Ital J Gender-Specific Med 2020; 6(3): 126-141

Gender differences in the 12-lead electrocardiogram: clinical implications and prospects

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Summary. Many sex differences exist in cardiac electrophysiology which are reflected on surface ECG. All gender-related differences in the repolarization features, including QT duration, J-ST voltages and T-wave morphology, become apparent at puberty, increase quickly and then progressively subside with advancing age. This suggests a strong role of the sex hormones, particularly testosterone, in modulating the ventricular recovery properties. Besides having a longer QT interval at baseline, women experience a greater increase in QT duration after exposure to QT-prolonging drugs, and consequently are more prone than men to develop torsade de pointes in both congenital and acquired long QT syndromes. On the other hand, the J-point elevation occurring in pubescent men – but not in women – may be the basis for male predominance in the Brugada and early repolarization syndromes, such as the higher event rate and worse prognosis reported in affected men. In postmenopausal women, several ECG variables proved to be strong predictors of morbidity and mortality from coronary heart disease, congestive heart failure and all-cause death. In women the ECG changes occurring during exercise test are less accurate than in men in detecting a coronary artery disease, but this difference can be mitigated by choosing wisely the diagnostic test and using other stress data beyond the ST-depression alone. The ECG is a valuable diagnostic and prognostic tool, whose clinical yield can be further enhanced if sex differences are properly taken into account.

Key word. Sex, gender, gender differences, electrocardiogram.

Differenze di genere nell'elettrocardiogramma a 12 derivazioni: implicazioni cliniche e prospettive future

Riassunto. L'elettrofisiologia cardiaca presenta numerose differenze di genere che si riflettono sull'ECG di superficie. Tutte le differenze di genere relative alla ripolarizzazione ventricolare, come la durata dell'intervallo QT, l'ampiezza di J-ST e la morfologia dell'onda T, cominciano a manifestarsi con la pubertà, aumentano rapidamente e in seguito si attenuano progressivamente con l'avanzare dell'età. Questo comportamento suggerisce un forte ruolo degli ormoni sessuali, in particolare del testosterone, nella modulazione del recupero elettrico ventricolare. Oltre ad avere un QT più lungo in condizioni basali, le donne incrementano maggiormente quest'intervallo quando esposte all'azione di farmaci QT-prolunganti e, pertanto, sono più inclini degli uomini allo sviluppo di torsione di punta, tanto nella sindrome del QT lungo congenita quanto in quella acquisita. D'altra parte, l'elevazione del punto J che si osserva alla pubertà negli uomini ma non nelle donne potrebbe essere alla base della prevalenza maschile nelle sindromi di Brugada e della ripolarizzazione precoce, nonché della maggior incidenza di eventi e della prognosi più severa descritti nei maschi affetti. In donne in età postmenopausale alcune variabili ECG sono risultate fortemente predittive di morbilità e mortalità da cardiopatia ischemica, scompenso cardiaco e da tutte le cause. Nelle donne le modifiche ECG durante test ergometrico sono meno accurate nel documentare una coronaropatia rispetto agli uomini, ma una scelta ragionata del test diagnostico e l'utilizzo di altri parametri della prova da sforzo oltre al semplice sottoslivellamento del segmento ST possono attenuare questa differenza di genere. L'ECG rappresenta un prezioso strumento diagnostico e prognostico, la cui valenza clinica può essere ancor più rafforzata se ne vengono opportunamente valorizzate e implementate le specificità di genere.

Parole chiave. Sesso, genere, differenze di genere, elettrocardiogramma.

Introduction

It is commonly believed that the surface electrocardiogram (ECG) is essentially identical in men and women, both in the presentation and in the interpretation of the main signs. In the last few years, however, several reports highlighted some gender-specific properties of cellular and clinical electrophysiology, leading to ECG differences between the sexes which can play a role in the management of various heart conditions. In this article we will review the most well-known sex-related differences in cardiac electrophysiology and their translation on ECG morphology and measurements. The potential diagnostic and prognostic value of the ECG by gender in several cardiovascular diseases will also be discussed.

Cellular electrophysiology

Sex-based changes in cellular ion channel function and transmembrane ionic currents have been well documented in various species, including humans. Although

these differences are partially explained by the effects of sex hormones, other determinants – including genetics, hemodynamics, intercellular conduction and autonomic tone – could play a significant role.

Na^+ channel function and transmural distribution of I_{Na} are affected by sex hormones, as demonstrated in the canine left ventricle, where female subepicardial and subendocardial layers show a smaller I_{Na} amplitude. Such transmural dispersion in amplitude of I_{Na} in females is corrected by testosterone, leading to similar Na^+ current amplitude and distribution as in males. On the other hand, in castrated male dog ventricles a transmural I_{Na} dispersion has been found, like the one identified in female ventricles.[1]

Repolarizing outward K^+ currents exhibit a lower density and are slower in females than in males. In healthy human transplant donor hearts, a reduced expression of many genes encoding for K^+ channel subunits (including HERG, Kir2.3, minK, Kv1.4 et al.) has been observed in women versus men.[2] In female murine hearts, total I_k, transient outward K^+ current (I_{to}) and slow delayed-rectifier K^+ current (I_{Ks}) show lower densities in the presence of higher estrogen levels, supporting a direct effect of estrogen on the K^+ channel function.[3] In addition, sex-based differences in transmural distribution of I_k in dog hearts lead to an increased heterogeneity of transmural ventricular repolarization in females, making them more susceptible to ventricular arrhythmias than males.[4]

Gender differences also affect the Ca^{2+} channel function; indeed, in female canine ventricles greater L-type Ca^{2+} channel (I_{CaL}) currents have been measured with respect to males.[4]

The above ionic current changes are reflected in differences in the female cardiomyocyte action potential (AP) shape compared with males. In women the ventricular cells show a longer AP duration, slower recovery dynamics and a greater transmural heterogeneity of AP duration than in men. In men the AP recorded from ventricular myocytes has a more prominent phase 1 repolarization (notch) than in women, especially in the epicardial layer. Sex hormones are able to affect the AP morphology and the cellular electrophysiology of the heart through a modulation of the ion channel function and current densities (Figure 1).

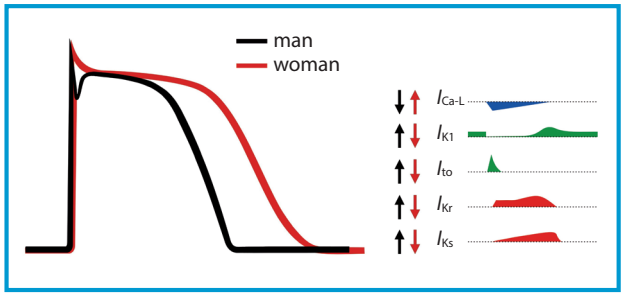

Figure 1. Morphology of ventricular action potential (AP) in women (red) and men (black). Women show longer AP duration and slower phase 3 repolarization than men. In men, the ventricular AP has a more prominent phase 1 notch than in women. Some ion-channel currents believed to be involved in generating these differences (primarily inward depolarizing L-type Ca^{2+} current and outward repolarizing K^+ currents) and their possible hormonal modulation are shown. Red and black arrows indicate the estrogen and testosterone effects, respectively. Upward arrows = increasing effect. Downward arrows = decreasing effect.

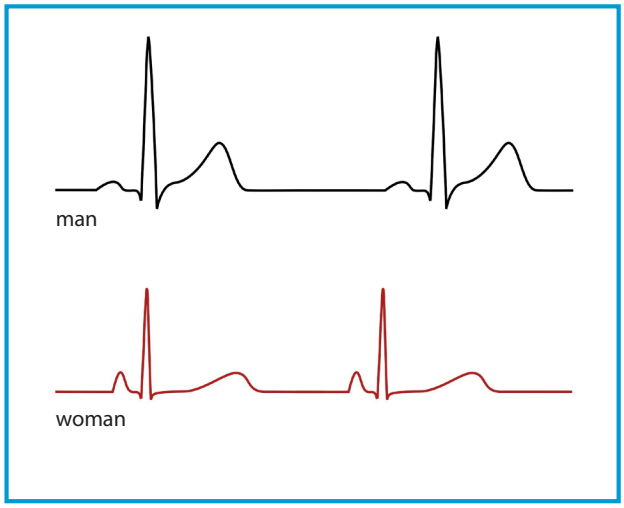

Figure 2. Gender differences in surface ECG. Compared with men (black), women (red) have faster sinus rate, taller and shorter P wave, shorter PR interval, lower and narrower QRS complex, longer QT/JT interval, lower J-point and ST-segment amplitude, lower and wider T wave. See text for further explanation.

Electrocardiogram by gender

Sex differences in AP configuration generate differences between men and women in baseline ECG intervals and morphologies (Figure 2). In addition, the smaller size of the female heart could play a role in shortening some time intervals in comparison with men.[5] As general features, the ECG in women shows narrower and taller P waves, narrower and lower QRS complexes, shorter PR intervals, longer QTc intervals, lower and wider T waves, compared to that in men. These differences have been detected in all ethnic groups. We should be aware, however, that the stated ECG dissimilarities between the sexes have to be intended as average, rather than individual properties. In a very recent investigation by Attia et al., artificial intelligence algorithms applied to standard 12-lead ECG proved to be capable of identifying the patient's sex (with an over 90% accuracy) and age (within 7 years). An ECG-predicted age exceeding the actual age by >7 years suggested a greater burden of disease.[6] Table 1 lists the main gender-based differences in the surface ECG.

Table 1. The most relevant sex-based differences in standard ECG

ECG parameters	Men	Women
Heart rate	↓	↑
Heart rate variability	↑	↓
P wave amplitude	↓	↑
P wave duration	↑	↓
PR interval	↑	↓
QRS amplitude	↑	↓
QRS duration	↑	↓
QT interval	↓	↑
JT interval	↓	↑
QT dispersion	↑	↓
T wave amplitude	↑	↓
T wave duration	↓	↑
J point amplitude	↑	↓
ST amplitude	↑	↓

Resting heart rate and heart rate variability

The mean sinus rate at rest is higher in women than in men by 2 to 6 beats per minute.[7-9] Such a difference persists even after complete autonomic denervation obtained with propranolol and atropine administration; this, therefore, supports a major role of an enhanced intrinsic sinus node automaticity in women,[9] likely mediated through a higher activation rate of the I_f current in the pacemaker cells of the sinoatrial node.[10] This behavior of the sinus node properties in women could explain why the so-called "inappropriate sinus tachycardia" – an uncommon disorder characterized by persistently increased heart rate out of proportion to metabolic or physiologic needs – mostly occurs in young female patients.[11]

Heart rate variability (HRV), a well-known index of autonomic modulation of the heart, is lower in women than in men, both in supine and standing positions. Among the frequency-domain parameters of HRV, women show lower values of total power spectrum and low-frequency power, whereas there is no sex difference in the high-frequency band.[8,12-14] This implies a predominance of the vagal tone in women, likely an expression of the estrogen effect.[14] In conditions of estrogen deprivation, such as after ovariectomy or menopause, all the HRV indexes measured by time- and frequency-domain methods show an increase in the sympathetic tone, whereas estrogen replacement therapy is able to quickly restore the original autonomic condition and the physiological sympathovagal balance.[15]

P wave and PR interval

P-wave amplitude is greater in women than in men, but it decreases progressively with aging in both sexes. P-wave duration is significantly shorter in women compared to men.[15]

Sex differences in PR duration have been investigated extensively. In several studies, the PR intervals resulted shorter in women than in men.[5] Data from the MESA cohorts show that women have shorter P-wave and PR durations in all ethnic groups.[16] Short PR intervals in females may result in a non-ischemic ST segment depression, due to the superimposition of the atrial repolarization wave (Ta wave).[17] The above gender differences may be explained by the smaller size of the female heart, which leads to shorter activation times.[5] Since both P-wave morphology and PR interval have been proposed as prognostic markers for an increased risk of several cardiovascular outcomes, including atrial fibrillation, stroke and all-cause mortality,[18-21] the definition of normal ranges stratified by gender and their clinical implementation should be considered mandatory.

QRS complex

The QRS complexes show shorter duration and lower amplitude in women as compared to men.[5,22] This gender difference occurs in all ethnic groups, and persists even after adjustment for left ventricular mass and body weight.[22,23] The smaller QRS complexes in women make the voltage-based ECG criteria for the diagnosis of left ventricular hypertrophy less accurate than in men. The use of gender-specific Cornell voltage criteria (sum of R wave in lead aVL and S wave in lead V3, having recognized cut-off points of >20 mm in women and >28 mm in men) improves significantly the accuracy of ECG for the detection of left ventricular hypertrophy in both sexes.[24]

QRS duration has been shown to be a risk marker for sudden cardiac death (SCD) in study groups with a specific heart disease, including congestive heart failure[25,26] and coronary artery disease,[27] irrespective of the patient's gender. Moreover, in a population-based random cohort of men, the QRS duration, as a continuous variable, also was an independent predictor for the risk of SCD.[28] To date, it is not known whether the relation between QRS width and SCD also applies in the general community-based female population; studies focused on this topic are needed.

Being the QRS complexes in women narrower than in men, the normal duration ranges in relation to gender should be taken into account, particularly in some clinical settings, such as intraventricular conduction disturbances and cardiac resynchronization therapy (CRT). In patients with congestive heart failure and left bundle branch block, women usually respond to CRT in the presence of QRS durations of 130 ms or more, whereas no responses have been reported in men with a QRS width less than 140 ms.[29] This implies that women are better candidates than men for CRT, as any QRS duration may reflect a greater degree of ventricular dyssynchrony compared with men, considering the above sex differences in normal values.[30] Given the better CRT efficacy expected in women, such a treatment could be administered earlier than in men, in the presence of less widened QRS complexes.

QT interval

Since the initial report by Bazett,[31] many subsequent studies demonstrated that the QT interval is longer in women than in men. Moreover, women's ECG shows longer QoT (from Q wave to T-wave onset) and QT_{peak} (from Q wave to T-wave apex) intervals and longer ST segment than men's ECG.[32] Such findings reflect the longer AP duration and, in particular, the slower repolarization process observed in female ventricular cardiomyocytes (Figures 1 and 2). In addition, women undergo a greater lengthening of the QT interval as the heart rate slows, so that the sex-based differences become more pronounced at increased cycle lengths.[32,33] The QT interval on the surface ECG measures the total time of activation of the ventricles and their recovery to the resting state, and is the sum of the QRS complex plus the JT interval. Since women have narrower QRS complexes, the longer QT intervals versus men are entirely caused by significantly longer JT intervals, that is by a prolonged ventricular repolarization. Analyzing the ECGs of 760 healthy subjects aged 0 to 88, Nakagawa et al. found that rate-corrected JT intervals, both JT_{peak} (from J point to the peak of the T wave) and JT_{end} (from J point to the end of the T wave) were longer in women aged >20 than in men of the same age, and stated that the difference was due to a shortening of these intervals around puberty in men.[34] In addition, a more recent investigation by Vicente et al. on the ECGs from 2,235 healthy subjects aged 18 to 78 revealed that among all the QT subintervals – represented by depolarization, early repolarization and late repolarization times (Figure 3) – the sex- and age-related differences in QT interval, with shorter values in healthy adult men than in women, were fully explained by differences in the duration of the early component of repolarization, which is reflected on ECG by the JT_{peak} interval. A testosterone effect on ventricular ion-channel currents, especially a decrease in L-type calcium current, has been invoked as the most likely mechanism to explain the JT_{peak} and QT shortening in postpubertal men.[35]

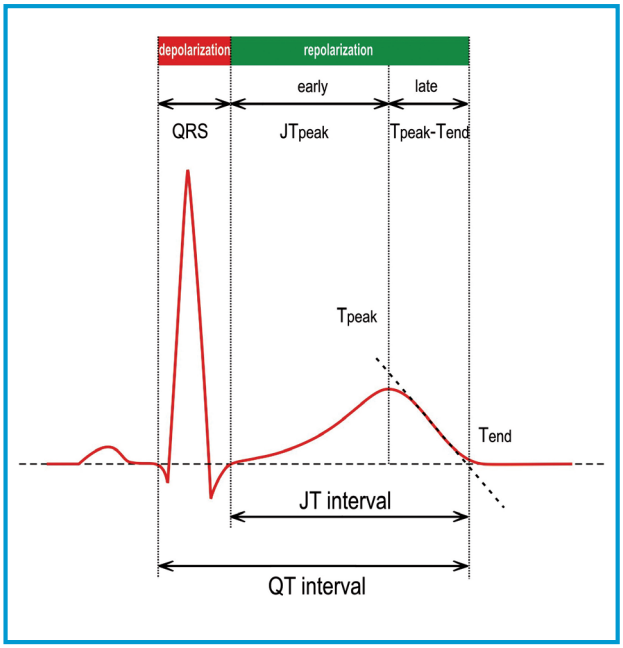

Figure 3. The QT interval is the sum of QRS complex (ventricular depolarization) and JT (JT_{end}) interval (ventricular repolarization). The JT_{end} interval, in turn, in the sum of JT_{peak} (early repolarization) and T_{peak}-T_{end} (late repolarization) intervals. Thus, the QT interval results from 3 subintervals: QRS, JT_{peak} and T_{peak}-T_{end}. The longer QT interval in women is due entirely to a longer JT_{peak} interval being both QRS complex and T_{peak}-T_{end} interval shorter than in men. The tangent method for T_{end} detection is also illustrated. From 35, modified.

The gender difference in QT duration is potentially relevant, because in women it can lead to a greater susceptibility to life-threatening arrhythmias, such as a rare form of polymorphic ventricular tachycardia known as torsade de pointes (TdP), as compared to men. In addition, women have a steeper course of the QT/RR relationship than men, i.e. a greater QTc difference at slower than at faster heart rates, a factor potentially predisposing to bradycardia-dependent arrhythmias.[32]

There is a strong evidence that sex-steroid hormones play a key role in determining the gender-related differences in QT interval duration, likely as expression of their effects on myocyte ion-channel function and ionic currents, especially inward L-type Ca^{2+} and outward K^+ currents, as previously discussed.[2,3,7,8,30,32-38] A study reported longer QT intervals in castrated compared to normal men and shorter QT intervals in women with virilization syndromes compared to healthy women and castrated men.[38] In athletes taking large doses of anabolic steroids, shorter rate-corrected QT (QTc) intervals have been found.[8] During childhood there is no gender

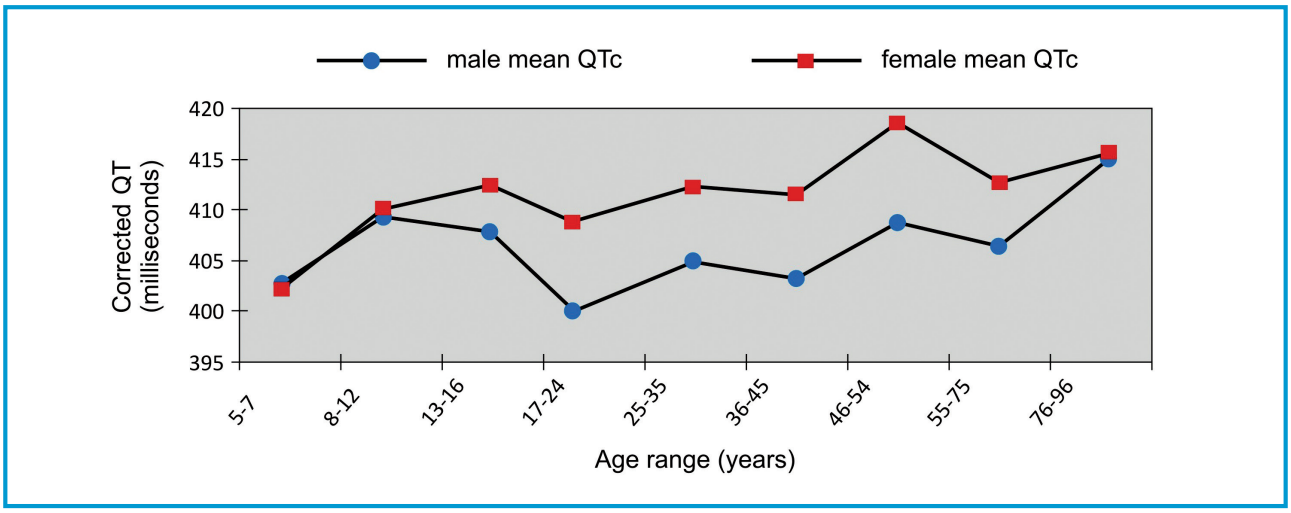

Figure 4. Age distribution of the QT interval durations by gender. From 32, modified.

difference in QTc duration, which appears at the time of puberty, when this interval shortens in boys, whereas it undergoes only a little change in girls. Sex difference persists until the age of 60-65, when the QTc gradually increases in men, becoming similar to that in women (Figure 4).[8,32,36] In view of these temporal dynamics, separate gender- and age-specific cut-point values for normal, borderline and prolonged rate-adjusted QT interval have been identified (Table 2).[39]

These observations suggest a major role of the testosterone effect in modulating the ventricular repolarization.[8,30,32-38] The detection of androgen receptors in ventricular cardiomyocytes seems to support this mechanism.[36,40]

Conflicting evidence, instead, illustrates the effects of female hormones on QT interval duration. It has been reported that the baseline QT interval fluctuates in women during the menstrual cycle, showing shorter values during the luteal phase, thus suggesting that the QT-prolonging effect of estrogen may be counteracted by progesterone.[41] However, in other studies no changes in QT interval duration were documented in relation to the menstrual cycle.[42] On the other hand, in postmenopausal women it has been shown that hormone replacement therapy with estrogen alone is able to prolong the QTc interval,[43] whereas progestin-estrogen replacement does not affect the QTc duration. These findings strongly suggest that estrogen and progesterone have opposite influences on ventricular repolarization, with a protective effect of progesterone against the estrogen-induced QT prolongation and the arrhythmic risk.[44]

The well recognized sex-based differences in ventricular repolarization and QTc interval duration have direct implications on the epidemiology and clinical outcomes in both congenital and acquired long QT syndromes (LQTS).

Table 2. Cut-point values (ms) for normal, borderline and prolonged QTc interval (Bazett's formula) by age group and sex

QTc interval	Age 1 to 15	Adult men	Adult women
Normal	<440	<430	<450
Borderline	440-460	430-450	450-470
Prolonged	>460	>450	>470

From 39, modified.

The LQTS International Registry shows a female predominance in congenital LQTS and a worse prognosis in adult women, with a 3-fold higher risk of cardiac events (syncope or cardiac arrest due to ventricular tachyarrhythmias) than in adult men. In particular, among LQTS patients aged 16 to 40, the cumulative probability of a first cardiac event is significantly higher in LQT1 and LQT2 females (carrying gene mutations responsible for a loss of function in K^+ channel currents I_{Ks} and I_{Kr}, respectively), whereas no sex difference occurs in the LQT3 genotype (due to a mutation leading to a gain of function in Na^+ channel current). By contrast, before puberty (≤15 years of age) the risk of experiencing malignant arrhythmias is significantly higher in LQT1 males than in LQT1 females, whereas no gender difference in the cardiac event rate has been found among LQT2 and LQT3 carriers.[45] The above data further strengthens the possible QT-prolonging effect of estrogen leading to an increased risk of TdP in adult women and, even more, the QT-shortening effect of testosterone resulting in a beneficial role against the arrhythmic risk in adult men.[8,30,32-38] Most likely the gonadal hormones affect the ventricular repolarization properties by mod-

ulating the function of K^+ channels, but not that of Na^+ channels.[45]

Several reports showed that women are more prone than men to abnormal QT prolongation during the exposure to drugs or other conditions (such as bradycardia, electrolyte imbalances, cerebral injury) able to delay the ventricular repolarization and increase the AP duration. In addition, in the presence of acquired QT interval prolongation, women are more susceptible to develop TdP than men, with about 65-75% of drug-induced TdP occurring in women. Thus, female gender is thought to be an independent risk factor for acquired LQTS and related ventricular arrhythmias.[32,33,36] The mechanisms underlying this gender-based difference, however, are not fully understood. Although the female sex-steroid hormones may play a role in increasing the propensity towards acquired LQTS and TdP in women,[30,33,36,37] reports of a similar susceptibility in both premenopausal and postmenopausal women[46] suggest that other factors, including genetics and sympathetic tone, should be taken into account.[30] It has been speculated that a K897T polymorphism of the HERG channel gene, frequently detected in females and affecting the heart repolarization properties, may prolong the QT interval and, therefore, partially explain the greater vulnerability to acquired LQTS in women.[33] As an alternative explanation, sex-based differences in susceptibility to drug-induced QT prolongation and TdP may reflect a decreased risk in men, due to the protective effect of testosterone, rather than an increased risk in women.[30,32-38,40]

Another potentially relevant sex-related difference in the 12-lead ECG is the QT dispersion, defined as the difference between the longest and the shortest QT intervals. It has been reported that QT dispersion is greater in men than in women, but it exhibits prominent circadian variation. An increased QT dispersion can play a critical role in the genesis of life-threatening ventricular tachyarrhythmias and SCD.[8,36]

J point and ST segment

Age- and gender-related differences in J-point and ST-segment amplitudes and morphologies have been well documented. Both J point and ST segment are significantly higher in adult men than in age-matched women, whereas no sex difference is apparent before puberty.[32] A study by Ezaki et al. analyzing the precordial leads V2 and V5 of ECGs recorded from 640 healthy subjects (310 males, 330 females) aged from 5 to 89 demonstrates that in both leads the J point and the ST segment undergo a marked elevation after puberty in males, but not in females. The J-ST peak is observed in males between 20 and 29 years of age in both chest leads; then, with advancing age, a gradual and progressive reduction is observed after the 3rd decade of life. In adult subjects of both sexes, the lead V2 displays considerably higher J-ST levels than the lead V5. As a result, in both precordial leads the J-ST amplitudes are significantly higher in post-pubertal males compared with females of the same age, and this gender difference is much more pronounced in lead V2 than in V5. These findings strongly suggest a possible role of testosterone in modulating the early phase of ventricular repolarization and, subsequently, in generating the reported sex differences in J-ST. According to this hypothesis, the dynamic age-related changes in J point and ST segment occurring after puberty in males mimic precisely the behavior of plasma testosterone concentration, which increases around puberty, peaks at the age of 20-30, then it decreases gradually over time, due to the physiologic effects of aging (Figure 5). By contrast, the female sex hormone, which also markedly increases at puberty, exerts only a little effect on phases 1 and 2 of the ventricular AP, since no changes in J-ST voltages are observed in pubescent females. In order to validate the influence of testosterone on initial ventricular repolarization, the same study also evaluated the ECG effects of androgen-deprivation therapy in

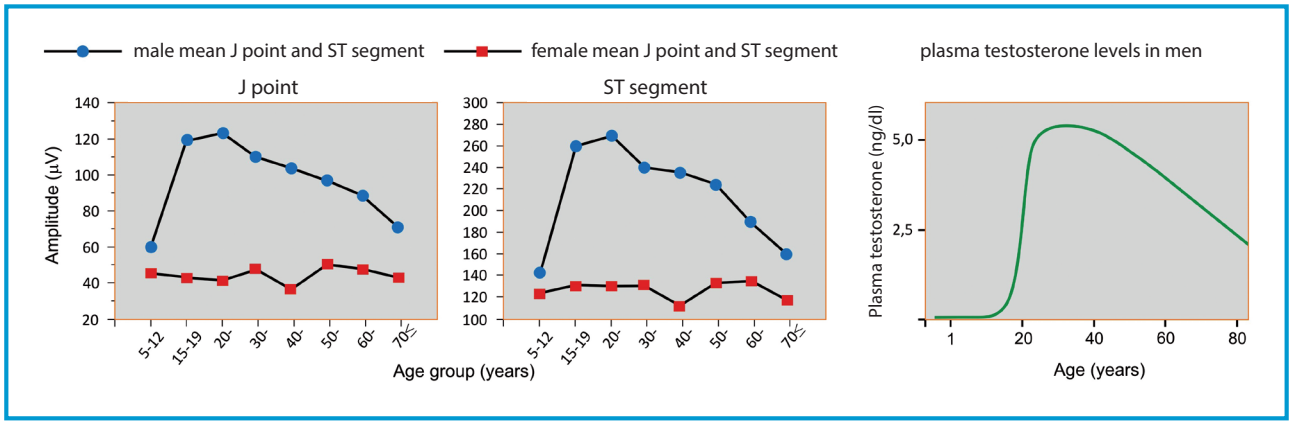

Figure 5. Effect of age and gender on J-point and ST-segment amplitudes (lead V2). The right panel illustrates age-related changes in testosterone blood levels in men. From 47, modified.

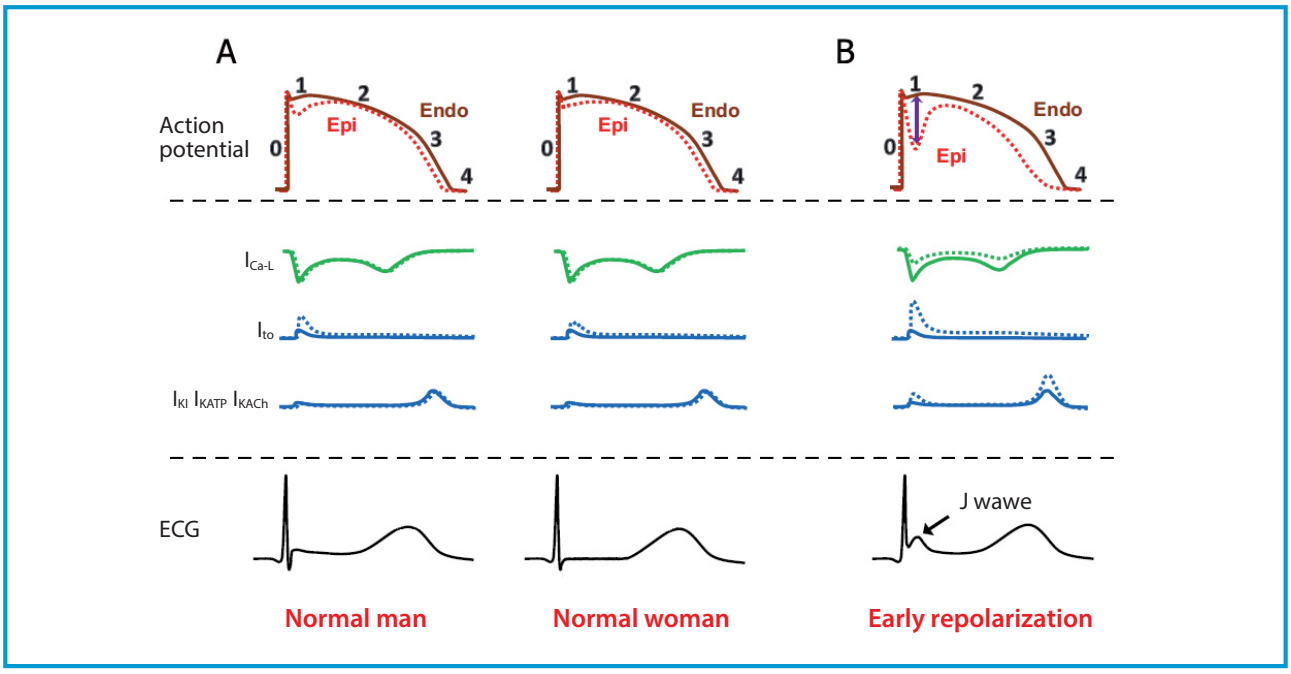

Figure 6. Ionic and cellular mechanisms underlying sex differences in J point and ST segment with related ECG findings. Epicardial AP and some corresponding currents are depicted with dotted lines, endocardial by solid lines. A. In normal men, epicardial AP shows a prominent notch, due to larger phase-1 I_{to} compared with endocardial AP. This causes some transmural voltage gradient during the early phases of ventricular repolarization, reflected in a trivial J-point, with or without ST-segment elevation. In healthy women, epicardial AP has a modest phase-1 I_{to}-mediated notch so that little transmural gradient is generated and the ECG displays lower J-point and ST-segment amplitudes compared to men. B. An exaggeration of the epicardial notch resulting from enhanced I_{to} accentuates the transmural voltage gradient and the endocardium-to-epicardium current flow at phase 1, leading to the inscription on ECG of a J wave (early repolarization). A concomitant decrease of I_{CaL} generates a phase-2 transmural gradient which manifests itself as ST-segment elevation.

I_{CaL} = inward calcium currents; I_{to} = transient outward current; I_{K1} = inward rectifier current; I_{KATP} = adenosine triphosphate-sensitive current; I_{KACh} = acetylcholine-activated current.

21 prostate cancer patients receiving neoadjuvant treatment with a gonadotropin-releasing hormone agonist (leuprorelin or goserelin) and/or an anti-androgen drug (bicalutamide) before radical prostatectomy. Compared with the tracings recorded before androgen-deprivation therapy, after therapy the J point and the ST segment are considerably lower and closely similar to those observed in age-matched female controls. These observations further support the key role of male sex hormone in determining the gender differences in J-ST amplitudes after puberty, through a direct modulation of early ventricular repolarization.[47]

It has been suggested that a prominent transient outward K^+ current (I_{to})-mediated phase 1 notch in the ventricular epicardium AP, but not in the endocardium AP, may generate a transmural voltage gradient during early ventricular repolarization that could appear on ECG as a J-point elevation. Voltage gradients occurring later in the AP (phase 2) are the basis for an upward displacement of the ST segment.[47-53] Even in normal subjects, some degree of transmural heterogeneity in phase 1 and/or phase 2 repolarization voltages may develop, due to the much smaller I_{to} present in the endocardial layer compared with the epicardial and the mid-myocardial, thus accounting for a trivial J-point/ST-segment elevation.[47-49] The above ionic and cellular mechanisms exhibit marked gender differences in adulthood, being I_{to} density in ventricular epicardium higher in males than in females, likely as a testosterone effect leading to enhanced K^+ channel function. In addition, testosterone may decrease I_{CaL}[35] more in epicardium than in endocardium.[49] This results in greater transmural voltage gradients at phases 1 and 2 in males and, therefore, may provide a mechanistic explanation for the higher J-point and ST-segment amplitudes observed in men versus women after puberty (Figure 6A).[47]

An amplification in epicardial net repolarizing current during the early phases of ventricular AP accentuates the phase 1 notch (spike-and-dome morphology of epicardial AP) and enhances the endocardium-to-epicardium voltage gradient, leading to the inscription on the surface ECG of J waves with or without ST-segment elevation: the so-called "J-wave syndromes", including Brugada syndrome (BrS) and early repolarization syndrome (ERS) (Figure 6B).[47-53] The prominent J-point and ST-segment elevation occurring at puberty in young

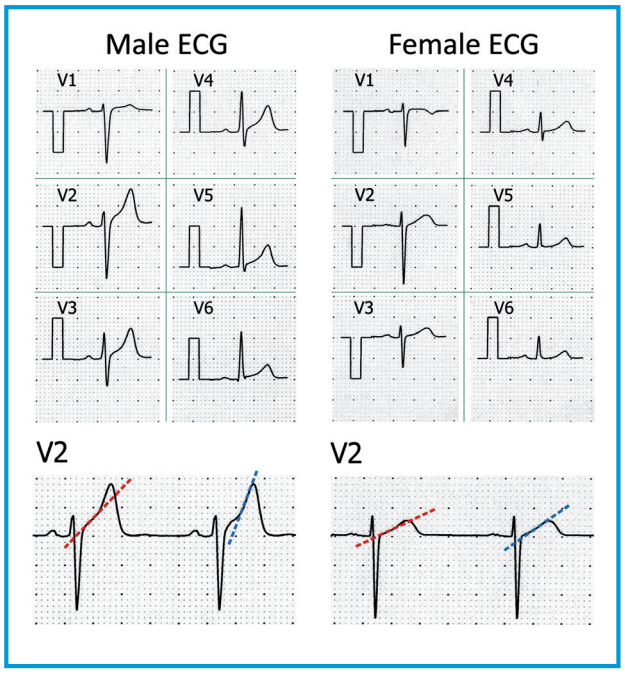

Figure 7. Sex differences in ventricular repolarization (precordial leads).

Left: ECG from a 32-year-old healthy man. Right: ECG from a 34-year-old healthy woman. At the bottom of each panel an enlargement of lead V2 is shown. Oblique dashed lines indicate the steepness of the ST segment (red) and that of the ascending limb of the T wave (blue). The typical male ECG displays higher J-point amplitude, shorter and steeper ST segment, taller T wave, with a steeper ascent compared to female ECG. In addition, the narrower and lower QRS complex in female ECG than in the male one should be noted.

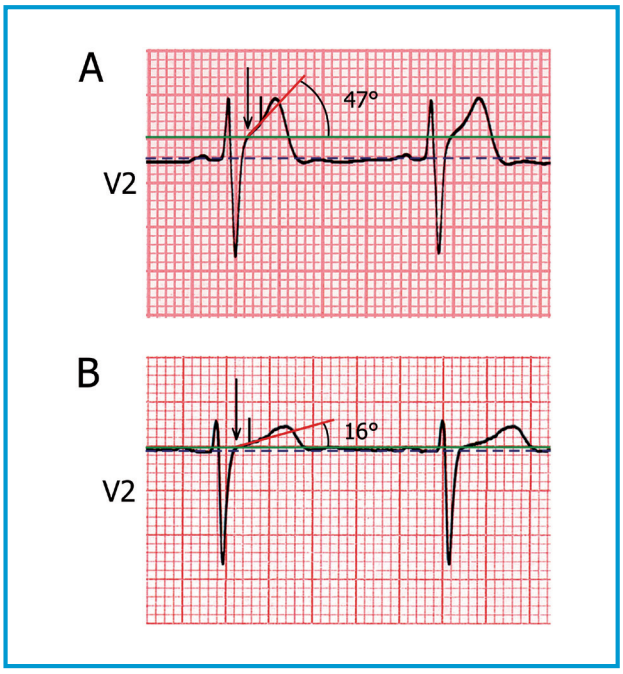

Figure 8. Sex-specific patterns of early ventricular repolarization. Method for pattern determination in precordial leads V1 to V4. Two sequential QRS complexes are selected in the lead displaying the highest J point (in this example, V2). A horizontal dashed blue line is drawn to connect the onset of these two QRS (Q-Q line); a horizontal solid green line parallel to Q-Q line is drawn at the level of the J point: this is considered as baseline. The arrow marks the J point; the short vertical line indicates 60 ms after the J point; the oblique red line connects the J point with the point inscribed 60 ms later. The distance between the 2 horizontal lines represents J-point amplitude. The ST angle is that between the oblique line and the baseline. A. Male pattern: the J-point amplitude is 0.25 mV and the ST angle is 47°. B. Female pattern: the J-point amplitude is 0.04 mV; in addition, the ST angle is 16°. Further explanation in the text. Adapted from 58.

males might have a clinical relevance with reference to the J-wave syndromes, which indeed are both characterized by a strong male predominance (>75% in BrS, >80% in ERS).[52] The testosterone-induced J-point and ST-segment elevation in pubescent men could favor the phenotypic expression of J-wave syndromes and, thus, contribute to this male predominance.[47,52-54] In addition, among patients with J-wave syndromes, males have a worse prognosis than females[8,49,52,53,55,56] and androgen-deprivation therapy has shown to decrease significantly both the ST-segment elevation and the arrhythmic events in Brugada patients. Similar hormonal modulation may be expected in ERS.[53]

According to the aforementioned gender differences in J-point and ST-segment amplitudes, the *2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation* state that an ongoing STEMI should be suspected when a suggestive clinical picture is associated with ST-segment elevation (measured at the J point, in at least two contiguous leads) ≥2.5 mm in men <40 years (≥2.0 mm in men ≥40 years), or ≥1.5 mm in women in leads V2-V3 (and/or ≥1.0 mm in women in the other leads).[59]

Other sex-specific features of ventricular repolarization developing at puberty in men are: a steeper ST-segment slope; a shorter ST-segment (the JoT interval) duration; a steeper ascent and a higher amplitude of the T wave, in comparison to women (Figure 7).[32,57,58]

Based on two ECG variables (the amplitude of the J point and the angle between the ST segment and the baseline – the so-called "ST angle") analyzed in the precordial leads V1 to V4, gender-specific patterns of early ventricular repolarization have been identified in normal tracings.[57,58] The "male pattern" is characterized by a J point ≥0.1 mV and a steeper ST segment course expressed by a ST angle ≥20° in at least one of the V1 to V4 leads; the "female pattern" is defined by a J point <0.1 mV in each of the leads V1 to V4. An "indeterminate pattern" occurs when the J point is ≥0.1 mV, but the ST angle is <20° in each of the four chest leads (Figure 8). The distribution by age of repolarization patterns is significantly different between genders. In females, the patterns show a nearly uniform distribution from puberty to

advanced age, with an about 80% prevalence of the female pattern. In males, by contrast, the prevalence of male pattern is relatively low in children, increases quickly at puberty, reaching 91% between 17 and 24 years of age and finally, with further advance in age, declines gradually to 14% in the oldest subjects, in which the prevalence of female pattern proportionally grows until it becomes dominant. The indeterminate pattern occurs in about 10% of cases in both sexes. The gender differences in the distribution of the ventricular repolarization patterns are subsequent to age-dependent changes in the prevalence of male pattern in males, being the pattern distribution in females substantially constant over time. These findings strengthen even more the testosterone hypothesis to explain the differences between men and women in the early ventricular repolarization.[32,38,58] Focusing on the precordial leads V1 to V4 we can readily recognize, in most normal ECGs, the typical male and female patterns, even with a simply visual approach. It would be clinically useful to recognize whether an atypical distribution of the repolarization patterns among genders (for example, a male pattern in young adult females or vice versa) is associated with a different risk of TdP and SCD, an attractive hypothesis which, however, needs to be tested.[32,58]

T wave

Several studies reported that in women the T waves are lower in amplitude and longer in duration compared to pair-matched men; this, in association with longer QT intervals, reflects a slower repolarization mechanism in women. A sex difference in T-wave amplitude has been found in all age groups, except for 5 to 7-year-old children.[32,58,60] In addition to differences in amplitude, the T waves show marked gender-related dissimilarities concerning morphology and duration, which become more apparent around puberty. In both male and female young adults the descending limb of the T wave is faster than the ascending one. In men, however, the ascending limb has a steeper slope, resulting in a shorter oT-aT interval (from the onset to the apex of the T wave) and shorter T-wave duration compared to women.[32] The question whether the descent of T wave displays a different steepness between the sexes has long been debated in the past, with conflicting conclusions.[32,57] In recent years, a great attention has been paid to this issue, and particularly on gender differences in the duration of the terminal component of the T wave, i.e. the time interval from the peak to the end of the T wave (T_{peak}-T_{end} interval, Figure 3).[34,35] Such interval is believed to be a marker of transmural dispersion of ventricular repolarization, whose prolongation would identify patients at increased risk of arrhythmic death.[34,35,61] In the study by Nakagawa et al. the T_{peak}-T_{end} interval was significantly shorter, and the T_{peak}-T_{end}/JT_{end} ratio was significantly smaller in adult women aged >20 years than in men of corresponding age.[34] Similar findings resulted from the study of Vicente et al., who observed that in healthy women aged over 18 both QRS complex (depolarization) and T_{peak}-T_{end} interval (late repolarization phase) were significantly shorter than in men, in contrast with a longer JT_{peak} interval (early repolarization phase), responsible for an increased QTc duration.[35] The considerably shorter T_{peak}-T_{end} intervals found in healthy adult women compared to men suggest that the transmural dispersion of the left ventricular repolarization may be smaller in women, irrespective of a longer total repolarization time. This feature might be a beneficial property, able to exert a protective action against ventricular tachyarrhythmias, and could partially explain the lower incidence of SCD in women despite longer QTc and JTc intervals and higher risk of TdP compared to men.[34,35]

The T-wave shape and duration – together with other ECG variables, such as QTc and JTc intervals and the features of J point and ST segment – can make it possible to distinguish the tracing of a man from that of a woman.[57,58]

Another clinically relevant ECG feature is the T-wave polarity. Inverted (negative) T wave in the right precordial leads is a normal finding in infants aged >48 hours, and persists during the first decade of life but, as children grow older, a gradual reversal of T-wave polarity occurs, leading after puberty to the adult repolarization pattern, characterized by negative T waves confined to V1. Sometimes a T-wave inversion (TWI) up to leads V2/V3 is detected beyond the pubertal age (the so-called "persistence of juvenile pattern of repolarization"), a pattern usually deemed to be devoid of clinical significance. Indeed, while a general agreement exists that TWI in inferior and/or lateral leads in young (black or white) individuals may reflect an underlying cardiomyopathy and warrants further investigation, it is also well recognized that healthy adolescents of all ethnic origins, as well as adolescent athletes and black adult athletes, frequently display TWI in anterior leads beyond V1 as an expression of normal variant, physiological adaptation to exercise or ethnicity. In a cohort of Italian children undergoing pre-participation screening, Migliore et al. found TWI in 5.7% of the subjects, with a predominant localization in the right precordial leads (≥2 contiguous leads V1 to V3). In both sexes the prevalence of right precordial TWI was almost identical, and decreased significantly with increasing age (8.4% in children aged <14 vs 1.7% in those ≥14), complete pubertal development and greater BMI. Incomplete pubertal development was the only independent predictor for the persistence of right precordial TWI beyond lead V1.

It is worth noting that 2.5% of postpubertal adolescents with inverted T waves, all exhibiting complete pubertal development, were diagnosed with an early cardiomyopathy (arrhythmogenic right ventricular cardiomyopathy in 3 cases with right precordial TWI, hypertrophic cardiomyopathy in 1 individual with TWI in lateral leads).[62] In a large cohort of 14,646 young, white adults – including 20% of athletes – Malhotra et al. detected anterior TWI beyond V1 (≥2 adjacent leads V1 to V4) in 2.3% of cases, more frequently in women than in men (4.3% vs 1.4%, respectively) and more commonly in athletes (especially those engaging in endurance sports) than in nonathletes (3.5% vs 2.0%, respectively). The highest prevalence of anterior TWI was observed in female athletes (6.5%), the lowest prevalence in male nonathletes (1.1%). Almost 80% of the anterior TWI was confined to leads V1 to V2, and after further evaluation resulted in a poor diagnostic yield for heart disease. This implies that such ECG pattern could be considered an innocent finding in asymptomatic subjects without a family history of cardiomyopathy or premature SCD. Anterior TWI extending beyond lead V2, by contrast, was very rare, occurring in only 1.2% of women and 0.2% of men. This pattern may raise concerns about an underlying cardiomyopathy and, therefore, may justify a careful diagnostic workup, particularly when associated with J-point or ST-segment depression. The mechanisms postulated to explain sex difference in the prevalence of anterior TWI in adults but not in prepubertal boys and girls include hormone modulation, different levels of sympathetic innervation and increased breast tissue in women around puberty, able to affect chest lead placement.[63]

Repolarization abnormalities

Nonspecific T-wave and/or ST-segment abnormalities are far more common in women than in men (Figure 9). Based on population studies, these repolarization abnormalities have been long believed to be of poor clinical and prognostic value in women.[64] In patients with suspected coronary heart disease (CHD), the presence of ST-T abnormalities in a baseline ECG is associated with a higher prevalence and severity of resting and stress-induced myocardial perfusion defects in men, whereas no significant difference has been shown in women with normal or abnormal ST-T morphology at rest.[65]

A later study by Rautaharju et al., however, evaluated hazard ratios (HRs) for ECG variables for combined nonfatal and fatal CHD events and for CHD mortality, by means of a large scale Cox regression analysis of 38,283 postmenopausal female participants in the Women's Health Initiative (WHI) trial, during up to 9.2 years of follow-up. The authors reported that several ECG variables, including ventricular repolarization abnormalities, were important predictors of future CHD events and CHD death in postmenopausal women. In particular, a wide QRS/T angle and the ECG finding of an old myocardial infarction (ECG-MI) turned out to be the strongest predictors of CHD events, with HRs of 1.90 and 1.62, respectively. In addition to wide

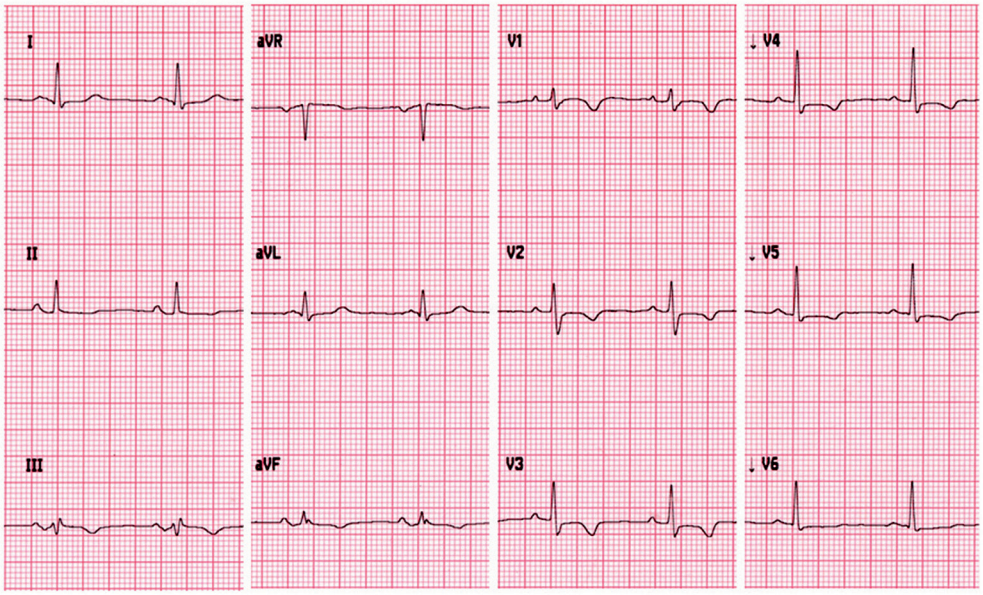

Figure 9. Nonspecific repolarization abnormalities in a healthy 43-year-old woman complaining of atypical chest pain (no CAD detected with stress echocardiography and coronary CT scan).

QRS/T angle, other repolarization variables, including T-wave amplitudes in V1 and V5, mean ST amplitude in V5, STV5 gradient (increase of ST voltage from the beginning to the end in lead V5) and QT prolongation were also significant CHD event predictors. QRS/T angle, ECG-MI and high QRS nondipolar voltage were the strongest predictors of CHD mortality, with HRs of 2.70, 2.41 and 2,18, respectively. The following five ECG abnormalities were identified as dominant CHD mortality risk predictors: wide QRS/T angle, ECG-MI, high QRS nondipolar voltage, reduced HRV, and QT interval prolongation (in cardiovascular disease-free women only). This study demonstrates that in postmenopausal women the ECG variables related to ventricular repolarization are as important in predicting CHD events and CHD mortality as some well-defined depolarization abnormalities, such as the finding of an old myocardial infarction. In particular, in women with and without previous cardiovascular disease (CVD), a wide QRS/T angle, which reflects an abnormal sequence of ventricular repolarization, has been found to be among the strongest and dominant ECG predictors of future CHD events and death. Even in the absence of an overt CHD, a wide QRS/T angle should be considered as an expression of a subclinical abnormality.[66] However, many of the above ECG abnormalities, although being clinically relevant, may not be easy to detect and characterized by clinicians without computer assistance. In agreement with these results, data from the Cardiovascular Health Study provide further evidence that there is no significant difference between men and women in the relative risk of mortality for ECG repolarization abnormalities.[67] In a subsequent investigation on postmenopausal, asymptomatic women without a history of prior CVD, participating in the estrogen plus progestin arm of the WHI trial, a significant association was found between major and minor baseline and incident ECG abnormalities (as defined by Novacode criteria) and increased long-term CHD and CVD events, irrespective of any hormone replacement therapy. In addition, data from this study demonstrate that the ECG provides incremental information for the risk stratification of cardiovascular morbidity and mortality beyond the traditional risk factors.[68]

The ECG is also a useful tool in predicting the risk of incident congestive heart failure (CHF) and all-cause mortality. Rautaharju et al., using the same cohorts of postmenopausal women in the WHI trial, identified a variety of ECG abnormalities, mostly related to ventricular repolarization, which were significant independent predictors of incident CHF, with six of them displaying a dominant predicting power. Among these dominant ECG predictors, a wide spatial QRS/T angle was the strongest, with a nearly 3-fold increased risk of incident CHF. Two other repolarization variables (ST depression in V5 and tall T wave in V1) and two depolarization-related criteria (high QRS nondipolar voltage and ECG-MI) were all associated with an over 2-fold increase in the incident CHF risk. Regarding the risk prediction of all-cause mortality, the strongest dominant variables were ECG-MI, wide QRS/T angle and low amplitude of T wave in lead V5, with a >2- to 3-fold risk increase in CVD women, but a substantially lower risk in the CVD-free group.[69] Since these studies are focused on postmenopausal women, they provide little or no information about the prognostic value of ECG criteria in younger age groups of women, as well as in men. Nevertheless, more recent data from the screening of large ECG databases (~50,000 patients) over 6 months in 2 hospitals revealed that a high QRS score of ≥5 (index of myocardial scar) and a wide QRS/T angle of ≥105° (expression of spatial discordance between depolarization and repolarization vectors) predict an increased 1-year all-cause mortality (8.8-13.9% compared to 3.8-5.5% in subjects not meeting these ECG thresholds), including SCD, in both women and men. Interestingly, these ECG markers exhibited an independent prognostic yield, despite a preserved or only moderately reduced left ventricular ejection fraction (LVEF), therefore adding a predictive value in death risk-stratification over LVEF alone.[70] In view of their critical importance as predictors of hard cardiovascular outcomes, including CHD, CVD, incident CHF events, all-cause mortality and SCD, the ventricular repolarization abnormalities, and particularly the QRS/T angle – together with the aforementioned depolarization (QRS) changes – should never be overlooked, especially in women where these ECG findings are often underestimated, or ignored as inconsequential.

Changes during exercise stress testing

Exercise stress testing is the most commonly used non-invasive method to diagnose a coronary artery disease (CAD), and an exercise stress ECG is often performed as the first-line diagnostic strategy in the assessment of angina, in both men and women. The main diagnostic ECG change during exercise testing consists of a horizontal or down-sloping ST-segment depression ≥0.1 mV (1 mm) in one or more leads, persisting for at least 0.06-0.08 s after the J point. In about 15% of patients, such a diagnostic ST-depression occurs later, in the recovery phase of the test. There is a general agreement that the diagnostic accuracy of the exercise ECG is lower in women than in men, with sensitivity usually being worse than specificity.[71-75] In a meta-analysis of exercise ECG testing in women the sensitivity and specificity for ST-segment depression were 61% and 70%, respectively; a meta-analysis in men showed diagnostic sensitivity

and specificity of 68% and 77%, respectively.[74] Women undergoing an ECG stress test have a higher rate of false-positive results than men.[71-75] Therefore, in women the positive predictive value of ST-segment depression during exercise testing is significantly lower than in men (in a study, 47% versus 77%, respectively); the negative predictive value, however, is similar in both sexes (78% in women versus 81% in men)[74] (Table 3). As a consequence, a positive ECG stress test is very useful in predicting the presence of a significant CAD in symptomatic men, but not in women. By contrast, in women a negative test is quite useful in effectively ruling out a diagnosis of CAD.[71,75] The mechanisms leading to these gender differences in the accuracy of stress-induced ST-segment depression are not completely understood. Some of the most reliable explanations are the following: 1) a higher prevalence and degree of resting ST-segment and/or T-wave abnormalities in women, making more difficult the interpretation of the ECG changes during exercise; 2) a lower prevalence of severe CAD in women less than 60 years old compared with men; 3) the inability of many women to exercise to maximum aerobic capacity, which prevents the induction of ischemia, thus limiting the ability of the stress test to accurately identify an underlying CAD; and 4) a digoxin-like effect of estrogen on ST-segment shape, especially during exercise. The estrogen theory is supported by some observations: in premenopausal women with no CAD, the ST depression during exercise varies with the menstrual cycle; among postmenopausal women with no demonstration of CAD, those receiving estrogen replacement therapy are more likely to undergo stress-related ST-segment depression compared with those who are not on estrogen replacement.[72,74]

Although a positive exercise ECG testing provides some diagnostic information in women, no prognostic implication has been shown with regard to cardiovascular and all-cause mortality, in contrast to both the diagnostic and prognostic values demonstrated in men.[74]

The appropriate recommendations for exercise stress ECG for diagnostic purposes must take into account the pre-test probability (PTP) of CAD, which in a given patient influences the post-test risk of CAD, according to Bayes' theorem. PTP is based on simple clinical features, including the presence of traditional cardiovascular risk factors. Major determinants of PTP are age, gender and the nature of symptoms (Table 4).[71-75] Noninvasive diagnostic testing is most useful in patients with an intermediate PTP-predicted likelihood of CAD. Based on these principles, the 2014 AHA Consensus statement on the role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease provides evidence-based guidelines on the diagnosis of CAD in women by noninvasive testing.[71] As shown in Table 4, the clinical PTPs for CAD are systematically higher in men than in age- and symptom-matched women, except for the older age groups (>60 years), in which PTPs become the same in both genders.[71-75] Accordingly, although the options for noninvasive diagnostic tests are similar for both men and

Table 3. Diagnostic value of exercise-induced ST-segment depression in the detection of CAD in men and women

	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
Men	68	77	81	77
Women	61	70	78	47

NPV, negative predictive value; PPV, positive predictive value.
Adapted from 74.

Table 4. Exercise testing: pre-test probability of coronary artery disease by age, sex and symptoms

Age (y)	Sex	Typical/definite angina pectoris	Atypical/probable angina pectoris	Nonanginal chest pain	Asymptomatic
30-39	Men	Intermediate	Intermediate	Low	Very low
	Women	Intermediate	Very low	Very low	Very low
40-49	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Low	Very low	Very low
50-59	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Intermediate	Low	Very low
60-69	Men	High	Intermediate	Intermediate	Low
	Women	High	Intermediate	Intermediate	Low

Modified from 73.

women, testing appropriateness is usually lower in women, and the 2014 AHA Consensus statement recommends exercise ECG as the first stress test of choice in the evaluation of symptomatic, intermediate-risk (10% to 90% PTP) women who are able to exercise and display a normal baseline ECG.[71] In the 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes, the PTPs of obstructive CAD traditionally based on age, gender and symptoms have undergone major revisions with respect to the 2013 version of the same guidelines, being the new PTPs consistently lower than previously predicted. However, the identification of patients with obstructive CAD, especially in the presence of a new PTP of 5-15%, is improved by assessing the overall clinical likelihood of CAD, based not on PTP alone, but also on the evaluation of several PTP modifiers able to increase (traditional risk factors of CVD, resting ECG changes, abnormal exercise ECG, coronary calcium by CT, LV dysfunction suggestive of ischemia) or decrease (normal exercise ECG, no coronary calcium by CT) the probability of a CAD. Owing to the better diagnostic performance of imaging tests, current ESC Guidelines recommend either noninvasive functional imaging for myocardial ischemia (in high clinical likelihood) or coronary CT angiography (in low clinical likelihood), instead of exercise ECG, as the initial test for diagnosing obstructive CAD. Exercise ECG may be considered as an alternative first test when noninvasive imaging is not available. However, since the findings on exercise ECG are modifiers of PTP strongly affecting the clinical likelihood of CAD, the test results – keeping in mind the above mentioned limitations in women – remain of crucial importance in the diagnosis and management of symptomatic patients in whom a chronic coronary syndrome is suspected.[75]

Very important additional information can be obtained if the ECG stress testing is evaluated beyond the ST-segment changes alone.[71,75] Indeed, in women the use of several exercise parameters, such as heart rate response, heart rate recovery, blood pressure response, symptoms, workload achieved, in conjunction with stress-related ST-segment depression, is able to enhance significantly the diagnostic accuracy of the ECG stress test and, also, to provide relevant data for the patient's prognostic assessment.[71,72,74,75]

Key messages

- Sex differences exist in each component of the ECG. Compared with men, women show higher and narrower P wave, lower and narrower QRS complex, lower and wider T wave, shorter PR interval.
- QTc interval is longer in women than in men from puberty up to 60 years of age. In addition, women develop greater drug-induced QTc prolongation compared to men and, thus, are more prone to torsades de pointes, in both congenital and acquired LQTS.
- J point and ST segment are higher in men than in women. This difference starts at puberty, peaks at 25-30 years of age, then gradually decreases. Such sex-related behavior may explain the male predominance in J-wave syndromes (BrS and ERS) and the worse prognosis in men.
- Gender differences in QTc interval and J point/ST segment are related to the ability of sex hormones, especially testosterone, to modulate the ion-channel function and current densities that are involved in ventricular repolarization. Weaker and controversial is the effect of estrogen.
- A careful analysis of the ECG by gender provides very valuable diagnostic and prognostic information, which allows to optimize the patient management in several clinical settings.

Conclusions

Although it is becoming increasingly recognized that the standard 12-lead ECG shows several sex-related differences regardless of ethnicity, to date physicians still tend to overlook this important knowledge and usually, in reporting the test results, little or no information is provided about the relationship between the patient's gender and ECG features. Nonetheless, a careful recognition of gender differences in the ECG and their implementation in routine medical practice will further enhance the clinical value of this simple, cost-effective and widespread available tool. In a short-term perspective, it would be advisable that certain ECG findings which have a well-documented sex-specific role as diagnostic and prognostic markers in a variety of pathological conditions, including inherited arrhythmia syndromes, coronary heart disease, left ventricular hypertrophy and congestive heart failure, are applied in a systematic fashion with reference to the patient's gender, in order to intensify prevention strategies, optimize therapeutic management and improve clinical outcomes.

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Author contribution statement: all Authors are responsible for the content and have read and approved the manuscript.

Conflict of interest statement: the Author declare no conflicts of interest.

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