Establishing Normal Ranges for ECG Intervals in a Normal Healthy Population

J. Olbertz¹, R. Lester¹ and M. Combs² ¹Celerion, Tempe, AZ, USA, ²Celerion, Lincoln NE USA

INTRODUCTION

The acquisition of ECGs as a screening tool for enrollment of normal healthy subjects is an essential component of qualifying subjects for early clinical research studies. Incumbent in this screening process is determining what constitutes a normal interval reference range in this population thereby ensuring that the original intent of the enrollment criteria is satisfied.

To date, there is a paucity of data to define normal ECG interval ranges in a large homogeneous healthy subject population (1, 2). Previous population-based studies are limited by a number of factors. In some cases a relatively small sample size was used thereby compromising the ability to subset subjects by gender, age, ethnicity and other covariates. Other studies have used a heterogeneous composition of subjects who may have underlying cardiovascular or other disease states which therefore may not permit clear demarcation of normal from abnormal Results can also be difficult to interpret when the dataset used includes variation in ECG cart acquisition technology and varied measurement algorithms, including use of manual interval measurements employing variable reader methodology. As such, the primary objective of this exploratory analysis was to interrogate an ECG database to establish reference ranges for heart rate (HR), PR, QRS, QTcB (QT corrected for HR using Bazett's method), QTcF (QT corrected for HR using Fridericia's method) and JT intervals in a cohort of healthy adult subjects comprehensively screened in a controlled phase I clinic. A secondary objective was to determine the impact of the covariates of gender, age, body mass index (BMI), and time of day the ECG was acquired on these parameters.

Figure 1: ECG intervals



METHODS

The data set for this exploratory analysis was created using screening digital ECG data from all healthy subjects accepted into early phase clinical studies in Celerion's proprietary ClinQuick database from 01 Jan 2005 to 31 Oct 2014. There were 39,386 complete tracings identified of which 83 (0.02%) were excluded due to at least one implausible non physiologic value for HR, PR, QRS or QTc intervals. Also, during this time frame the same individual may have been included in multiple studies and for the purposes of this project, replicate ECGs from the same subject within the same year were excluded from the analysis dataset. Lastly, it was assumed that there was no meaningful correlation in an individual's results from year to year.

The following covariates were included in the analysis datasets: site (Belfast, Northern Ireland UK; Lincoln, Nebraska; Neptune, New Jersey; Montreal, Quebec; and Phoenix, Arizona), age in years (25 and under, over 25 to 35, over 35 to 45, over 45 to 55 and over 55), gender (male or female), BMI in kg/m², time of day of ECG collection (12am to before 10am, 10am to before 12:30pm, 12:30pm to before 3pm, and 3pm to before 12am), ethnicity (Black, Caucasian, Hispanic, or Other), and ECG equipment (General Electric (GE) Mac 1200, Global Instrumentation (GI) M12R, or Hewlett Packard (HP) Pagewriter).

following formulae (3,4): RR(msec) = 60000/HR $QTcB(msec) = QT/(RR)^{1/2}$ $QTcF(msec) = QT/(RR)^{1/3}$ JT(msec) = QT - QRS

STATISTICAL ANALYSIS

Descriptive statistics were calculated for all endpoints and covariates. Summary statistics (N, arithmetic mean, standard deviation (SD), coefficient of variation (CV), median, minimum, and maximum) were calculated for all continuous variables and number and percentage were calculated for all categorical variables.

Normal ranges for each of the ECG parameters were constructed by calculating the 2.5th and 97.5th percentiles overall and by site, age, gender, and ethnicity following current standards for establishing reference ranges for laboratory testing values (5). The impact of site, gender, age, BMI, ethnicity, and time of day of ECG acquisition on these ECG parameters was also assessed.

In order to better determine which (if any) of the covariates listed might have a meaningful impact on normal range, the endpoints were analyzed for statistical significance. A simple ANOVA model was performed using the PROC MIXED procedure in SAS to analyze each covariate. The least squares means and corresponding 95% confidence intervals (CI) were calculated. Since this was an exploratory analysis, no adjustment was made for multiplicity.

The parameters QRS, QT, PR and HR were extracted from the ClinQuick database. The remaining ECG parameters (QTcB, QTcF, RR and JT) were derived using the

RESULTS

Table 1: Database composition

Covariate	Level	Number	Percentage
All		39303	100
Site	BFS	3094	8
	LNK	10625	27
	MTL	11180	28
	NEP	4316	11
	PHX	10088	26
Age	<=25	10734	27
	>25 to <=35	12381	32
	>35 to <=45	9495	24
	>45 to <=55	4953	13
	>55	1740	4
BMI	<=21	3231	8
	>21 to <=25	15924	41
	>25 to <=29	15553	40
	>29	4595	12
Sex	F	13168	34
	Μ	26135	66
Time	12am<10am	6383	16
	10am to <12:30pm	12767	32
	12:30pm to <3pm	12131	31
	3pm to <12am	8022	20
Race	Black	4141	11
	Caucasian	27607	70
	Hispanic	6606	17
	Other	949	2
Equipment	GE Mac 1200	33080	84
	GI M12R	4333	11
	HP Pagewriter	1890	5

Table 2: Observed normal ranges representing 2.5th and 97.5th percentiles and suggested inclusion criteria for healthy subject studies based on these normal ranges.

	Observed Normal Range		Suggested Healthy Subject		
	Low	High	Inclusion Criteria		
QT	333	450	≤ 450		
QTcB	350	446	≤ 450		
QTcF	351	438	≤ 450		
HR	47	88	50-100		
PR	120	196	≤ 200		
QRS	72	112	<u><</u> 110		
JT	243	358	<u>≤</u> 350		

Table 3: Impact of gender on ECG interval measurements (msec) shown as LS Means (95% CI).

Endpoint	Fem	ale-Male	Female		Male	
QRS	-7.94	-8.13, -7.74	85	84.21, 84.79	92	92.18, 92.7
QT	5.14	4.53, 5.75	387	386.33, 388.16	382	381.28, 382.94
QTcB	14.14	13.72, 14.56	405	404.02, 405.29	391	389.94, 391.09
QTcF	11.10	10.7, 11.49	399	397.92, 399.1	387	386.88, 387.95
HR	2.74	2.53, 2.95	66	66.01, 66.65	64	63.31, 63.88
PR	-5.43	-5.83, -5.04	154	153.43, 154.62	159	158.92, 160
RR	-0.04	-0.05, -0.04	0.926	0.92, 0.93	0.968	0.96, 0.97
JT	13.08	12.49, 13.67	303	301.86, 303.63	290	288.87, 290.47



Figure 2. Mean QTcF, QTcB, and QT interval measurements trend higher with both age and BMI with minimal changes in HR. Whereas the JT interval appears to increase with age but not BMI. Time of Day had minimal impact on interval measurements.

DISCUSSION

- Major advantages of this exploratory analysis include the use of a large ethnically diverse population of healthy subjects, use of modern digital equipment for acquisition of ECGs, and high precision computer derived measurements. In addition, this is the first known large cohort evaluation of normal ranges for JT interval (Table 1).
- The normal ranges for ECG intervals established in this analysis are applicable to the screening of healthy subjects for entry into early clinical research studies. They may not reflect normal values in the general population with similar demographics and therefore should not be used to screen for cardiac or other disease pathology in this latter category of individuals (Table 2).
- The difference in QTcF between the genders in the overall database was observed to be 13 msec. This difference was 11 msec when adjusted for race, site, age, BMI, and equipment (Table 3). This 2 msec (11 msec vs 13 msec) difference in QTcF although statistically significant with this large sample size, is not clinically significant.
- There was a clear trend towards higher values in QT, QTcB, QTcF, and PR intervals with increasing age and BMI without a corresponding increase in HR. Whereas the JT interval appears to increase with age but not BMI (Figure 2).
- Although some statistically significant differences in ECG intervals were observed depending on time of day, the differences ranged from 1.8 msec (QTcF) to 3.2 msec (JT) which is not considered clinically significant (Figure 2).
- There was a statistically significant adjusted 13 msec longer JT interval in females compared to males while there was an 8 msec adjusted shorter QRS in females relative to males which was also statistically significant. The observation that gender influenced multiple ECG parameters is not surprising. However, it is noteworthy that the prolonged QTc intervals seen in women compared to men were primarily due to delayed ventricular repolarization since QRS intervals were overall shorter in females than males. This underscores



the potential value of routinely deriving the JT interval, especially in situations where the QT interval is prolonged, to determine if this lengthening is due to prolongation of the QRS interval (ventricular depolarization), the JT interval (ventricular repolarization) or both (Table 3).

Since the JT interval is heart rate dependent, calculation of the JTc interval (HR corrected JT interval) may be more useful than the uncorrected JT measurement especially when there is a prolonged QTc interval in the presence of a high heart rate (4, 5). Currently, there is no consensus on the optimal method of calculating the JTc interval beyond simple alternatives such as subtracting the QRS from the corrected QTc interval.

CONCLUSION

This database is the largest of its kind in healthy subjects employing digital acquisition technology and computer assisted interval measurements of PR, QRS, QT and HR intervals. It also provides data on normal values for the calculated QTcB, QTcF and JT intervals. The latter measurement denotes ventricular repolarization and may be useful when a prolonged QT interval is seen in the presence of an abnormally long QRS value. Data presented here provide a frame of reference for normal JT ranges in a healthy subject population in order to assist the clinician with discerning differences between ventricular repolarization and depolarization when a prolonged QT interval is observed.

Common ECG inclusion criteria used for early clinical studies can vary depending on anticipated effects and therapeutic class of the study drug. This data provides a scientific basis for establishing normal range criteria to be used in consideration of ECG-related inclusion and exclusion criteria for early clinical studies assuming no prior evidence of cardiac pathology. This work also adds to the body of knowledge for better understanding impact of age, gender, ethnicity and BMI on those normal ranges for ECG interval measurements.

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