heart rate, blood pressure (both systolic and diastolic), and mean arterial pressure. However, for QT intervals, a significant condition by period interaction was only obtained with the Bazett method of QT adjustment ($p < 0.001$) whereas they were not statistically significant in the Fridericia and Sagie calculations. To follow up on this important point, paired t-tests were calculated to compare the adjusted QT values obtained with the three methods of calculation. These tests revealed that the QT values obtained with the Bazett method were in all instances higher than those obtained via the Fridericia or Sagie ($p < 0.001$).

4.2. STUDY #2. CORRECTED QT DURING EXERCISE TEST

Rest and exercise values of the studied variables are summarized in Table 5. With exercise, heart rate significantly increased, and the uncorrected QT interval duration significantly shortened. From the corrected QT values, QTBc significantly prolonged, whereas the other four previously published methods yielded nonsignificant changes.

Table 5. Comparison of heart rate and QT interval values of 20 subjects at rest and at exercise

	rest	**2-min**	**4-min**	**6-min**	**p**
Heart rate (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#

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

More specifically, QTFc and QTLc values tended to decrease, but QTHc and QTNc remained virtually stable throughout the protocol (Figure 8).

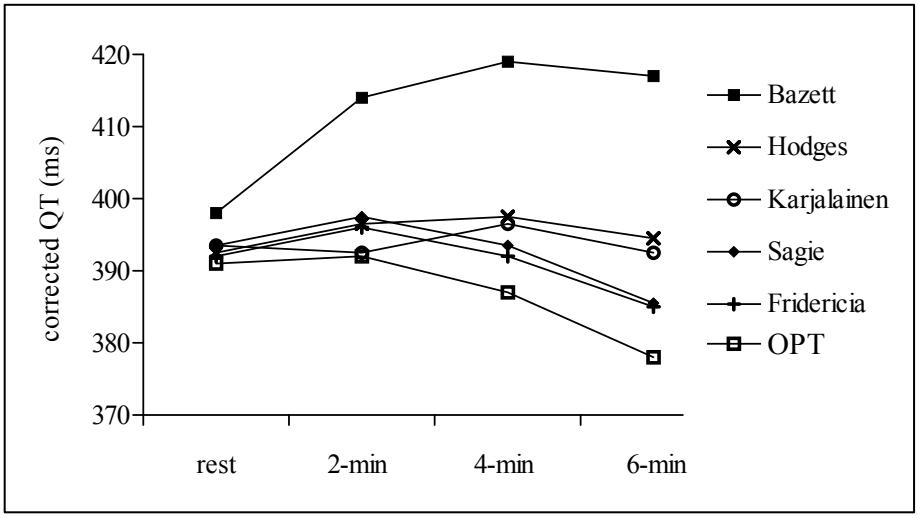

Figure 8. Mean QTc values given by different heart rate correction methods at rest and at 2-min, 4-min and 6-min during exercise. A significant QTc prolongation is indicated by the Bazett formula (p=0.0007), whereas Fridericia, Sagie, Hodges and Karjalainen methods show no significant change. OPT formula derived from pooled study data show significant QTcopt-par shortening (p=0.013).

The study specific optimization resulted a value of 0.299 for the coefficient α, yielding the study specific equation: $QTcopt\text{-}par = QT/RR^{0.299}$. Using this formula, a significant shortening of the corrected QT interval during exercise was detected. Correlation analysis of RR and corrected QT data given by each correction method revealed, that only the newly defined study specific equation eliminated completely the heart rate dependence of corrected QT (near-zero correlation: r = -0.00009), and the correlation coefficients of the previously published methods were considerably different from zero (r = 0.3594 for Bazett, r = 0.0675 for Fridericia, r = 0.0464 for Sagie, r = 0.2162 for Hodges, and r = 0.1562 for Karjalainen). The correlation between uncorrected QT and heart rate and the profound remaining correlation despite adjustment between QTBc and heart rate is shown in Figure 9.

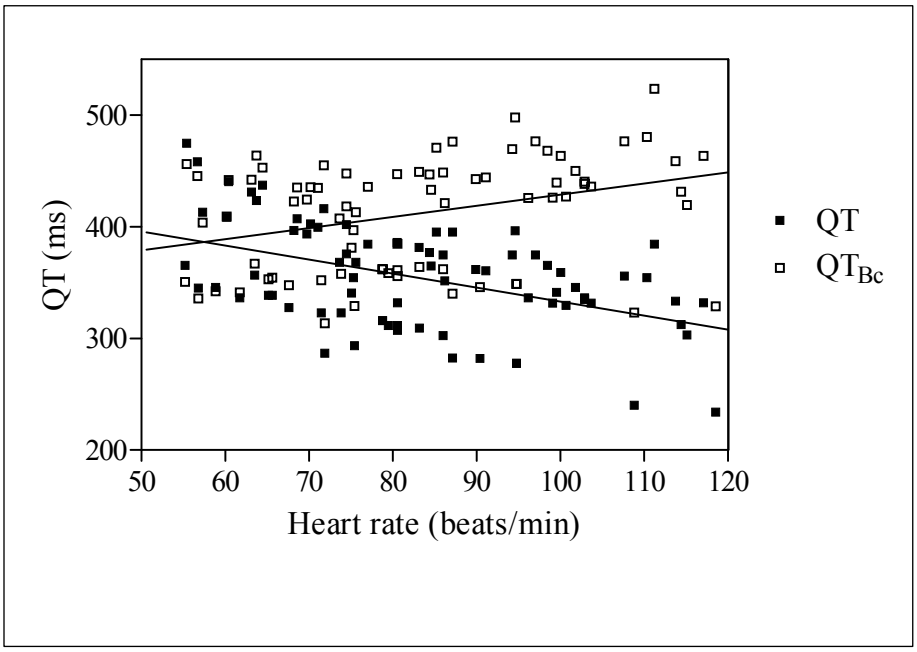

Figure 9. Relationship between heart rate, uncorrected QT and QTBc during exercise in healthy subjects. A significant negative (QT) and positive (QTBc) correlation was found with heart rate ($p<0.0001$ and $p=0.0011$, respectively).

4.3. STUDY #3. CORRECTED QT OF 31 PATIENTS DURING A 3-MINUTE MENTAL ARITHMETIC

From the 31 participants, depressed LV function was present in 9 patients, and LV hypertrophy was detected in 5 patients. Left bundle branch block was revealed in 3 and right bundle branch block in 2 patients. A medical history of ischemic heart disease and previous MI was present in 12 and 9 patients, respectively. At the time of the experiment 14 patients was on amiodarone, 2 patients on propafenone and one patient was taking flecainide. At the end of the 3-minute MA, a significant increase in heart rate and blood pressure, and a significant decrease of the uncorrected QT interval duration was measured. The mean QTc and QTLc did not change significantly (Table 6).

Table 6. Variables of 31 patients before (0) and in the 3rd minute of a mental arithmetic

	0 min	3 min	P
HR (beats/min)	70±14	73±15	< 0.05
SBP (mmHg)	132±19	137±17	< 0.05
DBP (mmHg)	79±11	84±11	< 0.05
QT (ms)	432±65	425±64	< 0.05
QTBc (ms)	460±53	462±50	Ns
QTLc (ms)	449±52	448±50	Ns

Data are expressed as means. HR=heart rate; SBP=systolic blood pressure; DPB=diastolic blood pressure; QTBc = Bazett corrected QT time; QTLc = Sagie corrected QT time.

In 14 subjects QTBc increased by 17±10 ms and QTLc increased by 12±8 ms. In 17 subjects QTBc decreased by 10±10 ms and QTLc decreased by 12±9 ms (Figure 10).

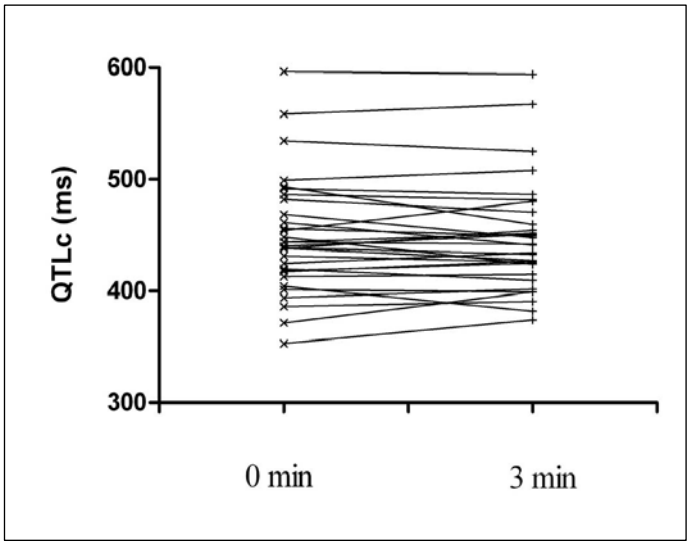

Figure 10. QTLc values of 31 patients at baseline (0 min) and at the end of a 3-min mental arithmetic.

4.4. STUDY #4. CORRECTED QT OF 20 HEALTHY SUBJECTS DURING A 1-MINUTE MENTAL ARITHMETIC

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 7).

Table 7. 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-	401±17	412±19†	405±22	430±15	424±15	425±15
QTCOPT-	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. STUDY #5. THE EFFECT OF VIDEO GAME ON THE QT INTERVAL

The cut-off value of 5/min increase in heart rate during video game classified 13 subjects as stress-responders and 33 subjects as non-responders. Table 8 shows that in stress-responders, the mean QTc values obtained by all correction methods were significantly higher during video game than in the PRE and POST periods, whereas QTc did not change in non-responders. The increase in heart rate during video game 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 8. Results of 46 healthy volunteers exposed to a simple video game challenge. Corrected QT values before (PRE), during (DUR) and after (POST) the game yielded by different correction methods. The α values in the different correction equations are also indicated

	QTc	α	PRE (ms)	DUR (ms)	POST (ms)	P
Non-respond. (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-respond. (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

Data are means ±SD. 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. STUDY #6. THE EFFECT OF ACTIVE AND PASSIVE MENTAL STRESS ON THE QT INTERVAL

4.6.1. Subject-specific QT Interval Correction

A total of 450 ECGs were prepared during the study. ECGs obtained at rest and during mental stress were all suitable for analysis, but 37 exercise ECGs had to be discarded because of inadequate quality due to muscle noise. Consequently, the participant-specific QT/RR relationship could be evaluated using 11.0±1.9 (minimum = 7) ECGs per subject. Heart rate changes induced during the study 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). This adjustment of QT for heart rate successfully abolished the correlation between uncorrected QT and heart rate (Figure 11).

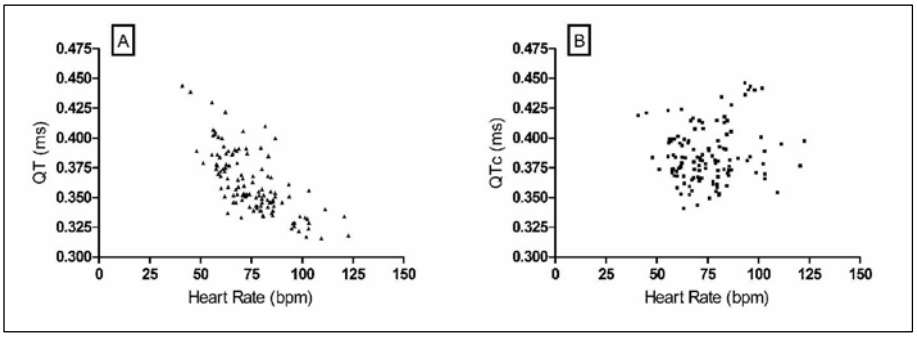

Figure 11. Subject-specific QT interval correction. Uncorrected QT and corrected QTc data of 30 subjects obtained in four mental stress periods are plotted against heart rate. In panel A, a highly significant correlation is present between the uncorrected QT time and heart rate (r = -0.7132, p < 0.0001). In panel B, as a result of the subject-specific correction method, QTc and heart rate do not correlate (r = 0.1144, p = 0.2136, ns).

4.6.2. QT Interval Changes

Participants' blood pressure was in the normal range (systolic 118±11 mmHg, diastolic 82±10 mmHg) except for one subject who had a slightly increased systolic value (150/85 mmHg). Heart rate and QTc values in the six study periods are shown in Table 9.

Table 9. Heart rate and individually corrected QT intervals in six study periods

	Rest I	**AMS I**	**AMS II**	**PMS I**	**PMS II**	**Rest II**
HR (bpm)	67±12	88±16*	80±11*	67±12	67±12	68±12
QTc (ms)	380±26	390±24†	386±25	382±22	384±21	382±22

HR = heart rate. Data are means ± SD. *p < 0.0001; †p = 0.0004.

Heart rate was significantly increased during both periods of AMS ($p < 0.0001$), PMS did not elicit significant heart rate changes. During AMS, an early significant QTc prolongation could be observed (AMS I, $p = 0.0004$), but QTc measured between 30 and 40 seconds (AMS II) was not significantly changed. During PMS no significant QTc changes could be detected.

4.6.3. T Wave Changes

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. From the 14 subjects with bifid T waves, 8 presented bifid T waves during both AMS and exercise, and 6 subjects developed bifid T waves only during exercise (Table 10).

Table 10. Subjects with T wave changes during one ore more study conditions. From the total of 30 subjects and 15 conditions only affected ones are presented.

Subject	AMS I	AMS	Ex. 9	Ex. 10	Ex. 12	Ex. 14	Ex. 15
2			o			o	O
5	+	+	+		+	+	+
6	+		+,o		+	+	
7	+		+		+		
8	+,o		+,o	+	+	+	
9						+	
11			+			+	
14			+				
15			o			+,o	
16			+				
17				o			
18					o		
19					+		
21	+	+	+				
23	+,o		o		+	o	
24	o						
26	+					+	
27	+	+	+			+	

Ex. = isometric exercise. + = bifid T wave; o = T wave inversion.

The number of ECGs with bifid T waves varied from 1 to 6 in affected participants, and bifid T waves seemed to appear more frequently at higher heart rates (Figure 12).

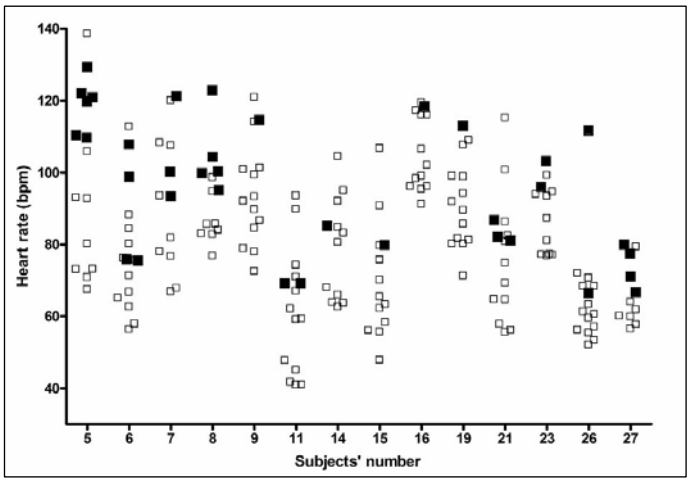

Figure 12. This graph illustrates the heart rates for 14 (out of the 30) participants who have developed bifid T waves during at least one study period. Open squares indicate normal T waves; filled squares indicate bifid T waves. Although bifid T waves seem to appear at higher heart rates, this observation cannot be the only explanation.

Conditions associated with multiple cases of bifid T waves were as follows: standing, arms by side (9 cases), AMS I (8 cases), standing, balanced on tip-toes (8 cases), skiers' squat (6 cases), and AMS II (3 cases). During PMS no T wave changes could be observed.

T wave inversion occurred in 4 subjects who also presented T wave notching, and in 4 subjects T wave inversion developed on its own. T wave inversion occurred exclusively in the "inferior" leads (Mason – Likar II, III, aVF), and were often "heralded" by the baseline ECGs, as in 5 cases T waves were initially negative in at least one inferior lead. In one case (subject 24), a very flat baseline positive T wave in aVF turned slightly inverted. In another case (subject 8), T waves in some study conditions might have been classified as biphasic or inverted, though based on the dynamics of T wave contour changes we rather thought this as a variant of T wave notching (Figure 13).

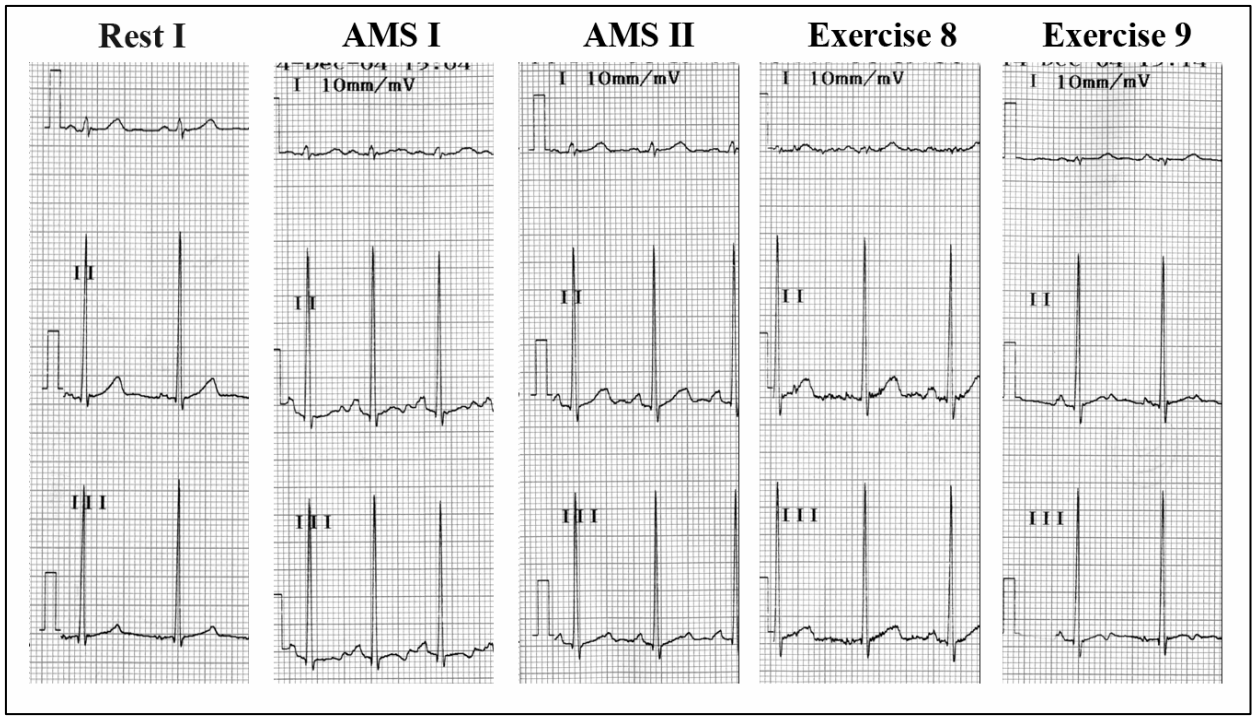

Figure 13. Five representative ECGs from subject No. 8. QT interval prolongation and T-wave notching is present early in AMS (AMS I). Both QT duration and T-wave normalize later in AMS (AMS II). Heart rate is nearly identical in exercise 8 and 9 but QT duration and the shape of the T-waves are distinct: T-waves become bifid again in exercise 9.

In another case (Subject 15), T wave inversion (with a slight positivity of the terminal part of the T wave suggesting some biphasic tendency) developed in lead III that was not heralded by concomitant T negativity on the baseline ECG (Figure 14).

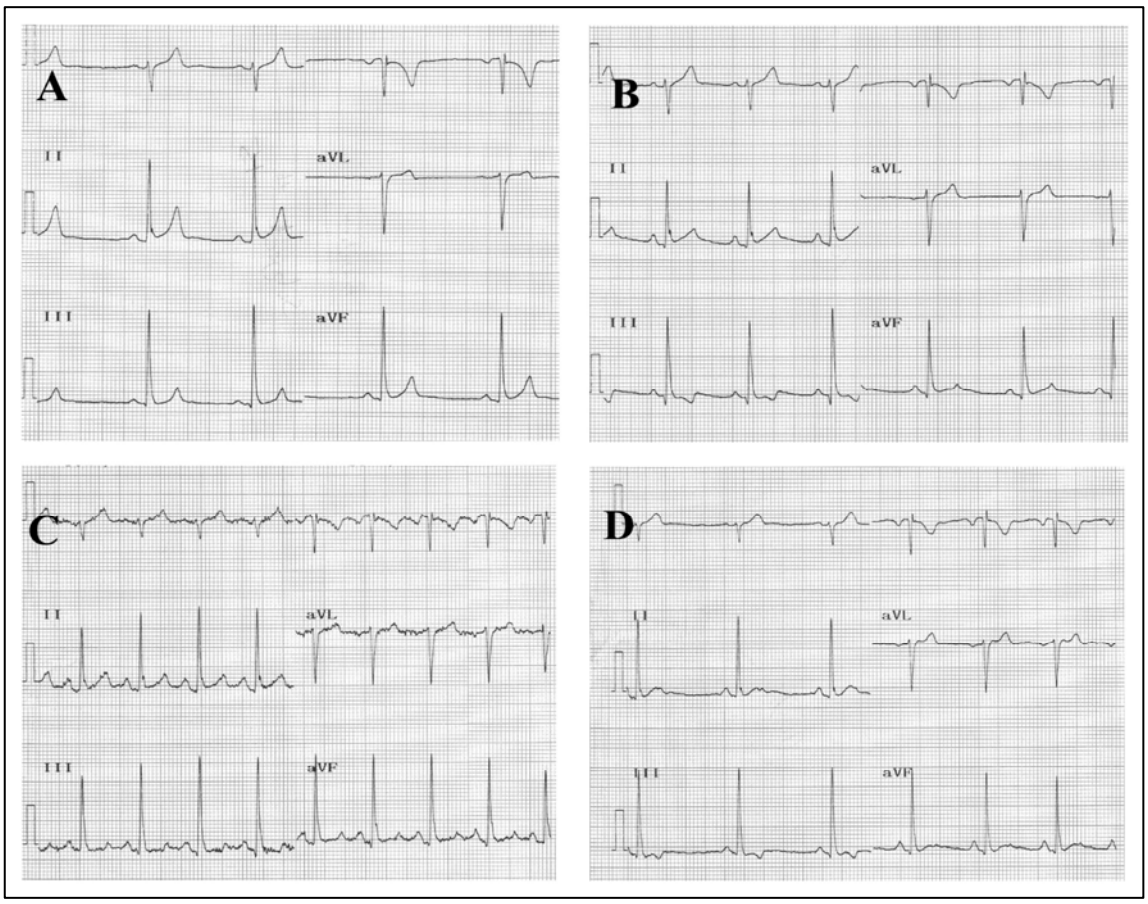

Figure 14. Four representative ECGs from subject No. 15. At baseline, T wave is upright and has normal contour in leads II, III, and aVF (**A**). In exercise condition no 9, T-wave inversion (with a slight positivity of the terminal part of the T wave suggesting some biphasic tendency) developed in lead III (**B**). Somewhat flattened but still upright T-waves are present in exercise condition no 12 (**C**). Bifid T waves in leads II and aVF and inverted T wave in III appearing simultaneously suggest that in this case the same T wave alteration may have different manifestations depending on the projection of the T vector (**D**).

One more representative ECG for QT interval prolongation and bifid T waves is shown in Figure 15.

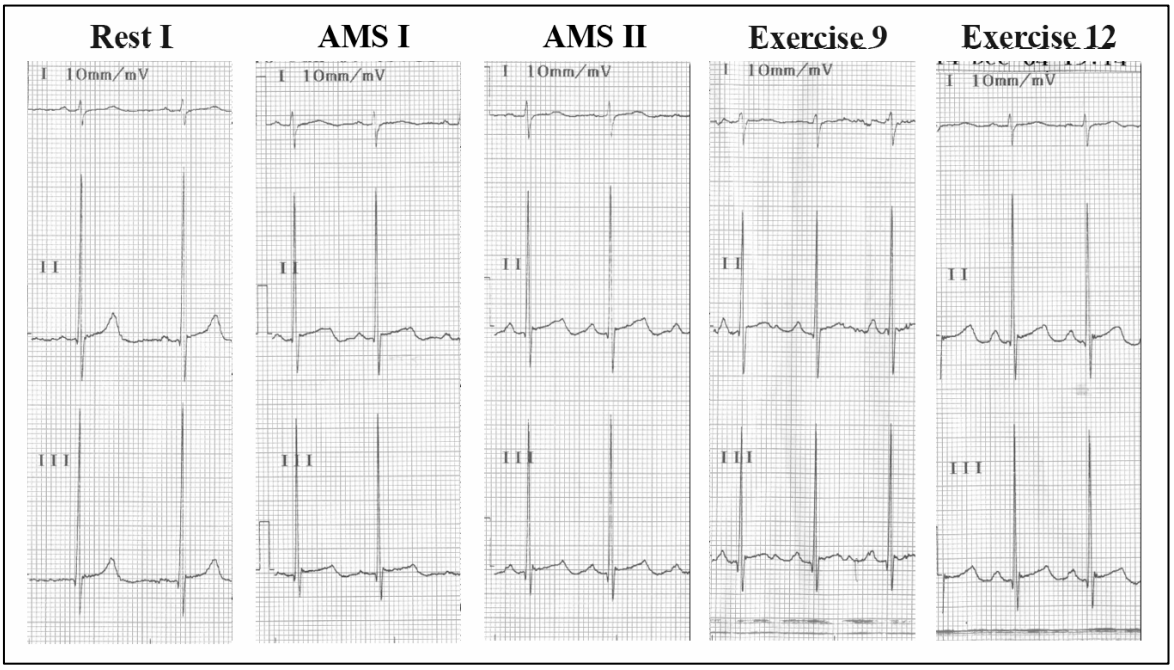

Figure 15. Subject No. 21 presents a substantial QT interval prolongation in AMS I that persists through AMS II. QT prolongation is also present in exercises 9 and 12. The incipient T wave notching in AMS becomes clearly visible in exercise 9.

4.6.4. Likert Scores

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. DISSCUSSION

5.1. THE EFFECT OF SMOKING ON THE QT INTERVAL

Previous published reports provided conflicting data on the effect smoking on the QT interval duration. Romero Mestre (175) found no significant differences in the duration of the QTBc interval between smokers and non-smokers. Ileri (176) reported that QTBc is significantly longer in smokers compared to nonsmokers, whereas Dilaveris (197) revealed marginally prolonged QTBc in smokers. Fauchier (177) found that among men who smoked, the number of cigarettes smoked per day was positively related to the corrected QT duration after adjustment for age. They applied the formula $QT_k=QT/RR^k$, where the rate correction index "k" was determined from the best-fit regression between variables QT and RR. Importantly, their value of "k" (0.354 for men and 0.338 for women) was very close to 1/3, the value for Fridericia's formula (15). On the contrary, Karjalainen (36) using the nomogram method for correcting QT found that smoking was associated with the shortening of the corrected QT interval. Apparently, regardless of the method used for heart rate correction, data on the effect of chronic smoking on the QT interval are conflicting, and the effect of acute smoking has not been adequately studied. Consequently, we examined directly the effect of the first morning cigarette on the QT interval duration in habitual smokers after an overnight cessation of smoking (Study #1).

Our study is the only published placebo controlled experiment where the effect of acute smoking was evaluated on the QT interval using QT correction formulae considered more accurate than Bazett's (198). Our data confirm previous reports indicating that acute cardiovascular effects of cigarette smoking include an increase in heart rate and blood pressure as a result of enhanced sympathetic activity (178, 189). In accord with our results, the QTBc interval has been reported to be significantly prolonged immediately after cigarette smoking by Canale (178). In contrast to the significantly increased QTBc values after smoking, we found that neither QTFc nor QTLc was increased after smoking and sham smoking (Table 5). In agreement with others, in case of heart rate changes, we attribute the alterations of QTc most likely as distortion resulting from the inaccuracy inherent in the Bazett method (27, 180, 199).

The mechanisms by which cigarette smoking may lead to cardiovascular events include endothelial dysfunction, accelerated atherosclerosis, increased platelet aggregation, increased fibrinogen levels, coronary vasoconstriction, and increased carbon monoxide levels (200, 201). Acute cardiac events such as ventricular fibrillation and sudden death are increased by cigarette smoking, particularly in the presence of preexisting coronary disease (202). Habitual smokers also have an increased sympathetic drive at rest, and acute exposure to cigarette smoke has powerful sympathetic excitatory effects (203). It was also demonstrated in canine ventricular myocytes that nicotine, the main constituent of tobacco smoke, blocked multiple types of K^+ currents involved in the repolarization process (204). QT interval prolongation has been associated with a lowered ventricular fibrillation threshold and with the occurrence of sudden cardiac death thus may represent a link between smoking and life-threatening ventricular arrhythmias (100).
Our finding, that the QTFc and QTLc values remained unchanged does not necessarily mean that cigarette smoke has no effect on ventricular repolarization. The powerful sympathetic excitatory effect of smoking, influencing sympathetic drive to muscle blood vessels, to skin, and to the heart has been described previously (189). Most human and animal studies have shown that the sympathetic system exerts a shortening effect on refractory periods and QT duration, while the parasympathetic system prolongs both these variables (37, 158). It is possible that in our study, the QT shortening effect of sympathetic activation and the QT prolonging effect of nicotine counterbalanced each other, so that the QTFc and QTLc intervals remained unchanged.

5.2. SHORTCOMINGS OF THE BAZETT METHOD

Heart rate plays a substantial role in the variation of the length of the QT interval. In an effort to correct for this effect, and to make it possible to compare QT intervals obtained at different cycle lengths, a rate normalized QT is used. The object of applying this correction is to normalize the QT at a given heart rate to the value that it would have had at a rate of 60 bpm. Many equations have been developed for QT correction and as it was detailed in 1.2.3., mainly the first published and most widespread Bazett equation has been criticized and shown to be inappropriate, especially at high and low heart rates (24, 158-160, 180, 199). It was also shown, that the Bazett's formula performed poorest

at all heart rate subranges among the QT prediction formulas compared (180, 199). To assess differences in QTc yielded by different correction formulae, in Study #1 besides Bazett's we corrected QT intervals according to Fridericia and Sagie too (15, 24). These latter formulae have been shown to be reliable at normal heart rates (180, 199). Our results demonstrate the importance of using an adequate method for QT correction as acute smoking elicited a significant QTc prolongation as shown by the Bazett method, whereas the Fridericia and Sagie methods indicated no change (Table 4).

Study #2 was conducted to further assess this problem (205). We selected exercise testing to induce heart rate changes in order to compare different QT correction methods in a relatively clear condition of sympathetic preponderance. Graded exercise leads to sympathetic overdrive, acidosis, and increased body temperature which trigger various physiological reflexes (206). Heart rate increases linearly with increasing work rate, and stroke volume increases initially at the onset of exercise, and then reaches a plateau. The initial increase in heart rate is mediated by vagal withdrawal, subsequent increases being mediated at the sinoatrial node by sympathetic stimulation through the cardiac nerves and circulating catecholamines (206). It was also reported, that in patients with high degree atrioventricular block treated with fixed rate ventricular pacing, physical stress (exercise) induced significant QT interval shortening (169). We speculated that a correction method that works well should indicate the shortening of the QTc, and any method showing QTc prolongation should be clearly regarded as inadequate, because QTc shortening is the predicted physiologic response to sympathetic influence (37, 158, 169).

In Study #2, besides previously published methods the recently introduced study specific method was also applied (30). We found substantial differences in the results depending on the QT correction method used (Table 5 and Figure 8). Specifically, Bazett values increased, Karjalainen and Hodges values remained constant, and in accord with others, we found that QTc intervals yielded by Fridericia and Sagie decreased with exercise (207, 208). The remaining correlation between heart rate and QTc was in concert with this finding as most correlation remained after the Bazett method (Figure 9) and the optimized study specific correction formula performed best; besides showing the expected QTcopt-lin shortening with exercise, completely removed the dependency of QTc on heart rate as shown by the near zero correlation (4.2).

5.3. THE EFFECT OF MENTAL STRESS ON THE QT INTERVAL

5.3.1. Rationale for Using Mental Stress in Cardiology

Though rarely applied in the everyday practice, mental stress testing has an established role in the diagnosis of ischemic heart disease. Epidemiological studies indicate that psychosocial factors both contribute to the development of CAD, and increase risk of cardiac dysfunction and the likelihood of cardiac events in susceptible patients with established disease (209, 210). One possible method to assess cardiac function is to measure transient ischemic responses to standardized mental stress tests, because mental stress-induced myocardial ischemia is analogous to exercise stress ischemia, except that the stimulus is psychological rather than physical (211).

More importantly from the point of our research, recently some reports were published where laboratory mental stress was successfully applied to induce electrical instability in susceptible individuals, thus offering a potential tool to identify subjects with excess arrhythmic risk (152, 212, 213). Further, in recent years, LQTS has been extended to encompass the reduced repolarization reserve (i.e., decrease in net repolarizing current even though different potassium channels may compensate each other to secure the repolarization process) attending remodeling of the ventricular myocardium that accompanies dilated and hypertrophic cardiomyopathies, as well as congestive heart failure (88, 214-218). It was also shown that silent gene carriers of the LQTS and patients with acquired LQTS or impaired myocardial repolarization reserve often present little or no QT interval prolongation at rest, in these patients, the QTc interval is only intermittently prolonged (219). Also, other studies have suggested that the frequency of asymptomatic LQTS gene carriers in the general population is greater than previously considered (220). This may not be detected, even if repeated standard 12-lead ECGs are recorded several times on different occasions and the longest QTc intervals are taken into consideration. Besides exercise testing, pharmacologic provocations to induce QT interval prolongation, thereby bring up subjects with concealed LQTS has been reported, also it was shown that QT adaptation to mental and exercise stress in healthy people and in patients with LQTS is different (168, 221, 222).

These previous results turned our interest towards mental stress testing, because in the setting of a community hospital and general cardiac department like SFH, though LQTS

is rare, patients with potentially reduced repolarization reserve due to structural heart disease (cardiomyopathies, heart failure) are common. Also, a number of patients take various antiarrhytmic drugs that are known to block one ore more ionic channels responsible for repolarization. We supposed that mental stress might be a feasible tool to detect impaired repolarization reserve (heralded by excess QT prolongation) in such individuals, thus warranting an increased concern for arrhythmic risk or drug related pro-arrhythmia. The clinical convenience of mental stress for such a purpose seemed obvious, because this method is cheap, non invasive and can be applied to subjects with limitations to exercise testing. Therefore, Study #3 was organized to assess the method of mental stress in a variety of patients also with structural heart diseases and/or taking antiarrhythmics (181).

5.3.2. Individual Response to Mental Stress

In Study #3, mental stress applied in the form of a simple MA elicited no change of the QTc interval assessed by the means of the 31 patients measured at the end of the 3. minute (Table 6). However, though a generic response was not revealed, it was obvious, that in some individuals the QTc prolonged and in others shortened (Figure 10). The limited number of subjects did not allow a thorough subgroup analysis, but seemingly, the QT response was not related to LV hypertrophy, impaired LV function, medical history of ischemic heart disease or antiarrhythmics.

QTc was computed by the Bazett and Sagie methods in this trial. We presume that using any other correcting method would have led to the same result. Because of the inherent profound heart rate dependency, the Bazett method has the most propensity to show significant QTc differences in case of heart rate changes. This QTBc prolongation should be clearly regarded artificial if other methods fail to support this (24, 27, 180, 199). Consequently, if QTBc values are not different, there is no reason to expect that any other correcting method yield significantly differing QTc-s.

MA is probably the most frequently used active mental stressor; this stressor was used in three out of our six studies. The amount of reaction of the autonomic nervous system depends on commitment; therefore every effort should be done to motivate participants. In Study #3 the cohort was recruited from hospital patients with advanced age, and after completing the experiments we judged MA as impractical in this subset. First, in these

elderly patients the lack of motivation to achieve the maximal performance was apparent during the tests and was reflected by the minor (still significant) overall heart rate and blood pressure increases. It is of note that the blunted heart rate response might also be caused by the use of beta-blockers commonly prescribed for such patients. Further, some subjects simply gave up computing after the initial unsuccessful attempts. Therefore, the 3-minute study duration proved to be too long, as most participants seemingly got tired and sympathetic activation was gradually decreasing despite being apparent in the beginning of tests.

In Studies #4 and #5 we further examined the finding that the QT response to MA is different across individuals (223, 224). We enrolled younger subjects and applied shorter stressing sessions that assured more intense sympathetic activation. In Study #4 a younger subset of subjects was enrolled (35 ± 12 years) and a 1-minute MA was used, in Study #5 male university students participated (21 ± 1 years) and video game playing was used as mental stressor. In Study #5, in-stress QT/RR data were obtained and averaged from two ECGs recorded in the first 10 seconds and in the 60 – 70. seconds of the video game. This concept was successful as reflected by the more substantial heart rate responses as presented in Tables 7 and 9.

5.3.3. The Relationship between Cardiovascular Reactivity and QTc Changes

The results of Study #3 suggested that the response to mental stress is not generic, substantial individual differences exist. For example, a simple comparison of men with women in terms of QT response upon MA may lead to completely erroneous conclusions if the differences in individual response patterns are not taken into account (225, 226). Importantly, it was shown that individuals with a repressive-defensive coping style may display stronger cardiovascular and endocrine responses to acute challenges (227-229). Some other psychometric variables accountable for such differences were listed as well as the concept of CVR was introduced in 2.3. We hypothesized that the QT response might be related to the CVR, so that subjects could be classified according to CVR that would also characterize these individuals in terms of the QT response. To test if the association between CVR and QT response is not stressor specific, in Study #5 we used video game playing that has been found to elicit changes of laboratory measures of CVR (230-232).

In Studies #4 and #5, using stress induced heart rate changes, stress responsive and non-responsive groups could be formed. Classification according to CVR (stress responders vs. non-responders) using a cutoff point of 5 bpm increase in heart rate successfully discriminated subjects that responded with QT interval prolongation from those who did not: a significant QT interval prolongation upon MA and video game was found only in stress responders. The use of optimized correction formulae in Studies #4 and #5 assured that the heart rate dependency of QT changes was minimalized. Consequently, this reinforced the validity of our findings: MA and the video game elicited QTc prolongation in stress responders reflected a real physiological phenomenon not merely an artifact resulting from inappropriate QT interval correction.

5.3.4. QTc Interval Prolongation at the Onset of Active Mental Stress

Contradictory previous findings on the effect of mental stress on the QT interval were detailed in 1.6.9. Briefly, a case report and a study using ambulatory ECGs reported QT prolongation upon mental stress, whereas five laboratory based studies reported QT interval shortening (165-169). Multiple reasons could be explored for this disagreement, amongst others; the use of different correction methods (some used no QT adjustment for heart rate at all!) and the variety of stress protocols, see also in 1.6.9. Yet we realized one further important difference between reports on QT prolongation and shortening: the timing of ECG sampling. Those that reported QT prolongation sampled ECGs immediately upon stress initiation; those reported QT shortening analyzed ECGs prepared after several minutes of stress launch.

This unresolved issue and the results of Studies #3-5 inspired us to organize Study #6, where ECG sampling encompassed also the initiation of the mental stress and QT correction was performed by the subject specific method (28). In this study young male university students were enrolled, the high level of commitment was reflected by the marked heart rate response during AMS (Table 9). Also importantly, in this study QT intervals were individually corrected, and currently only this method is considered suitable for trials where QT interval durations are compared at different heart rates (26). The most important contribution of Study #6 is that a significant QT interval prolongation presents early in AMS: in the first 10 seconds (Table 9). In this study the first QT measurement was carried out just at the launch of the stress periods, with this

method we successfully detected the initial QT interval prolongation at the onset of AMS that other investigators have failed to observe.

Adjustment of QT to changing heart rate is a dynamic phenomenon consisting of fast adaptation phase and slow adaptation phase. Franz (2) showed that after rapid change in heart rate, fast adaptation phase of repolarization usually lasts 30-60 seconds followed by a 2-minute slow adaptation. We propose that a part of the QT prolongation we noted was due to a delay in heart rate adaptation and only the remaining fraction was caused directly by the AMS, unfortunately the setting up of this study did not allow the quantification of these proportions.

5.3.5. The Effect of Passive Mental Stress on the QT Interval

In Study #6, we were first to compare the effect of active and passive mental stress on the QT interval. In this study, PMS had no significant effect on heart rate and QT interval duration. The perceived level of stress was below the midpoint of 4 on the 7-point Likert scale both for AMS and PMS, so the stressors were not strong in terms of subjective perception. Really, particularly young subjects, accustomed to shocking images and acoustic effects via media appear difficult to be stressed passively, yet it cannot be excluded that a more aggressive passive stressor might have induced significant cardiac changes. However, despite the low perceived level we still observed significant effects of AMS on the QT interval, indicating that even mild AMS may induce changes in cardiac repolarization.

5.4. BIFID (NOTCHED) T WAVE

We observed with surprise that almost half of our subjects (14 out of 30) developed bifid T waves in one or more study periods. The set up of this study does not allow a comprehensive interpretation of this phenomenon, only some comments can be added. Bifid T waves seemed to appear at higher heart rates, but high heart rate is unlikely to explain the evolution of bifid T waves by itself, as bifid T waves also occurred at lower heart rates (Figure 3). In the background of T wave notching, underlying excess sympathetic activity was suggested (233, 234). We also hypothesize that the overt sympathetic predominance characterizing the onset of AMS and the final phase of the 3-

minute isometric physical exercises might have played a role in inducing the T wave notching.

5.4.1. Prevalence and Conditions Associated with Bifid T Waves

"Splitting" or "notching" of T waves has been reported due to the effect of quinidine and flecainide, accompanied by prolonged and normal QT interval duration, respectively (235, 236). In a LQT2 model using d-sotalol, prolongation of mid-myocardial cell AP duration was observed in arterially perfused canine left ventricular wedge preparations causing an interruption in the down-slope of the T wave (phase 3 repolarization) and giving rise to bifurcated T waves and apparent T-U complexes (237, 238, 239). Notched T waves have been reported in humans and in normal dogs after exposure to sotalol (237, 240). Bifid T waves are also common in patients on amiodarone (unpublished observation, GA). From 101 pediatric patients taking cisapride, one was found to develop bifid T waves in all leads (241). Classic causes of notched T waves include left ventricular hypertrophy, digitalis glycosides, and ischemic heart disease, in the geriatric population they are most commonly associated with psychoactive drugs or CNS disorders (242).

A remarkably high number of bifid T waves were reported in a study that enrolled 30 patients with Duchenne progressive muscular dystrophy and 50 age-matched controls (233). In this cohort, notched T waves were observed in 46.7% of patients and in 20.0% of controls. Bifid T waves were reported less frequently by others, as the presence of bifid T waves has been noted only in a minority of the general population, with a prevalence of 2.8% among 4,000 consecutive tracings analyzed by Watanabe (243) and 3.0% of 3,980 normal subjects reported by Ishikawa and Ohnuma (244). In a younger population of 1510 healthy subjects aged 14 to 40 years that was studied by Berdin (245), bifid T waves in the right precordial leads were present in 6.15 % .

5.4.2. Exercise, Sympathomimetic Agents and Bifid T Waves

Atterhog (246) found that primary T wave aberrations of fifteen healthy young males consisting mainly of notches in the T wave were eliminated by beta-adrenergic blockade in thirteen cases and physical exercise decreased all the T wave aberrations. In contrast,

as reported by Watanabe (243), exercise accentuated the bifid nature of the T wave in 12 of 18 subjects with otherwise normal electrocardiograms (243).

Bifid T wave has been traditionally considered as one of the diagnostic signs of LQTS, more typically LQTS2 (71, 247, 248). Exercise or pharmacological testing of subjects with suspected LQTS has been suggested to induce morphological changes of the T wave to pick up silent gene carriers or to discriminate between the main genotypes.(188, 249). During exercise test QT prolongation and T wave changes have been reported in LQTS patients as well as in non-carrier LQTS family-members, but not in healthy controls (249, 250).

It was shown that EPI infusion elicited T wave notching in one third of normal subjects, and approximately half of the male and all female healthy volunteers developed bifid or biphasic T waves on isoproterenol infusion (188, 249-251). In a subsequent study, at baseline, 97% LQT1, 71% LQT2, and 94% control subjects had normal T wave profiles. During EPI infusion, bifid T waves were more common in LQT2 than in LQT1 (75% vs. 26%,). However, EPI-induced bifid T waves were also present in 34% of controls (252). In another study, an oral glucose tolerance test was performed in LQTS patients and in controls without QT prolongation. The LQTS group had 100% incidence of changes in T wave morphology, such as biphasic, bifid or notched T wave, whereas no subject exhibited T wave changes in controls (253).

In the study of Toivonen (162), ambulatory electrocardiography was performed in 30 healthy physicians during emergency calls while they were on duty in the hospital. Samples were taken before and during the first 30 s after the calls. During arousal, the T wave was inverted in 19 subjects, and biphasic in 4 subjects. This finding was reinforced recently by Dweck (245), when using Holter monitors, marked T-wave morphology changes, including T-wave flattening and inversion, were observed in night-arousal events. Of note, neither of these two studies revealed bifid T waves upon arousal.

In summary, first, notched T waves were present on resting ECGs of healthy individuals with an incidence of 2.8 – 20 % in various reports. Second, as a result of provocations with EPI and isoproterenol, T waves became bifid in one third of subjects with initially normal T waves. Third, the effect of exercise on bifid T waves is not clear, as it was reported either to accentuate or even normalize T wave aberrations in healthy subjects.

Most importantly, to best of our knowledge, the phenomenon that mental stress or exercise may induce bifid T waves in healthy subjects with normal baseline ECGs has not been reported thus far.

Recent studies on myocardial wedge preparations indicated the transmural dispersion of repolarization as one possible cause of bifid T waves (237). Consequently the appearance of bifid T waves in pathological conditions has been speculated to provide a substrate for reentry and life threatening arrhythmias (255). As both local (nondipolar i.e., not included in the main cardiac dipole, or heart vector) and global (dipolar) repolarization components may contribute to the genesis of T waves on the body surface ECG, the relative contribution of each of these two repolarization forces to T wave aberrations may vary among different clinical conditions (256). Further research is needed to elucidate this problem.

5.5. EMOTIONS AND INHOMOGENIOUS REPOLARIZATION

A number of possibilities underlie the mechanism by which emotion may influence repolarization homogeneity in the myocardium in the absence of ischemia through the altered autonomic activity. Animal studies have shown that sympathetic stimulation causes a temporary (not steady-state) status during which AP-s shorten nonhomogeneously, thereby creating dispersion of repolarization (257). Therefore, the speed of the intervention and the rate of adaptation are likely to be important in some situations that is evident from the reports of Toivonen (163) and Dweck (245), and also finds support from our results. Regional differences in receptor density and regional differences in neural traffic to the heart are alternative possibilities. Several animal studies have created increased dispersion of repolarization or refractoriness by stimulation of sympathetic nerves, which shortens action potential duration selectively in the regions supplied by the stimulated nerves (87, 258). The right and left cardiac sympathetic nerves are asymmetrically distributed on the ventricles (259). Therefore, one possible mechanism for diverse repolarization changes in response to different mental stimuli would be that central brain processing might result in asymmetrical distribution of neural traffic to the heart. Such a possibility, although speculative, receives support from recent increasing evidence for regional cortical representation of

different emotions, and different cardiovascular responses when emotion engages different cortical areas (260, 261). Finally, a link between stress and arrhythmia was implied whereby mental stress elicited asymmetrical activation at the level of the midbrain was associated with an asymmetrical neural input to the heart, hence enhancing the repolarization inhomogeneities which predispose to arrhythmias (262).

6. CONCLUSIONS

Acute smoking elicits a profound sympathetic response. The smoking induced QTBc prolongation is an "artifact", we found no QTc prolongation with more reliable correction methods. The practical meaning of QTc interval depends on the correction formula used. The Bazett formula will probably remain a routine clinical use, but it should be noted that anytime when heart rate increases, the Bazett method will probably show an artificial QTBc prolongation. Though the Fridericia and Sagie methods appear better in such circumstances, precise result can only be obtained by fitting the correction equation to the studied data set or subject.

The mental stress elicited QT response is individual and seems to be related to CVR. In stress-reactors a QTc interval prolongation could be identified during mental stress, which is most pronounced upon stress initiation. Our research has shown a correlation between mental stress induced changes in autonomic balance and ventricular repolarization including QT interval prolongation and T wave notching. These findings suggest the possibility of a mechanism linking emotional stress with arrhythmia in the absence of ischemia. At present, there is no established parameter of the standard 12-lead EKG to quantify dispersion of ventricular repolarization. It is clear, though, that this cannot be reliably estimated by simple manually derived indices such as the visually assessed T wave shape or QT duration measurements. However, our observations on the standard 12-lead ECG are in strong agreement with reports on mental stress induced repolarization changes assessed by most sophisticated methods like microvolt TWA, TCRT (total cosine R to T; cosine of the angle between the spatial QRS and T vectors) and TWR (T-wave residua; i.e. proportion of the non-dipolar components of the T wave) (152, 212, 213, 262, 263).

Further work is needed to elucidate the mechanisms involved: for example, whether central cortical processing or local sensitivity at the level of the myocardial cell may be responsible. These preliminary observations that have been made on young healthy subjects need to be extended to patients with coronary artery disease in whom any regional autonomic effects on repolarization inhomogeneity would be expected to be magnified as a result of mental stress–induced ischemia.

7. NEW FINDINGS

1. We have 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.

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

3. We have found that the QT response to mental stress is not generic; the response depends on cardiovascular reactivity.

4. We 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.

5. 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.

8. ACKNOWLEDGEMENTS

This research was carried out at Saint Francis Hospital, Budapest and at the School of Life Sciences at Nottingham Trent University, Nottingham U.K. First of all, I would like to express my thanks to all the participants in the studies, that they understood the importance of this research, for their patience and commitment to complete the tests.

Further, I would like to express my thanks to the former Directors of Saint Francis Hospital, **György Kozma** M.D. and **Gyula Kerkovits** M.D. and the present director **Ádám Tahy**, M.D.,Ph.D. who not only inspired me to undertake this research and gave continuous support, but also allowed me to conduct research in the Hospital and devote enough of my power to accomplish this mission. I would like to thank prof. **András Varró** for giving me an opportunity to join his team at Department of Pharmacology and Pharmacotherapy at the University of Szeged, and I could start my Ph.D. work under his guidance. I am particularly indebted to prof. Varró for introducing me to the exciting scientific area of myocardial repolarization that inspired me to study the QT interval on surface ECG. I would also like to express my gratitude to my friend and major co-author, **Attila Szabo** Ph.D., who turned my interest towards mental stress and helped me with permanent valuable theoretical and practical advices. I am deeply indebted to prof. **László Rosivall** for his crucially important support that helped me to get ahead with my work when I felt lost because of troubled circumstances. I am grateful to prof. **Béla Székács** for his patience and support when I did research on renal prostanoids under his supervision as a medical student. I am thankful to prof. **József Borbola** for his very important guidance when I started my dissertation work.

I am principally grateful to **George Szele** M.D. for the opportunity to take part in a great professional adventure: a three year medical partnership program sponsored by the US AID. That project was like a reward for me and offered SFH the possibility to get on its own way. Special thanks to prof. **Lajos Papp** for his friendship, advices and support he gave always when needed!

I would like to extend my thanks to my research-mates at SFH and at NTU for the stimulating cooperation, who also co-authored many papers on QT interval research, in alphabetic order: **Caroline Buckenham** M.D., **Andrea Dunai** M.D., **Gyöngyvér**

Ferencz M.D., **Tímea Nagy**, M.D., **Eszter Simon**, M.D., **Richard Spooner**, M.D., and **Zsófia Trummer** M.D.

Further, I wish to thank deeply my professional trainers on internal and cardiovascular medicine for their kind attention and patience, in chronological order: **Tamás Solymosi**, M.D., **Sarolta Ságí**, M.D., **Cristopher J. Leet**, M.D., **Robert G. Matthews** and **John T. O'Brien** M.D.

I would like to thank my many friends and colleagues at Saint Francis Hospital, Prince William and Fairfax Hospitals, Virginia, USA with whom I have had the pleasure of working over the years, these include **Jenő Jánosy** M.D., **Gyula Kóczán** M.D., **Károly Madarasi** M.D., **István Greschik** M.D., **László Gábos** M.D., **László Tóth** M.D., **Sándor Mohay**, M.D., **Piroka Turbucz**, M.D., **Tamás Haba** M.D., **Éva Donkó** M.D., **Viktor Győző** M.D., **Klára Baltási**, R.N., **Éva Benke** R.N**.**, **Ivan Harangozo** M.D., **Baikunth Singh** M.D., **Andres Alisuag** M.D., **Janet Hoffman** MBA., **Judy Carleton**, **Kathleen Tyrell** R.N., **Jane Dolan** R.N., **Donna Beebe** R.N., **Rosemary Brindle** R.N. and **Linda Ohler** R.N.

And last but not least, let me thank my family who have been most patient and understanding with me throughout my endeavors, particularly my wife, **Rita** for her loving patience and helping me during all the years!

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10. PUBLICATIONS

10.1. PUBLICATIONS DIRECTLY RELATED TO THE THESIS

10.1.1. Full Articles

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.
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4. 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.
5. 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.

10.1.2. Letters to the Editor

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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.
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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.
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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.
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