**Ethnicity-specific normal limits of the electrocardiogram: Distributional regression model analysis in six different ethnicities from a multi-ethnic cohort study**

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Abstract 298/300

Background: Age, sex, and ethnicity influence the electrocardiogram (ECG), yet current guidelines ignore ethnic differences, potentially leading to misdiagnosis and inadequate treatment for specific population groups. This study aimed to establish normal ECG-limits for multiple ethnicities to improve the differentiation between health and disease.

Methods: ECGs from the multi-ethnic HELIUS cohort study were collected, comprising six ethnicities from Western-European (Dutch), South Asian-South American (South Asian-Surinamese), Middle-Eastern (Turkish), Northern-African (Moroccan), African-South American (African-Surinamese), and Sub-Sahara Western-African (Ghanaian) descent. Various approaches, including both detailed standard and vectorcardiographic ECG-evaluations, and distributional regression analyses, were employed to determine normal limits.

Results: We included 11,276 apparently healthy participants (age 39±12 years, age range 18-71, 61% female). Normal limits for participants from Dutch (Western-European) descent were consistent with current guidelines. Many differences based on age, sex and ethnicity were found for both conduction and repolarization intervals, spatial parameters (e.g. sum absolute QRS-T integral) and disease-criteria (e.g. ECG-criteria for left ventricular hypertrophy(LVH)). Compared to a Dutch-reference, e.g., participants from Sub-Saharan African-descent (African-Surinamese/Ghanaian), showed increased upper limit of PR-interval in older (≥40 years) males (230/221ms versus 215ms), decreased upper limit of QRS-duration in older females (102/98ms versus 107ms), more high QRS voltage (10/17% versus 6%) in contrast to a decreased upper limit of sum absolute QRS-T integral (324/300mV.ms versus 347mV.ms) in younger males. ECG-criteria for LVH were very high (>67%) in younger males from Sub-Saharan African-descent) but very low (<8%) in older female participants from Turkish/Moroccan descent.

Conclusion: This study established age, sex, and ethnicity-specific normal limits for ECG parameters across diverse ethnicities – which are probably more accurate than current guidelines. We highlight the importance of considering ethnicity, in addition to age and sex, when evaluating ECGs. These results have implications for global guidelines in determining health and disease based on normal and abnormal ECG features.

Introduction

World-wide, the electrocardiogram (ECG) is used in the evaluation of patients with (potential) cardiovascular disease. Importantly, every ECG is unique, and differences exist between individuals, while also within individuals the ECG evolves with, e.g., aging or the development of comorbidities. Besides well described ECG-influencing factors like age and sex, earlier studies have shown that ECG-parameters also differ among subjects of different ethnicities. For example, previous studies have defined ethnicity-specific normal limits for conduction and repolarization intervals and axes for healthy subjects of Chinese, Nigerian and Indian descent, among others.(1-6) However, these studies were limited by scale or number of ethnicities. Moreover, from the lack of detailed insights in variability based on age, sex, and ethnicity, the realization currently emerges that determination of cardiac disease is troubled. For example, in apparently healthy individuals there is a highly ethnicity-dependent variability in the prevalence of ST-segment elevation exceeding ST-segment-elevation myocardial infarction (STEMI) thresholds as defined by European, American as well as World Heart Federation guidelines.(7) The scale of this variability goes from 0.0% false-positive prevalence rates to >45% in certain subgroups. As current international guidelines are predominantly based on data from subjects of Western-European descent, these findings suggest that these guidelines potentially result in over- and under-diagnosis of STEMI among patients of non-Western-European descent.(8-10) Neither current ECG diagnostic guidelines, nor commercial ECG equipment algorithms, take ethnic differences into account for many ethnic groups and normal ECG-limits for people from several large areas have not yet been described. This suggests over- and under diagnosis of cardiovascular disease in specific ethnic groups, aside age and sex, and, subsequently, in either over-treatment, suboptimal, insufficient or even lack of treatment.

With the current study, we aimed to establish normal ECG-limits recognizing ethnic variability, besides variability based on age and sex, to increase our understanding of ethnic differences between healthy subjects and to promote appropriate decision making.

Methods

For this observational study, baseline and follow-up data were collected from the population-based multi-ethnic HELIUS (Healthy Life in an Urban Setting) study. A detailed description of HELIUS has previously been published. (11, 12) It’s goal is to evaluate differences in the (causes of the) unequal burden of disease and clinical disease course across different ethnic groups, and to ultimately improve ethnicity-specific health care. Initial inclusion at baseline (2011-2015) consisted of almost 25,000 participants, who were randomly sampled according to ethnic origin (i.e. Western European (Dutch), South Asian-South American (South Asian-Surinamese), Middle-Eastern (Turkish), Northern-African (Moroccan), African-South American (African-Surinamese), and Sub-Saharan Western-African (Ghanaian) origin). From this cohort, medical history data retrieved from questionnaires were combined with physical examinations, blood test results and ECG diagnoses to identify ‘apparently healthy’ participants without apparent cardiovascular disease, significant co-morbidities (like diabetes mellitus), or on potentially ECG-modifying drugs. Furthermore, from a selection of participants, follow-up data was available to assess whether initial ‘apparently healthy’ determination was still valid (as initial evaluation could have interfered with potential sub-clinical disease that only surfaced during follow-up). We collected standard 12-lead supine resting ECGs (GE MAC5500, 500 samples/sec). ECGs were thoroughly evaluated, including both visual assessment by a cardiologist, as well as automated analyses using the Modular ECG Analysis System (MEANS) program which were then manually verified and re-analyzed.(7) For early repolarization pattern (ERP) assessment, the University of Glasgow ECG core laboratory fully automated evaluation was utilized.(10, 13, 14) Multiple ECG-measurements were derived from these data.(10, 13, 14) Ethnicity-specific normal limit curves for each of these ECG-measurements were developed using the 2.5th and 97.5th centile curves derived from univariate distributional regression models (Generalized additive models for location, scale, and shape; GAMLSS), where the ECG-measurements are modelled against age and sex using a distributional regression approach. Lastly, to assess the validity of the normal limits derived from the apparently healthy (baseline) cohort, we compared those results and GAMLSS percentile curves with the follow-up cohort using the same methods. A complete overview of the methods, including an extensive description of study design and data collection, participant inclusion and exclusion, ECG analyses, definition of normal limits using GAMLSS and percentiles, and comparison with the follow-up data are described in the Supplementary Methods section in the Supplementary Material.

**Results**

*Study population.*

After exclusion criteria were applied, 11,276 apparently healthy participants were identified at baseline (see Figure 1). From these apparently healthy participants, follow-up data until December 31st, 2020, was available for 4,293 participants (38%, mean time to follow-up 73±13 months). During follow-up 735/4,293 participants (17%) developed arterial disease, diabetes mellitus and/or hypertension, leading to a final follow-up dataset of 3,558 participants with an ECG at baseline who remained apparently healthy during follow-up. The apparently healthy population had a mean age of 39±12 years and 61% were female, range 18-71. For the follow-up cohort, mean age (at baseline) was 40±12 years and 61% were female, range 18-71. Baseline characteristics of both the baseline and follow-up cohort are depicted in Table 1. Figure S1 shows the distribution of age and sex in the cohort.

The prevalence of ECG-abnormalities according to international guidelines was significantly different among ethnicities. For example, the prevalence of early repolarization pattern (ERP) for the African-Surinamese (30%) and Ghanaian (40%) participants was higher than other ethnicities (19-23%) (p <0.001). Furthermore, prevalence of ECG-criteria for left ventricular hypertrophy (LVH) was very high (67% for ESC hypertension guideline criteria and 24% for composite criteria) in the Sub-Saharan African-descent (African-Surinamese/Ghanaian), but very low (6 and 3% for the different criteria respectively) in older female participants from Middle-Eastern/Northern African (Turkish/Moroccan) descent.

An overview of these ECG measurements, stratified by ethnicity in the apparently healthy population are depicted in Table 2. Table 3 shows the prevalence of the high QRS-voltage criteria stratified by age group, sex and the Dutch, African-Surinamese and Ghanaian combined and Turkish and Moroccan combined.

*Normal limits – GAMLSS*

For the apparently healthy population, sex and ethnicity specific normal limits curves were created by fitting ECG-data to age with GAMLSS models and percentile curves were derived from the fitted models. Figures 2 and 3 show GAMLSS normal limits curves of QRS-duration for all ethnicities, stratified by sex. An overview of all curves for all ECG-intervals and axes for each of the six ethnicities, stratified by sex, can be found in Appendix 1 of the supplementary material. We compared GAMLSS percentile curves of each ethnicity to that of the Dutch participants. We chose to only compare the other ethnicities to the Dutch participants because the latter match the population on which current ECG guidelines are based. For Ghanaian and African–Surinamese males, P-wave duration, PR-interval, QT/QTc and T-wave axis were all significantly different when compared to the Dutch (p-values ranging from <0.001 to 0.023). For South Asian–Surinamese males the only differences that were significant were QRS-duration and QT-interval (p<0.001 and p=0.015, respectively). Furthermore, normal limits for QRS duration were significantly different for females of all other ethnicities compared to Dutch females. Lastly, also for spatial QRS-T angles significant differences were found between both males and females of each ethnicity, compared to the Dutch. For example, for the Ghanaian participants the GAMLSS curves of both males and females were significantly different, with p-values of 0.016 and 0.038, respectively.

*Normal limits – percentiles*

For the apparently healthy populations the mean, standard deviation (SD), and the 2.5th and 97.5th percentile were determined for each ECG-parameter, stratified by sex, age group and ethnicity. As reference standard, normal limits as agreed on by the AHA/ACCF/HRS were used, which are shown in Table S1 (16-19). African-Surinamese and Ghanaian groups exhibited differences with the Dutch, with increased upper limit of PR-interval in older males (230 and 221ms versus 215ms) and decreased upper limit of QRS-duration in older females (102 and 98ms versus 107ms). The upper limit of QTc (Bazett) for older females (age >40 years) was higher in Ghanaians (444ms) than the other ethnicities (458-465ms). A full overview containing the tables for all six ethnicities can be found in Appendix 2.

*Comparison with healthy after follow-up population*

The GAMLSS derived percentile curves of each ethnicity and sex for the baseline cohort were compared to those of the follow-up cohort. In almost all instances there were no significant differences found, suggesting that the results from the baseline cohort are indeed representative of an apparently healthy population. An overview of this comparison is presented in Table S2 of the supplementary material. For percentile curves for the GAMLSS models fitted with the follow-up cohort data, see Appendix 3.

Discussion

In this study we evaluated the influence of age, sex and ethnic origin on the ECG using GAMLSS models to develop and evaluate normal limits curves for individuals from six different ethnicities with origins from around the globe. To our knowledge, this is the largest study on this topic to include a wide variety of different ethnicities and include both detailed standard ECG as well as detailed vectorcardiographic ECG-data. Our results show that there are indeed significant ethnicity-based differences for most ECG-parameters besides differences based on sex and age. This suggests that when evaluating ECGs also ethnicity should be considered, besides age and sex, because of the large influence of ethnic origin on normal limits. This is important because determination of normal vice versa also determines abnormal, which in turn translates to the determination of health or disease and treatment considerations.

Besides evaluating the role of ethnicity as an influencing factor of the ECG in general, the aim of this study was indeed to determine normal limits for specific ethnicities, which putatively represent larger areas around the globe. First, the normal limits that we developed for the Dutch population mirror current AHA/ACCF/HRS ECG guidelines, besides a slightly higher upper limit P-wave duration (136 vs 120ms), PR-interval (210 vs 200ms) and QRS-duration (115 vs 110ms) in males. Therefore, the normal limits of the Dutch population, in general, fit reference values of current ECG-guidelines and by comparing the normal limits curves of other ethnicities to that of the Dutch participants, we can indirectly compare our results to the guidelines.(16-19) For example, for male individuals from Sub-Sahara African origin (both African-Surinamese and Ghanaian participants) P-wave duration and PR-interval were significantly longer. Although these people came to The Netherlands from different continents, we did expect similar results for both, because the African-Surinamese population, as the name suggests, were forcefully migrated from Western-Africa to South-America (Surinam), during slave trades.(10) When comparing the prolonged P-wave duration and PR-interval with that of previous studies, there are some conflicting results. For example, a prolonged P-wave duration was also found in apparently healthy Nigerian males and healthy ‘blacks’, while other studies found the PR-interval to be within reference limits.(1, 2, 5, 20) Another finding was that the upper normal limit for QRS-duration among females not of Western-European descent was significantly shorter than for Dutch females. This could mean that for these ethnicities the current guidelines are too “loose” and that in some cases, a borderline QRS-duration could coincide with underlying structural heart disease/cardiomyopathy.(21)

Besides ethnicity-specific normal limits for ECG-intervals and axes, we also estimated the prevalence of multiple ECG-abnormalities in our apparently healthy cohort (i.e. false positives). Both LVH-criteria and ERP were more prevalent in both the African Surinamese and Ghanaian, compared to the other ethnicities and in particular the Turkish and Moroccan females. These findings are in line with previous studies showing a higher prevalence of (ECG based) LVH-criteria and ERP in healthy ‘black’ subjects compared to ‘whites’.(22, 23) Therefore by properly setting (ECG based) LVH-criteria for ‘blacks’, the number of LVH-criteria met based on current guidelines would be reduced. Further analysis of both LVH-criteria and ERP in HELIUS, also in the non-healthy participants of the cohort, was out of the context of the current study but will be the subject of future research by our group.

Previous research regarding the spatial QRS-T angle identified three categories, values up to 105° are considered normal, 105–135° is borderline abnormal and >135° is abnormal, where this last category associated with fatal cardiac arrhythmias in a general population.(24) When looking at the GAMLSS curves, the upper limit of the spatial QRS-T angle seems to increase with age but seems to not exceed the 135 degree limit in any of the ethnicities, therefore fitting the current categories. The ventricular gradient, however, decreases with age, which could possibly be due to smaller areas-under-the-curve of a single heartbeat due to diminished QRS-T voltages. However, as laid out in previous studies and as can be concluded from this study’s broad interpercentile range, the ventricular gradient is highly variable between persons.(25, 26) This absence of strict normal limits, renders it less suitable for single ECG diagnostics without comparing the ECG to a previously made ECG from the same individual.(7, 27) The upper normal limit of both ventricular gradients and sum absolute QRS-T integrals of participants of Sub-Saharan African descent was found to be lower than participants from Dutch descent, in contrast to LVH-criteria, which were more prevalent in participants from Sub-Saharan African descent. Both the ventricular gradient and the sum absolute QRS-T integral are markers for heterogeneous or abnormal repolarization, therefore suggesting that the presence of LVH-criteria in Sub-Saharan Africans does not lead to abnormal repolarization and therefore would not increase the risk of cardiac events, in contrast to patients with actual LVH or hypertrophic cardiomyopathy.(25, 28, 29) However, more in-depth research should be performed to further investigate this association.

For this study, we chose to develop normal curves using GAMLSS models. Application of GAMLSS is growing and the World Health Organization for example recommended GAMLSS for the development of child growth standards.(30) Besides normal limits, other applications of these models have been found, e.g. the development of survival curves to predict mortality during the COVID-19 pandemic, illustrating the versatility of using these models.(31, 32)

*Clinical applicability*

The normal limits presented can be used directly when in doubt if certain ECG-measurements are pathological for persons not of Western-European descent. Moreover, ECG interpretation programs could easily incorporate ethnicity aside age and sex to improve diagnostic accuracy. This is important, because when looking at the distribution of ethnicities worldwide, the population of Western-European descent comprises less than a fifth of the global population.(33) Comparison of percentile curves derived from our baseline cohort with those of the follow-up cohort, showed that they were mostly identical, empowering the clinical significance of these findings. It is striking to note, like earlier studies, that several ECG-criteria differ so much based on age, sex, and ethnicity. This implicates that either disease is not recognized (e.g. because a patient does not reach cut-off values while being out of range for his/her own reference) or that disease is implicated while in fact the findings are within normal limits. The basis of acceptable false-positive and false-negative results from our current global guidelines based on data mainly from Western-European descent, is thus very much challenged in patients not from Western-European descent and coincide with apparent sex/age differences. This notwithstanding, intra-patient ECG-evaluations may often prove very valuable.

Although our participants were all living in the Netherlands, we suggest that these results can be extrapolated to the countries of origin of our participants not from Dutch descent. Moreover, as people from neighboring countries often share similar backgrounds, we even suggest extrapolation of these data to wider areas rather than countries. For example, we do not consider people from Dutch descent to have meaningful different ECG-characteristics than, e.g., people from English, French or German descent. The same holds for our other participants. Hence, we believe that crude areas like Western-Europe, or Northern-Africa are reasonable extrapolations of these data until more detailed evaluations and are at least a lot better than current guidelines. Putatively, our participants from sub-Sahara African descent are comparable to ‘black’ cohorts, while our participants from Dutch descent would compare to ‘white’ cohorts. Furthermore, many countries and certainly large metropoles around the globe now have multi-ethnic populations, therefore a more ethnicity-specific ECG analysis strategy can prove more useful than current guidelines. Still, to evaluate the generalizability of these criteria and normal limits, external validation in another cohorts is needed, ideally in the original country/area of each ethnicity.

*Limitations*

The world consists of much more ethnicities than the six evaluated in this study, meaning that in future research, more data from other ethnicities must be included to further develop normal limits like those that were developed in this study. As migration routes can vary considerably per country and over time, in many countries the specific country-based origin of our study-participants may feel irrelevant. However, as explained above, we specifically suggest broadening the area of origin of these participants. Additionally, although extensive baseline examinations were performed for each participant, follow-up data was not (yet) available in almost two-thirds of our cohort. Therefore, in most of the apparently healthy participants, it remains unknown if they did not have sub-clinical underlying disease. However, we showed our derived normal limits in patients still without apparent cardiovascular disease during follow-up were comparable to the whole group. While many of our selection criteria to determine if patients were healthy or not, were questionnaire based, aside examinations (e.g. blood pressure) and blood tests (e.g. fasting glucose, hemoglobin-A1c, creatinine), there could also be differences in self-reporting due to differences in healthcare quality, access to healthcare and literacy among ethnicities, potentially influencing our results. However, HELIUS data collection is still ongoing and hopefully in the future, we can collect more follow-up data to increase our accuracy. Other limitations in this study are that the 10-second ECG-recording only gives a snapshot of each patient, and that despite an appreciable age-range and a fair distribution around the 40-year split between younger and older individuals, we did not include all ages (<18, >71 years). In particular, the number of older subjects was low. Lastly, electrocardiographic measurements will always contain error-margins, although we used systematic and very detailed approaches including manually verified automatic waveform recognition and assessment by experienced cardiologists.

Conclusions

Current international guidelines on normal limits for ECG-parameters, and thereby the distinction between normal and abnormal ECGs, are mainly based on data from participants of Western-European descent. However, there are many (important) differences to be considered in assessing ECGs of subjects with different ethnic backgrounds, which even go beyond both age and sex. Therefore, we suggest that ethnicity-specific normal limits as defined in this study should be considered for use when assessing ECGs from patients with a non-Western-European background and to take ethnicity into account aside age and sex for the development of new ECG criteria.

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