INSULIN RESISTANCE AND ELECTROCARDIOGRAPHIC ALTERATIONS IN NON-OBESE INDIAN PATIENTS WITH HYPERTENSION.

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Abstract

Background:

Heart disease risk has been associated with cardiac steatosis. The relationships between cardiac steatosis, aberrant electrocardiograms (ECG), and specific metabolic syndrome symptoms (MetS) were studied.

Method:

This prospective study was conducted from July 2021 to August 2022 at Patna Medical College & Hospital, Patna, and laboratory data and a 10-lead ECG were compared between 35 men without the MetS and 30 men with the MetS. Using 1.0 T magnetic resonance (MR) spectroscopy, the myocardial triglyceride (MTG) content was determined, and epicardial and pericardial fat was imaged using MR. SPSS 22.0 for Windows was used to conduct all statistical analyses. The Kolmogorove-Smirnov test was used to determine whether continuous variables were normal.

Results:

Compared to participants without the MetS, men with the condition exhibited higher levels of MTG in their epicardial and pericardial fat depots ($p < 0.002$). Patients with MetS had greater heart rates ($p < 0.002$), longer PR intervals ($p < 0.043$), a shift of the frontal plane QRS axis to the left ($p < 0.002$), and lower QRS voltage ($p < 0.002$). There was an inverse relationship between the frontal plane QRS axis and the QRS voltage and MTG content, waist circumference (WC), body mass index (BMI), TGs, and fasting blood glucose. Measures of insulin resistance were associated adversely with the QRS voltage, but high-density lipoprotein cholesterol correlated positively. The frontal plane QRS was determined by the MTG content and hypertriglyceridemia, while the QRS voltage was predicted by the WC and hyperglycemia.

Conclusion:

Several alterations on the 10-lead ECG appear to be related to both the MetS and cardiac steatosis. In people with MetS, the frontal plane QRS axis is displaced to the left and the QRS voltage is reduced. In obese people with cardiometabolic risk factors, the presence of left ventricular hypertrophy may be understated by standard ECG criteria.

Keywords: cardiac steatosis, electrocardiogram, metabolic syndrome symptoms, Submitted: 2023-03-05 Accepted 2023-03-21

1. INTRODUCTION:

The mortality from coronary artery disease and cardiovascular disease (CVD) has been highly cor-

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related with abnormalities in the resting electrocardiograph (ECG). A rapid, non-invasive test for early CVD identification is the 12-lead electrocardiogram [1, 2]. Numerous ECG abnormalities or changes are associated with obesity, including leftward shifts of the P, QRS, and T wave axes, different variations in P wave morphology, low QRS voltage, various markers of left ventricular (LV) hypertrophy, T wave flattening in the inferior and lateral leads, and lengthening of the QT interval [3]. Yet, little is known regarding the relationship between ECG abnormalities and metabolic syndrome (MetS), particularly its distinct elements.

Myocardial triglyceride (MTG) content in humans can now be determined using proton magnetic resonance spectroscopy (1 H MRS) [4]. The following research found that type 2 diabetes mellitus (DM), decreased glucose tolerance, and obesity all had higher MTG content [5–7]. The myocardial fat deposition has negative metabolic effects, such as compromised lipid oxidation, oxidative stress, and mitochondrial abnormalities. The detrimental consequences of the buildup of lipids and other toxic byproducts of free fatty acid (FFA) metabolism within myocardial tissue are thought to be reflected in this cardiac lipotoxicity [8, 9]. A growing body of evidence from animal studies shows that myocardial lipotoxicity reduces LV function and encourages cardiac fibrosis and apoptosis [10].

The major objective of this research was to investigate the relationship between cardiac steatosis and ECG abnormalities in participants with and without cardiometabolic risk factors, which are included in the definition of the MetS. Investigating the connection between ECG anomalies and the various MetS components was our second objective.

2. METHODS:

2.1. ***Study Design:***

This prospective study was conducted from July 2021 to August 2022 at Patna Medical College & Hospital, Patna

2.2. ***Inclusion Criteria:***

The subjects were divided into two groups according to the following standards: 1) having a waist circumference (WC) $\geq$90 cm and 2) having one abnormal finding by the MetS harmonized definition

2.3. ***Excluded Criteria:***

Based on medical history, physical exam, and standard laboratory tests (blood counts, creatinine, aspartate aminotransferase, alanine aminotransferase, thyroid-stimulating hormone, sodium, and potassium levels), there are no known acute or chronic diseases. Type 2 diabetes, significant alcohol consumption (defined as more than 10 g per day), and treatment with lipid-lowering therapy other than statins are also excluded.

Only men were included because women's lipid metabolism is altered by hormonal factors or the use of contraceptives. Angiotensin receptor was being used to treat hypertension in 3 patients, and statins were being used to treat dyslipidemia in 1. There were 7 cases of critical ECG parameters being missed. 65 people remained in the research population after this. The patients were recruited for a period of 12 months (July 2021 to August 2022).

The samples were taken in March 2021 from all the participants meeting the inclusion criteria.

The requirements for the MetS were met by thirty participants. For these subjects, myocardial ischemia was ruled out by coronary angiography or adenosine stress MR perfusion. The study's concept was approved by the Patna Medical College & Hospital Ethics Committee, and each participant gave their signed informed permission.

2.4. ***Electrocardiogram analysis***

All individuals had their resting 10-lead ECGs recorded using a Siemens Sicard 360 electrocardiograph. At a paper speed of 40 mm/s and an electric signal amplification of 2 mV/cm, examinations were recorded. The recordings were used to determine the heart rate, P duration, PR interval, QRS duration, QT and QTc intervals, P,

QRS and T-axes, P (II), S(V1), and R(V5) amplitudes. The maximal amplitudes of the S wave in lead V1 and the R wave in lead V5 or V6 were added to determine the QRS voltage.

2.5. ***Research into biochemistry***

After an overnight fast, blood samples were taken on the day the EKG was being recorded. The Konelab analyzer performed an automatic analysis of TG, HDL-C, apolipoprotein B, and total serum cholesterol. The Friedewald formula was used to determine the concentration of low-density lipoprotein cholesterol. Glucose levels at fasting and after a meal were measured using a Hitachi 917 or a Modular analyzer and the hexokinase technique. The level of serum insulin was measured using a double-antibody radioimmunoassay. The following formula was used to construct the insulin resistance index for the homeostasis model assessment: (fasting plasma glucose x fasting plasma insulin) < 22.5.

2.6. ***Measurement of myocardial triglyceride content***

A 1.5-T (whole-body MR imager) was used for the cardiac imaging, which was also quantified, as previously mentioned. Using end-systolic cardiac cine pictures, the spectroscopic volume of interest was located within the interventricular septum, and data acquisition was double-triggered to end-exhalation and end-systole. Spectra were gathered using 30 and 5 acquisitions, respectively, with and without water suppression. The ratio of fat to water (%) was used to express the myocardial TG content.

2.7. ***The measurement of pericardial and epicardial fat***

To calculate the amount of epicardial and pericardial fat, the regions of adipose tissue in a 4-chamber orientated picture were quantified. Adipose tissue that is between the myocardium and the visceral strip of the pericardium is known as epicardial fat. All phases of the cine images were examined to determine the location of the epicardial fat layer, and measurement was done on the end-diastolic image using a conventional radiologic workstation. The same end diastolic 4-chamber orientated picture was used to assess pericardial fat, which is a continuation of the thoracic or mediastinal adipose tissue outside the parietal pericardium.

2.8. ***MRI of the heart and evaluation of the left ventricle***

During a breath hold, cine sequences were recorded utilizing a retrospective electrocardiographically gated steady-state free precession gradient echo sequence in the 4-chamber, 2-chamber, and LV short-axis orientations. From base to apex, a stack of short-axis cine series (usually 10 slices) was collected, spanning the whole LV. The LV's volumetric analysis was examined with specialized post-processing tools (Argus, Siemens). End-diastolic volume and mass were indexed to the subject's body surface area, and LV ejection fraction and mass were also given [15].

2.9. ***Statistical evaluations***

SPSS 22.0 for Windows was used to conduct all statistical analyses. The Kolmogorove Smirnov test was used to determine whether continuous variables were normal. If necessary, variables were transformed using logarithms. All models included age as a confounding factor. For categorical variables, data are given as frequencies or percentages, for continuous variables with a normally distributed distribution, as means SD, and for skewed variables, as medians (range). The Mann-Whitney U test, unpaired t-test, and the chi-square test were used as necessary to analyze between-group differences. The frontal plane QRS axis and the QRS voltage, respectively, were selected as dependent variables in stepwise multivariable linear regression analyses based on univariate studies. The following cardiometabolic elements were taken into consideration: TGs, insulin resistance measurements, blood pressure parameters, HDL cholesterol, and apolipoprotein B. Statistical significance was defined as a p-value $<$ 0.04.

3. RESULTS:

Provides an overview of the clinical and biochemical features of the research cohort. The subjects who had the MetS were older than the subjects who did not. Compared to the group without the MetS, the MetS group had a higher percentage of current smokers. Those with the MetS had higher levels of total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B, fasting glucose, fasting insulin, and the HOMA-IR index than those without the MetS. Across the two study groups, there were significant differences in the lipid profiles. BMI and WC were higher in subjects with the MetS than in subjects without the MetS, as was to be predicted.

The MTG content was higher in persons with the MetS than in participants without the MetS (0.86%, 0.30-2.32 vs. 0.44%, 0.13-1.38, p <0.002). A similar difference was seen in the epicardial and pericardial fat depots (792 mm^2, 384-1752 and 1488 mm^2, 751-6130 vs. 540 mm^2, 250-128 and 561 mm^2, 65-1581, p <0.002 for both) between participants with and without the MetS. The LV ejection % was typical in each research participant. When compared to the group without the MetS, the LV end-diastolic volume indexed to body surface area was lower in the MetS group (66 $mL/m^2 \pm$ 11 vs. 83 mL/m^2 ±10, p <0.001).

Although LV mass was similar between the groups, participants with the MetS had lower LV mass indexed to body surface area than those without the MetS (56 g/m2±8 vs. 61 g/m^2 ±6, p <0.008). In subjects with the MetS compared to participants without the MetS, the LVGFI, a novel measure of cardiac performance, was considerably lower (40% (31-50) vs. 43% (34-54), (p <0.002).

Compared to the group without the MetS, the MetS group had a longer PR interval and a higher heart rate. There was no difference in the QRS duration across the study groups. The QT interval was longer in those without the MetS than in those with the MetS, although the QTc interval was similar in the two groups. Compared to the group without the MetS, the frontal plane QRS axis migrated further to the left in the MetS group. The frontal plane QRS axis of three members of the MetS group met the criteria for left axis deviation. The P- and Taxes also tended to shift more to the left in the MetS group than in the control group, although this did not achieve statistical significance. The P and S amplitudes in leads II and V1 were comparable throughout the study groups. In comparison to those in the group without MetS, subjects in the MetS group had reduced R amplitudes in lead V5 and QRS voltage (Table 2).

The frontal plane QRS axis and the QRS voltage were inversely linked with MTG content, WC, BMI, TGs, and fasting glucose in age-adjusted univariate analyses. The frontal plane QRS axis, apolipoprotein B, and blood pressure measurements were all inversely correlated. Additionally, fasting insulin, the HOMA-IR index, the LV end-diastolic volume, and mass indexed to body surface area all showed negative correlations with the R amplitude in lead V5 and the QRS voltage. About WC, BMI, TGs, and apolipoprotein B, the P axis showed an inverse correlation. Importantly, the P-axis, the P amplitude in lead II, the R amplitude in lead V5, and the QRS voltage are all linked with HDL cholesterol. The epicardial or pericardial fat did not correspond with any of the ECG parameters.

In addition, no significant correlations between P duration, PR intervals, QRS duration, QT interval, QTc interval, or T-axis were found in the study. Age and hypertriglyceridemia were found to be significant predictors of the frontal plane QRS axis in multivariable regression analysis. 27.8% of the variation in the frontal plane QRS axis was explained by the model. Accountability of the model increased only by 5.1% percentage points when MTG content was introduced. The QRS voltage was determined by WC and hyperglycemia. The model's responsibility did not increase by adding MTG content. WC continued to be a major influence on the QRS voltage even when glucose was substituted by fasting insulin or the HOMA-IR index.

Table 1: **Characteristics of the research population's biochemical and clinical conditions**

Parameter	Mets Present	MetS absent	P-Value
Age (years)	45 ±5	41 ±7	0.002
BMI (kg/m2)	30	23.4	<0.002
Height (cm)	181 ±5	181 ±4	0.882
Waist circumstances (cm)	107.0	86.9	<0.002
Current smoker (%)	31%	12%	0.055
Systolic blood Pressure (mm/hg)	131 ±13	114 ±11	<0.002
Diastolic blood Pressure (mm/hg)	87 ±8	76 ±5	<0.002
Total cholesterol	5.28	4.63	<0.002
LDL cholesterol	3.31 ±0.6	2.52 ± 0.66	<0.002
HDL cholesterol	1.01 ±0.1	1.52 ±0.37	<0.002
Triglycerides	2.00	0.77	<0.002
Apolipoproein-B	113 ±24	73 ±16	<0.002
fP-glucose	5.7	5.1	<0.002
fS-insulin	9.2	2.8	<0.002
HOMA-IR index	2.5	0.5	<0.002

Table 2: **Individuals in the study population's electrocardiograms.**

Parameter	Mets Present	MetS absent	P-Value
Heart rate (1/min)	63±10	55±6	<0.002
P duration	111±13	107±11	0.297
PR interval	177±31	164±18	0.043
QRS interval	94±7	97±7	0.161
QT interval	400±32	418±26	0.020
QTc interval	412±25	404±21	0.132
P axis	28±27	40±22	0.050
QRS axis	12±28	45±28	<0.002
T axis	20	27	0.075
P (II) mV	0.08	0.11	0.115
S (V1) mV	-0.77±0.34	-0.091±0.31	0.143
R (v5) mV	1.25±0.41	1.70±0.37	<0.002
QRS Voltage	2.35	3.02	<0.002

4. DISCUSSION:

To the best of our knowledge, this is the first study that has looked at the interactions between a thorough survey of ECG factors and cardiac steatosis using MR technology in a significant non-diabetic cohort of abdominally obese men without clinical CVD [11, 13]. Myocardial and epicardial fat levels were both w2- and w3-fold higher in subjects with the MetS, respectively, as well as the pericardial fat depot [14, 15]. According to our findings, males who are abdominally obese and have cardiometabolic risk factors also exhibit higher myocardial lipid accumulation in insulin-resistant states, including those in which participants have type 2 DM and impaired glucose tolerance [5–7].

However, there hasn't been much research into these ECG characteristics in people with MetS. Previous studies analyzing the electrocardiogram in obesity have shown trends towards the left axis

and low QRS voltage as the most common modifications [16, 17]. We discovered that the frontal plane QRS axis changed noticeably more to the left in the MetS, and the QRS voltage was lowered, which is consistent with previous data published by Bacharova et al. [17]. The P and T wave axes also shifted to the left, albeit these results were only marginally significant. Our results demonstrate that the PR interval was longer in participants with the MetS, which is consistent with earlier studies [18, 19].

The evaluation of the interaction between ECG anomalies and intramyocardial TG assessed by MR technology is a novel discovery of this study. To the best of our knowledge, only one prior study [20], which included 30 hearts at necropsy, has demonstrated a relationship between subepicardial fat content and a reduction in total 12-lead QRS voltage. The frontal plane QRS axis and MTG content showed an inverse connection in our age-adjusted univariate analyses. The QRS voltage also showed an inverse relationship with MTG content. MTG content was an independent marker of the frontal plane QRS axis but not of the QRS voltage after age, BMI, and WC adjustments.

The increased amount of adipose tissue in the chest wall that affects the resistance of the current flow and the distance between the precordial electrode and the heart is thought to be the cause of obesity's attenuation of ECG amplitudes. It is interesting to note that neither the frontal plane QRS axis nor the QRS voltage were significantly correlated with the pericardial or epicardial fat masses in the current investigation. Evidence, however, suggests that low voltage is not a noteworthy aspect of an obese subject's ECG. According to Frank et al. [21], growing obesity was associated with an increase in QRS voltage, and after weight loss, a drop in QRS voltage was observed in obese participants. The etiology of this shift in obesity is unknown, even though leftward shifts in the P-wave, QRS, and T-wave axes have been described [16, 21].

The relationship between ECG anomalies and other MetS components has only been briefly examined in a few publications [23, 24]. According to Kim et al. [23], the main causes of ischemia ECG abnormalities in younger and older participants, respectively, were hyperglycemia and hypertension. Central obesity and high fasting blood glucose were linked to both major and mild ECG abnormalities, according to research by Ebong et al. [24], whereas low HDL cholesterol was only linked to severe ECG abnormalities. In the current univariate analysis, TGs, HOMA-IR, fasting glucose, and fasting insulin were all negatively linked with QRS voltage. In multivariate studies, WC and hyperglycemia were predictors of the QRS voltage, while hypertriglyceridemia was an independent determinant of the frontal plane QRS axis.

In multivariate studies, WC and hyperglycemia were predictors of the QRS voltage, while hypertriglyceridemia was an independent determinant of the frontal plane QRS axis. Importantly, WC continued to be the best predictor of the QRS voltage even when glucose was substituted by fasting insulin or the HOMA-IR index.

The link between LV mass and LV dimensions is not taken into consideration by the most widely used indicator of LV performance in clinical practice, the LV ejection fraction. LVGFI, a unique parameter that integrates LV structure and global function, was just introduced [15]. The evaluation of LVGFI takes into account the LV ejection fraction, LV concentric remodeling, and LV mass indices.

Cardiovascular events have been linked to considerable risk when the LVGFI value is below 36%. Intriguingly, we demonstrate that LVFGI was considerably decreased in participants with MetS, indicating a higher risk of cardiovascular events and corroborating the idea that concentric rather than eccentric cardiac remodeling occurs in MetS.

5. CONCLUSION:

The impairment of the structure and function of the LV, which may lead to an elevated risk for cardiac events, may be sped up by the metabolic abnormalities connected to several cardiometabolic risk factors, particularly visceral obesity as shown

by WC. Conventional 10-lead ECGs are less sensitive in obese patients than they are in lean and normal-weight people, therefore ideally, cardiac imaging should be linked with the ECG.

6. STUDY LIMITATION:

Instead of digitally generated ECG recordings, conventional 10-lead ECGs are used, which limits the study of ECGs to the most fundamental parameters that can be evaluated with accuracy. Although the findings are inconsistent, gender and age may both affect the severity of cardiac steatosis [25]. As a result, this study only included men, and the data were age-adjusted. However, recent studies have shown that MTG content is rising in obese, insulin-resistant women as well [26], suggesting that women may have even more dramatic LV remodeling in MetS than males [27]. Finally, the cross-sectional nature of this study restricts our capacity to draw any conclusions about causality.

7. ACKNOWLEDGMENTS:

The skilled laboratory effort of Patna Medical College Hospital, Patna is heartily acknowledged by the researchers.

8. LISTS OF ABBREVIATIONS:

CVD: Cardiovascular disease;
BMI: body mass index
WC: waist circumference.
DM: Diabetes Mellitus
FFA: free fatty acid;
HOMA-IR: homeostasis model assessment insulin resistance
ECG: electrocardiogram;
LV: left ventricular
1H MRS: proton magnetic resonance spectroscopy
MetS: metabolic syndrome
LVGFI: left ventricular global functional index
TG: triglyceride
MTG: myocardial triglyceride
HDL-C: High-density lipoprotein cholesterol

9. CONFLICT OF INTEREST:

The authors state that they have no conflicts of interest.

10. FUNDING:

No outside funding was used for this study.

11. PUBLISHER DETAILS:

Publisher: Student's Journal of Health Research (SJHR)
(ISSN 2709-9997) Online
Category: Non-Governmental & Non-profit Organization
Email: studentsjournal2020@gmail.com
WhatsApp: +256775434261
Location: Wisdom Centre, P.O.BOX. 148, Uganda, East Africa.

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