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An Improved QT Correction Method for use in Atrial Fibrillation and a Comparison with the Assessment of QT in Sinus Rhythm

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Abstract

Background: Conventional QT corrections may be inappropriate inatrial fibrillation (AF) due to RR variability and QT lag. Existing formulashave been modified by the formula RRmod to account for this lag. Wedeveloped a novel correction formula for use in AF (QTAF) based onthe slope ΔQT/ΔRRmod and report its performance in AF.We also compare QTAF obtained in AF with rate-independentcorrections in NSR.

Materials and Methods: A total of 3063 RR/QT pairs from 28 patients with AFwere measured, 22 of whom also had measurements during sinus rhythm. QTc (theBazett equation), QTLC (the Framingham linear correction), and QTAFwere calculated utilizing RRmod, and the rate-independence of eachformula in AF tested. Mean QTAF values in AF were compared to QTintervals corrected with QTLC in normal sinus rhythm.

Results: ΔQTc/ΔRRmod andΔQTLC/ΔRRmod slopes were significantlynon-zero whereas ΔQTAF/ΔRRmod was not. QTLCand QTc corrections were imperfect at extremes of RRmod whileQTAF was constant. QTAF corrections in AF were shorterthan QTc or QTLC corrections in NSR.

Conclusions: QTAF is a novel QT correction with adefined relationship to correction in NSR that performs better than existingstrategies.

Introduction

Background

Atrial fibrillation (AF) is a common problem for whichantiarrhythmic drugs (AADs) are often prescribed.[1,2] The most dangerous complication of AAD therapy isventricular proarrythmia, including torsades de pointes, the risk of which islargely predicted by a prolonged QT.[3] Theability to accurately measure the QT interval before and during the AAD therapyof AF is therefore critical.

Since QT duration varies with heart rate, formulasthat "correct" the QT based on the immediately preceding cycle (CL) are commonlyused. While universally accepted in sinus rhythm (SR), this approach has beenquestioned in AF. Previous stud-

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ies have shown that more remotely preceding CLsexert an additional, though smaller effect on the QT, a phenomenon known as QTlag.[4-6] Underconditions of relative CL stability such as SR, this effect can be ignored. InAF, however, an incident QT may be preceded by CLs of variable durations whoselagging effect on the QT may be manifest, and thus must be accounted for inrate corrections to make them optimally meaningful.

Replacing the term "RR" (the R to R interval inseconds) in existing QT correction formulas with RRmod, a weightedaverage of the previous 5 RR intervals, has been shown to improve their abilityto normalize QT intervals in AF, and has been suggested as a method foraddressing QT lag.[7] Recently, Larroude et.al. described the relationship between QTand RRmod (ΔQT/ΔRRmod) in AF in patients withparoxysmal AF.[8] ΔQT/ΔRR slopes have been successfully used in SRto construct correction formulas that improve on the inaccuracies in thecommonly used Bazett formula.[9-12] Specifically, the Framingham correction (QTLC) was designed using ΔQT/ΔRRas measured in SR, and has been shown in that rhythm to yield corrected QTvalues that are more stable than those obtained by Bazett's formula over a widerange of cycle lengths.[13] We hypothesized thatΔQT/ΔRRmodcould be used to construct a linear QT correction formula (QTAF)that would similarly yield a rate-independent correction in AF. We chose tocompare it to conventional formulas modified by RRmod; QTLCbecause of its utility in SR, and QTc given its ubiquity in QTcorrection (see Table 1 for list of QT correction formula abbreviations).

Table 1 List of abbreviations

Abbreviation	Legend	Formula
QTc9	Bazett correction	QTc=QT/(RR)1/2
QTLC13	Framingham correction	QTLC=0.154*(1-RR)+QT
QTAF	AF correction	QTAF=0.126*(1-RRmod)+QT
RRmod7	Modified RR interval	(5*RR1 + 2*RR2 + RR3 + RR4 + RR5)/10
QTx	Corrected QT intervals using QTc, QTLC, or QTAF	

Since AADs are often continued after conversion to SR,and previous studies have suggested intrinsic differences in repolarizationbetween AF and SR,[14-16] weadditionally sought to define the relationship between QTAF measuredduring AF and commonly used

correction formulas employed in SR. In this way, wehoped to define a rate-independent AF -specific formula that could be utilizednot only to judge AAD risk in AF, but also to approximate AAD risk in SR.

Population and data collection

Telemetry data was obtained from 28 randomly selectedmedical and surgical inpatients at New York-Presbyterian Hospital who had AFduring their hospitalization.Approximately 60 seconds of telemetry data wasretrieved for each patient. For patients with paroxysmal AF data collectionstarted with the last five available sinus beats. Otherwise, the start time fordata collection was random. Deidentified data, along with demographic,medication, and echocardiographic information, were provided to theinvestigators. The IRB of Columbia University approved the protocol. Becausedeidentified data was used, the requirement for informed consent was waived.

QT and RR measurements

Telemetry was recorded using a five-lead wearable unitand wireless monitoring system (PatientNet Monitoring System, GE Healthcare,Piscataway, NJ) with a sampling rate of 200Hz and a 10mm/mV gain selection.Three-lead strips (I, II, and V1) were printed at a paper speed of 25mm/sec.RRand QT intervals were manually measured with a resolution of 10ms in theclearest of the three leads available. Measurements were performed by one oftwo readers (AS or JG).The RR interval was defined as the time elapsed betweenthe initial deflections of adjacent QRS complexes. The QT interval was definedas the time elapsed from the initial inscription of the QRS to the point wherethe T-wave of the same beat intersected the isoelectric segment. In the casethat the T-wave did not return to baseline before the onset of the followingP-QRS in SR or QRS in AF, the QT interval was taken to be the onset of the QRSto the extrapolated point at which the T wave would have intersected theisoelectric point had the following P-

QRS or QRS not occurred.[17] VPCs during AF were excluded, as were the 4subsequent RR/QT pairs.

QTx and RRmod calculations,and analysis of ΔQTx /ΔRRmod in AF

For each beat in AF, RRmod was calculatedas RRmod = (5*RR1 + 2*RR2 + RR3 + RR4 + RR5)/10) .[7] In order to account for QT lag, the original formulas for QTLC andQTc were modified from the original by substituting the term "RR"for RRmod as follows; QTc=QT/(RRmod)1/2[9] QTLC=(1-RRmod)*0.154+QT(13). Since the value for ΔQT/ΔRRmod inAF has been reported as 0.126 (8), QTAFwas calculated as QTAF= (1-RRmod)*0.126 + QT. In order to allow forcomparisons between patients, QTx data from each patient (where QTx represents QTc, QTAF, or QTLC)was normalized as deviation from that patient's mean QTx. Normalized QTx vs. RRmod was then plotted for eachformula.ΔQTx/ΔRRmodfor each correction formula was calculated, and deviation from a slope of 0determined using linear regression. A perfect correction should be rate independent; thatis, QTx should not vary withRRmod, and ΔQT/ΔRRmod should have a slope of 0.The primary hypothesis was that QTAF would yield a rate-independentcorrection in AF, whereas QTLC and QTc corrections wouldnot. In addition to pooled data, individual data was analyzed by averagingindividual ΔQTx/ΔRRmodslopes and comparing the means. Each correction formula's performance at extreme RRmodvalues was examined by dividing RRmod into quartiles. Deviation fromthe mean QTxin the first andfourth quartile of RRmod was calculated for each patient. The datafrom corresponding quartiles were then pooled and compared to an idealdeviation of 0.

QT corrections in Sinus Rhythm and comparison toatrial fibrillation

Since the equation describing the relationship betweenQT and RRmod in AF has a nearly equal slope but a lower y-interceptthan that in SR (8), our secondary hypothesis wasthat optimally corrected QT values in AF would be lower than optimallycorrected values in SR, while comparisons made between AF and SR using a lessideal formula would fail to show a difference. We used QTAF as anexample of an optimal correction in AF, QTLC as an optimalcorrection in SR, and QTc as a less ideal correction.

For subjects with paroxysmal AF, QTc and QTLC valueswere calculated for each of the last five sinus beats preceding the initiationof AF using their original formulas, and the minimum QTc and QTLC from eachpatient was recorded (QTc(min) and QTLC(min)).Only AF initiations that did notinclude atrial ectopy during sinus rhythm were included for analysis. Minimumvalues were used in order to bias the results as much as possible towards thenull hypothesis.

The mean SR QTc(min) in the population as a whole wascompared to the mean QTc in AF calculated using RRmod. QTLC(min) was comparedto the overall mean QTAF measured during AF. Since the slopes of therelationships describing QT and ΔRRmodin SR and AF are roughly equal even though their y-intercepts are not,[8] QTAF was applied to the last five sinus beats, and theaverage QTAF calculated during SR was compared to the overall mean QTAF in AF.

Subgroup Analysis

Since some of the subjects were on drugs known toalter the QT interval at the time of data collection (digoxin, sotalol,amiodarone) and/or had baseline EKG abnormalities, we undertook a separateanalysis of the subset of subjects with normal ejection fractions, normalbaseline QRS morphologies, and who were not on the above drugs.
traction sheet. Quality assurance was provided by a single nurse at a central coordinating centre. The first 30 patients chosen were reviewed by the coordinating centre nurse to ensure accurate patient selection. Data on selected patients was then entered into an electronic database. Although interrater reliability was not formally assessed, before a specific ED was included in the trial, data from the first 25 patients entered into the database from that centre was reviewed by the coordinating center nurse to ensure consistency and accuracy of data abstraction throughout the various centres included in the study. The coordinating center nurse was also regularly in contact with the individual research nurses through phone calls and emails to

clear up any ambiguities in patient data. Unclear elements were resolved by the coordinating centre nurse in conjunction with the principal investigator, and missing elements were clearly identified as such. Finally, some pertinent information was included from those patients who had a primary diagnosis of recent onset atrial fibrillation or flutter but met exclusion criteria.

Data Analysis

Patients were first stratified into whether or not they received warfarin upon discharge from the ED. $CHADS_2$ score was calculated for each patient. We then analyzed the compiled data with descriptive statistics with 95% confidence intervals. Univariate analyses were conducted using T-test or Chi-square to select factors, including $CHADS_2$ score, associated with anticoagulation initiation. Multiple logistic regression was employed to evaluate independent predictors of anticoagulation after adjustment for confounders. Only variables with p-values less than 0.05 were included in multivariate regression analysis. Data analyses were conducted with SAS statistical software. (version 9.2; SAS Institute, Inc.).

Results

The initial RAFF study identified a total of 2,464 RAFF patients at the 8 involved ED centers over the 12 month period. Of these, 1,068 met the initial inclusion criteria. After exclusion of patients already receiving warfarin prior to presentation to the ED, a cohort of 633 patients remained. Table 1 describes the characteristics of this cohort. There were no significant differences between patients that received warfarin and those that did not.

Univariate analysis results are listed in table 2. Factors with the highest odds ratios were heparin administration in the ED (OR 10.14, 95% CI 5.77 – 17.83), cardiology follow-up organized in the ED (OR 5.66, 95% CI 2.91 – 11.00), having a new prescription of Metoprolol at discharge (OR 4.02, 95% CI 2.22 – 7.23), and having a new prescription of Diltiazem at discharge (OR 3.01, 95% CI 1.15 – 7.91). Notably, having a CHADs score of 2 or higher, while doubling the odds of receiving warfarin at discharge (OR 2.01), was not significantly different from having a $CHADS_2$ score of 1 or higher (OR 2.07). Major factors associated with lack of warfarin administration included electrical (OR 0.37, 95% CI 0.21 – 0.65) and medical (OR 0.26, 95% CI 0.16 – 0.44) cardioversion, and having a history of AF (OR 0.50, 95% CI 0.30 – 0.83).
Multivariate analysis demonstrated significant predictors of warfarin administration at discharge to again include heparin administration (OR 9.59, 95% CI 4.88 – 18.87), Metoprolol prescription (OR 9.59, 95% CI 4.88 – 18.87), cardiology follow-up (OR 5.61, 95% CI 2.62 – 12.02), and age by 10 year increments (OR 1.69, 95% CI 1.34 – 2.14). Odds ratios and confidence intervals are shown in table 3. Interestingly, it was found that while patients with a $CHADS_2$ score of 1 or greater had double the likelihood of warfarin administration, it no longer became an independent predictor after regression analysis.

Validation

A total of 58 RR/QT pairs were overread by a secondreader (JAR), and reread by the primary readers. Inter- and intraobservervariability was calculated using coefficients of variation (r2).Overall, interobserver variability was r2=0.998 for RR intervals and0.856 for QT intervals, and intraobserver variability was r2=0.995for RR intervals and 0.863 for QT intervals.

Statistical analysis

TComparisons of all continuous variables were performedusing paired Student's t-tests. Determinations of slopes and comparisons to aslope of 0 were performed using linear regression. Statistical significance wasdefined as $p<.05$. All tests were performed using a statistical softwarepackage (Prism 4.0c, GraphPad Software, San Diego, CA). Data is presented asmean ± SD. Since calculations involving QT and RR intervals were rounded to thenearest millisecond, rounding error may occur.

Results

Patient Characteristics and Data Collection

Patient characteristics are presented in Table 2. The populationwas 57% male. Twenty-two patients (79%) were surgical, and 6 (11%) weremedi-

cal. The mean age was 72.4 ± 11.5. Five patients (18%) had an abnormal EF(< 50%), and 7 patients (25%) had conduction abnormalities on their surfaceEKG. Nine (22%) were on Class III antiarrhythmic drugs at the time ofconversion to AF, and 5 (18%) were on digoxin.

A total of 3063 QT/RR pairs were counted in AF, a meanof 109 ± 25 pairs/patient (range 63-153). Due to the way RRmod iscalculated, the QT intervals associated with the first four RR intervals fromeach patient, or 112 total (3.6%), were excluded from QT/RRmodanalysis. Thirty-eight intervals (1.2%) were excluded because of poor dataquality. Exclusion of PVCs and the subsequent RR pairs removed an additional116 beats (3.8%). There was no atrial ectopy noted. 2797 QT/RRmodpairs were therefore included in the final analysis. One hundred ten QT/RRpairs were counted in SR, all of which were included in analysis.In AF, the mean RR cycle length was 543ms±155 (range270-1490), the mean RRmod cycle length was 538ms±124 (range305-1211) and the mean QT was 348ms±48 (range 250-620). In SR, the mean RRinterval was 757ms± 115 (range 520-1010) and the mean QT was 408ms±51(p<.0001 for comparison of both mean RR and QT intervals between AF and SR).

QT Relationships and Correction slopes

Slopes and p-values are presented in Table 3. Theslopes obtained for ΔQT/ΔRR and ΔQT/<ΔRRmod agree closely withpreviously reported values.[12, 20] The average of the individual ΔQTc/ΔRRmod and ΔQTLC/ΔRRmodslopes were both significantly non-zero, whereas the average ΔQTAF/ΔRRmod was not.

Normalized QTx vs. RRmod for the population as a wholeis shown in Fig. 1. The overall ΔQTc/ΔRRmod slope was -0.081 ± 0.005and the ΔQTLC/ΔRRmod slope was –0.014 ±0.003. Both were significantly non-zero. The ΔQTAF/ΔRRmod slope was –0.003 ±0.003, which did not significantly deviate from 0.

Correction performance at the extremes of RRmod

The three formulas were tested for performance at theextremes of RRmod (Fig. 2). QTc produced corrections onaverage 15ms ± 32 greater than the mean QTc in the first quartile ofRRmod and 11ms ± 28 less than the mean QTc in the lastquartile. Compared to QTAF, QTc corrections were onaverage 14ms ± 1 greater in the first quartile of RRmod and 11ms ± 1shorter in the last quartile. QTLC generated corrections that were 3ms ±19 greater than the mean QTLC in the first quartile of RRmodand 2ms ± 19 shorter in the last. Compared to QTAF, QTLCcorrections were on average 1ms ± 0.1 greater in the first quartile of RRmodand 2ms ± 0.2 shorter in the last. QTAF corrections in the firstquartile of RRmod were 1ms ± 18 greater the overall mean normalizedQTAF. In the last quartile, they were 0.1ms ± 18 greater than themean normalized QTAF. Neither difference was significantly nonzero.

Subgroup analysis

TThere were 11 patients with normal cardiac function,EKG, and not on AADs. The mean ΔQT/ΔRR slope was .086 ± .034 and the mean ΔQT/ΔRRmodslope was .111 ± .060, similar to those in the group as a whole. The mean ΔQTc/ΔRRmod slope was significantly non-zero (p<.0001),as was the mean ΔQTLC/ΔRRmod slope (p<.005), whereasthe average ΔQTAF/ΔRRmod was not (p>.05).

Comparison to Sinus Rhythm

Data for NSR was collected in 22 patients. The mean QTc(min)in SR was significantly less than the mean QTc in AF. Both QTLC(min)and QTAF in SR were greater than mean QTAF in AF (Fig.3). QTAF in SR was on average 22ms±11 greater than QTAFin AF, while QTLC(min) in SR was on average 20ms ± 10 greater.

Discussion

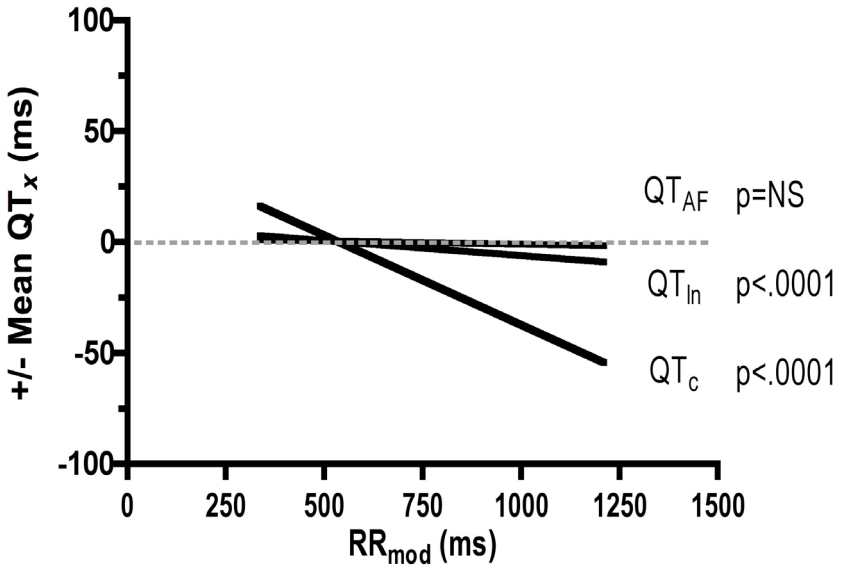
We report the performance of a novel QT correctionformula for use in AF, constructed by utilizing the linear relationship betweenthe QT interval and RRmod, the RR interval adjusted to account forQT lag.[8] QTAF yielded a more idealcorrection overall and at the extremes of heart rate than either QTcor QTLC, despite modifying these formulas by RRmod. Bystudying a subset with paroxysmal AF at the onset of arrhythmia, we werefurther able to investigate the relationship between opti-

Table 2

Baseline characteristics. Amio=Amiodarone. AVR=Aortic valve replacement p Op=Post-operative. BB=Beta blocker. CABG=Coronary artery bypass grafting. CCB= Calcium Channel Blocker. Dig=Digoxin. EF==Ejection fraction. EKG=Electrocardiogram. LAH=Left anterior hemiblock. LBBB=Left bundle branch block. LVH=Left ventricular hypertrophy. Maze=Maze procedure. MVR=Mitral valve replacement. PFO=Patent foramen ovale. RBBB=Right bundle branch block.

Patient	Age	M/F	Operation/ Dx	p-Op Day	EF	EKG	EKG LVH	Amio	So-talol	CCB	BB	Dig
1	58	M	CABGx4	3	Nml						Y	
2	85	F	AVR	1	Nml	LBBB			Y			Y
3	82	M	CABGx4/ MVR	7	30%	RBBB/ LAH					Y	
4	72	M	Urinary Retention		Nml					Y	Y	
5	85	F	MVR/Maze	2	45%				Y			
6	84	F	CABGx1/ AVR/MVR	14	Nml	RBBB		Y			Y	
7	50	M	MVR	0	Nml		Y					
8	58	M	PFO closure	3	Nml						Y	
9	76	F	Dementia		Nml						Y	
10	79	F	CABGx3, AVR	8	Nml						Y	
11	82	M	AVR	2	Nml	IRBBB				Y	Y	
12	61	M	AVR/CAB-Gx4	7	Nml			Y		Y		Y
13	78	F	CABGx5	3	Nml		Y	Y			Y	
14	80	M	CABGx3	2	35%	RBBB, LAH						
15	71	F	CABGx3	7	Nml			Y			Y	
16	76	M	Elective Stenting		Nml						Y	
17	66	M	Lymohoma		Nml						Y	
18	86	F	MV mass excision	2	Nml			Y			Y	
19	89	F	CABGx1, AVR	2	45%				Y			
20	77	M	Lung CA		Nml						Y	
21	66	M	Altered Mental Status		Nml					Y		
22	86	F	CABGX2	1	45%						Y	
23	52	M	MVR	1	Nml							
24	80	F	CABGX3	12	Nml						Y	Y
25	55	M	CABGx3	3	Nml						Y	Y
26	64	M	CABGx3	3	Nml	RBBB		Y				
27	61	M	AVR	2	Nml						Y	
28	67	F	ASD Closure	2	Nml	RBBB					Y	Y

Figure 1: Pooled normalized QTx vs. RR_{mod}

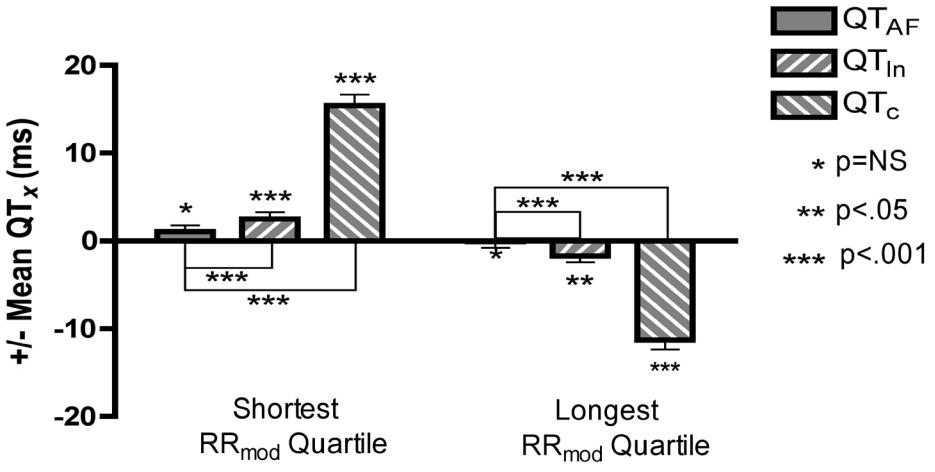


mally corrected QTintervals in AF and those in SR.

Linear QT corrections methods

Linear approaches to QT correction are based on theassumption that a first order relationship exists between QT and RR with aquantifiable slope (ΔQT/ΔRR). If, by convention, a patient's "true"QT is taken to be equal to the QT measured at a "standard" heart rate of 60, anoptimal correction would transform a raw QT measured at any CL into the "true"QT . If ΔQT/< ΔRR is known, this is achieved by calculating the differencebetween RR=1 sec and the measured RR (1-RR), multiplying that difference by ΔQT/ΔRR,and adding that product to the measured QT. In a perfect correction, there isno relationship between the corrected QT and RR, and the corrected QT vs. RRplot yields a line with a slope of 0 that intersects uncorrected QT vs. RR atRR=1 sec (Fig. 4). QTLC is an example of a linear equation, and hasbeen shown to achieve a QT correction that is substantially morerate-independent

Figure 2: The performance of each formula at the first and last quartile of RRmod, representing the shortest and longest RR_{mod} cycle lengths, respectively. P-values above and below bars are for comparisons with 0. P-values above and below brackets are for comparisons with QT_{AF}



than QTc1[3,18,19]

Most studies, including a large series with over 10000 patients, have validated a linear relationship between QT and RR for SR, bothon a population basis[13,18] as well as individually[19,20] and linear correction formulas perform at least equally well as non-linearmodels in SR.[13] Although a linear relationshipbetween QT and RR appears to be present in AF as well, <ΔQT/ΔRR in SR is notequivalent to ΔQT/ΔRR in AF[8,21] and does not account for QT lag. Corrections based onΔQT/ΔRRrelationships measured in SR will therefore be inaccurate in AF.

QT lag and RRmod

[RR]mod was proposed as a method ofaccounting for QT lag by Elhert, who showed that in AF, RRmodincreased the goodness-of-fit of three different QT-RR relationship models byanalysis of mean square residuals and Akaike information criteria.[7] Larroude subsequently showed that it allows for themeasurement of QT dynamics in AF, and renders previously divergent ΔQT/ΔRRrelationships in AF and SR nearly parallel. In that study, ΔQT/ΔRRmod in AF was reported to be 0.126 (8).The use of the formula QTAF = (1-RRmod)*0.126+QT wasbased on this data and the above rationale. RRmod considers only the five most proximalRR cycles. Thus, contributions of more distant RR intervals to an incident QTwill be ignored. The findings of pacing studies which have shown that an abruptand sustained change in cycle length causes an initial rapid adaptation in QTfollowed by a new steady state that requires several minutes to achieve, whilea brief interruption of the basic cycle length with a single premature stimuluscauses a perturbation in steady state that requires up to 10 beats to regain[4,22] suggest that while the majorityof the QT adaptation is dominated by more proximal RR intervals, there is asubstantial late component that would not accounted for using RRmod.It is notable, however, that these studies were done under conditions in whicha new steady state was allowed to develop. It is unclear what applicabilitythese studies have in AF, where sufficient variability may exist to precludethe development of a longer-term steady state. Thus, although RRmodincludes only the most proximal five RR intervals in correcting for QT lag, itlikely subsumes the most influential cycles, and presents a reasonable balancebetween corrective accuracy and ease of calculation.

QTAF

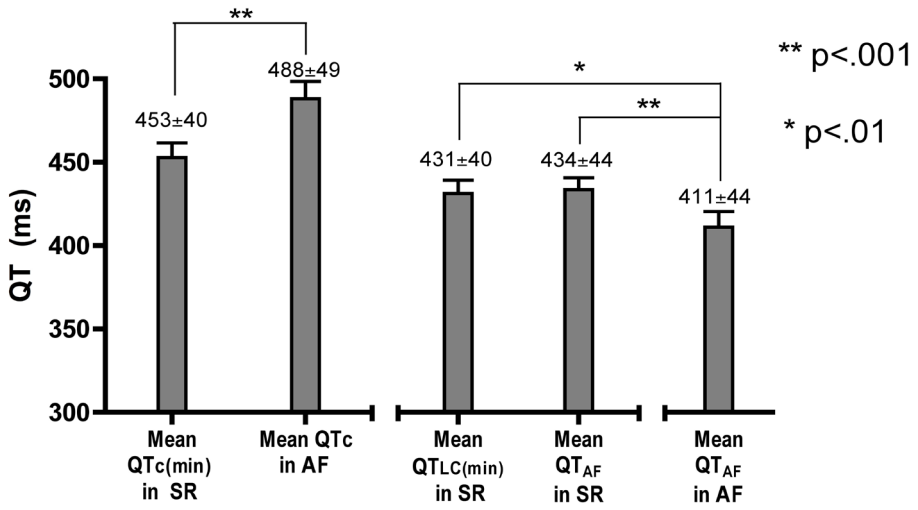
We confirmed that the relationship between QT and RRis adequately described by a first order equation, the slope of which (0.076)agrees well with the previously reported measurements of "7%" by Pai, et.al.[21] and 0.068 by Larroude.[8] We found that in distinction to the other correctionstested, QTAF values had no correlation to RRmod, anessential property of an ideal correction. This remained true at the extremesof RRmod.

The data on which QTAF was based wasderived in a cohort of medical subjects, including some with CHF,AAD use, andbaseline conduction abnormalities.We studied a similar group of largely-surgical subjects.Recognizing that it would be useful to determine theefficacy of QTAF in a population of otherwise normal subjects, wetested our primary hypothesis in our subset of subjects with normal EFs, no AADuse, and with normal baseline EKGs and found them to be no different than thelarger group. Since our institution has previously reported on alteration inrepolarization duration due to IVCD,[23] we alsotested our primary hypothesis with these patients excluded

Table 3 **Mean values of individually determined slopes. P-values indicate significance of difference from a slope of 0.egression Analysis**

Relationship	Mean Slope	Range	p-value
⚜QT/ ⚜RR	0.076 ± 0.030	0.016 ¬– 0.144	<0.001
⚜QT/ ⚜RRmod	0.114 ± 0.045	0.025 – 0.256	<0.001
⚜QTc/ ⚜RRmod	-0.239 ± 0.126	-0.390 – 0.162	<0.001
⚜QTLC/ ⚜RRmod	-0.045 ± 0.069	-0.314 ¬¬– 0.102	<0.01
⚜QTAF/ ⚜RRmod	-0.011 ± 0.043	-0.101 – 0.130	NS

Figure 3: Comparison of QT corrections in AF with corrections in SR. Min=Minimum. SR=Sinus rhythm. AF=Atrial fibrillation

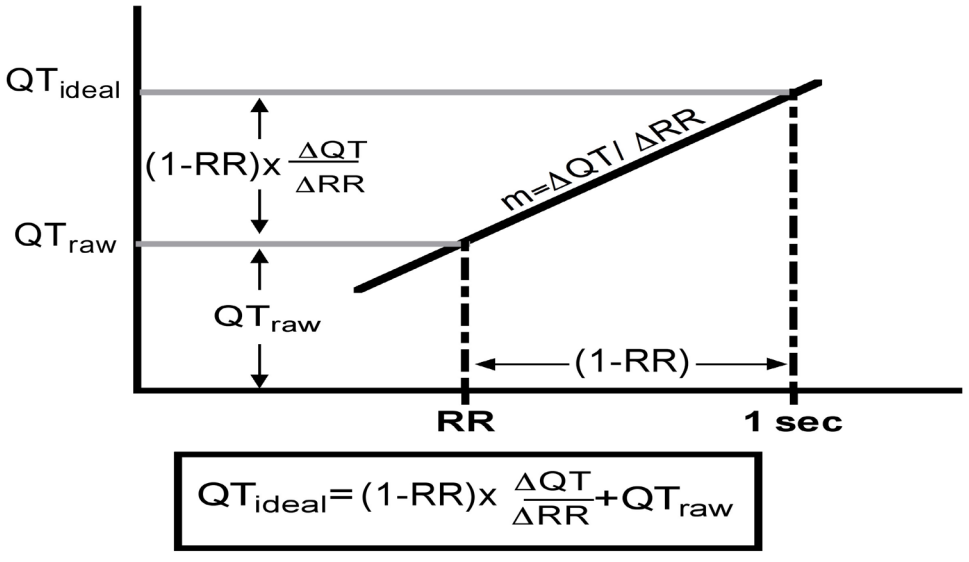


and found the sameresults. Although this study was not powered specifically to detect differences-between subgroups and further studies are needed to determine optimal QTcorrection strategies in individual populations, these data suggest that QTAFmay be applicable for a broad population of patients with AF.

Comparison to SR

Studies that have directly compared QT intervals in SRand AF using the Bazett correction have found the QT in SR to be either shorteror no different than that in AF.[15,24,25] However, other observations are consistent with theinterpretation that the QT may be shorter in AF compared to SR. For example, inthe study of Larroude et. al., although ΔQT/ΔRRmodin SR was nearly parallel to that for AF, the AF relationship had both a lowery-intercept and a lower QT at the "standard" heart rate of 60 .[8] The observations that a gain-of-function mutation inKCNQ1, which would be expected to shorten repolarization, can cause AF,[15] and that excessive QT prolongation[16] and torsades de pointes[14] can both be seen during infusion of Ikr blockers for the

Figure 4: PThe basis behind QTAF=(1-RR)*0.126+QT. In order to transform the QT at a given RR (QTraw) to the "ideal" QT at RR=1000ms, ⍵QT/⍵RR is multiplied by the difference the two values recorded in seconds (1-RR). This value is then added to QT_{raw}.



pharmacologiccardioversion of AF, but generally only after conversion to SR, are similarlyintriguing in this regard. QT hysteresis, the observation that the timeconstant for QT rate adaptation during periods of heart rate acceleration isshorter than that for deceleration, has been suggested as one potentialmechanism for this difference .[4] Such adisparity in adaptation might favor an overall shortening of the QT in anirregular rhythm such as AF

Our data showed that while QTc was shorterin SR than in AF, optimally corrected QT intervals in AF (using QTAF)were shorter than those in SR (using QTLC). One explanation for thisdiscrepancy may be the Bazett equation's overcorrection of the QT at the fasterheart rates often seen in AF1[0-12].Since ΔQT/<ΔRRmod in AF has been reported to be approximatelyequal to that of SR,[8] QTAF wasapplied to the last five sinus beats before the initiation of AF and comparedto QTAF in AF, and the same results were obtained (Fig. 3). Giventhat we collected limited data in SR, and heart rates were significantly higherin AF than in SR, we were unable to directly compare QT intervals in SR and AFat similar values of RRmod.

Clinical Implications

These data imply that the use of Q_{Tc} and,to a lesser degree, QT_{LC}, fail to achieve rate-independentcorrections in AF, even after correction for QT lag. Clinicians using QTcin AF should account for an overcorrection of nearly 15ms compared with Q_{TA-}Fin the fastest quartile of RRmod, rates likely to be encountered inAF. Similarly, Q_{TAF} values should be considered underestimations ofthe duration of repolarization to be expected after conversion to SR. Theseobservations will aid risk stratification of AAD therapy both during AF andafter SR is obtained.

Limitations

The use of population-derived indices to construct acommon QT correction has the inherent limitation of discounting individual variabilityin ΔQT/ΔRR,producing skewed corrections in those individuals who differ substantially fromthe mean. Several studies have found substantial variability in ΔQT/ΔRRand some investigators have argued for an emphasis on individualized approachesto QT correction in key circumstances .[19,20] Individualizing QT corrections, however, may not be practical in mostcircumstances. For example, in our data set, the ΔQT/ΔRR slope of the first 10 data interval pairsdiffered from the ultimately derived slope by an average of 55%, suggestingthat relying on the limited number of QT/RR measurements that, withoutautomation, would be realistically made in daily clinical use, could yieldsubstantially inaccurate corrections. Additionally, despite the individualvariability seen, there is a very high degree of correlation in thepopulation-averaged slopes measured in this and previous studies,[5,19] suggesting that at least in AF,while individual variability may exist, the relationship is reasonably constantacross populations. Future work should concentrate on identifying the factors thatdrive this variability and assessing their clinical impact in terms of theability of a correction formula to predict hard endpoints, such as propensityfor polymorphic ventricular arrhythmia. Similarly, although QTAFperformed as well in patients with cardiac comorbidities as well as thosewithout, further work should be done to prove its efficacy in populations thatmight be expected to have variability in repolarization dynamics.

In the comparison of SR with AF, we studied patientsat the time of conversion from in order to minimize the confounding effects ofdifferential autonomic tone between the two rhythms. It is possible, however,that the autonomic milieu present at the point of conversion from SR to AF maynot be generalizable. It is also possible that the degree of RR variabilityseen in a population of patients with newly incident AF may not be the same asthat seen in a more chronic population. Similarly, while our population wasdiverse in terms of EF, diagnosis, use of antiarrhythmic drugs, and age, all ofthe patients in this subset had cardiac surgery. Whether these findings aregeneralizable to a larger population remains to be seen.

Conclusions

QT_{AF} is a novel QT correction formula,designed for use in AF, which exhibits correcting characteristics superior tothe current strategy. Average QT_{AF} values are shorter than QT_{LC}values

measured in SR, suggesting that the optimally corrected QT in AF isshorter than that in SR.

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