Original Research Article

PATTERN VARIATION IN ELECTROCARDIOGRAM T WAVE OF APPARENTLY HEALTHY IN-SCHOOL CHILDREN IN CHOBA, RIVERS STATE, NIGERIA.

Abstract

Background to the Study

Electrocardiographic patterns are graphical recordings of voltage versus time of the electrical waves of the heart using a resting 12-lead electrocardiographic machine Lilly, (2016). In children, the electrocardiogram (ECG) misinterpretation remains a problem and can result in clinical mismanagement. Gates, (2019). In electrocardiography, the T-wave represents the repolarization of the ventricles. T-wave inversions from V1 to V3 leads are frequently found and is normal in children (www.Patientcareonline.com). The aim of this study is to determine the T-wave pattern variation in apparently healthy in-school Nigerian children in Choba.

Methodology

A descriptive cross sectional was carried out to determine pattern variations in T wave inversion in in-school children across sex, age, and height. Simple random sampling method was used to select subjects from primary 1 to primary 6. A total of 135 in-school children were recruited from a population of 203 from 2 primary schools in Choba.

The subjects were randomly sampled across two sex groups (boys and girls) and three age group (5-8, 9-11, and 12-14). Trend in the weight, height and blood pressure were also observed. A resting 12- lead electrocardiograph, a seca standiometer, mercury sphygmomanometer and cuffs and a stethoscope etc were used. Data was collected using standard methods. The procedures were conducted by competent personnel.

Result:

The girls have significantly higher mean age, height, and weight than the boys ($p<0.01$). Diastolic blood pressure and systolic blood pressure between boys and girls showed no significant difference ($p<0.005$). The result also showed that distribution of T wave inversion has no sexual preference ($\times^2=0.702$; $p=0.873$). The result also showed correlation between measured variable in the study population.

Conclusion:

Distribution notwithstanding, T wave inversion in V1, V2, V3 of the right precordial leads are normal findings in apparently healthy children throughout their childhood ages.

Keywords: ECG, T wave Inversion, Children

INTRODUCTION

Electrocardiographic patterns are graphical recordings of voltage versus time of the electrical waves of the heart using a resting 12-lead electrocardiographic machine Lilly, (2016). In children, the electrocardiogram (ECG) misinterpretation remains a problem and can result in clinical mismanagement. Gates, (2019). In electrocardiography, the T-wave represents the repolarization of the ventricles. T-wave inversions from V1 to V3 leads are frequently found and is normal in children (www.Patientcareonline.com).

Olayinka and Lynn, (2014) in the work, T-wave inversion in electrocardiogram said that T- wave represented ventricular repolarization and the electrical forces resulting from recovery of activated ventricular muscle fibers to their resting states. They added that a major factor influencing T- wave configuration is the temporal and spatial patterns on myocardial excitation. Altered patterns of excitation secondarily alter the patterns of recovery and, thus, the formation of the T wave. Furthermore, they said that T-wave inversions as seen on electrocardiogram are associated with a variety of pathophysiologic states, including cardiac, Pulmonary and cerebrovasocular disease and acute electrolyte disorder.

T wave in children is normally upright after birth, inverted after the first week of life and becomes upright again after 6 years Liesel, (2011). Steve and Karen (2002) added that T wave in lead V1 inverts by 7 days and typically remain inverted until at least age 7 years.

Papadakis et al (2009) in the work prevalence and significance of T wave inversions in predominantly Caucasians athletes stated that t wave remains inverted in ages less than 16 years.

SUBJECT AND METHODS

Consent and Ethical Approval

This research was carried out in conformity with the Helsinki Declaration of 1975 as amended in 2000 (World Medical Association, 2002.)

Institutional ethical approval (UPH/R&D/REC/0434) was obtained from University of Port Harcourt Ethics Committee.

The Objectives and nature of the study was explained to each subject before enlistment. Informed consent was obtained from the parents and the head teachers of the schools before recruitment into the study

Subjects

A total of 135 Children were use for the study. They were within 5 -14 years of age. They were all in-school Nigerian Children in Choba.

Only apparently healthy in-school children were used.

Children with any form of health challenges like fever, cough, children under medication, heart palpitation, headaches etc. were excluded from the study.

Determination of Blood Pressure, Height, Weight

Blood pressure

Trained personnel were used to examine the blood pressure of the children. Blood pressure were measured using mercury sphygmomanometer and appropriate size cuffs after the participants had been seated in a chair for 5 minutes with the backs supported. Blood pressure was measured for 3 times at an

interval of 2 minutes and the mean of the second and third measurements was taken as the blood pressure. (Hiroyuki Takase et al., 2016)

$$MAP = \frac{SBP + 2DBP}{3}$$

Body weight and height

The body weights of the children were collected and recorded using standard heights without shoes and weights wearing light clothes in all participants. They were measured in metres (m) and kilograms (kg) respectively using standard scale (Seca model).

To ensure accuracy in the readings, the children were asked to remove shoes, wrist watches, necklaces and anything's that could interfere with the correct readings of ECGs, blood pressures, body weights and heights (Guo-Zhe et al., 2013).

Determination of ECG parameters

A Cardiovit AT-2plus model standard resting 12- lead electrocardiogram (Schiller AG, Altgasse 68 CH 6341, Bear Switzerland) was used to determine electrocardiographic patterns of the hearts of the subjects (children) in accordance with American Heart Association, American college of cardiology/Heart Rhythm society (AHA/ACCF/HRS) recommendations (Kligfield et al;2017). The subjects rested first, then they were asked to lie on a couch in supine position, exposing only their trunk. (The girls were allowed light gowns). The limb leads were placed on their wrist and on their ankles. The chest leads were placed at appropriate points on their chests (Sembulingham and Prema,2007). Cotton wool swap was used to sterilize the point the leads were placed. Electrode gel was then applied to enhance conductivity of electrical impulses from the heart to the leads.

Statistics

Variance was set at infinity and a P-value ‹ 0.05 was considered significant.

Results obtained is presented as Mean ± SD where necessary.

RESULTS

List 1 : The result of this work is given in a graph and five tables using mean SD as follows

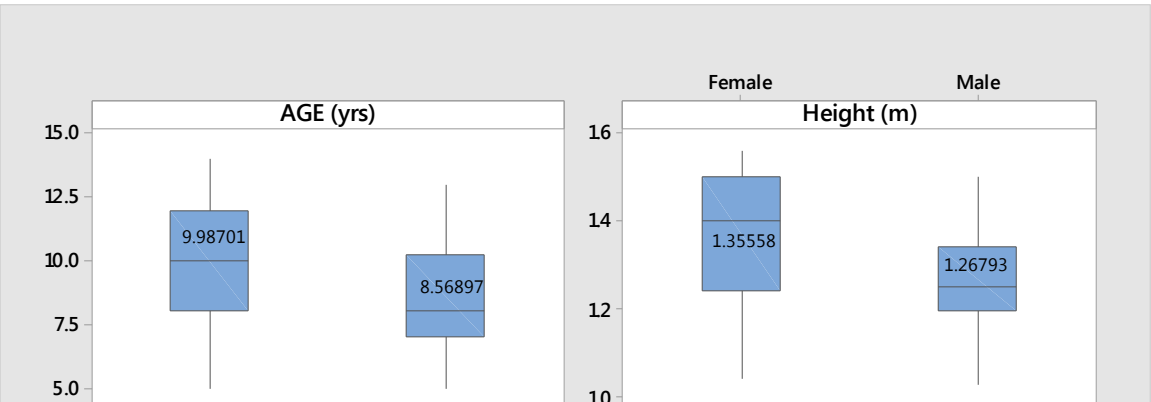

Figure 1:The mean age, height and weight of the male and female children

The mean age, height and weight of girls were 9.98±2.30 years, 1.36±0.14m, and 30.60±9.16kg while boys were 8.87±2.12years, 1.27±012m, and 25.17±6.02kg respectively. The difference in the values were significantly different in boys and girls (P<0.01); with girls having significantly higher mean values.

Table 1: The test of mean difference of the systolic and diastolic blood pressures (SBP& DBP) of the children

SEX	N	SBP (mmHg)	T-test		DPB (mmHg)	T-test	
		Mean±SD	T-Value	P-Value	Mean±SD	T-Value	P-Value
Male	56	87.20±12.40	-4.16	0.000	55.90±11.60	1.26	0.210
Female	77	96.20±12.30			53.40±10.70		

P value < (0.05)

The mean SBP was significantly higher in girls (96.20±12.30mmHg) when compared to boys (96.20±12.30mmHg) (t=4.16; P<0.001), while the SBP was higher in boys 55.90±11.60mmHg when compared to girls 53.40±10.70mmHg; however, the difference was not significant (P>0.05)

Table 2: The test of mean difference in t-axis value of the male and female children

SEX	N	T AXIS	T-test	
		Mean	T-Value	P-Value
Male	58	55.40±25.1	1.37	0.174

Female	77	49.60±24.1

The mean t-axis value was higher in boys (55.40±25.1) when compared to girls (49.60±24.1). However, the difference was not significant (0.174)

Table 3: Distribution of the t-wave inversion in boys and girls and test of association

Sex	T WAVE INVERSION				Chi-Square Analysis		
	NIL	V1	V1-V2	V1-V3	Chi-Square	DF	P-Value
Female	8 (10.39)	12 (15.58)	33 (42.86)	24 (31.17)	0.702	3	0.873
Male	8 (13.79)	10 (17.24)	25 (34.1)	15 (25.86)			
Total	16 (11.85)	22 (16.3)	58 (24.96)	39 (28.89)			

Both boys (25; 34.1%) and girls (33; 42.86%) had more of V1-V2 inversion when compared with other T-wave inversions; however, the distribution in the population has no sexual preference (χ^2=0.702; P=0.873).

In the male subjects the T wave inversions at V1 and V2 was more frequent than in V1 and V1 to V3. While in females the same V1 to V2 inversions were also more frequent when compared to inversions at the prercordial leads.

Comparing the male and female inversions at V1 and V2, the females have a higher percentage of V1 and V2 inversions (42.86%) than the males (34.1%). However, it was not statistically significant (χ^2=0.702; P=0.873).

Table 4: Distribution of the ST-segment in boys and girls and test of association

	ST SEGMENT			Chi-Square Analysis		
Sex	No	Yes	E	Chi-Square	DF	P-Value
Female	74 (96.1)	1 (1.3)	2 (2.6)	0.127	3	NA

Male	55 (94.83)	1 (1.72)	2 (3.45)
Total	129 (95.56)	2 (1.46)	4 (2.96)

The value of girls that have no ST segment elevations 74(96.1) is more than that of the boys 55(94.83). However, it was not statistically significant.

Table 5: The correlation between measured variables in the study population

Variables		Height (m)	WT (kg)	SBP (mmHg)	DBP (mmHg)	T AXIS
AGE (yrs)	R	.732**	.708**	.702**	.337**	-0.048
	P-value	0	0	0	0	0.581
Height (m)	R	1	.719**	.574**	.198*	-0.164
	P-value		0	0	0.022	0.057
WT (kg)	R		1	.555**	.281**	-0.143
	P-value			0	0.001	0.098
SBP (mmHg)	R			1	.501**	-0.041
	P-value				0	0.64
DBP (mmHg)	R				1	-0.134
	P-value					0.123

Note: Significant at * 0.05, ** 0.01; r=Pearson's correlation

Age correlates positively and significantly with height (0.732), weight (0.708), SBP (0.702), DBP (0.337) and negatively with T axis (-0.048) but not significant.

Height correlates positively and significantly with weight (0.719), SBP (90.574), DBP (O.198) and negatively with T axis (-0.164) but not significant.

Weight correlates positively and significantly with SBP (0.555), DBP (0.281) and negatively with Taxis (-0.143) but not significant.

SBP correlates positively and significantly with DBP (0.501) and negatively with T axis (-0.041) but not significant.

DISCUSSION OF FINDINGS

T wave inversions in the right precordial leads (V1 to V2) is normal in children and it is important to observe and identify the prevalence and, or, pattern variations of these inversions in children age groups, height and weight. The information can be very helpful in predicting normal T wave morphology in children and any cardiomyopathy that could be associated with it as well as other physiological imbalances.

In this study, T wave inversions were seen in age groups 6 and 7 years. This agrees with Liesel (2011) who said that T wave inversions begin after 6 years. My finding also agrees with Steve and Karen (2002) who said that T wave in V1 inverts by 7 days and typically remain inverted until at least age 7 years.

This study showed that age, height and weight have no association with T wave inversions, because T wave inversions were present in all the age groups, weights and heights of the children used for the study. This is in line with Papadakis et al (2009) in the work prevalence and significance of T wave inversions in predominantly Caucasians athletes. In this study there is a significant difference in the mean age, mean height and mean weight between boys and girls with the girls having significantly higher mean values. This is also in line with Papadakis et al (2009).

What this study also reveals is that T wave inversions were found in all age groups, heights and weights in the apparently healthy in-school children and this indicated no myopathies showing that this occurrence is normal in children which agrees with Dickinson (2005) in his work normal ECG in children and adolescence; were it was stated that more children of 3-5 years old had inverted T wave in V2 and few of 8-12 years old had inverted T wave in V2. Age, heights and body weights were not said to have interfered with this occurrences in any wave.

From this study, it was observed that there were no pattern variations in T wave inversion. Dickinson (2005) reported that throughout childhood, the T wave pattern, particularly the precordial leads is very different to that of adult and there is a progressive change in T Wave axis from birth to early adult life.

This study also compared mean systolic blood pressure and mean diastolic blood pressure in boys and girls and showed that there was no significant difference. This agrees with Schinichiro et al (2013) were he said that systolic blood pressure and diastolic blood pressure were associated with prevalence of ischemic-like ECG.

The test of mean difference in T axis value of the male and female children did not also show any significance. Although, the males were seen to have higher mean values than the females which is as a result of the simple random sampling method that was used in the study.

The study also evaluated T wave inversions in the boys and girls and reported that a higher number of children had more T wave inversions in V1-V2 when compared to T wave inversions in V1 only and V2 only. This finding is in contrast with Aapo et al (2012), in his work, T wave inversions in right precordial leads of a 12-lead electrocardiogram in 5-6 years age group subjects, were he reported that T wave inversions in V1-V2 were found in only 4 out of 10,957 subjects.

This study also revealed that T wave inversions in V1-V2 or V1-V3 had no sexual preference in line with Aapo et al (2012).

CONCLUSION

This study has found out that T wave inversions at V1, V2, and V3 are present in all childhood ages, although the inversion at V1 and V2 were found to be predominant compared to inversion at V1 only, V2only, and V3 only. Therefore, T wave inversion are normal findings in apparently healthy children.

REFERENCES

Aapo, L.; Aro, M.D.; Olli, A.; Anttonen, M.D.; Jani, T.; Tikkanen, B.M.M.; Juhani, J.M.D.; Tuomas, K.M.D.; Harri, A.; Rissanen, M.S.C.; Antti R.M.D.; Haicki, V. and Huikuri, M.D. (2012). Prevalence and Prognostic Significance of T-wave Inversions in Right Precordial Leads of a 12-Lead Electrocardiogram in Aged Subjects.*Circulation AHA.112. 098681 circulation. 2012, 125, 2575-2577*

Adedoyin, D.; Allinsegon A.; Ebele, U.; Adewumi A. and Sarah J. O. (2016). Electrocardiographic Study in Adult Homozygous Sickle Cell Disease Patients in Lagos, Nigeria.*Journal of tropical mediating volume 2016, article 4214387.5 pages*

Afolabi, J.K. and Omokhodion, S.I. (2014). Electrocardiographic Patterns in Apparently Healthy Nigerian Children in Illorin, Nigeria.*Department ofpardiations and child health, university of illorin, illorin Teaching Hospital, PMB 1495, illorin, vol.11*

Akinwusi, P.O.; Akintunde, M.D. and To Ogongbamigbe M.D. (2010). Cardiovascular and Electrocardiographic Changes in Nigerian with a Normal Pregnancy.*Cardiovascular journal of Africa PMID: 21556448.*

Alpert, M.A., Terry, B.E., Cohen, M.V., Fan, T.M., Painter, J.A., Massey, C.V. (2000). The Electrocardiogram in Morbid Obesity. *PMID: 10758940*

Aneil, M., Harshil, O., Sabiha, G. Helder, D. Lynne, M., Rajay, M. Ahmed, M., Michael W., Michael P. Sanjay, S. (2014). Prevalence and Significance of Anterior T-wave inversion in Females.*Heart jnl. 2014-306118.103.vol.100, issuesuppl 3*

Ary, L.; Goldberger, M.D., FACC,…Alexei Shrilkin, M.D. PhD. (2018). In Goldberger's Clinical Electrocardiography (ninth edition).*Book ISBN: 9780323 508773 by Elsevier.www.Elsevier.com*

Bill Gates, (2019). MIT Technology. How we'll invent the future.*MIT Technology*

Brooks Walsh, M.D. (2015). Persistent Juvenile T-wave Pattern.*Life in fast Lane. Library*

Chatterjee, S. (2011). ECG Changes in Subarachnoid Haemorrhage: A synopsis.*Netherlands heart journal. PMD 22020856.*

Christina, S.M.; Liisa, B. and Lars L. T-wave Abnormalities, High Body Mass Index, Current Smoking and High Lipoprotein Levels Predict the Development of Major Abnormal Q/Qs patterns 20 years later.*PMID: 16519804 PMID: PMC 1420329*

ECG Interpretation (2019). *Nurses learning network*

Edemeka, D.B.U. (2004). The Electrocardiogram in Healthy Nigerians Residents in Lagos State.*Global journal of pure and applied science, vol.10 No, 4 (2004).*

Fergus, J. Rugg-gunn, Lina N. (2009). In Blue Broks of Neurology.*www.amazon.com*

Guo-Zhe Sun (2013). Associationbacteria Obesity and ECG Variables in Children and Adolescents.www. *Ahajournals.com.circulation AHA. 109.192216. circulation. 2009,119: e 489-e517.*

Guyton and Halls (2012). *The heart. Saunders, 12th edition, pages 101 to 110*.

Hanna, E.B and Glancy, D.L. (2011). ST-Segment Depression and T-wave Inversions: Classification, Differential Diagnosis, and Caveats.*Cleveland clinic journal of medicine.*

Hiroyuki, T. (2016). Development of Hypertension in the General Population.*Medicine (Baltimore), PMID: 26039136.*

Hust, J.W. (1998). Naming of waves in the ECG, with a brief account on their Genesis.*Journal of history of medicine and Allied Sciences*.

Ibrahim, A. and Mu'uta, I. (2015). Electrocardiographic Pattern of Apparently Healthy Primary School Children Aged 5-15 Years in Kano Nigeria.*Doi: 10.403/2321-449x. 153280.vol.3 issue:1, page 12-17.*

Injure Park et al., (2015). Subarachnoid Hemorrhage Mimicking ST-Segment Elevation Myocandizy Infarction after Return of Spontaneous Circulation.*Clinical and experimental emergency medicine. Doi: 10.15441/ ceem.15.012. PMID 2775 2607.*

Interwoven, W. (1901). Un nouveau galvanometer.*Texas heart institute journal PMID. 18612490.*

Ishak, A.; Mansi, M.D. and Ira, S. Nash. (2004). Ethric differences in electrocardiographic Amplitude Measurements.*Annals of Saudi medicine doi: 10.5144/0256-4947, 2004.459.*

Johansson, B.V. Dan MedicinhistArbog, (22001).

Jordan, M; Prutkin, M.D., (2019). St and T-wave Changes.*Eca learning centre*

Liesel A.M.B. (2011). Pattern Recognition in Paediatric ECGs.*Continuing medical education vol. 29, No 11/12.*

Lilly Leonard, S. (2016). Pathophysiology of heart disease.*Pathophysiology of heart disease: A collaborative project of medical students and faculty, fifth, north American edition v3*

Madhur, D. B. (2016). Examining Left Axis Deviation.*Dol: 10.5 772/intechopen.69435.*

Marcus, F.I (2005). Prevalence of T-wave Inversion beyond V_I and in Young Normal Individuals and usefulness for the Diagnosis of Airhythmogenic Right Ventricular Cardiomyopathy/Dysplasia.*PMID: 15842973*

Marcus, F.I., McKenna, W.J. Sherrill, D., Basso, C., Bauce, B., Bluemke, D.A., Calkins, H., Corrado, D., Cox, M.G., Daubert, J. P., Fonta, Ine, G., Gear, K., Hauer R., Nava, A., Picard, M. H., Protonotarios, N., Saffitz, J.E. Samborn, D.M., Steinberg, J.S., Tandri, H., Thiene G., Towbin, J.A., Toatsopoulou, A., Wichler, T. and Zareba, W. (2010). Diagnosis of arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia: Proposed Modification of the Task force Criteria.*HHS public Access Dol: 10.1161/ circulation AHA.108.840827. PMID 20172911.*

Mark, Jonathan, B. (1998). Atlas of Cardiovascular Monitoring. *Atlas of cardiovascular monitoring*

Maron, B.J. (2002) Hypertrophic Cardiomyopthy: A systematic Review.*PMID:11886323*

Michael, P.; Sandeep, B.; John, R..; Jayesh, M; Sami, F.; Iora, C. and Sunjay, S. (2009). Prevalence and Significance of T-wave Inversions in Predominantly Caucasian Adolescent Athletes.*Eur heart journal, 2009, Dec,30 (23): 2947.*

Migliore, F. Zozi, A., Michieli, P., Perezzolo, M. M., Siciliano, M., Rigato, I., Bauce, B., Basso, C., Taozza, D., Schiavon, M., Iliceto, S. Thiene, G. and Corrado, D. (2012). Prevalence of Cardiomyopathy in Italian Asymptomatic Children with Electrocardiographic T.wave Inversion at preparticipatoryScreening.*www. Ahajournals.org circulation AHA. 111. 055673. Circulation: 2012; 125: 529-538.*

MPB Goonetileke, UA Jayarathna, PmWMadanayake, HAM inthisar, DR palangasinghe. PS Hehiarachhi, UK Eydage, ADY Gayan, MDSA Dil;rukshi, PK RakshithaRukmal, (2013) Assessment of the age, where juvenile T inversion pattern in right precordial leads of an ECG changes to the adult upright T wave pattern. *Sri Lanka journal of child health. 2013; 42,205-208.*

Nelson, I; Oguanobi, B.J.C.; Onuwbere, S.O.; Ike, B.C.; Anisuiba, E.C.; Ejim, O.G. and Ibegbulam (2010). Electrocardiographic findings in adult Nigerians with Sickle Cell Anaemia.*Journal of tropical medicine vol. 2016. Article ID: 4214387.*

Nelwan, S.P.; Meij, S.H.; Van Dam, T.B. and Koro, J.A. (2001). Correction of ECG Variations Caused by Body Position Changes and Electrode Placement during ST-T Monitoring.*PMID: 11781959 Pubmed mobile*.

OlayinkaAfolabi Brown MD, D. Lynn Morris, MD Vincent M. Figueredo, MD (2014). Enstein Heart and vascular institute, Enstein medical center, Philadelphia, PA, Jefferson medical college, Thomas Jefferson University, Philadelphia, PA. *Pubmed mobile*.

Os OGAH MBBS, MSc, FWACP, OOolaSapo, MBBS, MSC, FWACP and DM Ojji MBBS, FWACP (2010). Electrocardiographic Left Ventricular Hypertrophy with Strain Pattern Prevalence, Mechanisms and Prognostic Implications.*Pubmed mobile, PMID: 18320088 DMCID: PMC 3975313.*

Papadakis, M., Basavarajaiah, S., Rawlins, J., Edwards, C., Malcan, J. Firoozi, S. and Carby, L. Sharmas (2009). Prevalence and Significance of T-wave Inversions in Predominantly Caucasian Adolescent Athletes. *Eur heart journal.*

Rivera-Ruiz, M. Cajalvilca, C. Varon, J. (1927). Einthoven's string galvanometer. The first electrocardiograph.*Texas heart institute journal.*

Rogers, Mark, C (1969). Historical Annotation: Sir John Scolt. Burdon-Sanderson (1928-1905). A Piooneer in electrophysiology.

Salah, A.M.S.; Rene Bloo and Andries, S. (2014). Cardiac and non-cardiac causes of T-wave inversion in the precordial Leads in adults subjects: A Outich ease Series and REVIEW of the Literature.*Pubmed mobile PMD: 25717356 PMCID: PMC 4325305.*

Samuel, A. A. (Paed), John AkintundeOladotunOkeniyi (2015. Electrocardiographic abnormalities and Dyslipidemia Syndrome in Children with /sickle Cell Anaemia.*PMCID: PMC 4816931 and premaelectroearoliogram. Essentials of human.*

Sembulingham, S. (2014). 7th edition. Essentials of Human Physiology.*Physiology. Jaypeebrothers medical publishers, 4th edition, py 506-511*

Steve Goodacre and Karen Mcleod, (2002) Paediatric electrocardiography. *BMS publishing group, BMS. 2002, Jun 8, 324 (7350): 1382-1385. PMID; 12052812.*

Suprect, W. and Anuj, C. (2016). Effect of Changes in Body Position on Resting Electrocardiogram in Young Healthy Adults.

Taro, T. (2017). Takemi program in international health.*www.globalhealth.harvard.edu*.

US preventive Services Task Force; Curry, SJ; Krist, A.H.; owens, DK; Barry, MJ; Caughey, AB; Dvidson, KW; Doubeni, CA; Epling J.W; Kemper, A.R.; Kunik, M; Landefeld C.S; Mangione, C.J; Silverstein, M; Simon, M.A.; Tseng, C.W and Wong, J.B. (2018). Screening for cardiography: US preventive services Task force recommendation statement.*Pubmed mobile*

Verouden, N.J.; Koch, K.T.; Peters, R.J.; Henriques, J.P.; Baan, D.; Schaaf, R.J. Vander, Vis, M.M.; Tijssen, J.G. and Piek, J.J. (2009). Resistant Precordial Hyperacute T-wave signify approximal left anterior descending artery occlusion.*Heart, 2009 Dec, 95(23): 1951-2. PMID: 19620137*

Waller A.D, (1887): A Demonstration on man of electromotive charges accompanying the heartbeat.*The journal of physiology. J Physiol. 1887 oct. 8/5: 229-234 dol: 10. 1113/ J physiol. 1887. Sp000257.*

World Medical Association, 2002. "World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects.," *J. Postgrad. Med., vol. 48, no. 3, pp. 206-208.*