View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by UCL Discovery

Clinical Trials and Regulatory Science in Cardiology 26 (2017) 1–6

Contents lists available at ScienceDirect

Clinical Trials and Regulatory Science in Cardiology

journal homepage: www.elsevier.com/locate/ctrsc

High prevalence of ST-elevation, early repolarization, and left ventricular hypertrophy during the eligibility assessment for an HIV vaccine trial in young, healthy Tanzanians☆

Philipp Mann[a,b,*,1], Patricia Munseri[c,1], Marco Missanga[d,1], Johnson Lwakatare[c,1], Mohamed Janabi[e,1], Emanuel Kapesa[d,1], Merlin L. Robb[f,g,1], Michael Hoelscher[a,h,1], Sheena McCormack[i,1], Muhammad Bakari[c,1], Leonard Maboko[d,1], Eric Sandström[j,1], Arne Kroidl[a,h,1]

[a] Division of Infectious Diseases and Tropical Medicine, Medical Center of the University of Munich (LMU), Munich, Germany
[b] Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA
[c] Muhimbili University of Health and Allied Sciences (MUHAS), Dar es Salaam, Tanzania
[d] NIMR Mbeya Medical Research Center (MMRC), Mbeya, Tanzania
[e] Muhimbili National Hospital, Dar es Salaam, Tanzania
[f] Walter Reed Army Institute of Research (WRAIR), Rockville, MD, USA
[g] The Henry M. Jackson Foundation, Rockville, MD, USA
[h] German Center for Infection Research (DZIF), partner site Munich, Germany
[i] Medical Research Council Clinical Trials Unit, University College London, London, United Kingdom
[j] Venhälsan, Karolinska Institutet, Södersjukhuset, Stockholm, Sweden

ARTICLE INFO

Keywords:
ECG
Africa
ST-elevation
Early repolarization
MVA vaccine

ABSTRACT

Background: Vaccinia based immunizations have caused myo/pericarditis and vaccine study volunteers are monitored by ECG. We report ECG outcome obtained during the screening period for an HIV vaccine trial.
Methods: ECG was performed in healthy Tanzanian volunteers. ECG abnormalities and findings interfering with the interpretation of myo/pericarditis were subject to study ineligibility. We determined the prevalence of left ventricular hypertrophy (LVH) defined by the Sokolow-Lyon (SL) or the Cornell index, ST-elevations and early repolarization (ERP) in association with gender, age, BMI and body height by regression analysis adjusted for gender and age.
Results: In 257 volunteers (median age 23 years, 63% males) overall positivity for LVH defined by SL or Cornell criteria was seen in 20.6% and 3.5%, ST-elevations ≥ 0.1 mV or ≥ 0.2 mV in 77.8% and 38.1%, and ERP in 23.4%. Positive SL criteria were associated with male gender (PR 7.84, $p < 0.001$) and lower age (PR 0.70, $p = 0.002$), and associated with increased body height and lower BMI in univariate analysis. Positive Cornell criteria were only associated with lower age (PR 0.44, $p = 0.010$). ST-elevations ≥ 0.2 mV were associated with male gender (PR 8.05, $p < 0.001$) and lower age (PR 0.81, $p = 0.003$), and ERP with male gender (PR 2.86, $p < 0.001$). Vaccine study ineligibility due to ECG findings was concluded in 22.1% of the screening population.
Conclusions: High prevalence of LVH according to SL in association with ST-elevation and ERP is especially

☆ **Acknowledgement of grant support**
The Swedish Institute for Communicable Disease Control (SMI) {now Public Health Agency of Sweden} and the Muhimbili University of Health and Allied Sciences (MUHAS) sponsored the TaMoVac 01 HIV vaccine study. The European and Developing Countries Clinical Trials Partnership (EDCTP, Grant CT.2006.33111.007), the German Ministry of Education and Research (BMBF, Grant 01KA0801), the Swedish International Development Cooperation Agency (Sida) and the Swedish Embassy in Tanzania provided financial support for the TaMoVac 01 HIV vaccine study.
Any potential conflicts of interest, including related consultancies, shareholdings and funding grants:
The authors report no relationships that could be construed as a conflict of interest. None of the funding organizations had any influence on the study conduct or its data analysis.
Clinical Trials Registration: The trial is registered at the World Health Organization International Clinical Trials Registry Platform, with registration number PACTR2010050002122368.
* Corresponding author at: Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., Mail Stop E3-300, Seattle, WA 98109, USA
E-mail address: pmann@fredhutch.org (P. Mann).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

http://dx.doi.org/10.1016/j.ctrsc.2017.03.001
Received 22 November 2016; Accepted 31 March 2017
Available online 10 April 2017
2405-5875/ © 2017 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).

found in young and male Africans. ECG variations need to be considered for eligibility criteria in studies investigating potential cardiotoxic agents in Africa.

1. Introduction

With changing lifestyles and increasing urbanization, cardiovascular disease is increasingly prevalent in sub-Saharan Africa [1]. Electrocardiogram (ECG) is a non-invasive, widely available tool to assess heart disease. Yet, the reference ranges for a valid interpretation of ECG tracings are derived from Caucasian populations and normal ranges for ECG findings in African populations are not very well defined [2,3,4], though many large scale studies in North American populations have pointed out differences in ECG findings between African Americans and Caucasian Americans.

It has been described that voltages in ECG may be higher in populations of African origin and ST changes are more frequent as compared to Caucasian populations [5,6,7]. In this respect, left ventricular hypertrophy (LVH) criteria that rely on left or right precordial voltage such as the Sokolow Lyon (SL) Index have been reported to be of low specificity favouring the Cornell criteria in African populations [8,9,10,11,12]. Independent of ethnic heritage, ST-elevation characterized by an elevation of the QRS-ST junction (J point) has been described to be present in up to 93% of young males [13,14]. Early repolarization (ERP) characterized by an ST-elevation of ≥ 0.1 mV in multiple leads, often associated with QRS notching or slurring (J wave), is usually viewed as a benign abnormality in young and asymptomatic individuals, but has been associated with an increased risk for ventricular arrhythmias and sudden cardiac death [15]. Frequencies of ERP in the context of ethnic background are discussed controversially, with some reports indicating an overall prevalence of 1–2% independent of race [16]. More recent reports indicate higher prevalence in populations with African heritage as compared to Caucasians [17,18,19].

Vaccinia virus based vaccines have been associated with myo/pericarditis [20,21] and volunteers participating in Modified Vaccinia Ankara (MVA) containing vaccine trials are usually ECG monitored for safety [22]. We recently conducted the TaMoVac01 multicentre phase II, MVA containing HIV vaccine trial in healthy volunteers from Tanzania [23] and encountered challenges during eligibility assessments due to high rates of abnormal ECG findings that could potentially interfere with the diagnosis of suspected vaccine induced myo/pericarditis. In a post hoc analysis we here investigate frequencies and factors associated with variable ECG findings in otherwise clinically healthy young Tanzanian volunteers and the related implications for MVA based vaccine studies.

2. Methods

2.1. Study settings and ethics statements

The study was conducted at the Muhimbili University of Health and Allied Sciences (MUHAS) in Dar es Salaam, and the National Institute for Medical Research (NIMR)-Mbeya Medical Research Center (MMRC) in Mbeya. Ethical approval for TaMoVac01 was obtained from the institutional review boards of the Muhimbili University of Health and Allied Sciences and the Mbeya Medical Research Ethics Committee. The Tanzania National Institute for Medical Research (NIMR), serving as the National Ethics Committee, and the Swedish Ethics Committee also approved the study. The study was conducted according to the principles of International Conference of Harmonization and Good Clinical Practice guidelines (ICH-GCP). All volunteers were provided with an information sheet and informed consent was obtained before any study procedures took place.

2.2. Study population and eligibility criteria

Volunteers for the TaMoVac 01 HIV vaccine trial were recruited from the Police, Prison forces, and a youth clinic in Dar es Salaam, as well as from the general population in Mbeya in Tanzania. Study volunteers aged 18 years or older underwent screening including medical history, complete physical examination, blood pressure and pulse rate assessments, laboratory analyses (complete blood count, ALT, direct and indirect bilirubin, random blood glucose and creatinine), urine analysis, serology testing for HIV, syphilis and hepatitis B as well as pregnancy testing in females. A 12-lead ECG was recorded during screening in order to exclude volunteers with evidence of cardiac disease and those with abnormalities that would potentially interfere with later diagnosis of MVA induced myo/pericarditis.

As the aim of this post hoc analysis was to investigate incidental ECG variations in a healthy African vaccine trial screening population, we excluded participants from the analysis who met at least one of the following criteria which could potentially lead to ECG abnormalities: HIV infection, evidence of current of past cardiac or cardio-vascular disease as assessed by medical history and physical examination, known hypertension or confirmed systolic blood pressure $>$ 140/90 mm Hg, known diabetes or confirmed moderate or above hyperglycaemia, severe anaemia (haemoglobin levels $<$ 9.0 g/dL), and moderate or above creatinine or ALT elevations to exclude significant renal or hepatic diseases. Severity grades were based on the DAIDS toxicity table (Division of AIDS, Natl. Institutes of Health, Bethesda, MD) [24]. We included women with a positive pregnancy test into this analysis if pregnancy was deemed to be at an early stage (first trimester).

2.3. ECG Data Acquisition and Interpretation

ECGs were acquired on a MAC 1200 electrocardiograph (GE Medical Systems) as supine 12-lead ECGs at 25 mm/s with 1 cm/mV. Two trained study physicians at each site interpreted ECGs on paper. A panel of two national and one international cardiologists reviewed the interpretations to reach a final consensus. As TaMoVac 01 was a safety study, volunteers with pathological ECGs or variations that could potentially interfere with the later interpretation of myo/pericarditis were excluded from enrolment in the vaccine trial. Pathological ECGs and variations leading to exclusion from the vaccine trial were defined as: (i) conduction disturbance such as complete left or right bundle branch block or nonspecific intraventricular conduction disturbance with QRS $>$ 120 ms, AV block of any degree, or QTc prolongation ($>$ 440 ms), (ii) significant repolarization (ST segment or T wave) abnormality, (iii) significant atrial or ventricular arrhythmia; frequent atrial or ventricular ectopy, and (iv) ST-elevation consistent with ischemia or evidence of past or evolving myocardial infarction.

In our post hoc analysis we assessed (i) the Sokolow-Lyon Index with S in V1 plus R in V5 or V6 required to surpass 3.5 mV [25], and (ii) the Cornell Index with S in V3 plus R in aVL required to surpass 2.0 mV in women and 2.8 mV in men [26,27] to meet criteria for LVH. ST-Elevation was recorded if there was an elevation of the QRS-ST junction (J point) of ≥ 0.1 mV or ≥ 0.2 mV in at least one lead [14,28]. ERP was defined as an elevation of the QRS–ST junction by at least 0.1 mV in at least two of the following leads: I, II, III, aVF, aVL, V4, V5 or V6 [29].

2.4. Data collection and statistical analysis

ECG, clinical and laboratory data were recorded in study specific case report forms, double-entered into an SQL database, compared and

corrected for data entry errors and then extracted for data analysis. The following outcomes were considered during statistical analysis: ST-elevations ≥ 0.1 mV and ≥ 0.2 mV, LVH as defined by Sokolow-Lyon and Cornell criteria and ERP. Comparisons of binary and continuous variables between groups were performed using the Wilcoxon rank-sum test. Repeated measures within the same individuals were performed using McNemar's exact test. Poisson regression with robust variance estimates was used to analyse associations of gender, age, body mass index (BMI), and body height (as an indicator for cardiac size) with the above outcome variables in univariate models, and in multivariate models adjusted for gender and age. For all statistical tests an alpha level of < 0.05 was used to define significance. All statistical analyses were performed using Stata statistics software (version 14, StataCorp, College Station, TX, USA), graphs were drawn in MS Excel.

3. Results

For the TaMoVac01 trial, 508 volunteers underwent screening procedures of whom 263 volunteers, who were not otherwise excluded, received ECG assessments. During the 70 weeks of active follow-up, no cardiac events were noted in the population enrolled in the vaccine study. Of those 263 participants, six were excluded from this analysis due to conditions that might lead to abnormal ECG readings. These conditions were: prior heart disease in two, hypertension in two, HIV infection in one, and significant alcohol abuse in one participant, respectively. Three females with positive pregnancy tests were kept in the analysis as pregnancies were at early stages. Baseline characteristics for the remaining 257 participants included in the analysis are shown in Table 1. In brief, 63% of participants were males, the median age was 23 years, and the median BMI 21.7 kg/m^2. Males were slightly but significantly older, taller, had a lower median BMI, had higher median systolic blood pressure, and had lower median heart rate (within normal ranges) as compared to females, respectively.

Overall positivity for LVH either defined by SL or by Cornell criteria was seen in 53 (20.6%) and 9 (3.5%) participants, respectively. ST-elevation with a threshold of ≥ 0.1 mV and ≥ 0.2 mV was seen in 200 (77.8%) and 98 (38.1%) participants, respectively, and ERP was detected in 60 (23.4%) participants. The prevalences of above outcomes stratified by gender are shown in Fig. 1. Significantly higher prevalences of LVH according to SL criteria, ST-elevations, and ERP were detected in males. LVH according to Cornell criteria did not show a significant gender difference, however, a trend towards a higher proportion was seen in females. As indicated above, the SL criteria for LVH were more frequently positive than the Cornell criteria. This was mainly due to the large difference between the prevalence of these two criteria in males (30.3% versus 1.9%, $p < 0.001$), whereas differences seen in females were not significant (4.2% versus 6.3%, $p = 0.727$).

In multivariate regression analyses adjusted for gender and age, positive SL criteria were significantly associated with male gender and younger age, whereas lower BMI and increased body height were significantly associated with SL only in univariate analysis (Table 2). In contrast, LVH according to Cornell criteria was significantly associated with younger age after adjusting for gender and age in multivariate analysis, but not for gender, BMI, or body height in neither uni-nor multivariate regression analysis. There were significantly higher proportions of concurrent ST segment elevations and ERP among participants with LVH as defined by SL criteria that were not observed with Cornell criteria. ST segment elevation and ERP were significantly associated with male gender in both, univariate and multivariate analyses, and with greater body height in univariate analysis. Additionally, ST elevation was associated with lower BMI in univariate analysis. An association with younger age was shown in multivariate analysis for ST elevations ≥ 0.2 mV. Of note, ERP in association with ST-elevation ≥ 0.2 mV was detected in 40 (15.6%) participants. 20 (7.8%) of those participants demonstrated ERP in association with ST-elevation ≥ 0.2 mV without high QRS amplitudes as indicated by positive SL criteria, which could potentially indicate a higher risk for catastrophic arrhythmias.

An ECG pattern of a participant with positive LVH SL criteria in combination with ST-elevation and evidence of ERP with notching of the J-point is shown in Fig. 2A and without positive LVH criteria but ST-elevation in Fig. 2B, which has been referred as a typical “male pattern”. In Fig. 2C an example of a participant with ERP is shown with ST-elevation in the limb leads and slurring of the QRS-ST junction which is referred to as a J-wave.

ECG findings leading to ineligibility during the screening period of the vaccine trial were detected in 58/263 (22.1%) volunteers with ECG assessments, and 41 (15.6%) volunteers were screened out only due to ECG abnormalities without meeting other ineligibility criteria. Apart from above described ST-elevation, ERP and left ventricular hypertrophy criteria, other findings leading to ineligibility were abnormal T-wave inversion ($N = 10$), Right Bundle Branch Blocks ($N = 6$) including one suspected case with a Brugada syndrome, Left Bundle Branch Block ($N = 1$), higher grade AV-Blocks ($N = 2$) and ectopic atrial rhythms ($N = 2$).

4. Discussion

There was an overall high rate of screen outs in our MVA vector containing HIV vaccine trial due to ECG findings in young and otherwise clinically healthy volunteers in Tanzania. The most commonly encountered ECG abnormalities were signs of left ventricular hypertrophy, ST segment elevation and ERP. Across all ECG abnormalities analysed, male gender and younger age were the predominant factors that influenced the occurrence of most probably clinically insignificant ECG variations. Factors related to body shape and fat distribution such as lower BMI or greater body height were associated with most abnormalities in univariate regression analysis.

Sokolow Lyon criteria presumably over-diagnosed left ventricular hypertrophy in males as compared to the Cornell criteria (30% vs 2%). In contrast, both LVH criteria were positive in females in about one out of twenty individuals and no significant difference in the prevalence between both criteria was seen. Similar results including gender differences with predominance in males presenting positive Sokolow Lyon criteria have been described from different studies conducted in Africa supporting the evidence that Cornell criteria in African popula-

Table 1
Volunteer characteristics and prevalence of left ventricular hypertrophy (LVH) by Sokolow Lyon and Cornell criteria, ST-elevation in any lead of ≥ 0.1 mV or ≥ 0.2 mV, or for early repolarization (ERB) by gender.

	Total $N = 257$	Male $N = 162$	Female $N = 95$	p value[#]
Age (years), median (IQR)	23 (20 to 28)	24 (20 to 29)	21 (19 to 26)	0.040
BMI (kg/m^2), median (IQR)	21.7 (19.8 to 24.1)	21.4 (19.6 to 23.3)	23.1 (20.2 to 25.6)	0.002
Height (cm), median (IQR)	164 (158 to 170)	168 (163 to 173)	157 (152 to 160)	< 0.001
BP systolic (mm Hg), median (IQR)	119 (110 to 121)	120 (110 to 125)	110 (104 to 120)	< 0.001
BP diastolic (mm Hg), median (IQR)	71 (69 to 80)	72 (69 to 80)	70 (66 to 80)	0.367
Heart Rate (beats/min), median (IQR)	67 (57 to 73)	62 (54 to 69)	72 (66 to 79)	< 0.001
LVH by Sokolow Lyon Index	53 (20.6%)	49 (30.3%)	4 (4.2%)	< 0.001
LVH by Cornell Index	9 (3.5%)	3 (1.9%)	6 (6.3%)	0.061
ST elevation ≥ 0.1 mV	200 (77.8%)	151 (93.2%)	49 (51.6%)	< 0.001
ST elevation ≥ 0.2 mV	98 (38.1%)	91 (56.2%)	7 (7.4%)	< 0.001
Early repolarization	60 (23.4%)	50 (30.9%)	10 (10.5%)	< 0.001

[#] p-value of Wilcoxon rank-sum test for comparisons of males versus females.

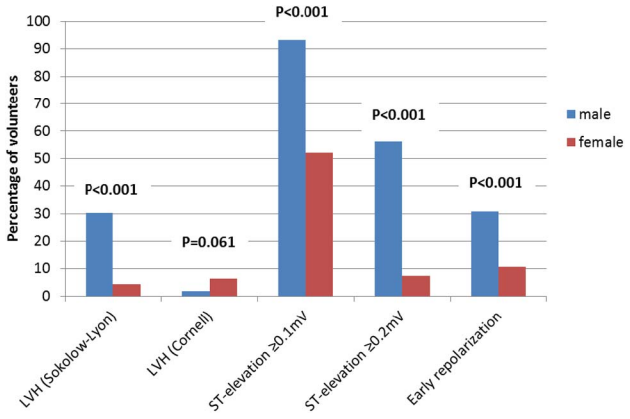

Fig. 1. Proportion of volunteers with positive ECG for left ventricular hypertrophy (LVH), ST-elevations and early repolarization by gender.

tions should preferentially be used and are less likely to suggest LVH [8,9,10,11,12].

Sokolow Lyon criteria have mainly been developed on white populations and reasons why these criteria are more likely to result into false positive LVH diagnosis in African origin populations have been attributed to socioeconomic and nutritional factors, differences in body shape, fat distributions, and physiological differences in ventricle sizes [30,31]. Higher QRS amplitudes in older populations of African-Americans as compared to white populations have been described for both men and women despite comparable left ventricular mass as measured by echocardiography, indicating racial differences which were partly explained by smaller lateral chest diameter in individuals of African origin [32]. As reviewed by Fraley et al. [33], higher BMI or obesity is known to lead to lower QRS voltages effecting especially ECG LVH criteria that rely on left or right precordial voltage such as the Sokolow Lyon Index. This is likely attributed to variable degrees of chest wall and epicardial fat which may result in increased distances of chest leads to the heart surface. Furthermore, difference in absolute cardiac size might explain gender specific differences in QRS amplitudes and body height has been described as a marker which correlates with left ventricular mass [34] impacting the prevalence of positive Sokolow Lyon criteria. High prevalence of positive Sokolow Lyon criteria especially in young and slender males in our analysis are therefore likely a result of lower BMI associated with younger age, racial characteristics of small lateral chest diameter, gender differences in cardiac size and chest wall impedance because of subcutaneous breast tissue, and lean body mass. As age was one of the predominant variables affecting both positive Sokolow Lyon and Cornell criteria, other factors such as age related myocyte atrophy might have already affected ECG readouts in our young population.

A high predominance of ST-elevation and J-point amplitudes ≥ 0.1 mV has been described as a typical male pattern in contrast to a female pattern which is more often represented with a J-point amplitude < 0.1 mV. ST-elevations have been associated with younger age and male gender in other studies, with proportions comparable to the ones found in our cohort [13,14]. Furthermore, significant differ-

Table 2
Factors associated with left ventricular hypertrophy (LVH) by Sokolow Lyon and Cornell criteria, ST-elevation in any lead of ≥ 0.1 mV or ≥ 0.2 mV, or for early repolarization (ERP) in univariate analysis and multivariate analysis adjusted for gender and age. The significance of bold is p < 0.001.

	Univariate analysis Total population (N = 257)		Multivariate analysis (adjusted for gender, age) Total population (N = 257)		Univariate analysis Males (N = 162)		Univariate analysis Females (N = 95)	
LVH (Sokolow Lyon)	PR (95% CI)	p value	PR (95% CI)	p value	PR (95% CI)	p value	PR (95% CI)	p value
Male versus female	7.18 (2.67 to 19.32)	< **0.001**	7.84 (2.92 to 21.06)	< **0.001**	**	**	**	**
Age, per 5 years increase	0.76 (0.61 to 0.96)	**0.020**	0.70 (0.56 to 0.88)	**0.002**	0.70 (0.55 to 0.89)	**0.003**	0.75 (0.34 to 1.61)	0.456
BMI, per kg/m^2 increase	0.90 (0.84 to 0.97)	**0.004**	0.97 (0.89 to 1.05)	0.423	0.93 (0.87 to 1.01)	0.075	0.91 (0.67 to 1.23)	0.529
Height, per 5 cm increase	1.32 (1.19 to 1.46)	< **0.001**	1.12 (0.96 to 1.31)	0.145	1.05 (0.89 to 1.23)	0.602	2.06 (1.58 to 2.70)	< **0.001**
ST elevation ≥ 0.1 mV	7.27 (1.82 to 29.02)	**0.005**	3.25 (0.78 to 13.50)	0.105	3.50 (0.53 to 23.12)	0.194	2.81 (0.30 to 26.43)	0.365
ST elevation ≥ 0.2 mV	4.99 (2.81 to 8.86)	< **0.001**	2.76 (1.53 to 4.98)	**0.001**	3.47 (1.80 to 6.68)	< **0.001**	**	**
Early repolarization	3.16 (2.00 to 4.98)	< **0.001**	2.57 (1.71 to 3.87)	< **0.001**	2.53 (1.61 to 3.98)	< **0.001**	**	**
LVH (Cornell)								
Male versus female	0.29 (0.07 to 1.15)	0.078	0.35 (0.09 to 1.41)	0.139	**	**	**	**
Age, per 5 years increase	0.41 (0.23 to 0.72)	**0.002**	0.44 (0.24 to 0.82)	**0.010**	0.17 (0.04 to 0.74)	**0.018**	0.61 (0.36 to 1.04)	0.072
BMI, per kg/m^2 increase	1.00 (0.82 to 1.20)	0.962	1.02 (0.82 to 1.24)	0.868	0.90 (0.60 to 1.34)	0.598	0.98 (0.81 to 1.19)	0.840
Height, per 5 cm increase	0.79 (0.52 to 1.19)	0.253	0.94 (0.49 to 1.77)	0.838	0.55 (0.31 to 0.99)	**0.045**	1.23 (0.60 to 2.55)	0.572
ST elevation ≥ 0.1 mV	2.28 (0.29 to 17.92)	0.443	4.50 (0.56 to 36.15)	0.158	**	**	4.69 (1.56 to 39.11)	0.153
ST elevation ≥ 0.2 mV	1.30 (0.36 to 4.73)	0.693	3.86 (0.53 to 28.06)	0.181	1.56 (0.14 to 17.00)	0.715	6.29 (1.37 to 28.76)	**0.018**
Early repolarization*	–	–	–	–	–	–	–	–
ST-elevation ≥ 0.1 mV								
Male versus female	1.81 (1.48 to 2.21)	< **0.001**	1.81 (1.48 to 2.22)	< **0.001**	**	**	**	**
Age, per 5 years increase	1.01 (0.96 to 1.08)	0.628	0.99 (0.94 to 1.04)	0.644	1.01 (0.96 to 1.05)	0.740	0.92 (0.76 to 1.13)	0.428
BMI, per kg/m^2 increase	0.98 (0.95 to 1.00)	**0.027**	0.99 (0.97 to 1.01)	0.331	0.99 (0.98 to 1.01)	0.495	0.98 (0.94 to 1.03)	0.456
Height, per 5 cm increase	1.10 (1.06 to 1.15)	< **0.001**	1.02 (0.98 to 1.06)	0.278	0.99 (0.96 to 1.02)	0.343	1.15 (1.02 to 1.29)	**0.018**
ST-elevation ≥ 0.2 mV								
Male versus female	7.62 (3.68 to 15.78)	< **0.001**	8.05 (3.89 to 16.67)	< **0.001**	**	**	**	**
Age, per 5 years increase	0.87 (0.75 to 1.01)	0.075	0.81 (0.71 to 0.93)	**0.003**	0.80 (0.70 to 0.93)	**0.003**	0.93 (0.54 to 1.59)	0.781
BMI, per kg/m^2 increase	0.95 (0.91 to 1.00)	**0.041**	1.01 (0.97 to 1.07)	0.486	0.98 (0.94 to 1.03)	0.433	1.04 (0.90 to 1.21)	0.604
Height, per 5 cm increase	1.20 (1.11 to 1.30)	< **0.001**	0.97 (0.89 to 1.06)	0.469	0.97 (0.88 to 1.06)	0.507	0.83 (0.58 to 1.21)	0.334
Early repolarization								
Male versus female	2.93 (1.56 to 5.51)	**0.001**	2.86 (1.52 to 5.38)	**0.001**	**	**	**	**
Age, per 5 years increase	1.14 (0.96 to 1.35)	0.123	1.10 (0.93 to 1.30)	0.281	1.10 (0.91 to 1.32)	0.339	1.11 (0.74 to 1.68)	0.616
BMI, per kg/m^2 increase	0.97 (0.91 to 1.03)	0.321	0.98 (0.92 to 1.05)	0.589	0.99 (0.92 to 1.07)	0.851	1.00 (0.91 to 1.09)	0.962
Height, per 5 cm increase	1.18 (1.05 to 1.31)	**0.004**	1.03 (0.90 to 1.19)	0.664	1.07 (0.92 to 1.24)	0.401	0.86 (0.59 to 1.26)	0.441

PR = prevalence ratio
* No data as no co-prevalence of LVH by Cornell with early repolarization.
** Cannot be estimated since outcome does not vary.

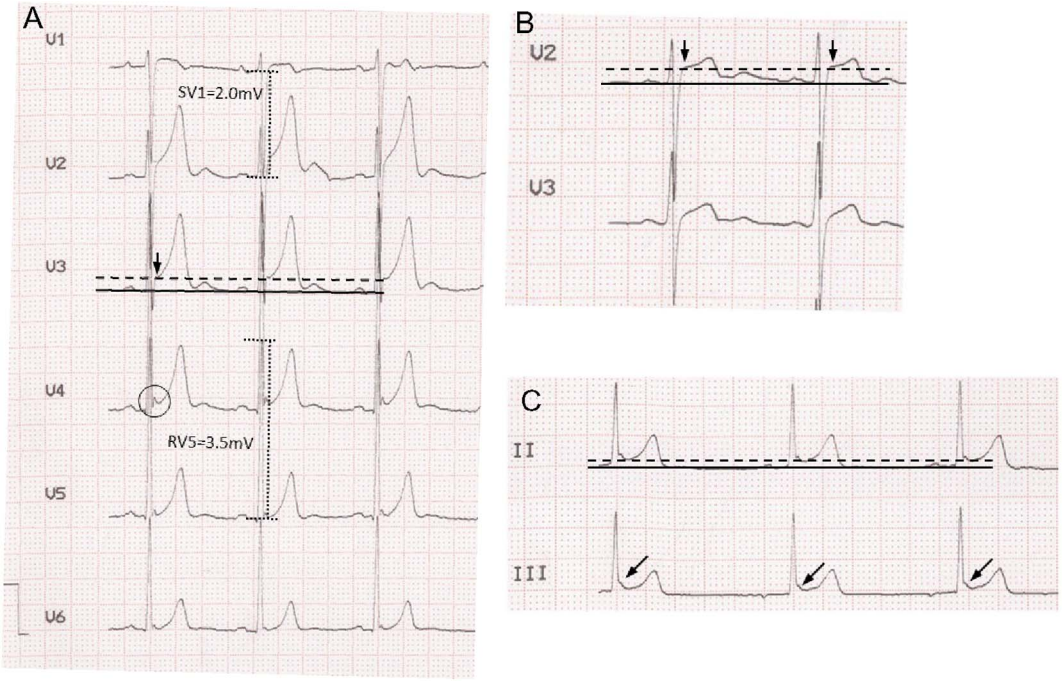

Fig. 2. A: Positive Sokolow Lyon criteria for LVH (dotted line SV1/RV5 > 3.5 mV), ST-elevation ≥ 0.2 mV (between Q-Q solid line and parallel broken line at the level of the J point, J point indicated by arrow) and notching of the J-point (circle) suggestive for early repolarization. B: ST-Elevation defined as an elevation of the QRS–ST junction (J point, arrow) by at least 0.1 mV in any lead ("male pattern"). C: Early Repolarization (ERP) with ST-elevation ≥ 0.1 mV and slurring of the QRS-ST junction (J-wave, arrow) in the limb leads.

ences in ST elevations among ethnic groups have been reported and were lowest in white populations as compared to African Americans who had the greatest ST elevations in leads I and V3 to V6 [35]. In the same study, BMI was inversely associated with ST-elevations which was also seen in our analysis. As we found a high co-variation of high QRS amplitudes as seen by positive SL criteria and ST-elevation, a possible reason for both findings is an increase in transmission of electrical currents from the heart to the electrodes secondary to less fatty tissue and related decreased distance/impedance. A pattern of ST-elevation consistent with positive criteria for ERP was hence predominantly found in young males in our analysis as well.

As recently reviewed by Ali et al. [15], the prevalence of ERP varies between 3% and 24% in the general population depending on the population studied with the highest prevalence seen in young males of African heritage and athletes [17,18]. As in our study population, ERP is usually incidentally diagnosed and considered benign with a negligible likelihood for developing catastrophic arrhythmias if asymptomatic, found in younger age groups, and co-prevalent with LVH on ECG [19,36,37,38,39]. On the other hand, individuals with ERP patterns associated with ST-elevation of ≥ 0.2 mV have been discussed to be of greater risk for fatal arrhythmias [40,41,42]. In our analysis this was found in 7.8% in the absence of high QRS amplitudes - possibly indicating a bias in transmission of electrical currents due to decreased chest wall impedance. The potential prognostic implications of these ECG patterns for fatal arrhythmias in a predominantly young and male African population would need to be determined.

A limitation of our analysis is that the study was not primarily designed to analyse ECG abnormalities and no cardiologic investigations other than clinical assessments and ECGs were performed. In this respect, no echocardiography or troponin evaluations were performed to support cardiac health or exclude morphologically abnormal cardiac conditions. As participants were of young age and clinically healthy by history and clinical examination, we feel that underlying cardiologic disease is unlikely in the vast majority of the individuals. No automated system was used to better standardize ECG analyses and all measurements were performed manually. As all ECGs were interpreted by at least two independent physicians and reviewed by a panel of experienced cardiologists, the likelihood of misinterpretations has been kept to a minimum.

In conclusion, high prevalence of LVH as defined by SL criteria, often associated with ST elevation and early repolarization predominantly seen in young, male, and clinically healthy Africans is a common finding that needs to be taken into consideration when screening for disease or eligibility criteria for potentially cardiotoxic investigational products. In the case of our MVA containing vaccine trial, ECG defined ineligibility was noted in at least 22.1% of the screening population who received ECG assessments. Screen outs due to ECG findings (11.3%) were reported for a North American MVA-containing vaccine trial in a predominantly Caucasian population [43]. The definitions for a "normal" ECG are largely based on references from Caucasian populations and do not necessarily translate into ECG findings in an African population. Investigations that evaluate differences in ECGs by ethnicity commonly refer to African-Americans or older African populations and are often associated with cardiovascular disease. Conversely, our data add to the scarcely available reports of ECG findings in young and healthy Africans. Main factors contributing to abnormal ECG patterns are likely caused by morphological chest characteristics and resulting distances of ECG electrodes to the heart in young African males. In African populations, Cornell criteria should be preferred for the interpretation of LVH by ECG as they appear to be less influenced by anthropomorphic variables and gender. The impact of ERP with ST-elevations ≥ 0.2 mV, especially in the absence of concomitant positive SL criteria as a risk factor for fatal arrhythmias needs to be further determined in young African populations.

Acknowledgements

The authors would like to thank Professor Bernard R. Chaitman, MD from the Saint Louis University School of Medicine for his ECG interpretations and expert advices. We thank Dr. Elmar Saathoff from the University of Munich (LMU) for statistical revision. We further would like to thank all the TaMoVac trial involved doctors and nurses not mentioned in the authors list for their contribution, especially Dr. Bahati Kaluwa from the NIMR-MMRC who tragically passed during the

study. We would also like to acknowledge the European and Developing Countries Clinical Trials Partnership (EDCTP), the German Ministry of Education and Research (BMBF) and the Swedish International Development Cooperation Agency (Sida) as funders of the TaMoVac01 trial.

References

[1] S. Kadiri, Tackling cardiovascular disease in Africa, BMJ 331 (7519) (Oct 1 2005) 711–712.
[2] K. Sliwa, G.A. Lee, M.J. Carrington, P. Obel, A. Okreglicki, S. Stewart, Redefining the ECG in urban South Africans: electrocardiographic findings in heart disease-free Africans, Int. J. Cardiol. 167 (5) (Sep 1 2013) 2204–2209.
[3] A. Dzudie, O. Milo, C. Edwards, G. Cotter, B.A. Davison, A. Damasceno, B.M. Mayosi, C. Mondo, O. Ogah, D. Ojji, M.U. Sani, K. Sliwa, Prognostic significance of ECG abnormalities for mortality risk in acute heart failure: insight from the sub-Saharan Africa survey of heart failure (THESUS-HF), J. Card. Fail. 20 (1) (Jan 2013) 45–52.
[4] M.J. Dewhurst, L.Y. Di Marco, F. Dewhurst, P.C. Adams, A. Murray, G.P. Orega, J.C. Mwita, R.W. Walker, P. Langley, Electrocardiographic reference values for a population of older adults in sub-Saharan Africa, Ann. Noninvasive Electrocardiol. 19 (1) (Jan 2014) 34–42.
[5] K. Somers, A.M. Rankin, The electrocardiogram in healthy East African (Bantu and Nilotic) men, Br. Heart J. 24 (Sep 1962) 542–548.
[6] L.L. Vitelli, R.S. Crow, E. Shahar, et al., Electrocardiographic findings in a healthy biracial population, Am. J. Cardiol. 9149 (97) (1998) 453–459.
[7] J.S1. Gottdiener, D.J. Reda, B.J. Materson, B.M. Massie, A. Notargiacomo, R.J. Hamburger, D.W. Williams, W.G. Henderson, Importance of obesity, race and age to the cardiac structural and functional effects of hypertension. The department of veterans affairs cooperative study group on antihypertensive agents, J Am Coll Cardiol. 24 (6) (Nov 15 1994) 1492–1498.
[8] I. Katibi, E.N. Clark, B. Devine, S.M. Lloyd, P.W. Macfarlane, Normal limits of the electrocardiogram in Nigerians, J. Electrocardiol. 46 (4) (Jul–Aug 2013) 289–295.
[9] P.W. Macfarlane, I.A. Katibi, S.T. Hamde, D. Singh, E. Clark, B. Devine, B.G. Francq, S. Lloyd, V. Kumar, Racial differences in the ECG–selected aspects, J. Electrocardiol. 47 (6) (Nov–Dec 2014) 809–814.
[10] M.A. Araoye, A.B. Omotoso, G.O. Opadijo, The orthogonal and 12 lead ECG in adult negroes with systemic hypertension: comparison with age-matched control, West Afr. J. Med. 17 (3) (Jul–Sep 1998) 157–164.
[11] M.J. Dewhurst, L.Y. Di Marco, F. Dewhurst, P.C. Adams, A. Murray, G.P. Orega, J.C. Mwita, R.W. Walker, P. Langley, Electrocardiographic reference values for a population of older adults in sub-Saharan Africa, Ann. Noninvasive Electrocardiol. 19 (1) (Jan 2014) 34–42.
[12] K. Sliwa, G.A. Lee, M.J. Carrington, P. Obel, A. Okreglicki, S. Stewart, Redefining the ECG in urban South Africans: electrocardiographic findings in heart disease-free Africans, Int. J. Cardiol. 167 (5) (Sep 1 2013) 2204–2209.
[13] B. Surawicz, S.R. Parikh, Prevalence of male and female patterns of early ventricular repolarization in the normal ECG of males and females from childhood to old age, J. Am. Coll. Cardiol. 40 (10) (Nov 20 2002) 1870–1876.
[14] R.G. Hiss, L.E. Lamb, M.F. Allen, Electrocardiographic findings in 67, 375 asymptomatic subjects, Am. J. Cardiol. 6 (Jul 1960) 130–142.
[15] A. Ali, N. Butt, A.S. Sheikh, Early repolarization syndrome: a cause of sudden cardiac death, World J. Cardiol. 7 (8) (August 26 2015) 466–475.
[16] M. Mehta, A.C. Jain, A. Mehta, Early repolarization, Clin. Cardiol. 22 (2) (Feb 1999) 59–65.
[17] S. Miyazaki, A.J. Shah, M. Haïssaguerre, Early repolarization syndrome – a new electrical disorder associated with sudden cardiac death, Circ. J. 74 (2010) 2039–2044.
[18] G.B. Nam, K.H. Ko, J. Kim, K.M. Park, K.S. Rhee, K.J. Choi, Y.H. Kim, C. Antzelevitch, Mode of onset of ventricular fibrillation in patients with early repolarization pattern vs. Brugada syndrome, Eur. Heart J. 31 (2010) 330–339.
[19] B. Surawicz, P.W. Macfarlane, Inappropriate and confusing electrocardiographic terms: J-wave syndromes and early repolarization, J. Am. Coll. Cardiol. 57 (15) (Apr 12 2011) 1584–1586.
[20] L.F. Mora, A.H. Khan, L.S. Sperling, Cardiac complications after smallpox vaccination, South. Med. J. 102 (6) (Jun 2009) 615–619.
[21] D.C. Cassimatis, J.E. Atwood, R.M. Engler, P.E. Linz, J.D. Grabenstein, M.N. Vernalis, Smallpox vaccination and myopericarditis: a clinical review, J. Am. Coll. Cardiol. 43 (9) (May 5 2004) 1503–1510.
[22] M.L. Elizaga, S. Vasan, M.A. Marovich, A.H. Sato, D.N. Lawrence, B.R. Chaitman, S.E. Frey, M.C. Keefer, MVA Cardiac Safety Working Group, Prospective surveillance for cardiac adverse events in healthy adults receiving modified vaccinia Ankara vaccines: a systematic review, PLoS One 8 (1) (2013) e54407.
[23] P.J. Munseri, A. Kroidl, C. Nilsson, A. Joachim, C. Geldmacher, P. Mann, et al., Priming with a simplified intradermal HIV-1 DNA vaccine regimen followed by boosting with recombinant HIV-1 MVA vaccine is safe and immunogenic: a phase IIa randomized clinical trial, PLoS One 10 (4) (2015) e0119629.
[24] DAIDS, Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, 1.0 ed., (2004).
[25] M. Sokolow, T.P. Lyon, The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads, Am. Heart J. 37 (2) (Feb 1949) 161–186.
[26] P.N. Casale, R.B. Devereux, P. Kligfield, R.R. Eisenberg, D.H. Miller, B.S. Chaudhary, M.C. Phillips, Electrocardiographic detection of left ventricular hypertrophy: development and prospective validation of improved criteria, J. Am. Coll. Cardiol. 6 (3) (Sep 1985) 572–580.
[27] J.E. Norman Jr., D. Levy, Improved electrocardiographic detection of echocardiographic left ventricular hypertrophy: results of a correlated data base approach, J. Am. Coll. Cardiol. 26 (4) (Oct 1995) 1022–1029.
[28] B. Surawicz, S.R. Parikh, Prevalence of male and female patterns of early ventricular repolarization in the normal ECG of males and females from childhood to old age, J. Am. Coll. Cardiol. 40 (10) (Nov 20 2002) 1870–1876 (Internet).
[29] S. Miyazaki, A.J. Shah, M. Haïssaguerre, Early repolarization syndrome – a new electrical disorder associated with sudden cardiac death, Circ. J. 74 (2010) 2039–2044.
[30] R. Devereux, E. Lutas, R. Casale, et al., Standardization of M-mode echocardiographic left ventricular anatomic measures, J. Am. Coll. Cardiol. 4 (1984) 1222.
[31] M. Koren, G. Menash, J. Blake, J. Laragh, R. Devereux, Comparison of left ventricular mass and geometry in black and white patients with essential hypertension, Am. J. Hypertens. 6 (1993) 815.
[32] P.M. Rautaharju, L.P. Park, J.S. Gottdiener, D. Siscovick, R. Boineau, V. Smith, N.R. Powe, Race- and sex-specific ECG models for left ventricular mass in older populations. Factors influencing overestimation of left ventricular hypertrophy prevalence by ECG criteria in African-Americans, J. Electrocardiol. 33 (3) (Jul 2000) 205–218.
[33] M.A. Fraley, J.A. Birchem, N. Senkottaiyan, M.A. Alpert, Obesity and the electrocardiogram, Obes. Rev. 6 (4) (Nov 2005) 275–281.
[34] G. de Simone, S.R. Daniels, R.B. Devereux, R.A. Meyer, M.J. Roman, O. de Divitiis, M.H. Alderman, Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight, J. Am. Coll. Cardiol. 20 (5) (Nov 1 1992) 1251–1260.
[35] V.K. Reddy, S.M. Gapstur, R. Prineas, L.A. Colangelo, P. Ouyang, A.H. Kadish, Ethnic differences in ST height in the multiethnic study of atherosclerosis, Ann. Noninvasive Electrocardiol. 13 (4) (Oct 2008) 341–351, http://dx.doi.org/10.1111/j.1542-474X.2008.00252.x.
[36] Olson K a, A.J. Viera, E.Z. Soliman, R.S. Crow, W.D. Rosamond, Long-term prognosis associated with J-point elevation in a large middle-aged biracial cohort: the ARIC study, Eur. Heart J. 32 (24) (Dec 2011) 3098–3106.
[37] A.L. Klatsky, R. Oehm, Cooper R a, N. Udaltsova, M.A. Armstrong, The early repolarization normal variant electrocardiogram: correlates and consequences, Am. J. Med. 115 (3) (Aug 2003) 171–177 (Internet). (cited 2012 Aug 2).
[38] R. Rosso, A. Halkin, S. Viskin, J waves and early repolarization: do not confuse me with the facts!, Heart Rhythm. 9 (2012) 1603–1604.
[39] S. Viskin, R. Rosso, A. Halkin, Making sense of early repolarization, Heart Rhythm. 9 (2012) 566–568.
[40] M. Haïssaguerre, N. Derval, F. Sacher, L. Jesel, I. Deisenhofer, L. de Roy, J.L. Pasquié, A. Nogami, D. Babuty, S. Yli-Mayry, et al., Sudden cardiac arrest associated with early repolarization, N. Engl. J. Med. 358 (2008) 2016–2023.
[41] R. Rosso, E. Glikson, B. Belhassen, A. Katz, A. Halkin, A. Steinvil, S. Viskin, Distinguishing “benign” from “malignant early repolarization”: the value of the ST-segment morphology, Heart Rhythm. 9 (2012) 225–229.
[42] J.T. Tikkanen, O. Anttonen, M.J. Junttila, A.L. Aro, T. Kerola, H.A. Rissanen, A. Reunanen, H.V. Huikuri, Long-term outcome associated with early repolarization on electrocardiography, N. Engl. J. Med. 361 (2009) 2529–2537.
[43] J. Sano, B.R. Chaitman, J. Swindle, S.E. Frey, Electrocardiography screening for cardiotoxicity after modified Vaccinia Ankara vaccination, Am. J. Med. 122 (1) (2009 Jan) 79–84.