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Normal values of the ventricular gradient and QRS-T angle, derived from the pediatric electrocardiogram☆

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ABSTRACT

Background: Normal values of the mathematically-synthesized vectorcardiogram (VCG) are lacking for children. Therefore, the objective of this study was to assess normal values of the pediatric synthesized VCG (spatial QRS-T angle [SA] and ventricular gradient [VG]).
Methods: Electrocardiograms (ECGs) of 1263 subjects (0–24 years) with a normal heart were retrospectively selected. VCGs were synthesized by the Kors matrix. Normal values (presented as 2nd and 98th percentiles) were assessed by quantile regression with smoothing by splines.
Results: Our results show that heart rate decreased over age, QRS duration increased and QTc interval remained constant. The SA initially decreased and increased again from the age of 8 years. The VG magnitude was relatively stable until the age of 2 years, after which it increased.
Conclusion: Normal values of the pediatric ECG and VCG (VG and SA) were established. These normal values could be important for future studies using VG and SA for risk stratification in heart disease in children.

Introduction

Vectorcardiography, especially the Frank vectorcardiogram (VCG), was a popular form of electrocardiography until it disappeared from the clinical routine in the seventies because it required special equipment and expertise. When computerized synthesis of the VCG from a 12-lead electrocardiogram (ECG) became feasible, it became clear that some vectorcardiographic variables, specifically the angle between the spatial QRS- and T axes (spatial QRS-T angle, [SA]) and the spatial QRS-T integral (ventricular gradient [VG]) [1] contained information that is not explored by standard 12-lead electrocardiography. Thus, the re-introduction of the VCG assumed the form of an add-on to the conventional 12-lead ECG. Both descriptors (VG and SA) have demonstrated additional diagnostic and prognostic value. Projection of the VG in an optimized direction is associated with right ventricular pressure and pulmonary hypertension [2, 3]. An abnormal (i.e., large) SA can improve prediction of sudden cardiac death after acute coronary syndromes [4] and overall mortality in a general population [5–7]. Normal values of the VG and SA in adults have been published [8–10]. Also, pediatric normal values obtained from Frank VCGs have been published [11]. However, up to now, pediatric normal values of SA and VG using a VCG that is synthesized mathematically from a standard 12-lead ECG are still lacking. Therefore, the objective of the current study is to determine pediatric normal values of SA and VG from a synthesized VCG, including their dynamics during growth.

Materials and methods

Study group

Normal subjects were retrospectively selected from the pediatric cardiology outpatient clinics of the Leiden University Medical Centre (LUMC) and the Academic Medical Centre Amsterdam, and from the first year of medical school at the LUMC (ECGs were made for educational purposes). The LUMC Medical Ethics Committee provided a statement of no objection for obtaining and publishing the anonymized data. The ECGs from the first year medical students are part of a larger

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database (The Leiden University Einthoven Science Project dataset) that was also used by Rijnbeek et al. [12] and Scherptong et al. [10]. All students gave written informed consent.

1011 children were selected because they visited the pediatric cardiology outpatient clinics and were declared normal after a full diagnostic work-up consisting of evaluation by a pediatric cardiologist, an echocardiogram and ECG. These healthy children were referred to the outpatient clinics because of an additional examination, for instance when a doctor at the consultation clinic heard a functional murmur during a routine check.

The age range of interest for our study was 0 days up to 18 years. By including 252 ECGs from first-year medical students (17–24 years), the data covered an age-range between 0 and 24 years, thus allowing for the use of a smoothing algorithm over the full age-range of interest in the statistical analysis. This resulted in a total study group of 1263 normal ECGs. Table 1 shows the age and sex distribution. Age categories between 0 months and 16 years are conform Rijnbeek et al. [13]. Age categories "16–20 years" and "20–24 years" were added to allow for the application of the smoothing algorithm at the age of 18 years.

Electrocardiogram recording

The 643 ECGs made in the LUMC were recorded with Mortara ELI 250 and 350 electrocardiographs (Mortara Instrument, Milwaukee, WI, USA) with a 1000 samples per second sampling rate; the 368 ECGs made in the AMC were recorded with MAC5500 electrocardiographs (GE Healthcare, Milwaukee, WI, USA) with a 250 samples per second (204 ECGs) or 500 samples per second (164 ECGs) sampling rate. The 252 ECGs of medical students at the LUMC were recorded with MAC5500 electrocardiographs (GE Healthcare, Milwaukee, WI, USA) with 500 samples per second sampling rate. All recordings were converted to ECGs with a 500 samples per second sampling rate.

Vectorcardiogram analysis

All ECGs were processed with the interactive research-oriented MATLAB (The MathWorks, Natick, MA) program LEADS (Leiden University Medical Centre, Leiden, the Netherlands) [14]. VCGs were synthesized by the Kors transformation matrix [15]. In brief, LEADS automatically removes baseline wander, deselects noisy beats, and computes an averaged beat in which it finds default onset of QRS, end of QRS (J point) and end of T landmarks. Subsequently, the LEADS analyst can adjust the beat selection and these landmarks, after which SA (angle between the mean QRS and T vectors) and VG (vectorial sum of the QRS and the T integrals) are automatically computed. All LEADS analyses were done by two analysts independently (VPK, CAS). In case of disagreement the definite positioning of the landmarks was collectively determined. Additionally to SA and VG, heart rate (HR), QRS duration and QT interval were stored. QTc was calculated with Bazett's formula.

Table 1
Age and sex distribution of the study group.

Age range	Total (M/F)
0–1 month	20 (12/8)
1–3 months	80 (44/36)
3–6 months	55 (24/31)
6–12 months	57 (24/33)
1–3 years	179 (101/78)
3–5 years	166 (81/85)
5–8 years	172 (99/73)
8–12 years	125 (76/49)
12–16 years	123 (70/53)
16–20 years	192 (91/101)
20–24 years	94 (34/60)
Total	1263 (656/607)

Age and sex distribution of the total study group.

Statistical analysis

Median, 2nd percentile and 98th percentile and their confidence intervals were continuously estimated as a function of age with quantile regression based on smoothing splines [16] with the COBS [17] extension of the statistical program "R" [18]. This smoothing operation allows for influences from younger and older children on the estimated value at a given age. In this respect it is a problem to estimate smoothed values at the end of the age span of interest (18 years): when the collected data ends at the age of 18 years, the smoothing at 18 years is only one-sided, and this creates a border effect in the terminal part of the regression curve. To solve this, we have added data of subjects until the age of 24 years. Adding data until the age of 24 years warrants absence of a border effect at 18 years, and introduces a border effect at 24 years. The latter is, however, not a problem because this is outside the age range of interest in the current study (up to 18 years). Spline knots were chosen at ages 0.08, 1, 5, 10, 15, 16, 17, 18, 19, and 23.6 years. The positions of these knots were determined by the distribution density of the data over the age range: knots were closer together at higher data densities and more distant with sparse data. The knots at ages 0.08 and 23.6 years correspond to the minimal and maximal ages in the data set. Tabulated data were based on the interpolated values in the middle of each of the age classes, at 1 month, 2 months, 4.5 months, 9 months, 2 years, 4 years, 6.5 years, 10 years, 14 years, and 18 years. Data at 22 years (middle of the highest age group) were not included in the table; these data served only to facilitate application of the smoothing algorithm at the age of 18 years.

Results

The total study group consisted of 1263 subjects, 1011 from the pediatric cardiology outpatient clinics and 252 medical students. Table 1 displays the age and sex distribution of the study group.

ECG and VCG variables

Fig. 1 displays the ECG variables as measured in all subjects of the study group as age-dependent scatter plots. These figures also contain the curves of the estimated medians and 2nd and 98th percentiles with their 95% confidence intervals. Fig. 1a shows a constantly decreasing median heart rate that stabilizes at higher ages. The larger confidence intervals at lower ages are caused by sparse data; this effect can be seen in all measured variables. The median QRS duration (Fig. 1b) showed a constant increase that has not yet stabilized at higher ages. The median QT interval (Fig. 1c) increased constantly and stabilized at higher ages. The median QTc interval (Fig. 1d) remained rather constant with a slight dip around age 3. Fig. 2 displays the VCG variables as measured in all subjects of the study group as age-dependent scatter plots. The median SA (Fig. 2a) initially decreased and increased again from the age of around 8 years and has not yet stabilized at higher ages. The median VG magnitude (Fig. 2b) was relatively stable until the age of around 2 years after which it increased without having stabilized at higher ages. Note that the figures display all data including the added normal subjects aged 18–24 years but that the median and the 2nd and 98th percentiles are only valid until the age of 18 years (see the Statistical analysis paragraph in the Methods section).

Table 2 shows the medians and 2nd and 98th percentiles for all ECG and VCG variables at the middle values of the age classes. Values from the highest age category in the study group (20–24 years) have not been included because of the presence of a border effect (see the Statistical analysis paragraph in the Methods section).

Discussion

In the dynamic period between birth and adulthood many structural and functional changes occur, which cause changes in the ECG as a

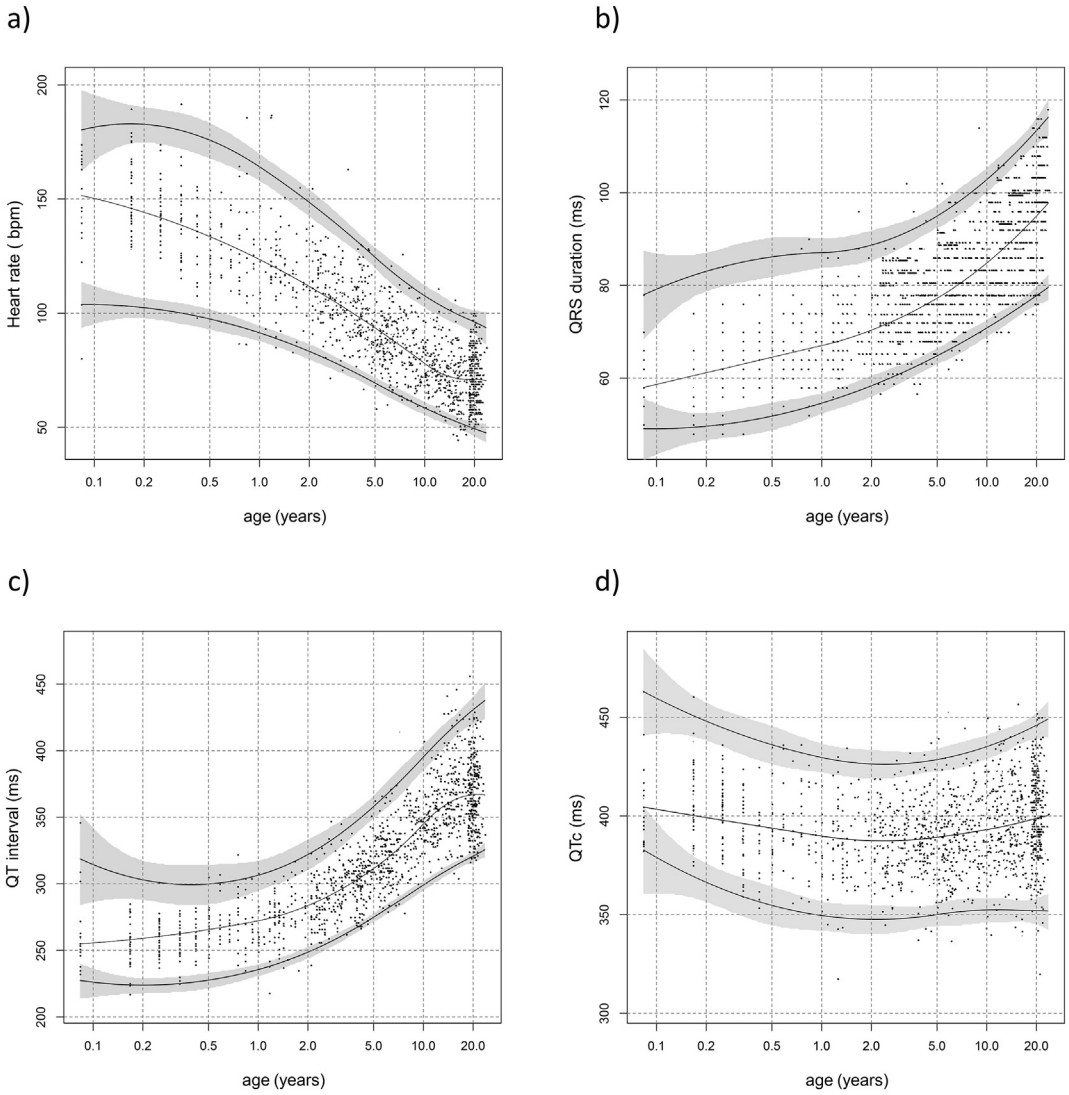

Fig. 1. Scatter plots of ECG variables versus age. The black curves show the estimated medians and 2nd and 98th percentiles. The 95% confidence intervals are shown in grey. a) Scatter plot of heart rate versus age. b) Scatter plot of QRS duration versus age. c) Scatter plot of QT interval versus age. d) Scatter plot of QTc versus age.

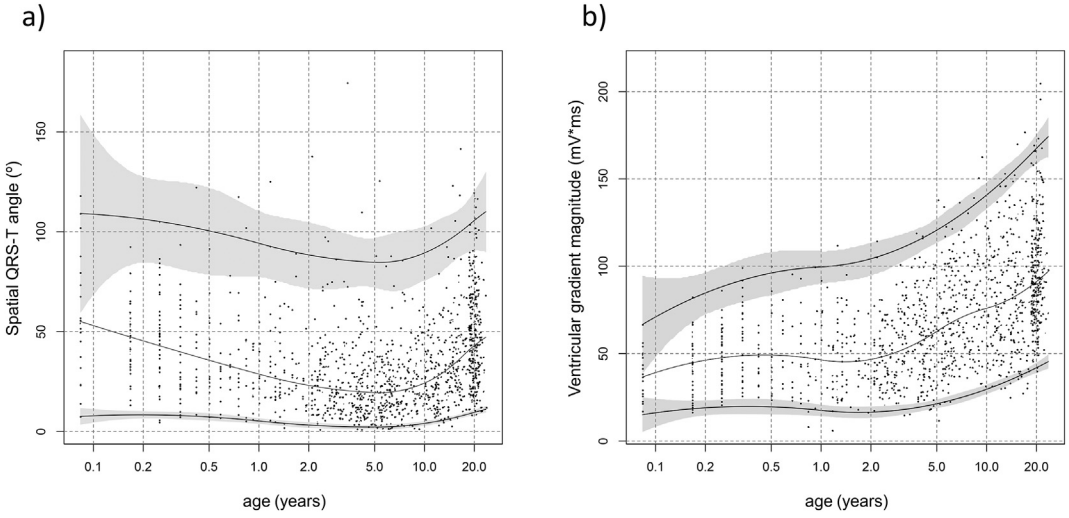

Fig. 2. Scatter plots of VCG variables versus age. The black curves show the estimated medians and 2nd and 98th percentiles. The 95% confidence intervals are shown in grey. a) Scatter plot of QRS-T angle versus age. b) Scatter plot of ventricular gradient versus age.

Table 2
ECG and VCG variables.

Age	HR (bpm)	QRS duration (ms)	QT interval (ms)	QTc[a] (ms)	SA (°)	VG (mV ∗ ms)
1 month	152 (104,180)	58 (49,78)	255 (227,319)	405 (383,463)	55 (8,109)	37 (15,67)
2 months	146 (103,183)	61 (49,82)	258 (224,305)	400 (369,451)	47 (8,107)	45 (18,82)
4.5 months	137 (99,179)	64 (51,85)	263 (226,299)	395 (358,440)	39 (8,103)	49 (20,93)
9 months	128 (94,170)	66 (53,87)	269 (232,303)	392 (351,432)	32 (6,97)	48 (19,99)
2 years	112 (83,149)	70 (58,89)	284 (249,322)	388 (348,426)	23 (3,88)	47 (17,104)
4 years	98 (73,131)	75 (63,93)	303 (268,348)	388 (349,427)	20 (2,85)	57 (20,116)
6.5 years	88 (65,118)	80 (67,98)	323 (284,371)	391 (351,431)	20 (2,85)	69 (24,128)
10 years	78 (59,108)	85 (71,103)	345 (299,395)	393 (352,435)	24 (4,89)	76 (30,141)
14 years	72 (54,101)	89 (74,108)	360 (310,414)	396 (352,440)	32 (6,96)	82 (35,153)
18 years	71 (51,98)	93 (77,112)	366 (318,426)	398 (352,444)	40 (9,102)	88 (40,163)

Global ECG and VCG variables. Data is shown as median (2nd, 98th percentile). Abbreviations: ECG = electrocardiogram, HR = heart rate, SA = spatial angle, VG = ventricular gradient, VCG = vectorcardiogram.
[a] QTc was calculated with Bazett's formula: QT / √(RR).

function of age. Several of the dynamic changes in electrocardiographic variables have to be explained by combined changes in the source of the electrocardiogram (the heart) and in the volume conductor between the heart and the body surface (the thorax). Some electrocardiographic variables are independent of the volume conductor and can be considered as cardiac properties (e.g., heart rate, QRS duration and QT interval). We will discuss these cardiac properties first.

ECG variables

Several studies have been published that determined the normal limits in the pediatric ECG [13, 19–22]. In our study group heart rate declined with age. Median values in the pediatric age groups correspond well with the median heart rate values as reported by Rijnbeek et al. [13]. Comparison of the 2nd and 98th percentiles show some differences in the lowest age groups; this is likely the consequence of limited sample size and a different statistical method to assess percentiles. The current study showed that the median resting heart rate in our study group stabilized after puberty. This stabilization is not evident from the study by Rijnbeek et al. [13]; our additional inclusion of a group of normal subjects aged 18–24 years allowed for an improved assessment of trends in the highest pediatric age range. The current study showed that median QRS duration constantly increases over all age groups, with no stabilization yet at the age of 18 years. QRS duration and trend roughly correspond to the pediatric normal values described by Rijnbeek et al. [13]. Rijnbeek et al. [13] have shown a significant difference in the 98th percentile of the QRS duration between boys and girls in the age groups “3–6 months” and “6–12 months”. However, this difference was maximally 7 ms and, hence, has limited clinical significance. Note that the trend at higher ages (18–24) cannot be interpreted because of a possible border effect caused by the smoothing algorithm. However, the study by Rijnbeek et al. [12] in subjects until 90 years of age, also showed this trend; in their study it appears that QRS duration only stabilizes at the mid 20's. Compared to the QTc values in the Rijnbeek publication [13] our median values are 10–15 ms shorter and show a U shape with a minimum around the age of 3 years. These differences are likely caused by different methods for determination of the end of the T wave. The LEADS program [14] determines the T wave in the heart-vector magnitude, computing the instant at which the tangent to the steepest slope of the terminal part of the T wave intersects zero. The ECG analysis program used by Rijnbeek et al. uses a template-matching method. Macfarlane et al. report QTc values in a large database of 1784 healthy neonates, infants, and children [23], which are strikingly similar to our values even though QTc in that study was corrected by the Hodges formula.

Spatial QRS-T angle

Several studies have shown, in an adult population, that an abnormal (i.e., large) SA can improve prediction of sudden cardiac death and overall mortality in a general population [6, 7]. Recently, Cortez et al. showed that a smaller SA rules out sustained ventricular arrhythmias in children with hypertrophic cardiomyopathy [24]. Our data showed that the median SA steadily decreased until the age of 8 years, after which the SA increased without stabilization in the highest age group. This could be caused by changes in the expression of action potential morphology differences between the endocardium and the epicardium over age. Additionally, the RV dominance in the infant heart gradually changes to LV dominance in the adult; which influences the QRS and the T vectors. However, we have to realize that these ECG-derived vectorcardiographic measures do not necessarily have the same physiologic explanation as in adults.

The trend in SA as observed by Rautaharju et al. [11] in pediatric Frank VCGs is comparable to our results; in their study the spatial angle between the QRS and STT integral vectors reaches its minimum in the age group 1.5–4.5 years after which it increases again. Edenbrandt et al. [25] studied the ECGs of 1792 healthy children; however, these ECGs were synthesized with the adjusted Dower matrix. Furthermore, the QRS-T angle was only determined in the transverse plane [25]. Altogether, the results of this study cannot be compared to our results. Another study by Dilaveris et al. [26] reports about ECGs recorded in 646 children with a mean age of 8.54 ± 1.86 years. Also in that study the inverse Dower matrix was used to synthesize the VCG. Moreover, the spatial QRS-T angle was computed as the angle between the maximum QRS and T vectors. In our study, we adopted the common definition, and computed the SA as the angle between the mean QRS and T vectors (i.e., the angle between the QRS and T axes). The limited age range and the methodological differences of the study by Dilaveris et al. [26] hamper comparison to our results. Normal values of SA have been published for young adults [10]. However, part of the ECGs used in that study [10] were also used in the current study and in that study the inverse Dower matrix was used to synthesize the VCGs. It has been demonstrated that use of the Kors matrix yields different SA values than the inverse Dower matrix [27]. Nowadays, the Kors matrix is generally accepted as the best VCG synthesis matrix [27, 28]. For this reason, VG and SA results were not compared to the results of current study.

Ventricular gradient

It has been shown in adults that the VG, a three-dimensional measure of ventricular action potential duration heterogeneity [29], has additional diagnostic value in the electrocardiographic detection of pulmonary hypertension [2, 3]. VG could potentially also be a valuable diagnostic tool in children with a congenital heart defect, especially those at risk of pulmonary hypertension. Our study showed that the median VG magnitude was relatively stable until the age of around 2 years after which it increased without having stabilized at higher ages. Rautaharju et al. [11], who measured the VG in Frank VCGs, report a different trend. They observed an initial increase in median VG value till around 100 mV ∗ ms at the age of around 6 years, after which a slight

decrease was observed till 90 mV ∗ ms at the age of 16 years. In contrast, our data showed a median VG value of 69 mV ∗ ms at age 6.5 years. Results in the highest age group of Rautaharju et al. [11] are comparable to our results. A possible explanation could be that the Kors matrix is less suitable for synthesizing Frank VCGs in children.

Even though there is little evidence of clustering of our normal values of the derived VG and SA around the mean, this is not unique for pediatric ECGs and not caused by the use of the Kors transformation. Also in adults, VG and SA do not cluster very well in matrix-derived-VCGs [10] and the same observation was done in the actual Frank VCG [27].

Diagnostic validity

At present, it is not clear to what extent a synthesized pediatric VCG by using the Kors matrix equals a Frank VCG. The Kors matrix has been developed with a database consisting of simultaneously recorded standard 12-lead ECGs and Frank VCGs in adults. It is likely that the Kors matrix will yield less accurate Frank VCGs the more the pediatric thoracic anatomy differs from the average adult's anatomy. This can be verified only when similar simultaneous 12-lead ECGs and Frank VCGs are recorded in children, which warrants further studies. Moreover, in this respect, the question arises as to how well a Frank VCG in children yields valid heart vector components (X, Y, Z). Actually, the Frank VCG rests on a physical model of an adult torso with homogeneous conduction characteristics (without lungs). When doing justice to the dynamic anatomy of human growth, separate models for various age stages should be developed. This would likely lead to different weighting coefficients in the Frank resistor network between the Frank electrodes and the X, Y and Z heart vector components. Corresponding ECG-to-VCG matrices could then be generated by simultaneously recoded 12 lead ECGs and the corrected Frank VCGs for each age group.

Following this reasoning, it is not likely that the Kors-VCG-derived metrics in a pediatric population have a diagnostic value that corresponds to the adult measurements. However, a consistently applied algorithm will still produce valid results. After an inventory of normal values as done in the current study, extreme values outside the normal range can be considered pathologic. A study group with various pathologies could reveal how much overlap exists between the normal and the abnormal group. For this purpose, future studies are needed. At this moment, it cannot be predicted if the metrics as provided in this study (SA and VG) will be able to separate normal from abnormal. Though, even when this would not be possible, it is still relevant to study individual trends by serial ECG/VCG analysis because any change in the individual ECG/VCG outside the spontaneous variability should be noted and interpreted within the clinical situation. The current study could be considered as a first step in this process.

Limitations

Our study is limited by the fact that the study data consists of a mix of ECG recordings sampled at 250 samples per second, 500 samples per second and 1000 samples per second. Rijnbeek et al. [30] demonstrated that the maximal positive and negative QRS deflections in pediatric ECGs recorded with a high-frequency bandwidth start to decrease with high-frequency cut-off values below <250 Hz; they conclude that the bandwidth of pediatric ECGs should be increased to 250 Hz. However, at present, not every clinic records ECGs with such high bandwidths and most ECG machines will have a bandwidth of around 0–150 Hz. Also, the average difference in pediatric ECG amplitude measurements with a higher bandwidth was shown by Rijnbeek et al. [30], to be in the order of 50 μV, which is not clinically relevant. Future studies should assess normal values of different age groups with changing bandwidth. The influence of low bandwidth on SA and VG is unknown. We assume, though, that this influence is limited, because these variables are integrals, and the amount of high-frequency energy content in the ECG is very small. Similar to Rijnbeek et al. [13], age categories "0–1 day"; "1–3 days"; "3–7 days" and "1–4 weeks" as used in the study by Davignon et al. [20] had to be combined into one category "0–1 month" because of the small number of subjects in the lower age groups. Therefore the reference values that we produced in these groups have to be used carefully. These age groups require further study. Furthermore, because of a small number of subjects in the lower age groups, we were not able to compare male to female values.

Conclusions

Normal values of the ventricular gradient and spatial QRS-T angle, derived from the pediatric electrocardiogram, were established. These normal values could be important for future studies using ventricular gradient and spatial QRS-T angle for risk stratification in heart disease in children.

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References

[1] Man S, Maan AC, Schalij MJ, Swenne CA. Vectorcardiographic diagnostic & prognostic information derived from the 12-lead electrocardiogram: historical review and clinical perspective. J Electrocardiol 2015;48:463–75.
[2] Kamphuis VP, Haeck ML, Wagner GS, Maan AC, Maynard C, Delgado V, et al. Electrocardiographic detection of right ventricular pressure overload in patients with suspected pulmonary hypertension. J Electrocardiol 2014;47:175–82.
[3] Scherptong RW, Henkens IR, Kapel GF, Swenne CA, van Kralingen KW, Huisman MV, et al. Diagnosis and mortality prediction in pulmonary hypertension: the value of the electrocardiogram-derived ventricular gradient. J Electrocardiol 2012;45:312–8.
[4] Lingman M, Hartford M, Karlsson T, Herlitz J, Rubulis A, Caidahl K, et al. Value of the QRS-T area angle in improving the prediction of sudden cardiac death after acute coronary syndromes. Int J Cardiol 2016;218:1–11.
[5] Kardys I, Kors JA, van der Meer IM, Hofman A, van der Kuip DA, Witteman JC. Spatial QRS-T angle predicts cardiac death in a general population. Eur Heart J 2003;24:1357–64.
[6] Waks JW, Sitlani CM, Soliman EZ, Kabir M, Ghafoori E, Biggs ML, et al. Global electric heterogeneity risk score for prediction of sudden cardiac death in the general population: the atherosclerosis risk in communities (ARIC) and cardiovascular health (CHS) studies. Circulation 2016;133:2222–34.
[7] Whang W, Shimbo D, Levitan EB, Newman JD, Rautaharju PM, Davidson KW, et al. Relations between QRS|T angle, cardiac risk factors, and mortality in the third National Health and Nutrition Examination Survey (NHANES III). Am J Cardiol 2012;109:981–7.
[8] Draper HW, Peffer CJ, Stallmann FW, Littmann D, Pipberger HV. The corrected orthogonal electrocardiogram and vectorcardiogram in 510 normal men (Frank lead system). Circulation 1964;30:853–64.
[9] Pipberger HV, Goldman MJ, Littmann D, Murphy GP, Cosma J, Snyder JR. Correlations of the orthogonal electrocardiogram and vectorcardiogram with consitutional variables in 518 normal men. Circulation 1967;35:536–51.
[10] Scherptong RW, Henkens IR, Man SC, Le Cessie S, Vliegen HW, Draisma HH, et al. Normal limits of the spatial QRS-T angle and ventricular gradient in 12-lead electrocardiograms of young adults: dependence on sex and heart rate. J Electrocardiol 2008;41:648–55.
[11] Rautaharju PM, Davignon A, Soumis F, Boiselle E, Choquette A. Evolution of QRS-T relationship from birth to adolescence in frank-lead orthogonal electrocardiograms of 1492 normal children. Circulation 1979;60:196–204.
[12] Rijnbeek PR, van Herpen G, Bots ML, Man S, Verweij N, Hofman A, et al. Normal values of the electrocardiogram for ages 16–90 years. J Electrocardiol 2014;47:914–21.
[13] Rijnbeek PR, Witsenburg M, Schrama E, Hess J, Kors JA. New normal limits for the paediatric electrocardiogram. Eur Heart J 2001;22:702–11.
[14] Draisma HHMS, Swenne CA, van de Vooren H, Maan AC, van Huysduynen BH, van der Wall EE, et al. LEADS: an interactive research oriented ECG/VCG analysis system. Comput Cardiol 2005:515–8.
[15] Kors JA, van Herpen G, Sittig AC, van Bemmel JH. Reconstruction of the Frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. Eur Heart J 1990;11:1083–92.
[16] Ng P, Maechler M. A fast and efficient implementation of qualitatively constrained quantile smoothing splines. Stat Model 2007;7:315–28.
[17] COBS—constrained B-splines (sparse matrix based). R package version 1.3–0. http://CRAN.R-project.org/package=cobs.
[18] R: a language and environment for statistical computing. http://www.R-project.org.
[19] Macfarlane PW, van Oosterom A, Pahlm O, Kligfield P, Janse M, Camm J, editors. Comprehensive electrocardiology. 2 ed. London: Springer; 2011.

[20] Davignon A. Normal ECG standards for infants and children. Pediatr Cardiol 1979: 133–52.
[21] Macfarlane PW, Coleman EN, Pomphrey EO, McLaughlin S, Houston A, Aitchison T. Normal limits of the high-fidelity pediatric ECG. Preliminary observations. J Electrocardiol 1989;22:162–8 [Suppl].
[22] Sun K. Normal ECG limits for Asian infants and children. Comput Cardiol 2005:455–8.
[23] Macfarlane PW, McLaughlin SC, Rodger JC. Influence of lead selection and population on automated measurement of QT dispersion. Circulation 1998;98:2160–7.
[24] Cortez D, Sharma N, Cavanaugh J, Tuozo F, Derk G, Lundberg E, et al. Lower spatial QRS-T angle rules out sustained ventricular arrhythmias in children with hypertrophic cardiomyopathy. Cardiol Young 2016:1–5.
[25] Edenbrandt L, Houston A, Macfarlane PW. Vectorcardiograms synthesized from 12-lead ECGs: a new method applied in 1792 healthy children. Pediatr Cardiol 1994;15:21–6.
[26] Dilaveris P, Roussos D, Giannopoulos G, Katinakis S, Maragiannis D, Raftopoulos L, et al. Clinical determinants of electrocardiographic and spatial vectorcardiographic descriptors of ventricular repolarization in healthy children. Ann Noninvasive Electrocardiol 2011;16:49–55.
[27] Schreurs CA, Algra AM, Man SC, Cannegieter SC, van der Wall EE, Schalij MJ, et al. The spatial QRS-T angle in the Frank vectorcardiogram: accuracy of estimates derived from the 12-lead electrocardiogram. J Electrocardiol 2010;43:294–301.
[28] Man S, Algra AM, Schreurs CA, Borleffs CJ, Scherptong RW, van Erven L, et al. Influence of the vectorcardiogram synthesis matrix on the power of the electrocardiogram-derived spatial QRS-T angle to predict arrhythmias in patients with ischemic heart disease and systolic left ventricular dysfunction. J Electrocardiol 2011;44:410–5.
[29] Draisma HH, Schalij MJ, van der Wall EE, Swenne CA. Elucidation of the spatial ventricular gradient and its link with dispersion of repolarization. Heart Rhythm 2006; 3:1092–9.
[30] Rijnbeek PR, Kors JA, Witsenburg M. Minimum bandwidth requirements for recording of pediatric electrocardiograms. Circulation 2001;104:3087–90.