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Age- and sex-based reference ranges for non-invasive ventricular repolarisation parameters

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Summary

Background: Some electrocardiographic parameters are able to assess indirectly ventricular repolarisation homogeneity. It is consequently essential to discriminate between normal and abnormal values in clinical decision-making. Considering there is still not a consensus about normal cut-off values, the aim of this study was to document reference intervals in all age groups of a healthy population, providing for age- and sex-percentile tables, which can be used easily and quickly in clinical practice.

Methods: We evaluated repolarisation markers in 606 sex-matched participants aged 1 day–94 years. Each subject underwent a 12-lead electrocardiogram at rest, and the following parameters were measured: QT, corrected QT, QTpeak, Tpeak-Tend, Tpeak-Tend dispersion, Tpeak-Tend/QT and QTpeak/QT ratio.

Results: A relationship was demonstrated between age and QTpeak, Tpeak-Tend, QT and QTc. In children, QTpeak, Tpeak-Tend and QT intervals increased linearly with age. In adolescents, all the three parameters remained stable. In adults, QTpeak and QT showed a further significant increase. On the contrary, Tpeak-Tend interval was longer in adults aged between 20 and 64 years than in participants aged 65 years or over, but the difference was not statistically significant. Male vs female participants showed longer Tpeak-Tend intervals; this sex difference was not statistically significant at birth and during childhood, whereas it was in adolescents and in adults.

Conclusions: Repolarisation parameters showed age- and sex-based variations, which are important to know to differentiate normal from pathological values.

1 | INTRODUCTION

Human ventricular wall comprises three electrophysiologically and functionally distinct cell types: epicardial, mid-myocardial and endocardial cells, with M cells showing the longest action potential (AP) duration; the intrinsic differences in AP duration lead to a transmural repolarisation heterogeneity among the layers.[1] In pathological conditions, transmural electrical differences in APs are amplified, with the consequent higher dispersion of repolarisation across the ventricular wall and the increased vulnerability to ventricular arrhythmias.[2]

Dispersion of ventricular repolarisation (DVR) can be assessed non-invasively using a 12-lead surface electrocardiogram (ECG). It has, in fact, been demonstrated, by means of monophasic action potentials recordings, that some electrocardiographic variables involving the terminal part of QT, such as the Tpeak-Tend (Tpe) interval, reflect indirectly DVR.[3]

Tpe interval in precordial leads, its dispersion and its ratio with QT in V5 have been suggested to provide an indirect and non-invasive assessment of repolarisation heterogeneity, and they have been evaluated in many cardiac and systemic diseases such as Brugada syndrome, long and short QT syndrome, hypertrophic cardiomyopathy,

arrhythmogenic right ventricular cardiomyopathy, coronary heart disease, heart failure, hypertension, diabetes mellitus, systemic lupus erythematosus and ankylosing spondylitis.[4–25]

Moreover, repolarisation markers have been studied in athletes and in non-morbidly obese populations.[26–30]

A relationship between Tpe duration and pacing-induced ventricular arrhythmia vulnerability has been demonstrated during electrophysiological study,[31] and data on large cohorts of patients have confirmed its utility as a risk stratification marker for sudden cardiac death and all-cause and cardiovascular mortality.[32,33]

It is consequently essential to discriminate between normal and abnormal values in clinical decision-making. Only few studies have assessed repolarisation markers in healthy subjects, and there is not a consensus about cut-off values; besides, elderly participants older than 81 years have never been involved.[34–36]

The aim of this study was to document reference intervals in all age groups of a healthy population providing for age- and sex-percentile tables, easy and quick to use in clinical practice.

What's known

- Some electrocardiographic variables are able to assess non-invasively repolarisation homogeneity. Markers such as the Tpeak-Tend, the Tpeak-Tend dispersion and the Tpeak-Tend/QT can be calculated manually by the physicians, obtaining information on susceptibility to ventricular arrhythmias.

What's new

- Ventricular repolarisation parameters show age- and sex-based variations. This article reports for age- and sex-percentile tables, which can be used easily and quickly in clinical practice.

2 | MATERIALS AND METHODS

2.1 | Study design and population

The study design was observational, retrospective and descriptive, enrolling healthy participants of both sexes, without age limits. All of the subjects performed a check-up visit and electrocardiogram in a hospital ambulatory setting, and we retrospectively acquired both their relevant clinical data and ECGs.

To study the distribution of the electrocardiographic variables in the different ages, we subdivided the sample into three groups on the basis of age (children, adolescents, adults), further subdivided into subgroups. The child group 1 was subdivided into subgroup 1A infants (between 1 day and 12 months), subgroup 1B toddlers (>1 year and ≤3 years), subgroup 1C preschoolers (≥3 years and ≤5 years), subgroup 1D middle childhood (between 6 and 8 years) and subgroup 1E late childhood (between 9 and 11 years).

The adolescent group 2 was subdivided into subgroup 2A young teens (between 12 and 14 years) and subgroup 2B teenagers (between 15 and 19 years).

The adult group 3 was subdivided into subgroups 3A (between 20 and 64 years) and 3B (≥65 years).

Clinical exclusion criteria were as follows: familiar history of arrhythmogenic disease and/or sudden death; personal history of heart disease, impaired glucose tolerance, diabetes, renal failure, hepatic or thyroid disease; and use of drugs or supplements.

Electrocardiographic exclusion criteria were as follows: atrial fibrillation, left or right bundle branch block, atrioventricular block, ventricular pre-excitation and pacemaker rhythm.

2.2 | Measurements and calculations

Each subject underwent a 12-lead ECG, using a standard digital recorder at a paper speed of 25 mm/s. The following commercially available electrocardiography machines were used: Philips Pagewriter PC 30, Philips Pagewriter Trim III, Esaote Mycardiopad XL and Cardioline Delta 360.

Every measurement was taken manually by one single observer. Evaluation of the intra-observer variability, calculated on 30 randomly chosen ECGs, was performed with two measurements of Tpe interval finding a high correlation (R>.9).

Corrected QT interval (QTc), QTpeak (QTp) interval, QTp/QT ratio, Tpe interval, Tpe-d and Tpe/QT ratio were calculated. QT intervals were measured from the QRS onset to the T-wave end, defined as the point where the descending part of the T-wave if positive or the ascending part of the T-wave if negative returns to the baseline of the TP segment.[37] When U-waves were present, the QT interval offset was measured to the nadir of the curve between T- and U-waves. When a bifid T-wave was present, the distance between the first and the second component was measured; if the time interval was ≤0.15 seconds, the second component was interpreted as a part of the T-wave; otherwise, the second component was identified as a U-wave.

Leads where the end of the T-wave could not be determined because of low-amplitude T-waves (<0.1 mV) were excluded from the analysis.

The QT interval recorded was the longest calculated in any ECG lead. The QT interval was corrected for heart rate (HR) using Bazett's formula (corrected QT=QT/√RR).[38]

QTpeak interval was measured in each precordial lead from the beginning of the QRS until the peak of the T-wave. In the case of negative or biphasic T-waves, QTpeak was measured to the nadir of the T-wave.[5] The QTpeak value reported was the longest interval obtained in all precordial leads.

The Tpe interval was measured in each precordial lead from the peak to the end of the T-wave. The longest interval obtained in all precordial leads was chosen as Tpe value.[5] The Tpe-d was defined as the difference between the maximum and the minimum Tpe interval in one single beat in the precordial leads.[5]

The Tpe/QT ratio was calculated dividing the Tpe interval by the QT interval, using lead V5.[10] The QTp/QT ratio was calculated dividing the QTpeak by the QT interval, using lead V3.[3]

2.3 | Ethics

The study was approved by the Institute of Sport Medicine (University of Palermo) and ethically performed according to the Declaration of Helsinki.[39]

2.4 | Statistical analysis

All analyses were performed using statistical analysis software R.[40]

Average values for electrocardiographic parameters were obtained by group and subgroup. Data are presented as mean ± SD and as estimates of percentiles.

To test for differences in variables between two groups, the unpaired Student's *t* test was used. One-way analysis of variance (ANOVA) was applied to compare means from three or more groups. Linear regression analysis was employed to determine the extent to which there was a linear relationship between continuous variables: repolarisation markers and age. Regression models were used to test the presence and the strength of association between continuous variables such as repolarisation markers and categorical variables such as sex. The models were applied for each subgroup to show differences in the association depending on age.

Statistical significance was set at $P<.05$.

3 | RESULTS

3.1 | Sample characteristics

Six hundred and six subjects, sex-matched, ranging in age from 1 day to 94 years and in sinus rhythm, were recruited. All participants were Caucasians with the exclusion of five subjects who were from Africa. No study participant had a personal history of heart disease, impaired glucose tolerance, diabetes, renal failure, hepatic or thyroid disease. They had no family history of arrhythmogenic disease and/or sudden death, and they were taking no drug or supplement. No subject had atrial fibrillation, left or right bundle branch block, atrioventricular block, ventricular pre-excitation or a pacemaker rhythm.

Study participants were subdivided into three age groups (see Methods for further details). The first group included 202 children aged 1 day-11 years, the second group comprised 202 adolescents aged 12-19 years and the third group consisted of 202 adults aged 20-94 years. All groups were sex-matched.

3.2 | Values of repolarisation parameters

Ventricular repolarisation markers of each group and the results from one-way ANOVA for group comparisons are shown in Table 1.

The 25th, 50th and 75th percentiles of QTpeak, Tpe, Tpe-d, Tpe/QT and QTp/QT together with the maximum value calculated for each parameter are presented in Table 2.

In Table 3, ventricular repolarisation parameters are shown after subdividing the study population into the following subgroups: infants (IA), toddlers (IB), preschoolers (IC), middle childhood (ID), late childhood (IE), young teens (IIA), teenagers (IIB), adults aged between 20 and 64 years (IIIA) and adults aged ≥65 years (IIIB). *P*-values from ANOVA, *t* tests and linear regression analysis are reported in the same table.

Percentiles of repolarisation parameters in the various subgroups are shown in Table 4.

HR of adolescents and adults ranged from 60 to 100 beats per minute (bpm), with the exclusion of only two participants. Newborns

TABLE 1 Repolarisation markers in children, adolescents and adults

Group	QT	QTc	QTpeak	Tpe	Tpe-d	Tpe/QT	QTp/QT
I (children)	309.8±38.4	401.7±25.0	243.2±30.6	70.5±13.0	21.0±9.5	0.21±0.02	0.78±0.03
II (adolescents)	356.9±22.2	401.9±21.0	275.5±21.3	86.2±9.5	25.9±9.8	0.22±0.02	0.76±0.03
III (adults)	372.6±26.1	407.3±19.8	291.1±24.5	87.1±9.5	27.3±9.0	0.21±0.02	0.77±0.02
P-value	<.05	<.05	<.05	<.05	<.05	<.05	<.05

Legend, QTc, corrected QT; Tpe, Tpeak-Tend interval; Tpe-d, Tpeak-Tend dispersion; Tpe/QT, Tpeak-Tend/QT; QTp/QT, QTpeak/QT.
Data are presented as mean±SD.
P-values are from ANOVA.

TABLE 2 Percentiles and maximum values of QTpeak, Tpe, Tpe-d, Tpe/QT and QTp/QT in children, adolescents and adults

Group	QTpeak	Tpe	Tpe-d	QTp/QT	Tpe/QT
I (children)	230-250-260 310	60-70-80 100	10-20-30 40	0.76-0.79-0.81 0.84	0.20-0.22-0.23 0.26
II (adolescents)	260-280-290 350	80-90-90 100	20-30-30 40	0.74-0.76-0.77 0.82	0.20-0.22-0.23 0.26
III (adults)	270-290-310 350	80-90-90 110	20-30-30 40	0.75-0.76-0.79 0.82	0.19-0.21-0.23 0.27

Legend. Tpe, Tpeak-Tend interval; Tpe-d, Tpeak-Tend dispersion; Tpe/QT, Tpeak-Tend/QT; QTp/QT, QTpeak/QT.
Electrocardiographic repolarisation parameters into each box are reported in the following order: 25th, 50th, 75th percentile (in the first row), maximum value calculated (in the second row).

TABLE 3 Repolarisation parameters in study population subdivided into subgroups according to age

Subgroup	QT	QTc	QTpeak	Tpe	Tpe-d	Tpe/QT	QTp/QT
IA	257.8±33.1	403.5±36.7	203.9±30.4	55.5±6.9	14.4±5.6	0.21±0.02	0.79±0.03
IB	286.5±26.9	404.0±23.6	228.8±24.8	62.3±7.8	17.3±7.9	0.21±0.02	0.81±0.02
IC	321.1±24.1	404.2±18.8	255.0±20.0	69.8±9.8	22.7±9.5	0.21±0.02	0.80±0.03
ID	329.8±19.0	399.3±25.8	258.6±18.2	76.4±9.4	23.4±9.6	0.21±0.02	0.77±0.03
IE	339.1±19.6	398.2±18.6	259.1±17.4	83.9±8.1	25.0±9.5	0.22±0.02	0.75±0.02
P-value[a]	<.05	>.05	<.05	<.05	<.05	>.05	<.05
IIA	355.9±21.3	402.0±20.7	275.1±20.7	85.9±9.3	25.5±9.9	0.21±0.02	0.76±0.02
IIB	358.0±23.2	401.8±21.3	276.0±22.1	86.5±9.8	26.3±9.7	0.22±0.02	0.75±0.03
P-value[b]	>.05	>.05	>.05	>.05	>.05	>.05	>.05
IIIA	367.6±25.3	401.4±19.7	284.7±23.4	88.3±8.4	26.8±9.8	0.21±0.02	0.76±0.02
IIIB	377.6±26.1	413.2±18.1	297.4±24.0	85.8±10.4	27.8±8.2	0.20±0.02	0.78±0.02
P-value[b]	<.05	<.05	<.05	>.05	>.05	<.05	<.05
P-value[c]	<.05	<.05	<.05	<.05	>.05	>.05	>.05

Legend, QTc, corrected QT; Tpe, Tpeak-Tend interval; Tpe-d, Tpeak-Tend dispersion; Tpe/QT, Tpeak-Tend/QT; QTp/QT, QTpeak/QT.
[a]*P*-value from ANOVA, [b]*P*-value from unpaired *t* test, [c]*P*-value from linear regression analysis assessing relationship between repolarisation parameters and age.
Data are presented as means±SD.

TABLE 4 Percentiles of QTpeak, Tpe, Tpe-d, Tpe/QT and QTp/QT in study population subdivided into subgroups according to age

Subgroup	QTpeak	Tpe	Tpe-d	Tpe/QT	QTp/QT
IA 1 day–12 months	190.0-200.0-212.5 280.0	50-60-60 70	10-10-20 30	0.20-0.21-0.23 0.25	0.77-0.80-0.82 0.83
IB 1<years>3	212.5-230.0-250.0 270.0	60-60-70 80	10-20-20 40	0.19-0.22-0.23 0.26	0.80-0.81-0.82 0.83
IC 3>years≤5	240.0-250.0-262.5 300.0	60-70-80 90	20-20-30 40	0.19-0.20-0.22 0.26	0.78-0.80-0.82 0.84
ID 6-8 years	250.0-260.0-270.0 290	70-80-80 90	20-20-30 40	0.20-0.21-0.22 0.26	0.75-0.78-0.80 0.82
IE 9-11 years	250.0-260.0-270.0 310	80-80-90 100	20-25-30 40	0.21-0.22-0.23 0.26	0.74-0.75-0.77 0.81
IIA 12-14 years	260.0-280.0-290.0 310	80-90-90 100	20-30-30 40	0.19-0.22-0.23 0.27	0.74-0.75-0.77 0.81
IIB 15-19 years	260.0-280.0-290.0 350	80-90-90 100	20-30-30 40	0.20-0.22-0.23 0.27	0.73-0.76-0.77 0.82
IIIA 20-64 years	270.0-280.0-300.0 340	80-90-90 110	20-30-30 40	0.19-0.21-0.23 0.26	0.74-0.76-0.77 0.81
IIIB ≥65 years	280.0-300.0-320.0 350	80-80-90 110	20-30-30 40	0.19-0.20-0.22 0.25	0.76-0.78-0.79 0.82

Legend. Tpe, Tpeak-Tend interval; Tpe-d, Tpeak-Tend dispersion; Tpe/QT, Tpeak-Tend/QT; QTp/QT, QTpeak/QT.
Electrocardiographic repolarisation parameters into each box are reported in the following order: 25th, 50th, 75th percentile (in the first row), maximum value calculated (in the second row).

showed HR in the range from 102 to 210 bpm, while only few children in other age range showed HR higher than 100 bpm.

The maximum value measured of Tpe ranged from 70 milliseconds in infants to 110 milliseconds in adults. The value of 110 milliseconds was present only in two study participants and was always associated with HR lower than 65 bpm. The maximum interval measured in participants with HR ≥65 bpm was 100 milliseconds.

3.2.1 | Age and repolarisation parameters

A relationship was demonstrated between age and the following parameters: QTpeak, Tpe, QT and QTc. No association was found between age and Tpe-d, Tpe/QT and QTp/QT.

In children, QTpeak, Tpe and QT intervals increased linearly with age. In adolescents, all the three parameters remained stable, not

showing statistically significant differences between the subgroups IIA and IIB.

In adults, QTpeak and QT showed a further significant increase from the subgroup IIIA to the subgroup IIIB. On the contrary, Tpe was longer in adults aged between 20 and 64 years than in participants aged 65 years or over, but the difference was not statistically significant.

3.2.2 | Sex and repolarisation parameters

With the aid of regression analysis, an association between sex and the following parameters was found: Tpe, Tpe/QT and QT ($P<.05$). Subsequently, regression models were applied to each subgroup, to study whether the relationship showed age-related changes. Repolarisation parameters and sex showed no association in the subgroups (IA, IB. IC, ID, IE) belonging to the first group ($P>.05$) for all the parameters studied.

A statistically significant association ($P<.05$) between Tpe, Tpe/QT and sex emerged in the subgroups IIA and IIB. A relationship between QTc and sex was absent in the subgroup IIA ($P<.05$) and present in the subgroup IIB ($P>.05$).

In the subgroup IIIA, there was an association between sex and Tpe, Tpe/QT and QTC ($P<.05$). In the subgroup IIIB, there was a statistically significant association between sex and Tpe and QTc, while the relationship between Tpe/QT and sex touched but not reached the statistical significance ($P=.052$).

In the subgroups IIA, IIB, IIIA and IIIB, women had faster HR than men (respectively 74.9±11.3 vs 79.8±9.2, 72.4±9.3 vs 80.2±10.3, 70.2±9.6 vs 74.0±9.0 and 71.4±11.5 vs 74.4±10.89). The difference was statistically significant in the subgroups IIA, IIB and IIIA.

Unpaired *t* tests were used to compare male and female participants in each subgroup (Table 5). Female participants showed longer QTc than male participants in the following subgroups: IIA, IIB, IIIA and IIIB. The difference was statistically significant in the last three

TABLE 5 Repolarisation parameters in female and male study participants subdivided into subgroups according to age

Subgroup	QT	QTc	QTpeak	Tpe	Tpe-d	Tpe/QT	QTp/QT	Sex
IA	258.4±38.6	402.5±39.3	205.8±35.6	54.7±7.7	14.7±5.1	0.21±0.03	0.80±0.03	F
1 day–12 months	257.0±26.9	404.8±34.6	201.8±24.3	56.5±6.1	14.1±6.2	0.22±0.02	0.79±0.03	M
	>.05	>.05	>.05	>.05	>.05	>.05	>.05	
IB	277.8±22.2	404.7±22.5	224.4±23.5	58.9±7.8	16.7±7.1	0.22±0.03	0.81±0.01	F
1<years>3	289.6±28.2	403.7±24.4	230.4±25.6	63.6±7.6	17.6±8.3	0.21±0.02	0.80±0.02	M
	>.05	>.05	>.05	>.05	>.05	>.05	>.05	
IC	318.8±26.2	402.9±15.5	254.7±21.5	68.2±8.8	21.2±9.3	0.21±0.02	0.80±0.03	F
3>years≤5	322.6±23.1	405.1±20.8	255.2±19.5	70.7±10.3	23.7±9.7	0.21±0.02	0.79±0.03	M
	>.05	>.05	>.05	>.05	>.05	>.05	>.05	
ID	324.3±18.6	400.1±27.5	255.2±18.3	74.8±10.3	23.8±9.2	0.21±0.02	0.77±0.03	F
6-8 years	334.8±18.3	398.5±24.9	261.7±18.0	77.8±8.5	23.0±10.2	0.22±0.02	0.77±0.03	M
	>.05	>.05	>.05	>.05	>.05	>.05	>.05	
IE	338.6±20.3	400.0±18.7	258.2±19.2	83.6±7.3	22.3±10.2	0.22±0.02	0.75±0.02	F
9-11 years	339.5±19.4	396.4±18.8	260.0±15.7	84.1±9.1	27.7±8.1	0.22±0.02	0.76±0.02	M
	>.05	>.05	>.05	>.05	>.05	>.05	>.05	
IIA	351.8±18.6	404.1±22.0	275.6±18.5	82.4±9.8	25.0±9.3	0.20±0.02	0.76±0.03	F
12-14 years	359.8±23.1	399.9±19.4	274.6±22.8	89.2±7.4	26.0±10.5	0.22±0.02	0.75±0.02	M
	>.05	>.05[a]	>.05	<.05	>.05	<.05	>.05	
IIB	354.2±19.1	407.6±18.3	273.4±17.3	84.0±10.3	28.0±9.0	0.21±0.02	0.76±0.03	F
15-19 years	361.8±26.4	396.1±22.7	278.6±25.9	89.0±8.6	24.6±10.1	0.23±0.02	0.75±0.02	M
	>.05	<.05	>.05	<.05	>.05	<.05	>.05	
IIIA	367.6±26.7	406.2±20.6	287.6±24.9	86.1±7.5	27.4±10.2	0.20±0.02	0.76±0.02	F
20-64 years	368.6±23.2	396.5±17.8	282.4±21.3	90.8±8.6	26.1±9.5	0.22±0.02	0.75±0.02	M
	>.05	<.05	>.05	<.05	>.05	<.05	>.05	
IIIB	376.6±27.1	416.7±21.2	298.8±24.9	83.4±9.6	27.8±7.4	0.20±0.02	0.78±0.02	F
≥65 years	378.6±25.3	409.9±13.9	296.1±23.2	88.2±10.7	27.8±9.0	0.21±0.02	0.77±0.03	M
	>.05	>.05	>.05	<.05	>.05	>.05[b]	>.05	

Legend, QTc, corrected QT; Tpe-max, Tpeak-Tend interval; Tpe-d, Tpeak-Tend dispersion; Tpe/QT, Tpeak-Tend/QT; QTp/QT, QTpeak/QT. *P*-values are from unpaired *t* tests.
[a]0.056, [b]0.052.

subgroups (P<.05), but did not reach the statistical significance in the subgroup IIA (P=.056).

On the contrary, Tpe was longer in boys than in girls in the subgroups IIA and IIB (P<.05) and in men than in women in the subgroups IIIA and IIIB (P<.05).

Higher Tpe/QT ratio was present in male participants of the subgroups IIA, IIB and IIIA compared with female participants of the same subgroups. In the subgroup IIIB, despite higher values in men than women, the difference just missed to reach the statistical significance (P=.052).

In both male and female participants, the precordial lead where the maximum value of Tpe was measurable was V3. The precordial lead with the shortest Tpe was V1. V3 was also the precordial lead where the maximum QTpeak was usually measured.

In the limb leads, the QT interval was found to be longest in lead DII, while in the precordial leads QT showed the maximum values in V3.

4 | DISCUSSION

Repolarisation parameters in healthy subjects have been investigated in few studies;[34,35,36] consensus about their measurement is still lacking and specific cut-off values remain arbitrary.

Our findings permit establishment of normal ranges of electrocardiographic ventricular repolarisation markers in healthy subjects over nine decades, providing percentile measures to allow comparisons with patients of the same age.

A close association emerged between some of the studied repolarisation markers and age and sex.

We have found that 75th percentile of Tpe increased constantly with age, from 60 milliseconds in infants to 80 milliseconds in middle childhood, reaching in the late childhood the value of 90 milliseconds and remaining stable in the following age groups. The maximum value measured of Tpe ranged from 70 milliseconds in infants to 110 milliseconds in adults. The value of 110 milliseconds was always associated with HR lower than 65 bpm. The maximum interval measured in participants with HR ≥65 bpm was 100 milliseconds.

Male participants showed longer Tpe intervals than female participants. In accordance with previous studies,[35] this sex difference was not statistically significant at birth and during childhood, while it was in adolescents and in adults.

From childhood to adolescence, Tpe interval in boys lengthened, whereas it did not show significant changes in girls, resulting as a mean, respectively, 7.6% and 5.6% shorter in female compared to male young teens and teenagers. In adults, women had a Tpe interval 5.2% shorter than men if aged between 20 and 64 years and 5.4% shorter if aged 65 years and over.

Contrary to Tpe interval, its interlead difference, the so-called Tpe-d, did not show any sex difference neither in children and teenagers nor in adults, confirming previous studies.[34]

Unlike Tpe, 75th percentile of Tpe-d did not show variations, with only a shift of 10 milliseconds in the passage from infants and toddlers to preschoolers.

In children and adolescents, the maximum value of Tpe-d found in our study was 40 milliseconds, which is shorter than that reported by others in subjects of the same age.[34] In adults, we found the same maximum value of 40 milliseconds.

It must be highlighted that Tpe from our data may be difficult to compare to other studies because we reported as value of Tpe the maximum obtained in all precordial leads while some studies on patients with cardiac or systemic diseases and/or healthy subjects reported Tpe measured in V5, or in V3.[21,35,36] However, our mean values for Tpe were similar to those found in healthy control subjects of the same age by a previous study using the longest precordial Tpe.[5] In our study, most of the participants showed the maximum value of Tpe in lead V3.

Neither Tpe/QT nor QTp/QT exhibited sex differences in childhood. On the contrary, male vs female young teens, teenagers and adults showed significant higher value of Tpe/QT, whereas in female participants, the slightly higher value of QTp/QT did not reach the statistical significance when compared to male participants.

Being both Tpe/QT and QTp/QT ratios, repolarisation parameters located as numerators and denominators, may affect their values. The higher Tpe/QT ratio value found in male participants reflected, in fact, the longer Tpe intervals showed by men.

Regarding age- and sex-based variations, QTpeak and QT exhibited the same behaviour. Both markers increased with age, without showing sex differences in the various age groups.

The longest QT interval value was more often measured in DII for the limb leads and V3 for the precordial leads, according to previous data from individuals without any repolarisation abnormality.[41,42]

To calculate the HR-corrected QT interval, Bazett's formula was used. It may lead to an overcorrection when HR is fast (>100 bpm) and an under correction when HR is slow (<60 bpm), but provides an adequate correction for HRs ranging from 60 to 100 bpm.[37] Outside the aforementioned range, the Framingham, Hodges and Rautaharju's corrections have more uniform rate correction over a wide range of HRs.[37] However, ECGs used in our study were registered in resting conditions and all, with the exclusion of only two ECGs, showed HRs for adolescents and adults in the range from 60 to 100 bpm, where most formulae provide almost equivalent results for the diagnosis of QT prolongation. Despite neonates showed HRs between 102 and 210 bpm and some children in other age range showed HRs higher than 100 bpm, we choose to use, for homogeneity of results, the same formula, which still remains the standard for clinical use. In fact, despite the limits of Bazett's formula, new HR correction formulae lack the simplicity needed for routine clinical use and have not been sufficiently validated in paediatric studies.[43,44] A recent study, analysing 702 ECGs, supported continued use of Bazett's formula in infants and young children,[45] and this correction of QT interval duration has been used in most of the neonatal studies, including a very large study of ECG screening newborns aged between 15 and 25 days, where Bazett's formula was used to identify potential cases of long QT syndrome, following the European guidelines for the interpretation of the neonatal electrocardiogram.[46,47]

In our study, we found a relationship between QT when corrected for HR by Bazett's formula and sex. In fact, in contrast to what showed by QT interval, a sex difference in QTc was present in all life stages, excluding childhood and young teen hood. In young teens, there was yet a sex difference, which did not narrowly reach statistical significance. Female participants from 15 to 64 years showed longer QTc intervals than men. From 65 to 94 years, the difference was still present, but no longer statistically significant.

The age and sex differences found in our study are probably hormone-related. Previous studies have, in fact, showed that sex hormones and gonadotropins may play a key role in the repolarisation process.[48] Another indirect influence can be mediated by the autonomic nervous system: women, in fact, showed higher resting HR than men, which determined longer QT intervals when corrected for HR.

4.1 | Limitations

One study limitation may be represented by the use of Bazett's formula, for the aforementioned reasons.

Another limitation is the use of manual measurements of repolarisation parameters made by one single observer. However, the advantages of computerised vs manual measures are still controversial. Van de Loo and colleagues found acceptable reproducibility using manual measurement of repolarisation parameters both in healthy subjects and in patients with acute myocardial infarction,[49] but these findings have not been confirmed by studies by Kautzner et al.[50,51]

On the other side also the use of automated assessment of repolarisation parameters may show some problematics associated, in particular, with the detection of T-wave end in the ECG signal, when T-wave morphology is particularly complex.[52,53] Moreover, the computer-based measurements show a reliability and a reproducibility significantly lower for complex parameter such as QT dispersion than for conventional ECG indices such as RR interval and QT interval.[52,53]

As a consequence, the clinical experience obtained through manual assessment of repolarisation markers may have some advantages compared to reproducible but incorrect measurements made by a computer, in particular when the ECGs are of poor quality and when the T-wave show complex and heterogeneous pattern difficult to interpret by a computerised algorithm.

Finally, considering the lack of international consensus on the definition of healthy status, we have subjectively, defined as healthy, individuals who was not known to suffer of any significant illness relevant to the study. Being a retrospective study, we were not able to collect full basal descriptive data (i.e. blood chemistry, body mass index or echo data) for all study subjects other than age and gender. However, absence of any exclusion criteria was carefully checked.

5 | CONCLUSIONS

Repolarisation parameters showed age- and sex-based variations, which is important to know to differentiate normal from pathological values.

The percentile distributions provided in this report are related to a study population that was healthy, sex-matched and ranging from 1 day to 94 years and can be used, easily and quickly, in clinical practice to compare an individual patient's repolarisation parameter to the values showed by a healthy reference group.

Moreover, our reference values could guide future research focusing on diseases and drugs, able to impair ventricular repolarisation with a consequent pathological modification of the relative electrocardiographic markers.

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DISCLOSURE

None to declare.

AUTHOR CONTRIBUTIONS

A. Braschi: study concept and design, data acquisition, measurements of repolarisation markers, data interpretation and drafting and approval of the final version of the article; M.G. Abrignani: data collection and analysis and drafting and approval of the final version of the article; V.C. Francavilla: data acquisition and drafting and approval of the final version of the article; V. Abrignani: data acquisition and drafting and approval of the final version of the article; G. Francavilla: data collection, critical revision of the manuscript and approval of its final version.

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