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ORIGINAL SCIENTIFIC PAPER

Investigation of ICAM-1 levels in hypertensive patients with fragmented QRS complexes

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ABSTRACT

Objective: Fragmented QRS (fQRS) detected on a 12-lead electrocardiogram (ECG) has been demonstrated to be a marker of myocardial fibrosis. Intercellular adhesion molecule-1 (ICAM-1) is a protein which plays an important role in fibro-inflammatory processes. In this study, we aimed to investigate the relationship between ICAM-1 levels and the presence of fQRS in hypertensive patients.

Methods: Ninety consecutive patients who were diagnosed with hypertension were included in the study. ECG and transthoracic echocardiography were performed to all patients. fQRS was defined as additional R' wave or notching/splitting of S wave in two contiguous ECG leads. Serum ICAM-1 levels were measured using the enzyme-linked immunosorbent assay method. Patients were divided into two groups according to the presence of fQRS.

Results: A total of 90 patients (female, 65%; mean age: 54.6 ± 8.5 years) were included in the study. fQRS was detected on ECG recordings of 47 (52.2%) patients. The demographic characteristics were similar between the groups. Left atrial diameter ($p = .003$), interventricular septal thickness ($p = .013$), posterior wall thickness ($p = .01$), left ventricular mass ($p = .002$), left ventricular mass index ($p < .001$), left ventricular hypertrophy ($p = .001$), and ICAM-1 levels ($p < .001$) were found to be significantly increased in fQRS(+) group. In multivariate analysis, only high ICAM-1 level was observed to be an independent predictor for the presence of fQRS (odds ratio: 1.029; 95%Confidence Interval: 1.013–1.045, $p < .001$).

Conclusion: A significant association exists between serum ICAM-1 levels and the presence of fQRS in hypertensive patients. The presence of fQRS may be used as an indicator of inflammation in hypertensive patients.

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Echocardiography; fragmented QRS complex; hypertension; inflammation; intercellular adhesion molecule; myocardial fibrosis

Introduction

Hypertension is an important public health problem which may lead to apparently prevalent serious complications [1]. Left ventricular hypertrophy (LVH) is one of the most important cardiovascular injuries caused by hypertension. LVH seen in hypertensive heart disease is not a simple increase in heart wall thickness, cardiac fibrosis and inflammation play fundamental roles and may be associated with adverse cardiovascular events [2].

Myocardial fibrosis is a dynamic structure that contains fibrotic and inflammatory cells [3]. Fragmented QRS (fQRS) is a depolarisation disorder that can be detected on a 12-lead electrocardiogram (ECG) and demonstrates a conduction delay induced by fibrotic myocardial tissues [4]. It has been reported that fQRS can manifest myocardial fibrosis in hypertensive patients [5].

Adhesion molecules are proteins that allow cells to adhere to each other or to the extracellular matrix. Intercellular adhesion molecule-1 (ICAM-1) is the major adhesion molecule that allows monocytes/macrophages to adhere to the endothelial surface and pass into the inflammatory zone [6]. It has been reported that ICAM-1 levels increase in hypertensive patients and it plays a key role in the fibro-inflammatory process [7]. In this study, we aimed to investigate the relationship between ICAM-1 levels and the presence of fQRS in hypertensive patients.

Material and methods

Consecutive patients with essential hypertension who referred to our cardiology outpatient clinic were

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included in this study. Patients with known or suspected coronary artery disease, rheumatic heart disease, cardiomyopathy, diabetes mellitus, pregnancy, systemic or metabolic disease, and atrial fibrillation were not included in the study. ECGs with typical bundle branch block, pace rhythm, or any kind of significant conducting abnormalities were also excluded from the study. Routinely obtained 12-lead ECG recordings were examined, and patients were divided into two groups as those with and without fQRS complexes. All patients provided a written or oral-witnessed informed consent, and the study protocol was approved by the local ethics committee (13-KAEK-200) of the hospital in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

Biochemical assessment

Venous blood samples were obtained from each patient following an overnight fasting and a 24-hour period of abstinence from alcohol and vigorous physical exercise for the determination of serum biochemical parameters. Routine serum biomarkers such as glucose, urea, creatinine, uric acid, bilirubin, alanine aminotransferase, aspartate aminotransferase, C-reactive protein, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, and complete blood count were calculated with standard laboratory methods (Beckmann Coulter aU5800 Autoanalyzer, Beckmann Coulter Inc, Brea, CA). In order to investigate serum ICAM-1 levels, venous blood samples were taken in 3.8% anticoagulant tubes with sodium citrate and centrifuged at 2500 rpm for 20 minutes at room temperature. The plasma samples, obtained after centrifugation, were stored at $-40\,^{\circ}C$, for further analysis. The quantitative determination of ICAM-1 levels in human plasma samples was performed with an enzyme-linked immunosorbent assay (ELISA) using a commercially available Human sICAM-1 Elisa kit (Human sICAM-1 Platinum ELISA Kit, eBioscience).

Diagnosis of hypertension

For the new diagnosis of hypertension, office blood pressure measurements or 24-hour ambulatory blood pressure measurements were taken into consideration. During office measurements, the results of at least two measurements were taken into consideration. Blood pressure measurements were performed while the patients were sitting comfortably on a chair with their feet stepping on the floor using a sphygmomanometer with an appropriately sized cuff (wrapping at least 80% of the forearm). Before blood pressure measurements, the patients were rested for at least 10 minutes and they were withheld from smoking and consumption of tea or coffee before 30 minutes. In these measurements patients with persistent blood pressures of $\geq$140/90 mmHg were considered to be hypertensive. Among patients whose blood pressures values were monitored on an ambulatory basis, those with average 24-hour, daytime, and night-time blood pressures values were of $\geq$130/80 mmHg $\geq$135/85 mmHg, and $\geq$120/70 mmHg, respectively, were considered as hypertensive individuals. Patients who had diagnosed with hypertension previously and had been using antihypertensive drugs for at least two months were also considered as hypertensive.

Detection and definition of fQRS

The standard 12-lead ECGs were obtained at a paper speed of 25 mm/s and amplitude of 10 mm/mv (low-pass filter range: 100–150 Hz, AC filter: 60 Hz) from all patients using Nihon Kohden Cardiofax ECG-9132 device. fQRS was defined as the presence of an additional R wave (R′), notching of the R or S wave, or the presence of fragmentation (more than one R′) in two contiguous leads on ECGs [5] (Figure 1). The ECGs were analysed by two independent cardiologists (L.B, M.K) blinded to the patient characteristics.

Echocardiography

All patients underwent transthoracic echocardiography (TTE) performed by the same cardiologist using Vivid 5 echocardiography device (GE Vingmed Ultrasound AS, Horten, Norway), and 3.2 mHz adult probe with the patient in the left lateral decubitus position. In all patients, the left ventricular posterior wall thickness (PWT), interventricular septal thickness (IVST), left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD) and left atrial diameter (LAD) were measured on the parasternal long-axis view. Left ventricular ejection fractions (LVEF) of the patients were calculated by using biplane Simpson's method. Left ventricular mass (LVM) was calculated based on Devereux formula [$LVM = 0.8\ (1.04\ (IVS + LVEDD + PW)^3 - (LVEDD)^3) + 0.6$], and body surface area was estimated using Mosteller formula [body surface area = (height (cm)$\times$body weight (kg)/3600)$^{1/2}$]. Left ventricular mass was divided by body surface area to estimate left ventricular mass index (LVMI). Based on the recommendations of European Society of Cardiology

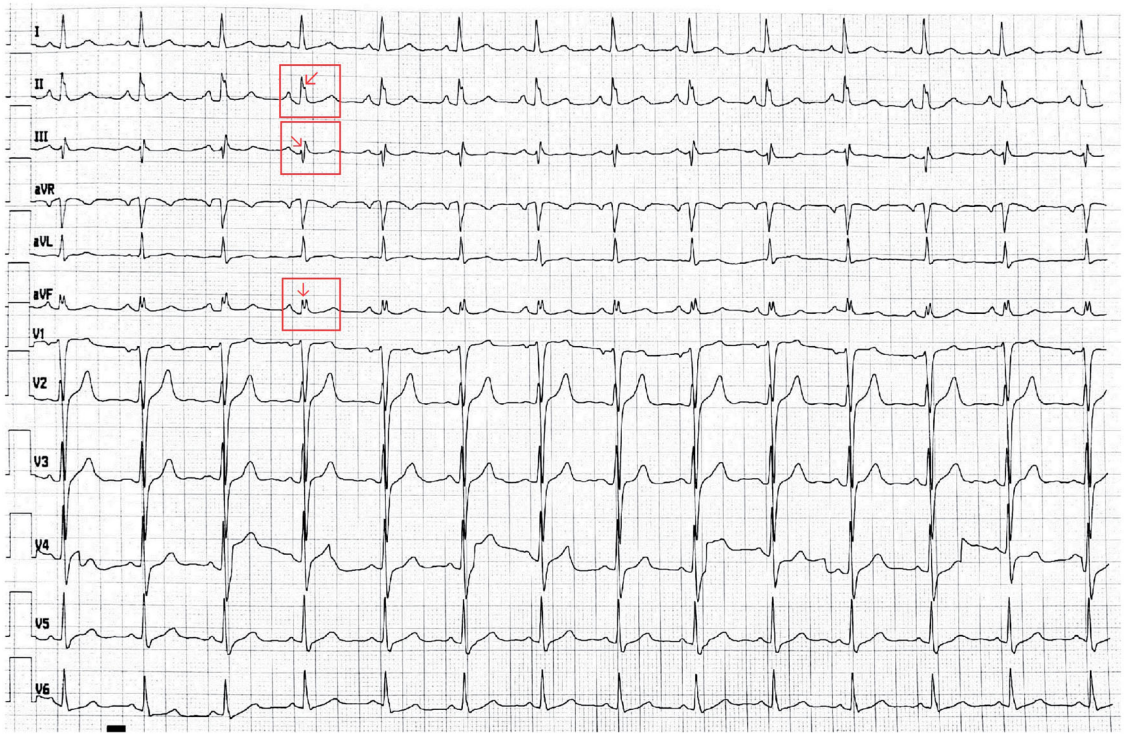

Figure 1. An example electrocardiography revealing the presence of QRS fragmentation in contiguous leads II, III and aVF (arrows show the notching of the R waves).

cut-off values of LVM indices for LVH were $>115\,g/m^2$ for men, and $>95\,g/m^2$ for women.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 19.0. (IBM Corp. Armonk, NY). Descriptive statistics were reported as mean ± standard deviation for continuous variables with normal distribution or median (25^{th}–75^{th} percentiles) values for continuous variables without normal distribution and as frequency with percentages for the categorical variables. The Shapiro–Wilk and Kolmogorov–Smirnov tests were used to test the normality of the distribution of continuous variables. Categorical variables were compared with Chi-square or Fisher exact tests. Student t-test or Mann–Whitney U-test was used to compare continuous variables as appropriate. Correlation analyses of continuous variables were assessed by Pearson or Spearman correlation tests. The significance level was accepted as $p < .05$ in all statistical analyses. A logistic regression analysis was performed in order to identify any independent associates of fQRS. A receiver operating characteristic (ROC) curve analysis was performed to evaluate the sensitivity, specificity, area under the curve (AUC) and confidence interval (CI) of ICAM-1 levels for predicting the presence of fQRS.

Results

A total of 90 patients (female, 65%; mean age: 54.6 ± 8.5 years) were included in the study. fQRS was detected on ECG recordings of 47 (52.2%) patients. Demographic, laboratory and echocardiographic characteristics of the patients with and without fQRS are presented in Table 1. Age and gender distribution were similar between patients with and without fQRS. There was no significant difference in terms of systolic and diastolic blood pressure measurements and heart rate values between the groups. Only body mass index was significantly higher in patients with fQRS ($p = .006$).

Routine serum biomarkers such as glucose, urea, creatinine, uric acid, bilirubin, alanine aminotransferase, aspartate aminotransferase, C-reactive protein, total cholesterol, HDL, LDL, triglyceride, and complete blood count parameters were similar between the patients with and without fQRS. Comparison of ICAM-1 levels between the groups revealed that ICAM-1 levels in fQRS(+) group were significantly higher than fQRS(-) group (515.5 ± 82.7 vs. 416.5 ± 63.7 ng/mL; $p < .001$) (Figure 2)

Echocardiographic parameters of the patients were compared between the groups. LAD ($p = .003$), IVST ($p = .013$), PWT ($p = .01$), LVM ($p = .002$), LVMI ($p < .001$), and the frequency of LVH ($p = .001$) were

Table 1. Comparison of the demographic, laboratory and echocardiographic characteristics of the patients with and without fragmented QRS complex (fQRS).

Variables	fQRS(+) (*n*:47)	fQRS(−) (*n*:43)	*p* value
Baseline Demographics			
Age, years	53.2 ± 9.1	56.7 ± 7.4	.285
Gender, male (*n*, %)	11 (23.4)	11 (25.6)	.810
Dyslipidemia (*n*, %)	5 (10.6)	11 (25.6)	.064
Smoking (*n*, %)	6 (12.8)	3 (7)	.489
Family History (*n*, %)	8 (17)	5 (11.6)	.467
BMI (kg/m^2)	31.5 ± 4.5	28.4 ± 5.1	.006
SBP (mmHg)	147.9 ± 18.8	144.3 ± 15.6	.338
DBP (mmHg)	84.3 ± 10.1	83.1 ± 10.9	.622
Heart rate (pbm)	77.7 ± 13.7	73 ± 10.4	.073
Laboratory			
Fasting Blood Glucose (mg/dL)	96.4 ± 11.1	95.7 ± 10.5	.774
Urea (mg/dL)	27.6 ± 9.6	33.4 ± 12.3	.224
Creatinine (mg/dL)	0.81 ± 0.17	0.77 ± 0.17	.263
Uric Acid (mg/dL)	4.91 ± 1.0	4.80 ± 1.0	.723
Total Bilirubin (mg/dL)	0.6 (0.4–0.9)	0.7 (0.5–0.8)	.677
Haemoglobin (g/dL)	13.4 (13–14)	13.4 (12.7–14)	.789
Platelet (×10^{3}cells/dL)	241.7 ± 49.9	243.3 ± 52.2	.881
LDL (mg/dL)	127.7 ± 29.8	137.5 ± 39.9	.194
HDL (mg/dL)	41 (35–49)	43 (38–52)	.296
Triglycerides (mg/dL)	169.7 ± 94.7	170.6 ± 97.7	.971
Total Cholesterol (mg/dL)	188.4 ± 29.9	205.1 ± 48.2	.060
ICAM-1 (ng/mL)	515.5 ± 82.7	416.5 ± 63.7	<.001
Echocardiography			
LVEF, (%)	65 ± 5.5	66 ± 4.9	.410
LAD, (cm)	3.65 ± 0.54	3.33 ± 0.45	.003
LVEDD, (cm)	4.6 (4.3–4.9)	4.4 (4.1–4.9)	.176
LVESD, (cm)	2.92 ± 0.45	2.94 ± 0.46	.807
IVST, (cm)	1.22 ± 0.19	1.12 ± 0.19	.013
PWT, (cm)	1.17 ± 0.17	1.07 ± 0.19	.010
LVM, (cm)	197.9 ± 50.3	165.4 ± 45.2	.002
LVMI, (cm)	106.5 ± 23.8	87.1 ± 20.9	<.001
RWT	0.51 ± 0.11	0.47 ± 0.11	.108
LVFS (%)	35.5 ± 4.1	35.4 ± 3.8	.926
LVCR, n(%)	10 (21.3)	13 (30.2)	.331
LVH, n(%)	27 (57.4)	10 (23.3)	.001

BMI: body mass index; BUN: blood urea nitrogen; DBP: diastolic blood pressure; HDL: high-density lipoprotein; ICAM: intercellular adhesion molecule; IVST: interventricular septum thickness; LAD: left atrial diameter; LDL: low-density lipoprotein; LVCR: left ventricular constrictive remodelling; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end systolic diameter; LVH: left ventricular hypertrophy; LVFS: left ventricular fractional shortening; LVM: left ventricular mass; LVMI: left ventricular mass index; PWT: posterior wall thickness; RWT: relative wall thickness; SBP: systolic blood pressure; (Continuous variables with normal distribution were expessed as mean ± standard deviation and continuous variables without normal distribution were expressed as median (25 th –75th percentiles)).

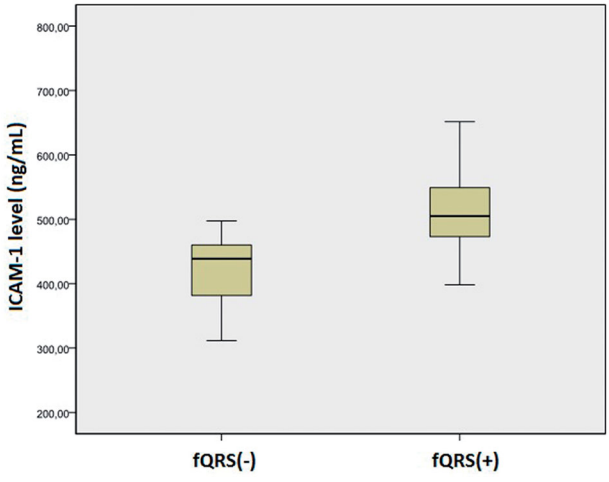

Figure 2. The comparison of serum ICAM-1 levels of patients with and without fragmented QRS complexes is represented as box-plot graphs.

found to be significantly increased in patients with fQRS (Table 1).

All univariate parameters significantly associated with fQRS in the dataset were included in multiple logistic regression analyses. By multivariate analysis, the only independent predictor of fQRS was the increased ICAM-1 levels [OR: 1.029 (95% CI: 1.013 to 1.045), $p < .001$] (Table 2). In ROC curve analyses, ICAM-1 values above 464.4 ng/mL, predicted the presence of fQRS with a sensitivity of 76.6% and a specificity of 76.7% (AUC: 845; 95% CI: 0.764 to 0.925; $p < .001$) (Figure 3).

Correlation analyses were conducted between the parameters in the dataset. There was a significant positive correlation between body mass index and ICAM-1 levels ($r = 0.281$; $p = .009$) (Figure 4).

Table 2. Multivariate regression analysis showing independent predictors of fragmented QRS.

	OR	95% CI	*p* value
Body Mass Index	1.090	0.932–1.274	.282
Left atrial diameter	1.030	0.202–5.244	.972
Interventricular septum thickness	0.814	0.001–1269.362	.956
Posterior wall thickness	0.304	0.000–370.253	.743
Left ventricular mass	0.996	0.956–1.038	.857
Left ventricular mass index	1.075	0.982–1.176	.116
Left ventricular hypertrophy	0.249	0.014–4.346	.341
ICAM-1	1.029	1.013–1.045	<.001

CI: confidence interval; ICAM: intercellular adhesion molecule, OR: odds ratio.

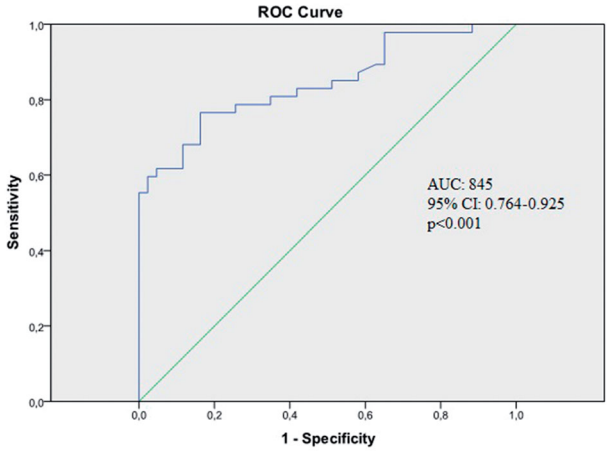

Figure 3. The receiver operating curve analysis provided that ICAM-1values above 464.4 ng/mL predicted the presence of fQRS with a sensitivity of 76.6% and a specificity of 76.7% ($p < .001$).

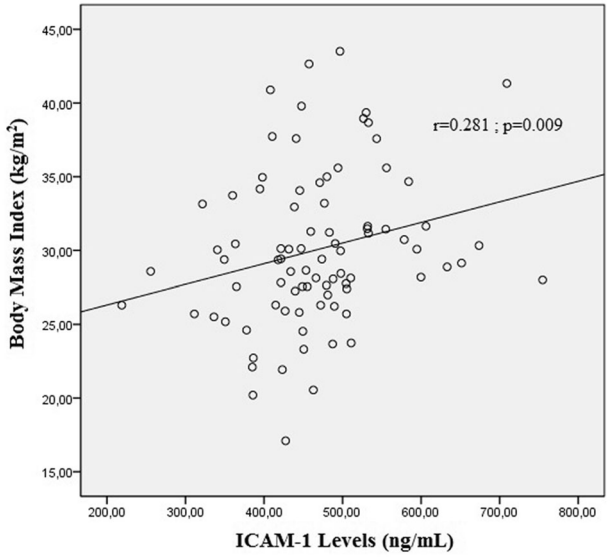

Figure 4. The scatter plot graph revealing the significant positive correlation between body mass index and ICAM-1 levels ($r = 0.281$; $p = .009$).

Discussion

In this study, it was observed that LAD, IVST, PWT, LVM, and LVMI were higher in the hypertensive patients with fQRS. Besides, LVH was more frequently observed in fQRS(+) group. Increased ICAM-1 levels were found to be associated with the presence of fQRS in hypertensive patients.

LVH is one of the most important cardiovascular injuries caused by hypertension and associated with increased mortality and morbidity. The main reason for this association is myocardial fibrosis. LVM is increased in LVH secondary to hypertension and extracellular collagen tissue increases excessively relative to myocytes, resulting in myocardial fibrosis [8].

Fragmented QRS is a depolarisation disorder that appears as a notch in the QRS complex on routine ECG recordings [9]. In our study, we found a significant and strong relationship between the presence of fQRS and LVH parameters in hypertensive patients. These fibrotic areas decrease the conduction speed of the electrical stimulation, which causes notching in the QRS complex. In previous studies, there was evidence that the presence of fQRS may demonstrate myocardial fibrosis in hypertensive patients [5].

There is increasing evidence that the inflammatory process is significantly involved in the fibrotic change of various disease conditions. In the hypertrophic hearts of hypertensive rats, inflammatory cells, especially macrophages, were found in the perivascular space with activated fibroblasts showing replication and extracellular matrix production [10,11]. Kuwahara et al. have demonstrated that pressure overload induced fibroinflammatory changes, preceding fibroblast proliferation, myocyte hypertrophy, and myocardial fibrosis in rats with an experimental aortic constriction [12].

Adhesion molecules allow cells to adhere to other cells or extracellular matrix molecules. Adhesion processes are required for cells to interact and to migrate to their destinations. ICAM-1 is the major adhesion receptor for monocyte/macrophage attachment to endothelial cells at the sites of inflammation. Kuwahara et al. have also demonstrated that ICAM-1 was upregulated in endothelial cells of the intramyocardial arterioles, especially in those adjacent to perivascular fibrosis in hypertensive rats [12]. Thus, a role of ICAM-1 was suggested in the fibrotic process in hypertensive hearts.

Multiple studies over the years have identified ICAM-1 as a critical regulator of leukocyte adhesion and transendothelial migration to allow tissue

infiltration in cardiovascular diseases [13,14]. Upregulated endothelial ICAM-1 levels were demonstrated in the human heart after myocardial infarction, concomitantly with cardiac inflammation and T-cell infiltration of the left ventricle [15]. Salvador et al. have demonstrated for the first time that ICAM-1 is necessary for pressure overload induced cardiac inflammation, fibrosis, and resulting cardiac dysfunction and heart failure. They provided an ICAM-1 dependent mechanism through which effector T cells are recruited into the left ventricle in response to pressure overload [16].

In the present study, we detected that increased serum ICAM-1 levels were higher in patients with fQRS. The probable cause of this condition is myocardial fibrotic tissue since there is increased inflammatory and fibrotic activity in this tissue [17,18]. ICAM-1 plays a key role in the fibro-inflammatory process by providing passage of leukocytes into this inflammatory region [6]. These data led us to hypothesise that ICAM-1 may mediate the inflammatory processes during pathological cardiac remodelling in hypertensive patients with fQRS.

Our study also found a correlation between BMI and serum ICAM-1 level. Previous studies have reported that obesity increases serum ICAM-1 levels and this increase may be caused by cytokines secreted from visceral fat tissue [19].

Detection of fQRS on a 12-lead ECG requires an optimal low pass filter setting (100 or 150 Hz). Fragmentation may be missed with a filter setting of 40 or 60 Hz. A low-pass filter is usually used to reduce electrical and musculature noises which influence the detection of fQRS [20].

The present study had some limitations. Firstly, the sample size is quite small. Second, only the patients with a QRS duration of $<$120 ms were included in the study. The last one was the lack of investigation for other inflammatory markers apart from ICAM-1 levels.

Conclusion

There was a strong and significant association between serum ICAM-1 levels and the presence of fQRS in hypertensive patients. This relationship may reveal an increased inflammation in such patients. fQRS which is an easily detectable marker from routine ECG recordings, may be used for risk classification in hypertensive patients.

Disclosure statement

All of the authors have no conflict of interest.

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