The influence of sex (and age) on the ECG - 2020

Dr. Andrés R. Pérez Riera

On the subject of the influence of sex (and age) on the ECG I send you a summary that I made of a recent "cornestone" manuscript by Peter W Macfarlane published 2 years ago in a chapter

Peter W Macfarlane The Influence of Age and Sex on the Electrocardiogram Adv Exp Med Biol. 2018; 1065:93-106. doi: 10.1007/978-3-319-77932-4_6. P. W. Macfarlane (*) Institute of Health and Wellbeing, University of Glasgow, Glasgow, Scotland, UK e-mail: peter.macfarlane@glasgow.ac.uk
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Abstract
The electrocardiogram (ECG) remains the most commonly used test in medical practice and as such requires to be interpreted with due care and attention to detail. The ECG changes rapidly from birth through childhood with age differences clearly related to increasing QRS voltages and a widening QRS complex. The only sex difference at this age is a slightly longer QRS duration in boys than girls. In adulthood, sex differences in QRS voltage are maximum in the under 40 age group and tend to minimize with advancing age. QRS duration is longer in males than in females, but little difference is made of this in diagnostic criteria. In a similar vein, ST amplitudes are higher in young males compared to young females with the difference diminishing as age increases. Corrected QT interval is longer in females than males. In summary, age and gender differences in the ECG are important and have been

incorporated into a variety of criteria for ECG interpretation. Physicians should be aware of the main sex differences in the ECG.
Keywords: Age; Automated ECG analysis; Databases; Diagnostic criteria; ECG; Ethnicity; JT interval; Normal ranges; QT interval; Reference values; Sex.

Introduction

It would be remiss to discuss the influence of age and sex on the electrocardiogram (ECG) without reference to the seminal work of Simonson, who published a book on differentiation between the normal and abnormal electrocardiogram in 1961 [**Simonson E, Harris R. Differentiation between normal and abnormal in electrocardiography. St Louis: Mosby; 1961**.]. Even before the advent of computer methods for measuring the components of the ECG, Simonson and his team drew up extensive tables of references ranges, more often called normal limits, of ECG measurements based on epidemiological studies. While there may be subtle differences between the 1961 measurements and those published more recently, Simonson nevertheless paved the way in pointing out differences in ECG measures between males and females and indeed between different races, as he had access to Japanese ECG databases in particular in addition to his own data from North American-based studies. Pipberger and his team in Washington, DC, led the way in automating ECG measurements [**Stallman EW, Pipberger HV. Automatic recognition of electrocardiographic waves by digital computer. Circ Res. 1961;9:1138–43**.].

He used the three orthogonal lead ECGs for his studies.

In the same part of the world, Caceres and colleagues also initiated methods for analyzing the ECG using computers [**Caceres CA, Steinberg CA, Abrahams S. Computer extraction of electrocardiographic parameters. Circulation. 1962;25:356–62**.], but they chose to use the standard 12 lead ECG.

Initially, the 12 lead ECG was recorded in four groups of three leads [**Caceres CA, Steinberg CA, Abrahams S. Computer extraction of electrocardiographic parameters. Circulation. 1962;25:356–62 Bonner RE, et al. A new computer program for analysis of scalar electrocardiograms. Comput Biomed Res. 1972;5:629–53**.], but nowadays the eight independent leads of the 12 lead ECG,

namely, I, II and V1–V6, are recorded simultaneously, greatly facilitating analysis through having time alignment of ECG appearances in all leads [**Macfarlane PW, Devine B, Clark E. The University of Glasgow (Uni-G) ECG analysis program. Comput Cardiol. 2005;32:451–4**].
The other limb leads III, aVR, aVL and aVF are easily calculated from leads I and II [**Macfarlane PW, Systems L. In: Macfarlane PW, et al., editors. Comprehensive electrocardiology. London: Springer-Verlag; 2011. p. 375–425.**].
In Glasgow, the development of automated ECG interpretation or as it was initially called locally, Computer-Assisted Reporting Of Electrocardiograms (CARE), followed a roughly similar route in that initially the three orthogonal lead ECG was used to develop data acquisition and measurement routines before the 12 lead ECG was analyzed in groups of three leads.
Ultimately, all 12 leads effectively recorded simultaneously were analyzed [**Macfarlane PW, Devine B, Clark E. The University of Glasgow (Uni-G) ECG analysis program. Comput Cardiol. 2005;32:451–4.**]. This chapter documents sex- and age-specific differences in ECG appearances for neonates, children and adults.
ECG changes observed in pregnant women are summarized elsewhere by Fu. [**Fu Q. Hemodynamic and electrocardiographic aspects of uncomplicated singleton pregnancy. In: Kerkhof PLM, Miller VM, editors. Sex-specific analysis of cardiovascular function. Cham: Springer; 2018. pp. 413–31**.].
Much of the following data is drawn from the databases acquired in Glasgow. These databases consist of the following 5 cohorts.

1. **Glasgow Adult Normal Database:** Throughout the late 1980s, a database of ECGs from apparently healthy adults was acquired in Glasgow [**Macfarlane PW, Veitch Lawrie TD. The normal electrocardiogram and vectorcardiogram. In: Macfarlane PW, et al., editors. Comprehensive electrocardiology. London: Springer; 2011. p. 483–546**.].
These volunteers essentially were recruited from local government and therefore consisted of persons from a variety of occupations from sedentary work in offices through teaching in schools to more manual work.

There was therefore a good cross section of the population involved. Each individual was screened by a physician to ensure that there were no known clinical problems and to ensure blood pressure was normal.
Blood tests and a chest X-ray were obtained in the first batch of volunteers but proved to be of no value, and these tests were later removed from the protocol.
Ultimately, a database of 1496 individuals aged from 18 to 82 years was compiled, and extensive tables of normal limits of various ECG parameters have already been published [**Macfarlane PW. Adult normal limits. Appendix 1. In: Macfarlane PW, et al., editors. Comprehensive electrocardiology. London: Springer; 2011. p. 2057–83**.].

2. Glasgow Pediatric Normal Database: Following the collection of the adult ECGs, it was also thought valuable to acquire 12 lead ECGs in healthy neonates, infants and children as there was no substantial database of ECGs from this age group available with all leads recorded simultaneously.
This was achieved through recording ECGs in the Royal Hospital for Sick Children in Glasgow, the Queen Mother's Hospital (Maternity Unit), and also through recording in day nurseries and schools.
In all cases, parental permission had to be obtained for the ECG recording. This remains a rather unique database through having over 500 ECGs recorded from neonates aged from birth to 6 days included in the 1784 entries from which normal limits were derived [**Macfarlane PW, et al. Normal limits of the high-fidelity pediatric ECG: preliminary observations. J Electrocardiol. 1990;22 (Suppl):162–8. 11.)(Macfarlane PW, McLaughlin SC, Rodger JC. Influence of lead selection and population on automated measurement of QT. Circulation. 1998;98:2160–7.)(Macfarlane PW. Paediatric normal limits. Appendix 2. In: Macfarlane P, et al., editors. Comprehensive electrocardiology. London: Springer; 2011. p. 2128–95**.].
Improvements in postnatal care mean that nowadays most new mothers leave hospital within 24–48 h of giving birth, and hence, it is no longer feasible to accumulate ECGs from children over the

first few days of life. Yet as will be shown, there are significant changes in the ECG at that period of development of a neonate [**Macfarlane PW, et al. Normal limits of the high fidelity pediatric ECG: preliminary observations. J Electrocardiol. 1990;22 (Suppl):162–8**.].
The availability of the database led to the extension of the Glasgow program to analyze and interpret ECGs from neonates, infants and children [**Macfarlane PW, et al. A new 12 lead pediatric ECG interpretation program. J Electrocardiol. 1990;23(Suppl):76–81.**].

3. Chinese Database: In order to compare the ECG of Caucasians versus Chinese, 503 ECGs were recorded from healthy individuals in Taipei Veterans General Hospital in Taiwan.
All volunteers had a normal cardiovascular system and were hospitalized for a variety of reasons.
The 12 lead ECGs were recorded on digital tape and sent to Glasgow for analysis [**Chen CY, Chiang BN, Macfarlane PW. Normal limits of the electrocardiogram in a Chinese population. J Electrocardiol. 1989;22:1–15**]. There were » equal numbers of men and women in this study, and the age range was 19–81 years.

4. Nigerian Database: As part of an MD thesis [**Katibi I. Establishment of normal limits of the electrocardiogram in healthy Nigerians using automated methods. Glasgow: Institute of Cardiovascular and Medical Sciences, University of Glasgow; 2011**], 1261 ECGs were recorded in and around Ilorin in central Nigeria from apparently healthy volunteers.
All ECGs were transferred to a database locally (Burdick, Wisconsin) and then sent to Glasgow for analysis using the same program as for the other databases. A full set of results was published [**Katibi I, et al. Normal limits of the electrocardiogram in Nigerians. J Electrocardiol. 2013; 46:289–95**]. Ages of the volunteers ranged from 20 to 87.

5. **Indian Database:** ECGs for this database were recorded in three separate centers in India, namely, at the Indian Institute of Technology Roorkee, NIT Jalandhar, and SGGS Nanded.
In all cases, the same model of electrocardiograph, namely, a Burdick Atria 6100, was used.
As for the other studies, all volunteers were apparently healthy with normal blood pressure and no history of cardiovascular disease.
The resulting reference ranges (normal limits) of the ECG in this population of 963 individuals aged 18–83 years were previously published [**Macfarlane PW, et al. Normal limits of the electrocardiogram in Indians. J Electrocardiol. 2015;48:652–68**.].

Database Summary All ECGs in the various databases were analyzed using the same version of the Glasgow program, and selected aspects of a comparison among the different groups have been published **[. Macfarlane PW, et al. Racial differences in the ECG – selected aspects. J Electrocardiol. 2014;47(6):809–8014**.].
It is important to stress that the same software was used for analysis in all databases.
Normal ranges were derived by excluding 2% of values at either end of a distribution in order to give a 96-percentile reference range.
For comparative studies [**Macfarlane PW, et al. Racial differences in the ECG – selected aspects. J Electrocardiol. 2014;47(6): 809–8014**], normal limits were computed from a knowledge of the mean regression line or directly with quantile regression.
Additionally, the sample quantiles, which incorporated smoothing with a window of 10 years, were computed and displayed. All statistical analyses were undertaken using the SAS v9.2 package.

Parameters studied

1. P Wave Amplitude

Given that cardiac muscle activation is essentially in a base to apex direction from the sinoatrial (SA) node with a mean direction which is roughly parallel to the lead II axis, the highest P wave amplitudes tend to be found in inferiorly directed leads such as II and aVF. In

general, ***there are no sex differences in terms of normal limits of P wave amplitudes. The normal upper limit of P wave amplitude in the limb leads is generally regarded as 0.25 mV for both males and females***.
Similarly, in children there are no sex differences in P wave amplitudes and no significant difference between pediatric and adult P wave upper limits of normal in the limb leads. In the precordial leads, the P wave configuration in V1 may be biphasic with an initial positive component and a terminal inversion. It has been suggested that the width of the terminal component multiplied by its amplitude, i.e. the Morris index [**Morris JJ Jr, et al. P wave analysis in valvular heart disease. Circulation. 1964; 29:242–52.**], provides a measure which increases in the presence of left atrial enlargement. A limit of 40 ms duration and 0.1 mV negativity, i.e. the width and depth of one small box on a conventional ECG display, gives a Morris index of 4 mVms, which is generally regarded as the upper limit of normal although the authors of the original paper **[. Morris JJ Jr, et al. P wave analysis in valvular heart disease. Circulation. 1964;29:242–52.**] used 3 mVms.
In right atrial enlargement, P waves in V1 and V2 can be upright. The upper limits of normal of the order of 0.15 mV in V1 and 0.175 in V2 were found in the Glasgow database for both males and females.
In children, slightly higher limits of normal are used, being 0.2 mV and 0.25 mV in V1 and V2, and so there is an age dependence on upper limits of normal P wave amplitude in these leads. There are no sex differences in these P wave amplitudes.

2. P Wave Duration

From the point of view of diagnosing an abnormal ECG, there are no sex differences in normal limits of P wave duration. Most textbooks will quote 120 ms as the upper limit of normal.??? (I disagree!)
From the point of view of automated interpretation, where all leads are recorded simultaneously, a slightly wider normal limit of 140 ms is often preferred????. (I disagree!)
Essentially, this relates to the fact that P wave onset does not occur simultaneously in all leads, while the same is true of P wave

termination. Thus, an interval from the earliest onset to the latest termination will be slightly longer than P wave durations measured in individual leads.
In the pediatric age range, it tends to be that 100 ms is also used as an upper limit of normal overall P wave duration with 80 ms in children under 1 year [**Park MK, Guntheroth WG. How to read pediatric ECGs. St Louis: Mosby; 1992**].
There are no sex differences in P wave durations in this age group.

3. QRS Complex Amplitudes

Perhaps the one component of the ECG where the greatest changes can be seen according to age and sex is the QRS complex.
Age-based changes can be seen, even in the first week of life, and so it makes sense to commence a review from that point.
The fetal circulation is decidedly different from adult circulation with blood short circuited from the RV to the aorta via the ductus arteriosus. Blood reaches the left side of the heart from the right atrium via the foramen oval.
The main effect is that, in the newborn, there is a so-called right ventricular preponderance which diminishes over the first days and weeks of life.
In summary, there are significant QRS amplitude changes, although there are no sex differences in QRS amplitudes in infants and children.
Change in S wave amplitude in V2 over the first few days and weeks of life is registered.
These data suggest that it is important to use the age of a neonate in days when interpreting an ECG.
In practical terms, this is essentially not done because healthy babies will be discharged from the hospital within a day or so after being born, whereas those with more significant problems such as congenital heart disease may have grossly abnormal ECGs not requiring fine adjustment of QRS voltages to determine abnormality.
Over the first years of life, S wave amplitude gradually increases as might be expected due to the natural growth of the child and, hence, increase in heart size.

Thus, age differences do play a role in ECG appearances in childhood. This does have relevance when the question of screening children, particularly for participation in sport, is considered. In the adult situation. Similar differences can be seen in other amplitudes such as the R wave amplitude in V5.
Thus, normal limits of R and S amplitudes are sex dependent. The reason why ECG amplitudes are sex and age dependent is linked to heart weight and body mass.
There are many publications showing that heart weight is higher in males than in females. Fuchs et al, [**Fuchs A, et al. Normal values of left ventricular mass and cardiac chamber volumes assessed by 320-detector computed tomography angiography in the Copenhagen General Population Study. Eur Heart J Cardiovasc Imag. 2016; 17:1009–17.**]
These researches, using computed tomography angiography, reported that the mean LV mass in males was 116 ±20 g and was 85 ± 14 g in females. This in itself might suggest that QRS voltages in males would be higher than in females due to increased LV mass generating larger electrical signals.
The indexed LV mass, i.e. LV mass indexed by body surface area (LVMI), was higher in males at 60 ± 9 g/m^2 as opposed to 49 ±7 g/m^2 in females. LVMI decreased with age in males but stayed level in females.
The difference in mean S wave amplitude in V2 between males and females lessens with increasing age.

A. Sokolow-Lyon Index for LVH

One of the most commonly used indices for reporting left ventricular hypertrophy (LVH) is the Sokolow-Lyon (S-L) index [**Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. Am Heart J. 1949;37:161–86**.].
This index was developed on 147 patients, 90% of whom were hypertensive with a mean blood pressure of 197/117 and 151 controls.
The authors did not detail the percentage of males and females in either cohort, and so sex differences in voltage were not assessed.

The controls had a mean age of 35.1 years, but the age of the patients was not stated. The maximum R amplitude in V5 in the controls was 2.6 mV. This has to be compared with a maximum value of 3.5 mV for males and 2.4 mV in females in the Glasgow normal population [**Macfarlane PW. Paediatric normal limits. Appendix 2. In: Macfarlane P, et al., editors. Comprehensive electrocardiology. London: Springer; 2011. p. 2128–95**.] and 3.5 mV for males and 3.8 mV for females in the Nigerian population [**Katibi I. Establishment of normal limits of the electrocardiogram in healthy Nigerians using automated methods. Glasgow: Institute of Cardiovascular and Medical Sciences, University of Glasgow; 2011.**].
Somehow or other, the index has remained embedded in ECG criteria for LVH since its inception.
The basic index is the sum of SV1+ RV5 amplitudes, although there are variations such as SV1 +max (RV5, RV6) amplitudes, because Sokolow and Lyon mixed the two in their article without giving separate criteria. The more commonly used SV1 + RV5 exceeded 3.5 mV in the hypertensive group in 48/147 individuals, i.e. its sensitivity in a training environment was 32.7%.
However, the important point to note here is that the index, as originally published, is neither age nor sex dependent. This is a very significant shortcoming.

Cornell Criteria for LVH

A group of cardiologists in Weill Medical College, New York, introduced an index for the detection of LVH from the ECG.
This was modified from the first publication in 1985 [**. Casale PN, et al. Electrocardiographic detection of left ventricular hypertrophy: development and prospective validation of improved criteria. J Am Coll Cardiol. 1985;6:572–80**.] to a later variation published in 1987 [**Casale PN, et al. Improved sex-specific criteria of left ventricular hypertrophy for clinical and computer interpretation of electrocardiograms: validation with autopsy findings. Circulation. 1987;75:565–72**.].
In a more recent study [**Dahlof B, et al. Characteristics of 9194 patients with left ventricular hypertrophy: the LIFE Study. Hypertension. 1998; 32:989–97**.], the threshold for females was

raised to 2.2 mV by reducing the difference between the male and female thresholds to 0.6 mV. The Cornell criteria most often used are: **RaVL + SV3 > 2:8mV in males RaVL +SV3 > 2:2mV** in females

These sex-based criteria have proved to be effective at all ages. In an assessment using the Glasgow database, it was shown that the Cornell criteria were essentially 94% specific in all age- and sex-based groups with the exception of females aged 40–49 where they were 91% specific [**Macfarlane PW, Clark E, Cleland JGF. New criteria for LVH should be evaluated against age. J Am Coll Cardiol. 2017; 70:2206–7**].

In the same study, the Sokolow and Lyon criterion specificity ranged from 64% in young males to 99% in older females.

The clear message is that criteria for LVH simply must be sex specific. If physicians wish to persist using the Sokolow and Lyon criterion, then it should be both an age- and sex-specific version that is used.

Romhilt-Estes Point Score System for LVH Romhilt and Estes introduced a point score system for the ECG diagnosis of LVH [**Romhilt DW, Estes EH Jr. A point-score system for the ECG diagnosis of left ventricular hypertrophy. Am Heart J. 1968; 75:752–8**].

These criteria made use not only of voltage changes but also ST-T segment changes, left axis deviation, left atrial abnormalities and a broadened QRS duration. They were not sex specific, but within Macfarlane laboratory, this author modified voltage criteria so that they were indeed age and sex dependent. This resulted in improved sensitivity as documented elsewhere **[Morrison I, Clark E, Macfarlane P. Evaluation of the electrocardiographic criteria for left ventricular hypertrophy. Anatolian J Cardiol. 2007;7(Suppl 1):159–63**].

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4. Right Ventricular Hypertrophy

There are no criteria for right ventricular hypertrophy (RVH) which are exceptionally sensitive and specific. Indeed, there are few, if any, criteria for RVH which are sex dependent. Previous reference to the neonatal ECG indicates that criteria for RVH are very definitely age dependent.

For the adult, an upper limit of 0.5 mV in V1 and/or R/S amplitude ratio > 1 in V1 are commonly cited, whereas for neonates and children, much higher threshold values are required to be used.

5. QRS Duration

In all of the adult populations studied, the mean QRS duration in males has been higher than in adult females.

In the Glasgow database, **the QRS mean duration was 96.4 ms in young males and 87.7 ms in young females.**

Similar changes were seen in different age groups, while in those aged **over 50 years, the mean QRS duration was 92.7 ms in males and 87.1 ms in females.**

Mean QRS duration varies with age and sex in the four different adult populations described earlier but with the much bigger influence being sex.

On the other hand, it has to be admitted that if a cardiologist were to be asked what the upper limit of normal QRS duration is, the answer would almost certainly be 120 ms for males and females.

There are few diagnostic criteria involving QRS duration which are sex dependent, but Strauss et al. introduced the concept of strict left bundle branch block (LBBB) which used a QRS duration >140 ms in men and 130 ms in women [**Strauss DG, et al. Defining left**

bundle branch block in the era of cardiac resynchronization therapy. Am J Cardiol. 2011;107:927–34.].
The need for such differentiation was related to deciding on which patients were most suited to cardiac resynchronization therapy.

6. ST-T Segment ST Amplitude

Although T wave amplitudes are generally not sex dependent, ST amplitudes are certainly age and sex dependent. Young males have higher limits of normal ST amplitude than young women, and older males have lower ST amplitudes than younger males [**Macfarlane PW. Age, sex and the ST amplitude in health and disease. J Electrocardiol. 2001; 34:235–41**.].
The ST amplitude varies with the precordial lead under consideration as well as age and sex. The sex-dependent changes for the upper limit of normal ST amplitude of V2–V4 in the Nigerian population database.
Some of the work in the author's laboratory led to the introduction of age- and sex-based criteria for ST elevation myocardial infarction (STEMI) as evidenced by the third universal definition of myocardial infarction published in 2012 [**Thygesen K, et al. Third Universal Definition of myocardial infarction. ESC/ACCF/AHA/WHF Expert Consensus Document. Circulation. 2009;53(11):1003–11.**].
This had been preceded by similar criteria in the recommendations of a working group on ST-T changes in acute ischemia and myocardial infarction [**Wagner GS, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram. Part VI: acute ischemia/infarction. A scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; The American College of Cardiology Foundation and the Heart Rhythm Society. J Am Coll Cardiol. 2009;53 (11):1003–1**1].
The age -and sex- specific criteria for ST change in diagnosing STEMI as listed in the third universal definition of myocardial infarction [**Thygesen K, et al. Third Universal Definition of myocardial infarction. ESC/ACCF/AHA/WHF Expert Consensus Document. Circulation. 2009;53(11):1003–11**.].

ST elevation criteria for acute myocardial ischemia in the absence of LVH and LBBB [**Thygesen K, et al. Third Universal Definition of myocardial infarction. ESC/ACCF/AHA/WHF Expert Consensus Document. Circulation. 2009;53(11):1003–11**.]: **New ST elevation at the J point in two contiguous leads with the cut points: J≥0.1mV in all leads other than leads V2-V3 where the following cut points apply: ≥0.2mV in men ≥ 40 years; ≥0.25mV in men < 40 years, or ≥ 0.15mV in women.**

Although ST amplitudes are sex dependent, in clinical practice they are not necessarily among the first thoughts of the cardiac electrophysiologist considering whether or not to undertake a percutaneous coronary intervention (PCI) in a patient with chest pain.

These more refined criteria are best applied via automated techniques where improvements in sensitivity can be noted [**Macfarlane PW, et al. Evaluation of age and sex dependent criteria for ST elevation myocardial infarction. Comput Cardiol. 2007; 34:293–6.) (. Clark EN, et al. Automated electrocardiogram interpretation programs versus cardiologists' triage decision making based on Teletransmitted data in patients with suspected acute coronary syndrome. Am J Cardiol. 2010;106:1696–702**.].

7. T Amplitude

There are clear sex differences in the upper limits of the normal precordial T waves. Diagnostic criteria acknowledge such differences when reporting tall T waves in precordial leads suggestive of hyperkaliemia or acute myocardial ischemia. ***The upper limit of normal in males is of the order of 1.4 mV and 1.0 mV in females.***

The only area where sex differences in T wave morphology are considered to be due to normal variation is in the right precordial leads where T wave inversion in V2 would be more frequently regarded as normal in females than in males.

The Glasgow data found 1.1% of healthy women had a negative component in the T wave in V2. There is also said to be racial

variation in that a small percentage of healthy young black males tend to have T wave inversion in right precordial leads, which is a normal variant [**Clark EN, et al. Automated electrocardiogram interpretation programs versus cardiologists' triage decision making based on Teletransmitted data in patients with suspected acute coronary syndrome. Am J Cardiol. 2010; 106:1696–702**.].

There have, however, been conflicting results in this connection, and their studies involving an indigenous Nigerian cohort did not show this feature [**Katibi I, et al. Normal limits of the electrocardiogram in Nigerians. J Electrocardiol. 2013; 46:289–95.**].

On the other hand, the prevalence of T wave changes in black athletes is much higher than in black controls [**Papadakis M, et al. The prevalence, distribution and clinical outcomes of electrocardiographic repolarization patterns in male athletes of African/Afro-Caribbean origin. Eur Heart J. 2011; 32:2304–13**.].

8. QT Interval

An important interval in the ECG is the QT interval because a lengthened QT can be due to a number of different causes and may result in death in some cases.

Hypokalemia and hypocalcemia, for example, are both known to increase the QT interval.

Drugs such as moxifloxacin can also increase the QT interval, and a recent comparative study of various computer programs has shown how each can detect even small changes in QT interval in a modest number of individuals after administration of the drug **[Kligfield P, et al. Comparison of automated measurements of electrocardiographic intervals and durations by computer-based algorithms of digital electrocardiographs. Am Heart J. 2014;167(2):150–159.e1**.].

Various congenital cardiac abnormalities can also result in a long QT interval, and in general terms, such a lengthened QT is associated with life-threatening cardiac arrhythmias.

QT interval varies with heart rate (HR), i.e. it shortens at increased HRs and lengthens at decreased HEs. This has led to the concept

of correcting the QT interval whereby an attempt is made to predict what the QT interval would be at a HR of 60.

The most commonly used formula for correcting QT is that of Bazett [**Bazett HC. An analysis of the time relations of electrocardiograms. Heart. 1920; 20:353–70**.]. This equation is QTc= measured QT / √RR: It has been suggested that the Bazett formula is probably the least accurate of all formulae, and its use is not to be recommended [**Vandenberg B, et al. Which QT correction formulae to use for QT monitoring? J Am Heart Assoc. 2016;5:e003264**.].

Other formulae include that of Hodges **[. Hodges M, Salerno D, Erlien D. Bazett's QT correction reviewed. Evidence that a linear QT correction for heart is better. J Am Coll Cardiol. 1993;1:694**], which is based on a linear correction. The equation used is QTc= QT + 175 (rate – 60).

Another formula that has increased in popularity recently is that of Fridericia [**Fridericia LS. Die Systolendauer im Elektrokardiogram bei normalen Menschen und bei Herzkranken. Acta Med Scand. 1920;53:469–86**.].

This is similar to Bazett but uses a cube root rather than a square root, i.e. QTc= QT^3 √rate/60)

Luo et al. [**Luo S, et al. A comparison of commonly used QT correction formulae: the effect of heart rate of the QTc of normal ECGs. J Electrocardiol. 2004;37(Suppl):81–9**0.] compared the different QT formulae and concluded that the Bazett correction was most often out of line with the other formulae.

A small sex-based difference in QT interval has been shown to occur with a mean difference between females and males being the order of 10 ms. The upper limit of normal QTc according to the 2009 guideline is 460 ms for females and 450 ms for males. [**Rautaharju PM, Surawicz B, Gettes LS. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram. Part IV: the ST segement and U waves, and the QT interval. A scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. J Am Coll Cardiol. 2009;53(11):982–91**.]

On the other hand, the international criteria for abnormal ECGs in athletes suggests using 480 ms for females and 470 ms for males **[. Drezner JA, et al. International criteria for electrocardiographic interpretation in athletes: consensus statement. Br J Sports Med. 2017; 51:704–31**].

9. JT/J-Tpeak/Tpeak-Tend Intervals

Other intervals which have been considered recently in relation to drug effects on the ECG [**Johannesen L, et al. Differentiating drug-induced multichannel block on the electrocardiogram: randomized study of dofetilide, quinidine, ranolazine and verapamil. Clin Pharmacol Ther. 2014; 96:549–58**.] include the JT interval (end QRS to end T), J-Tpeak (end QRS to the peak of the T wave) and Tpeak-Tend (peak of the T wave to end T).

The JT interval corrected for HR has been shown to be sex dependent in a study of 11,739 adult men and women **[. Rautaharju PM, et al. Assessment of prolonged QT and JT intervals in ventricular conduction defects. Am J Cardiol. 2004;93:1017–21**.].

The equation derived was JT_{RR} = JT -176 (60/HR -1 for women and +14 ms for men