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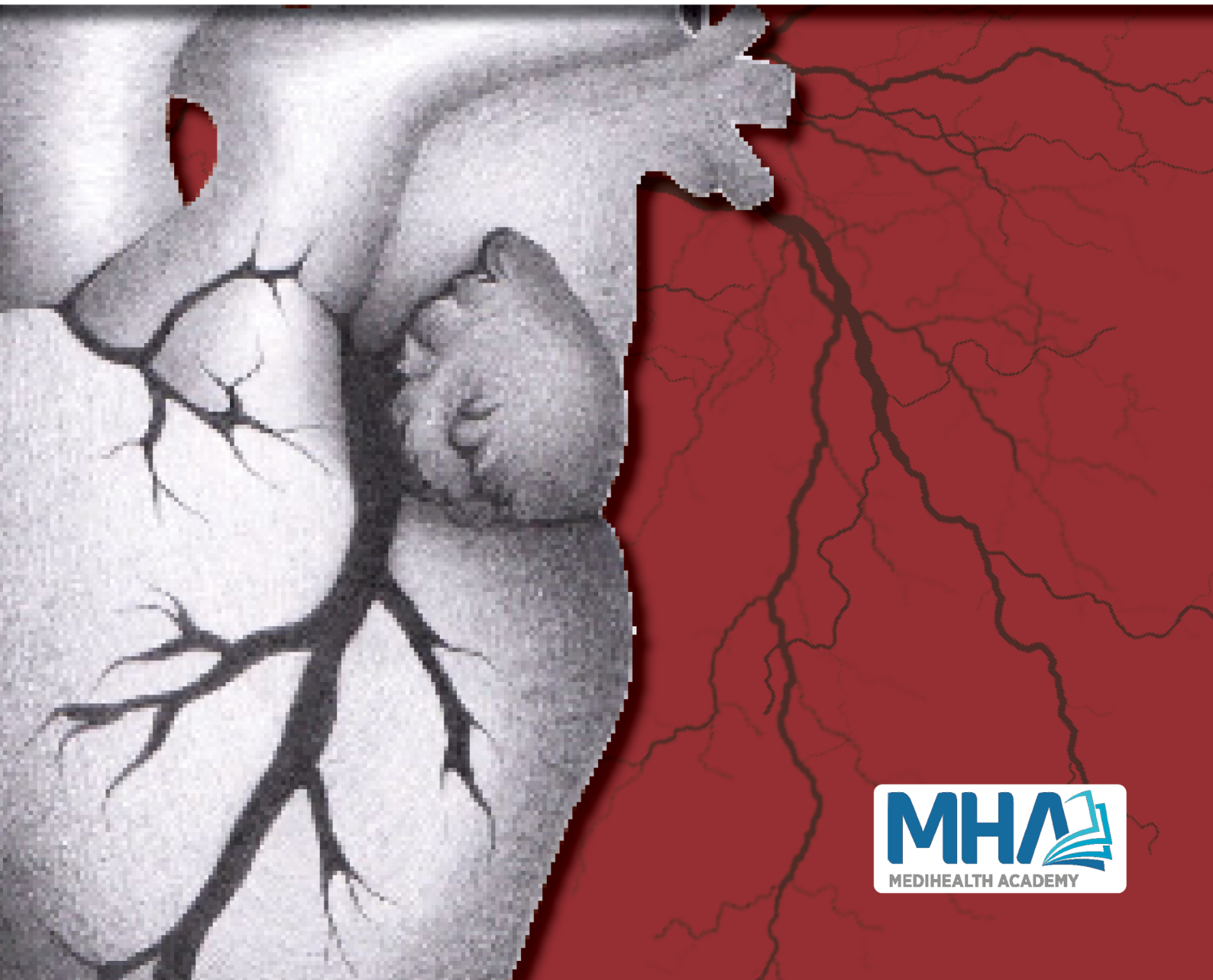

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Dear Colleagues,

I welcome to in the third issue of the Journal of Cardiology&Cardiovascular Surgery.

This issue includes 2 original articles, 2 case reports, and 1 review articles.

The research article entitled "*The relationship between neutrophil to lymphocyte ratio and diastolic dysfunction in patients with essential hypertension*" reveals the importance of inflammation as the pathogenesis of essential hypertension and the easy, fast, and useful tool for assessing diastolic dysfunction.

The second research article entitled "*Frontal QRS-T Angle in COVID-19 Patients with reduced left ventricular ejection fraction*" demonstrated the usefulness of frontal QRS-T angle as an indicator of disease severity in COVID-19 patients with reduced left ventricular function.

This is included 2 interesting case reports. The case entitled "*Successful treatment of concurrent acute migraine headache and atrial fibrillation with benzodiazepine administration*" was the first case of literature demonstrating beneficial effect of BZD in acute migraine headache and accompanying AF. The second case entitled "*Intravascular ultrasound application in the evaluation of left main coronary artery lesions*" emphasized the importance of IVUS in evaluationg left main coronary lesions.

The review entitled "*Approach to hypertension ın geriatric population*" highlighted the importance of patient based therapy in elderly with hypertension.

We believe that we will go further with your valuable contributions and we will mediate your valuable works to be included in the literature.

Sincerely,

İbrahim Halil İnanç, MD
Editor-in-Chief

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Original Article

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The relationship between neutrophil to lymphocyte ratio and diastolic dysfunction in patients with essential hypertension

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ABSTRACT

Aim: Diastolic dysfunction (DD), which often accompanies essential hypertension (HT), can progress to heart failure with preserved ejection fraction. Recent studies have shown an association between chronic inflammation and HT. In this study, we aimed to investigate the neutrophil lymphocyte ratio (NLR) in hypertensive patients with and without DD and the relationship between NLR and DD development.

Methods: The study included 50 patients with DD and 50 patients without DD. Left ventricular systolic and diastolic functions were evaluated by echocardiography in all patients. A complete blood count, C-reactive protein (CRP), and NLR were analyzed in blood samples obtained from the patients.

Results: There was no significant difference in demographic characteristics and biochemical values between the two groups. White blood cell count and NLR were significantly higher in the group with DD ($p<0.001$). There was a strong correlation between the presence of DD and NLR in hypertensive patients ($r=0.814$, $p<0.001$). Although CRP was between reference values in both groups, it was significantly higher in the group with DD compared to the group without DD (4.40±1.60 vs. 3.70±0.90, $p=0.020$).

Conclusion: NLR can be used to detect DD in patients with hypertension and is an easily accessible and inexpensive inflammatory marker.

Keywords: Hypertension, diastolic dysfunction, neutrophil/lymphocyte ratio.

INTRODUCTION

In 2/3 of patients with congestive heart failure (CHF), the clinical picture is a combination of systolic and diastolic dysfunction (DD), whereas left ventricular (LV) function is preserved in the remaining 1/3.[1] This clinical condition, which is thought to be due to DD, is not significantly different from systolic HF in terms of mortality, which further emphasizes the importance of detecting DD.[2] Essential hypertension (HT) is the most common comorbidity in patients with diastolic HF.[3] In patients with HT, the first cardiac change detected is LV DD, with or without left ventricular hypertrophy (LVH).

NLR, an inflammation parameter that has almost routinely begun to be included in laboratory results along with hemogram parameters, has been shown in many studies to have an important role in determining the severity and prognosis of many cardiovascular diseases, including HT.[4-14] Inflammatory mediators play an important role in myocardial contractility, remodeling, and endothelial dysfunction and have been shown to be associated with symptom onset and mortality.[15,16] However, studies showing the relationship between LV diastolic function and NLR are limited. In this study, we investigated the relationship between NLR and LV DD in patients with HT.

METHODS

Study Subjects

The study included a total of 100 patients admitted to the cardiology outpatient clinic between June and September 2013 with a diagnosis of HT. Fifty participants with grade I LV DD detected by echocardiography were accepted as the patient group. Fifty HT patients without LV DD were considered the control group. All patients were between 30 and 70 years of age, were on antihypertensive medication, and had normal electrocardiograms (ECG). Exclusion criteria were type II diabetes mellitus, coronary artery disease, other cardiac diseases (valvular heart disease, cardiomyopathy, HF, etc.), renal failure, recent cerebrovascular disease, and a history of alcohol and smoking. A physical examination,

outpatient blood pressure measurement, detailed background and habit questioning, and 12-lead ECG were performed in all patients.

Blood PressureMeasurement

After the patients had rested for at least 10 minutes, their blood pressures were measured in the supine position in both arms with a mercury sphygmomanometer with a suitable cuff by the same person based on Korotkoff phase I and phase V sounds. The blood pressures of subjects with elevated blood pressure were measured again 10 minutes later.

Laboratory Assessments

Biochemical measurements were analyzed in blood samples obtained after at least 12-14 hours of fasting. Fasting blood glucose, urea, creatinine, total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL) cholesterol, and triglyceride levels were measured in all patients. LDL Cholesterol: Calculated by the formula TK- [(TG/5) + HDL]. For an automated complete blood count, samples were collected from the antecubital vein in vacuum tubes containing EDTA (15% K3 EDTA 0.054 ml / 4.5 ml blood), and the samples were analyzed within 1 hour (Mindray BC 6800).

Echocardiographic Evaluation

With the patients in the left lateral decubitus position, echocardiographic measurements were performed by the same person in accordance with the recommendations of the American Society of Echocardiography using two-dimensional, M Mode, C-Doppler, and tissue Doppler with parasternal long axis, short axis, apical four-space, and five-space views. All echocardiograms were performed transthoracically with a Philips HD 11 xe Echo device. In accordance with the recommendations of the American Society of Echocardiography, all echocardiograms were performed by the same person and at midday to eliminate the effect of circadian changes on diastolic function. The intermittent Doppler sample was placed parallel to the flow (<20°) at the mitral valve cusps in the apical four-cavity view, and the mitral flow trace was obtained to obtain early mitral peak flow velocity (E), late mitral flow velocity (A), E/A ratio, and deceleration time (DT) of the E wave. To measure the deceleration time, the time between the peak of the E flow velocity and the point at which it decreased to the baseline was measured. The E/A ratio was calculated by finding the highest values of mitral valve E and A flow velocities. For isovolumetric relaxation time (IVRT) measurement, the transducer was directed towards the left ventricular outflow tract after placing the sample volume over the mitral valve cusps. When aortic Doppler flow was seen, the IVRT was found by measuring between the point where aortic flow ended and mitral flow began. In the apical four-cavity image, a 5-mm tissue Doppler sample volume was placed on the septal and lateral edges of the mitral annulus, and measurements were made. Ejection fraction, pulmonary venous systolic wave velocity/pulmonary venous diastolic wave velocity (PVs/PVd) were also measured with the Biplane Simpson model.

Statistics

The data obtained in the study were recorded in SPSS (Statistical Package for Social Sciences) version 18.0. The Kolmogorov-Simirnov test was used to determine that the distributions of the variables were normal. Normal distributions of continuous variables are presented as mean values and standard deviations. The statistical analysis of parametric variables between the two groups was performed using the student t test. Mann Whitney The U test was used for nonparametric variables. Qualitative variables were presented as percentages, and the correlation of variables was performed using the Chi-Square test. The relationship between variables was also evaluated by Pearson and Spearman correlation analyses. A probability coefficient of $p<0.05$ was considered statistically significant.

RESULTS

Of the 100 patients included in the study, 47 had stage I HT and 53 had stage II HT. There was no difference between the groups in terms of the HT stage distribution. There was no significant difference in baseline demographic findings between the two groups. There was also no significant difference between the two groups in terms of renal function tests, blood glucose, and lipid panels. E/A ratio, DT (ms), IVRT, and PVs/PVd ratio were significantly different in the echocardiography findings of the group with DD compared to the group without DD. White blood cell count and NLR were significantly higher in the group with DD ($p<0.001$). There was a strong correlation between the presence of DD and NLR in patients with HT ($r=0.814$, $p<0.001$). CRP was significantly higher in the group with DD compared to the group without DD ($p=0.020$) (**Table I, II**).

Table 1. Demographic and laboratory characteristics of the patients

	Group with diastolic dysfunction n=50	Group with nondiastolic dysfunction n=50	p
Age (year)	54,5± 7,7	52,6± 8,2	0,228
Gender (Male)	19	22	0,456
Glucose (mg/dL)	98,9± 15,3	97,3± 12,9	0,570
BUN(mg/dL)	15,4±4,1	14,4±4,3	0,241
Kreatinin (mg/dL)	0,7±0,2	0,7±0,1	0,956
LDL cholesterol(mg/dL)	113,3±32,2	104,2±29,	0,145
Total cholesterol(mg/dL)	190,6±39,1	186,3±35,8	0,566
Triglyceride (mg/dL)	157±56,1	159±55,2	0,862
HDL cholesterol(mg/dL)	45,6±13,1	47,5±10,2	0,418
WBC (10^3/mm^3)	8,8±1,6	7,6±1,7	<0.001
N/L ratio	6,1±2,7	1,6±0,7	<0.001
CRP mg/dL	4,4±1,6	3,7±0,9	0,020

(BUN: blood urea nitrogen, LDL: low-density lipoprotein, HDL: high-density lipoprotein,WBC: White blood cell, CRP: C-reaktif protein, N/L: neutrophil to lymphocyte ratio)

Table 2. Echocardiographic findings of the patients

	Group with diastolic dysfunction n=50	Group with nondiastolic dysfunction n=50	p
EF (%)	62,9± 3,1	65,8± 4,7	0,121
E/A	0.61±0.24	0.94±0.32	<0,05
DT (ms)	202±34	185±24	<0,05
IVRT (ms)	95±12	87±8	<0,05
(PVs/PVd)	0,96±0,31	0,71±0,21	<0,05
S' septum(cm/s)	6,8±1,1	7,3±1,21	0,066
E' septum (cm/s)	8,2±2,3	11,1±2,4	<0,05
E/E' septum	9,6±2,1	8,6±2,4	0,122
S' lateral (cm/s)	7,7±1,8	9,2±2	<0,05
E'lateral (cm/s)	9,6±2,3	13,1±2,8	<0,05
E/E' lateral	8,4±2,1	6,7±1,8	<0,05

(EF: ejection fraction, DT: deceleration time, IVRT: isovolumetric relaxation time, PVs/PVd: Pulmonary venous systolic wave velocity/pulmonary venous diastole wave velocity)

DISCUSSION

In our study, we found that white blood cells and NLR were significantly higher in the group with diastolic dysfunction. Considering that DD may progress to diastolic HF over time, this finding suggests that NLR may be used to predict the development of HF. In recent years, an association between HT and the presence of low-grade chronic inflammation has been demonstrated.[17] It is not known whether inflammation is a cause or a consequence of HT. Endothelial dysfunction may lead to HT, and HT itself may negatively affect endothelial function.[18,19] The vascular adventitia layer, which was previously considered only as a physical barrier, is now known to be an important source of free oxygen radicals that play an important role in the pathophysiology of HT. Collagen deposition in the interstitial space due to the inflammatory process leads to cardiac fibrosis. Cardiac fibrosis results in myocardial stiffness and DD.[20,21] Studies have found a correlation between low-grade systemic inflammation and high arterial stiffness and, progressively, ventricular stiffness and diastolic failure.[22,23] Dorfells et al.[24] proved that hypertensive patients have increased the release of IL-1 and TNF-α from peripheral blood monocytes compared to non-hypertensive patients. CRP, an inflammatory marker, has been shown to be higher in patients with essential HT compared to healthy subjects. In addition, some recently published studies have shown the presence of higher CRP levels in patients in the pre-HT stage compared to normotensive individuals.[25,26] Vasan et al. [27] showed that the inflammatory pathway is a very strong factor in cardiac remodeling and that systemic inflammatory markers (CRP, IL-6, TNF-α) are strong independent risk factors for HF. Masiha et al. [28] found a significant association between inflammatory markers and LVH in hypertensive patients. Inflammatory mediators were found to be higher in hypertensive patients with LVH compared to hypertensive patients without LVH.[29] In our study, CRP levels were found to be higher in patients with LVH due to HT, in accordance with the literature; therefore, it can be concluded that inflammation levels were higher. In recent years, NLR has been studied in all cardiovascular diseases, and the relationship between NLR and cardiovascular diseases has been shown. In parallel with this, it has been demonstrated that it is an independent marker of prognosis in HF, stable angina pectoris, and acute coronary syndromes.[8,11,30] In a study by Imtiaz et al.[31], NLR was found to be higher in hypertensive patients than in normal subjects. In a study by Demir et al.[32], NLR was found to be significantly higher in patients with non-dipper HT than in patients with dipper HT. It has been shown that there is a positive correlation between NLR and elevated blood pressure.[32]

In patients with hypertension, the autonomic nervous system can activate neutrophils, which can cause vascular system damage, penetrate the arteries, heart and kidney, drive fibrosis by secreting oxidants and proinflammatory molecules, and promote the recruitment of other immune cells for tissue inflammation.[33] The presence of these markers in individuals with normal blood pressure is associated with an increased risk of hypertension, whereas in patients with essential hypertension, levels of these markers are associated with target organ damage and may help predict the risk of cardiovascular events.[34] Many studies have investigated the effects of these inflammatory markers. Chronic inflammation can also trigger oxidative stress, which has been shown to be associated with hypertension and its consequences. This cycle of pathology contributes to the adverse outcomes of HTN patients.[35,36]

In our study, NLR was significantly higher in patients with diastolic dysfunction than in patients without DD. There was also a strong positive correlation between NLR and the presence of diastolic dysfunction. Possible pathophysiologic mechanisms that may explain this relationship are: inflammation, which is accepted as both a cause and a consequence of hypertension, may cause cardiac fibrosis, impair left ventricular compliance, and lead to the development of DD; and the inflammatory environment may contribute to the development of clinical/subclinical CAD and lead to the development of DD.[5,30] In our study, the high NLR in hypertensive patients with DD suggests that chronic inflammation plays a role in the development of DD.

Study Limitations

This study was conducted with a relatively small sample, and it may not be accurate in predicting its results for all HT patients. To confirm the results of this single-center study, a larger multicenter study with larger participation would be more appropriate. LV DD was determined only by some echocardiographic measurements and was not checked invasively, which may have led to some inaccurate results. Although patients with coronary artery disease were excluded, they may not have been fully excluded because coronary angiography and/or noninvasive ischemia were not investigated.

CONCLUSION

In conclusion, CRP, an inflammatory marker whose importance is well known in identifying high-risk patient groups in terms of cardiovascular disease, and NLR levels were found to be significantly associated with DD. NLR can be used as a biochemical marker to determine the presence of DD and predict the progression to HF in patients with HT.

ETHICAL DECLARATIONS

Ethic Committee Approval: The approval of the ethics committee, Kayseri Training and Research Hospital, dated 11.07.2013 and numbered 52332816/13084 was obtained

before the study, and it was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from the patients before the study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare. Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Frontal QRS-T angle in COVID-19 patients with reduced left ventricular ejection fraction

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ABSTRACT

Aim: The frontal QRS-T angle has been recognized as an indicator of ventricular repolarization heterogeneity, and a large frontal QRS-T angle has shown promise as a reliable predictor of cardiac mortality and morbidity. This study aims to investigate the impact of baseline frontal QRS-T angles on the clinical severity of COVID-19 in patients with reduced left ventricular ejection fraction (LVEF).

Methods: In our study, we employed data from COVID-19 hospitalized patients admitted between January 1, 2020, and December 1, 2020. We included patients who underwent echocardiography during their hospitalization and those had a reduced LVEF (<40%). Patient admission to either the intensive care unit or general ward was determined in accordance with criteria established in the Ministry of Health guidelines during the initial phase. Subsequently, patients were categorized into two groups: the severe illness group and the mild/moderate illness group.

Results: Between the two groups, statistically significant differences were observed in terms of QT durations. In the severe illness group, the QTc interval was measured as 427 milliseconds, while in the mild/moderate illness group, it was recorded as 415 milliseconds ($p < 0.001$).

Additionally, the frontal QRS-T angle was determined to be 91.80±31.41 degrees in the severe illness group and 67.88±27.7 degrees in the mild/moderate illness group. Once again, a statistically significant difference was identified ($p < 0.001$).

Conclusion: Our study differs from previous studies in that our population included only patients with reducedLVEF . We determined that the frontal QRS-T angle may be a good indicator of disease severity in COVID-19 patients with reducedLVEF.

Kew words: COVID-19, heart failure, infection, QRS-T angle

INTRODUCTION

SARS-CoV-2, the etiological agent of COVID-19, has exhibited rapid global dissemination, leading to over 630 million confirmed cases and more than 6.6 million fatalities as of November 11, 20221.

Although COVID-19 can present as asymptomatic or with mild symptoms, it can give rise to severe complications, such as severe acute respiratory distress syndrome (SARS), renal or multiple organ failure, cardiac arrhythmia and even fatality. The prognosis is impacted by concomitant systemic diseases like diabetes, hypertension, chronic heart failure, and coronary artery diseases.[2,3] Besides cardiac comorbidities influencing the prognosis of COVID-19, the infection itself exerts detrimental impacts on the cardiovascular system. The myocardial repercussions of COVID-19 encompass acute coronary syndromes, myocarditis, decompensated heart failure, pulmonary embolisms, and arrhythmias. These effects manifest a broad spectrum of electrocardiogram (ECG) abnormalities.[4]

While COVID-19 carries a high mortality rate, the available predictive indicators for mortality are relatively scarce. Recently, investigations have focused on inflammatory and hematologic parameters, as well as imaging scoring systems, such as the Coronavirus Disease 2019 (COVID-19) Reporting and Data System (CO-RADS) classification, to assess disease severity and predict short-term mortality.[5,6,7]

The frontal QRS-T angle has been identified as an indicator of ventricular repolarization heterogeneity and

a large frontal QRS-T angle is a good predictor of cardiac mortality and morbidity8. Change in the cardiac axis is one of the important electrocardiographic (ECG) finding in patients with COVID-19. In a study involving COVID-19 patients, mortality and mechanical ventilation requirement percentages were 67.8% and 66.1% in the frontal QRS-T angle >90° group, and 26.1% and 29.9% in the frontal QRS-T angle ≤90° group, respectively.[4,8] In a retrospective study comparing the data of polymerase chain reaction (PCR) positive and negative patients for COVID-19 in the study investigated the effect of the frontal QRS-T angle on disease severity. They found that frontal QRS-T increased significantly in severe illness patients.[9] When Mc Cullough et all. studied the ECGs of COVID-19 patients, they showed that 19.3% of the patients had an abnormal QRS axis10. The QT interval on surface ECG and the distance between the T wave peak and the endpoint can be used to assess myocardial repolarization.[11,12,13] The frontal QRS-T angle is simple to measure from the report portion of ECG devices.[14] Increased QRS-T angle indicates abnormal ventricular repolarization.[15] The available data regarding the association between the frontal QRS-T angle and the mortality rate as well as the clinical severity of COVID-19 patients is insufficient.

This study aims to determine the impact of baseline frontal QRS-T angles on the clinical severity of COVID-19 patients with reduced left ventricular ejection fraction.

METHODS

The study was carried out with the permission of Ethical Committe of Van Training and Researches Hospital Clinical Researches (Date:18.02.2021, Decision No: 2021-04). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. In our study, the data of COVID-19 hospitalized patients between 1 January 2020 and 1 December 2020 were used. Patients who underwent echocardiography during hospitalization and patients with reduced LVEF (<40%) were included ın the study. PCR negative patients, patients with bundle branch block in their ECGs, hemodialysis patients, patients under 20 years old, pregnant and lactating were excluded from the study. Besides, patients previously diagnosed with COVID-19 and followed up at home with medication were excluded. The patients were admitted to the intensive care unit or inward according to the criteria determined in the guidelines of the Ministry of Health during the first application. Patients were divided into two groups as severe illness group and the mild/moderate illness group.

In our center, routine ECGs are taken during the hospitalization of COVID-19 patients. Demographic and clinical characteristics, laboratory parameters, and length of hospital stay were obtained from the electronic medical records. Blood samples were analyzed for laboratory parameters such as urea, creatinine, sodium, potassium, glucose, D-dimer, hemoglobin, white blood cell, and C-reactive protein. Our study was approved by the local ethics committee.

Electrocardiography

At the time of initial hospitalization, the 12-lead ECGs of the patients were recorded (Tokyo, Japan, Nihon Kohden). The ECG calculations were performed in accordance with the guidelines. The automatic reports from the ECG machine included frontal QRS and T-wave axis. The frontal QRS-T angle on a 12-lead electrocardiogram was defined as: the QRS axis-T wave axis. In case the angle exceeded 180°, it was calculated by subtracting it from 36016,17

Statistical Analysis

Statistical Package for the Social Sciences 24.0 program was used. Descriptive statistics were given using frequency and mean ± standard deviation values. The relationship between numerical variables (heart rate, frontal QRS-T angle, QTc, QRS, CRP, WBC, lymphocites, D-Dimer, creatinine, BMI, Hbg, fasting glucose, sodium, potassium, urea, QT) evaluated with the independent sample t-test. Nominal/ordinal variables (sinus rhythm, diabetes mellitus, hypertension, smoking status, coronary artery desease, chronic obstructive pulmonary disease) were evaluated with two-way ANOVA and other numerical values were evaluated with ANOVA tests. p-values less than 0.05 and 0.001 were considered significant.

RESULTS

A total of 212 patients were included in the study. The mean age of patients was 65.32±11.53 years, and BMI was 28.77±3.62 kg/m2. It was seen that 51.4% of the mild/moderate illness group were male, 48.6% were female. While 48.5% of patients in severe illness group were female, 51.5% were male and 51.4% of patients in mild/moderate illness group were female, 48.6% were male. Both severe illness group (89.9%) and mild/moderate illness group (84.5%) sinus rhythms are mostly normal. The basic clinical and demographic characteristics, background, smoking history, laboratory values and ECG parameters were shown in **Table 1.**

There was no statistically difference in gender between the severe illness group and mild/moderate illness groups. When the severe illness group and mild/moderate illness groups were compared in terms of age, it was determined that the severe illness group was older. However, no significant differences in HT, DM, coronary artery disease, or smoking habit were found between the two groups. Chronic kidney disease, hemoglobin, WBC, lymphocyt, creatinine, urea, sodium, glucose, CRP, and D-dimer were different between the groups. **Table 2** also compares the ECG findings between the two groups. When the ECG findings were compared between the groups, the incidence of atrial fibrillation was found to be higher in the severe illness group than in the mild/moderate illness group, but this was not statistically significant (severe illness group=16/106 and mild/moderate illness group=11/109, p =0.235).

Mean heart rate was significiantly different between groups. The mean heart rate of the severe illness group was 88.27±18.64, the mean heart rate of the mild/moderate illness group was 80.85±14.11, and there was a significant difference (p< 0.001). Although the mean heart rate was higher in the severe illness group between the two groups, statistically significant results were found in terms of QT durations. QTc(427msec) in the severe illness group and QTc (415msec) in the mild/moderate illness group were calculated and there was significant statistical difference (p <0.001). The frontal QRS-T angle was 91.80±31.41 in the severe illness group and 67.88±27.7 in the mild/moderate illness group and significant statistical differece was found (p <0.000).

According to the results of the independent sample t test; angle [t(210)=-5.889, p=0.000], CRP [t(210)=-4.523, p=0.000], Hbg [t(210)=8.541, p=0.000], sodium [t(210)=-5.185, p=0.000] and urea [t(210)=-6.022, p=0.000] values are statistically significantly different between the groups (Table 2). According to independent sample t-test results, the mean of angle, CRP, sodium and urea were lower in mild/moderate illness group (angle=67.88±27.70; CRP=4.74±4.64; sodium=139.16±4.39; urea=42.18±12.23) than in severe illness group (angle=91.80±31.41; CRP=7.85±5.35; sodium=142.48±4.92; urea=52.88±13.62), while the mean Hbg was found to be higher in the mild/moderate illness group (13.98±1.66mg/dl) than the severe illness group (12.07±1.58mg/dl).

Two-way ANOVA was performed for the evaluation of nominal factors affecting the intergroup distribution, and ANOVA was applied for numerical factors. According to the two-way ANOVA test results, no nominal/ordinal factors affecting angle, Hbg, fasting blood sugar, sodium and urea were found (p>0.05). In addition, chronic kidney failure was found to affect the relationship between research groups and CRP [F(1)=73.05, p=0.007]. Accordingly, CRP values of patients in severe illness group ($\bar{x}$=3,44±3,78) with chronic kidney failure were considerably higher than those of patients in mild/moderate illness group ($\bar{x}$=11,68±3,26). According to ANOVA test results, no numerical factor affecting HBG, sodium and urea was encountered (p>0.05). In addition, it can be said that heart rate [F(1)=7.627, p=0.006] and fasting blood glucose level [F(1)=4.841, p=0.029] affect the intergroup distribution of the angle. In addition, it can be said that lymphocyte values [F(1)=19.392, p=0.000] and creatinine [F(1)=6.227, p=0.013] also affect CRP and intergroup distribution. Accordingly, the decrease in the angle of severe illness is affected by the low heart rate and fasting blood glucose. The distribution of intergroup distribution in CRP is affected by creatinine.

DISCUSSION

In the course of our investigation, it was discerned that there exists a noteworthy augmentation in the values of QTc duration and frontal QRS-T angle as the disease severity escalates. Our study distinguishes itself from previous research in that our study cohort exclusively comprised patients with reduced left ventricular ejection fraction. Our findings suggest that the frontal QRS-T angle could serve as a valuable indicator of disease severity in COVID-19 patients with compromised left ventricular function.

The frontal plane QRS-T (f(QRS-T)) angle, precisely defined as the angle between the vectors of ventricular depolarization (QRS axis) and repolarization (T axis), has been postulated as an innovative marker for assessing ventricular repolarization heterogeneity.[18]

The frontal QRS-T angle, which can be readily derived from the automated reporting section of electrocardiography (ECG) devices, is a highly valuable parameter. Its predictive significance has been demonstrated across various populations.[19,20]

Frontal QRS-T angle, as we are aware, serves as an indicator encompassing depolarization, repolarization, and heterogeneity and is easily quantifiable through ECG measurements. While observational studies have linked frontal QRS-T angle to mortality, the consensus on its association with both cardiac and all-cause mortality has not been consistently reinforced in numerous investigations .[21] In a groundbreaking study from 2003, spatial QRS angle emerged as a more robust predictor of mortality risk compared to traditional ECG parameters such as ST depression, T-wave inversion, and prolonged QT interval.[22]

It is unclear exactly how myocardial damage and arrhythmia caused due to COVID 19. Multiple organ failure is a hallmark of the advanced disease known as systemic inflammation.[23] Studies have shown that myocardial dysfunction in sepsis is caused by variables such as reduced contractility and altered cardiac conduction. Myocardial depression during sepsis is known to be correlated with the level of mediators and circulatory factors.[24]

In addition, it has been demonstrated that COVID-19 infection can induce autonomic dysfunction by activating the sympathetic nervous system and suppressing the parasympathetic system. This finding was highlighted in a study conducted by Del Rio R et al.[25]

Furthermore, a recent study comparing individuals who had recovered from COVID-19 to a healthy control group found that COVID-19 patients displayed a higher incidence of blunted heart rate response during exercise testing. This observation is believed to be a consequence of autonomic dysfunction.[26]

Previous research has concentrated on the spatial QRS-T angle, leaving the frontal QRS-T angle comparatively unexplored. The Finnish cohort research was the first large study to look into the relationship between the frontal QRS-T angle and sudden cardiac mortality. The study comprised 10.957 middle-aged people, and the risk of cardiac death was shown to be three times higher in the group with frontal QRS-T angles (>100°) than in the normal population.[27]

In examinations of COVID-19 patients, at least one ECG anomaly was observed. The major proposed mechanisms are cytokine storm, electrolyte problems, microthrombi, and coronary vasospasm.[28] Although practically all arrhythmias are encountered during COVID-19, sinus tachycardia is the most prevalent. Although both supraventricular and ventricular arrhythmias are common, ventricular arrhythmias are more fatal, as expected.[29] According to the literature, the rate of malignant arrhythmia in patients hospitalized with COVID-19 is as high as 16.7%; in patients hospitalized in the critical care unit, the rate can reach 44.4%.[30,31] Several ECG measurements have been proposed as potential indicators of malignant arrhythmias. Prolonged QTc and QTd due to ventricular repolarization abnormalities are risk factors that can enhance the likelihood of malignant arrhythmia.[32] In addition to these characteristics, we demonstrated that an increased frontal QRS-T angle could be an independent measure of disease severity. In our study, the difference in ECG (QTc, frontal QRS-T angle) between patients in the intensive care unit and those receiving the COVID-19 service suggests that the virus may impact ventricular depolarization and ventricular repolarization. This theory is supported by the fact that patients admitted to the COVID-19 service were similar to those admitted to the intensive care unit in terms of age and comorbidities. The frontal QRS-T angle, a simple ECG parameter, can aid in the management of COVID-19 patients and provide information on the severity of the disease throughout their follow-up. It can benefit in early care and decision-making until the findings of more advanced testing are available because it is

readily available within minutes of contacting patients.

Study Limitations

Firstly, our study only included a small number of participants. We lacked information on coronary artery disease and hormone status that could trigger arrhythmia in our study participants. Investigations by echocardiogram were performed while the infection was active. Our study confined the number of examinations to a minimum in order to protect healthcare personnel from prolonged interaction.

CONCLUSION

The frontal QRS-T angle, which can be easily derived from ECG, was shown to be high in patients in severe illness group. The clinical severity of COVID-19 disease can be predicted using an increased

Table 1. Clinical Features of Patients According to Study Groups

Variables	Severe illness group (n=109)		Mild/moderate illness group (n=103)	
	n	%	n	%
Gender(male)	53	48.6	53	51.5
Atrial fibrilation	16	15.5	11	10.1
Hypertension	55	36.9	64	58.7
Diabetes mellitus	68	66.0	78	71.6
Chronic kidney disease	88	85.4	100	91.7
Smoking	67	65.0	70	64.2
Coronary artery disease	71	68.9	78	71.6
Chronic obstructive pulmonary disease	82	79.6	92	84.4

Table 2. Distribution of Patients According to Clinical Values

Variables	Severe illness group	Mild/ moderate illness group	p-value
Heart rate	88.27 ±18.64	80.85±14.11	0.001
F-QRS-T angle(°)	91.80 ±31.41	67.88±27.70	<0.001
QT (msec)	430.5 ±2.92	416.8±3.76	0.004
QTc (msec)	427.56±16.84	415.33±39.86	0.004
QRS (msec)	96.95±15.94	92.32±19.48	0.059
LVEF (%)	36.44±5.23	34.65±6.21	0.233
CRP (mg/L)	7.85±5.354	4.74±4.64	<0.001
WBC (10^3 /µl)	8.72±4.78	7.42±6.06	0.086
Lymphocytes (meq/L)	1055.33±796.56	1346.62±704.06	0.005
D-Dimer	2870.22±9659.31	1117.96±786.63	0.060
Creatinine (mg/dl)	1.17±0.81	0.86±0.353	0.001
Hgb(g/dl)	12.07±1.58	13.98±1.66	<0.001
Glucose (Fasting) (mg/dl)	112.28±31.15	101.27±30.83	0.010
Na+2 (mEq/L)	142.48±4.92	139.16±4.39	<0.001
K+ (mEq/L)	3.79±0.67	3.83±0.37	0.629
Urea (mg/dl)	52.88±12.23	42.18±13.62	<0.001
BMI	29.16±3.32	28.40±3.86	0.127

ETHICAL DECLARATIONS

Ethic Committee Approval: The study was carried out with the permission of Ethical Committe of Van Training and Researches Hospital Clinical Researches (Date:18.02.2021, Decision No: 2021-04).

Informed Consent: Written informed consent was obtained from the patients before the study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare. Financial Disclosure: The authors declared that this study has received no financial support.

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Approach to hypertension in geriatric population

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ABSTRACT

Hypertension is a systolic blood pressure >140 and/or diastolic blood pressure >90, measured with the appropriate method and confirmed by repeated measurements. Hypertension is quite common in our country, as it is all over the world. Its prevalence increases with age. Isolated systolic hypertension is especially common among the elderly. Considering the increasing comorbidity with age, blood pressure regulation has a very important place in the geriatric group to prevent complications such as coronary artery diseases, chronic kidney diseases, and cerebrovascular diseases. During treatment, appropriate drug selection should be made, especially in geriatric individuals, by evaluating comorbidity and polypharmacy.

Keywords: Hypertension, geriatrics, polypharmacy

INTRODUCTION

Hypertension is a systolic blood pressure >140 and/or diastolic blood pressure >90, measured with the appropriate method and confirmed by repeated measurements.[1] The global prevalence of hypertension is approximately 30%, but this rate reaches 60% in advanced age.[2] Hypertension is quite common in our country, as it is in the whole world. The prevalence of hypertension reaches 70% in the 60-69 age group, 76% in the 70-79 age group, and 79.7% in the 80-year-old and older age groups. Due to the increased risk of hypertension in the geriatric patient group, blood pressure should be monitored at every visit to the doctor. Patients should be monitored carefully, especially since the incidence of isolated systolic hypertension increases with age. Hypertension may occur alone, but it is frequently associated with dyslipidemia and impaired glucose tolerance in advanced age, which increases cardiovascular risks. It can also cause comorbidities, such as chronic kidney disease and cerebrovascular disease, as well as unexpected death.[2,3]

WHAT IS APPROPRIATE BLOOD PRESSURE MEASUREMENT?

Although the gold standard is the arterial catheter, measurement from the brachial artery using a sphygmomanometer is preferred in clinical practice. For geriatric individuals, a validated automatic electronic upper arm control device may be used. In addition to the selection of the appropriate instrument, the appropriate environment and conditions are very important. When evaluating the measurement, the time of measurement, measurement during exercise or meal, or any condition that activates the adrenergic system should be known by the physician, as it will increase blood pressure. Preferably, the brachial artery is used in the measurement. It should be performed with at least 2 consecutive measurements and with separate measurements from both arms. The higher measurement between the arms should be taken as the basis. A measurement should be made from the right arm at the follow-up of the patient.[4,5]

Brachial artery atherosclerosis should be considered in elderly individuals. During measurement, a highly calcified brachial artery causes unreal elevations in blood pressure. This is also called pseudohypertension. Pseudohypertension should be suspected in elderly patients with disseminated atherosclerosis, in patients in whom the radial artery is still palpated despite cuff pressure exceeding auscultatory systolic blood pressure (Osler's sign), and in elderly individuals with persistently high blood pressure and resistant hypertension. Intra-arterial measurement, the gold standard method, is necessary for these patients.[5,6,7]

Orthostatic hypotension is a factor affecting hypertension regulation in elderly individuals. The presence or absence of orthostatic hypotension is diagnosed with a decrease of >20 mmHg in SBP or >10 mmHg in DBP by separate measurements performed while the individual is sitting and standing. In this condition, in which antihypertensive drugs such as salt restriction, high-dose diuretics, peripheral adrenergic blockers, and alpha blockers are involved in the etiology, effects on venous return and changes in cardiac output with advancing age are an etiologic factor on their own. Its evaluation is very important for the elderly, as it may lead to fainting, falls, and consequently life-threatening conditions.[8,9]

Another factor affecting proper measurement is white-coat hypertension. Considering this situation, it is recommended to confirm with a measurement taken in an environment where the individual feels comfortable. The two

most commonly used methods today are home blood pressure measurement and ambulatory blood pressure monitoring.[9]

STAGING

According to blood pressure level, the JNC-VI report is staged as follows (**Table 1**).

Table 1. Staging of blood pressure

	Blood Pressure (mmHg)		
Blood Pressure Stages	**Systolic**		**Diastolic**
Hypertension			
Stage 1	140-159	or	90-99
Stage 2	160-179	or	100-109
Stage 3	>180	or	>110
Isolated systolic hypertension	>140	< 90	

RISK FACTORS

Risk factors for hypertension are examined in two groups:

Group 1 = Non-modifiable risk factors: Age, gender, ethnicity, family history

Group 2 = Modifiable risk factors: Diet, sedentary lifestyle, obesity, psychosocial status, habits (such as alcohol, smoking, and drugs), irregular blood glucose regulation, dyslipidemia, obstructive sleep apnea, medications, etc.[10]

Although age is an unchangeable factor, it is very important to control the risk status that increases with age in geriatric individuals by keeping the modifiable risk factors under control with the necessary awareness and appropriate treatment.

ETIOPATHOGENESIS

There are many conditions in the etiopathogenesis of hypertension. Genetic factors, increased sympathetic system activity (increased heart rate, increased cardiac output, and peripheral resistance), renal factors (increased sodium load, renin-angiotensin-aldosterone system), impairments in vascular mechanisms (nitric oxide and endothelin secretion), obesity, insulin resistance, and obstructive sleep apnea can be listed. In the etiopathogenesis of hypertension in geriatric individuals, the following factors are at the forefront.[11] (**Table 2**).

Table 2. Physiological changes that occur with aging

* Changes in vascular structures are inevitable. Thickening of the intima and media and sclerosis of the arteries occur
* Cardiac output and heart rate decrease, and systemic vascular resistance increases
* Central obesity and insulin resistance develop with age
* There is a decrease in glomerular filtration
* Inadequate vasodilation is not achieved as a result of the decrease in B-adrenergic response with aging

HYPERTENSION AND POLYPHARMACY

Especially in geriatric individuals, polypharmacy is inevitable with the increase in chronic diseases. Therefore, it is very important to question the prescription drugs used in the clinical evaluation of hypertension. In addition, it is also necessary to question over-the-counter medications and dietary supplements, the frequency of use of which has increased with the development of alternative medicine. Glucocorticoids, non-steroidal anti-inflammatory drugs, sodium-containing agents (antacids), sympathomimetic agents (decongestants, anorectics), oral contraceptives, vascular endothelial growth factors (bevacizumab), tyrosine kinase inhibitors (sorafenib, sunitinib, etc.), calcineurin inhibitors (cyclosporin, tacrolimus), erythropoietin, agents containing stimulants such as cocaine and amphetamine, and neuropsychiatric drugs should be evaluated when hypertension is diagnosed.[12,13,14]

Whenever possible, medicines associated with increased blood pressure should be reduced, discontinued, or changed to alternative medicines.

TREATMENT APPROACH

The treatment algorithm and target values have been standardized in our country with the Hypertension Consensus Guideline. When starting treatment, not only the blood pressure value but also comorbid risk factors and chronic diseases should be evaluated. In previous years, increases in systolic blood pressure with age were considered physiologic and not treated. However, today, hypertension is thought to be the cause of diseases with high morbidity and mortality, such as cerebrovascular diseases and coronary diseases, in elderly individuals. A decrease in these complications is observed with hypertension regulation.15

Lifestyle modification should be recommended to all individuals, regardless of stage. Lifestyle modification should include keeping the body mass index in the normal range, limiting salt consumption, avoiding alcohol and smoking, abandoning a sedentary lifestyle, and avoiding stress.16 Subsequently, medical treatment should be shaped by evaluating risk factors. (**Table 3**).

Table 3. Treatment assessment according to risk groups with high blood pressure

Degree of blood pressure (mmHg)	No risk factors and no target organ damage	At least one risk factor except diabetes mellitus; no target organ damage	Risk factor, cardiovascular disease or target organ damage present
High-normal (130-139/85-89)	Non-pharmacological treatment	Non-pharmacological treatment	Drug treatment
Stage 1 (140-159/90-99)	Non-pharmacological treatment (up to 12 months)	Non-pharmacological treatment (up to 6 months)	Drug treatment
Stages 2 and 3 (>160/>100)	Drug treatment	Drug treatment	Drug treatment

Risk factors: Heart failure, renal failure, diabetes mellitus, smoking, advanced age, LDL (low-density lipoprotein) >130 mg/dl *
* Hypercholesterolemia is also very common. Dietary cholesterol intake should be restricted and controlled with medical treatment if necessary.

Medical treatment; In case of increased blood pressure (SBP=130-139mm and/or DBP=84-89 mmHg) and Stage 1 HT (SBP=140-159mmHg and/or DBP=90-99 mmHg), if there are no risk factors (coronary artery disease, diabetes mellitus, chronic kidney disease, smoking, advanced age, high cholesterol level), the patient should be followed up by trying lifestyle changes with priority. Medical treatment should be added if there is no response in the three-month periodic controls. (**Table 4**).

Table 4. Medical agents used in treatment
ACE inhibitors
ARBs
Diuretics
Calcium channel blockers
B-blockers

In stages 2 and 3 HT (SBP ≥160 mmHg and/or DBP ≥100 mmHg), medical treatment should be started immediately with lifestyle modification. Medical treatment may include diuretics, calcium channel blockers (CCBs), ACE inhibitors, ARBs, and anyone or combination of ARBs and B-blockers (except ACE inhibitors and ARB combinations). In patients with blood pressure ≥150/90 mmHg, it is recommended to start first-line treatment with combination therapy.[1,17]

There are issues to be considered in the treatment of geriatric individuals. The systolic blood pressure threshold for starting medical treatment for individuals aged 80 years and older has been raised. The targeted blood pressure values are set at 120-130/70-80 mmHg and are not tied to a clear number, suggesting a patient-based evaluation. However, although the blood pressure target set in geriatric individuals is almost close to the targets set in young individuals, it is kept slightly higher; 130-140/70-80 is considered being safer. While ESC/ESH, THUR, ISH, and Canadian Hypertension guidelines suggest that the blood pressure target can be kept lower in the elderly; JNC8, ADA 2021, and SEMT (Society of Endocrinology and Metabolism of Turkey) Diabetes guidelines state that the target range can be kept slightly higher within the benefit-benefit relationship, taking into account the functional and mental capacity of the elderly individual. According to the Hypertension Consensus Report, the targeted blood pressures vary according to age, but it is stated that it can be kept around 120-130/70-80 mmHg between 65-79 years of age.[14,17,18] Thus, individualized treatment with multidimensional evaluation in geriatric individuals is left open-ended.

Any of the four groups of drugs (diuretics, CCBs, ACE inhibitors, and ARBs) or a combination (except ACE inhibitors and ARBs) can be used in drug preference. However, in hypertensive patients over 65 years of age, drug compliance should be assessed before increasing the dose and number of drugs. Calcium channel blockers or diuretics should be the first choice in the treatment sequence. ACE inhibitors and ARBs are then recommended. B-blockers should be avoided unless there is a special indication. Especially in the frail elderly or those at risk of orthostatic hypotension, it is recommended to start treatment with a single drug and to increase the dose, and switch to the combination more slowly.[19,20]

The consensus among many of the above-mentioned guidelines and meta-analyses is that blood pressure control is the most important factor in reducing cardiovascular risk in all hypertensive patients, whether young or old. Even though the approach to hypertension treatment has been standardized by guidelines, an individual treatment algorithm should be established by evaluating lifestyle, comorbidities, and polypharmacy, especially in elderly individuals.[21]

CONCLUSION

The population is getting older all over the world, and elderly individuals have many comorbidities and are more vulnerable to frailty. Hypertension, the prevalence of which increases with age, is quite common in our country as well as in the whole world. Isolated systolic hypertension is especially common among the elderly. Considering the comorbidities in the elderly and the fact that the elderly is more vulnerable, diagnosis and treatment should be planned more sensitively in the geriatric group, paying attention to polypharmacy.

ETHICAL DECLARATIONS

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Case Report

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Successful treatment of concurrent acute migraine headache and atrial fibrillation with benzodiazepine administration

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ABSTRACT

Migraine and atrial fibrillation (AF) are common disorders in the general population in which autonomic nervous system takes role in the pathophysiological mechanism of both diseases. Migraine is a primary headache disease that is associated with significant debilitating symptoms and disability especially among young individuals and AF is associated with excess risk of morbidity and mortality. Interaction between migraine and AF has been a major interest since years at a pathophysiological and clinical level. Benzodiazepines (BZDs) are a class of psychotropic drugs that act through gamma amino butyric acid-A receptors located in the central nervous system. BZDs are widely used for their anxiolytic, anticonvulsant, sedative-hypnotic, and muscle relaxant effects. Herein, we describe a case of a patient presenting with concurrent acute migraine headache and AF attack and successful treatment of both conditions simultaneously with intravenous administration of BZD.

Keywords: Autonomic nervous system, atrial fibrillation, benzodiazepine, migraine.

INTRODUCTION

Migraine is a common primary headache disorder in which genetic and environmental components both involve in the pathogenesis. Characteristics of the disease include headache with repetitive, unilateral, and throbbing pattern usually accompanying photophobia and phonophobia. In addition, autonomic symptoms such as nausea, vomiting, flushing, lightheadedness, piloerection are common in migraine. Autonomic symptoms are mostly seen in migraine with aura and that paradoxical sympathetic hypersensitivity takes part during migraine attacks suggesting an important role for autonomic dysfunction in the pathophysiology.[1,2]

Atrial fibrillation (AF) is the most prevalent arrythmia type worldwide and associated with increased risk of morbidity and mortality. Akin to the migraine pathophysiology, alterations in autonomic nervous system functioning are the major drivers in AF pathogenesis.2,3 Therefore, interaction between migraine and AF has been a major interest since years at a pathophysiological and clinical level. Migraine is known to be a risk factor for AF development, but coexistence of AF and migraine headache has rarely been reported in the literature until now.[2,4,5]

Benzodiazepines (BZDs) are a class of psychotropic agents acting through gamma amino butyric acid (GABA)-A receptors which are ligand-gated and chloride-selective ion channels. Because BZDs reduce neuronal excitability, they are widely used in various neurologic and psychiatric conditions such as status epilepticus, anxiety, insomnia and delirium.[6] In this case report, we describe a case of a patient presenting with concurrent acute migraine headache and AF attack and successful treatment of both conditions simultaneously with intravenous (iv) administration of BZD.

CASE

A 47-year-old male patient with a history of migraine was admitted to our emergency department (ED) with the complaint of headache resulting with syncope. Initial evaluation revealed a heart rate of 100 beats per minute approximately and blood pressure of 110/70 mmHg. He had no fever and decreased oxygen saturation obtained from pulse oximetry. Neurological examination was normal and cardiac auscultation revealed irregular heart rate with no pathological sounds or murmurs. 12-lead electrocardiography obtained in the ED was consistent with AF accompanying high ventricular rate (**Figure 1**). Detailed anamnesis revealed no history of cardiac disease and risk factors except smoking. His headaches were very rare and associated with visual aura, irritability, and photophobia. However, he denied concomitance of syncope and/or palpitations during the previous attacks. He was on dexketoprofen treatment for

migraine prophylaxis for years. Laboratory tests including cardiac enzymes, natriuretic peptide level and thyroid function tests were all within normal limits. Cranial computed tomography and diffusion magnetic resonance imaging were also normal. Transthoracic echocardiography demonstrated mild mitral and tricuspid regurgitation with slightly increased left atrium diameter. Dexketoprofen and metoprolol was applied to the patient respectively through iv route but neither AF nor headache improved in two hours period. During this period the patient became agitated and anxious. Therefore, iv diazepam was applied to the patient and simultaneous termination of headache and conversion to sinus rhythm was observed in a few minutes (**Figure 2**). The patient was observed in the coronary intensive care unit for 24 hours and discharged from the hospital with beta blocker treatment in sinus rhythm and neurologically stable condition. Written informed consent was obtained from the patient.

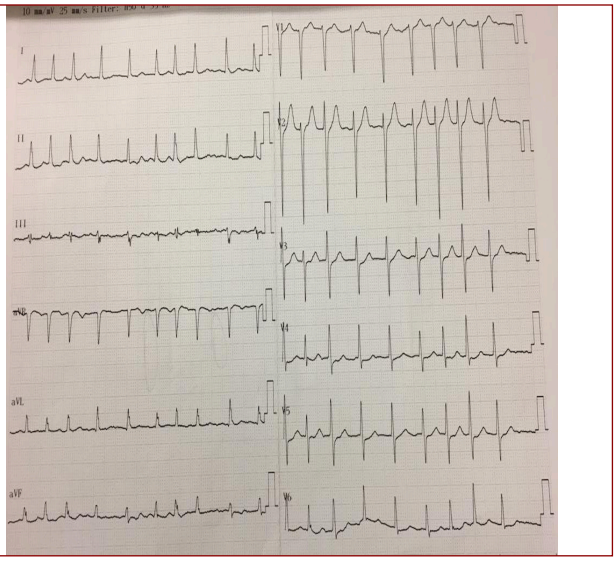

Figure 1. Admission 12-lead electrocardiography of the patient consistent with atrial fibrillation with high ventricular rate.

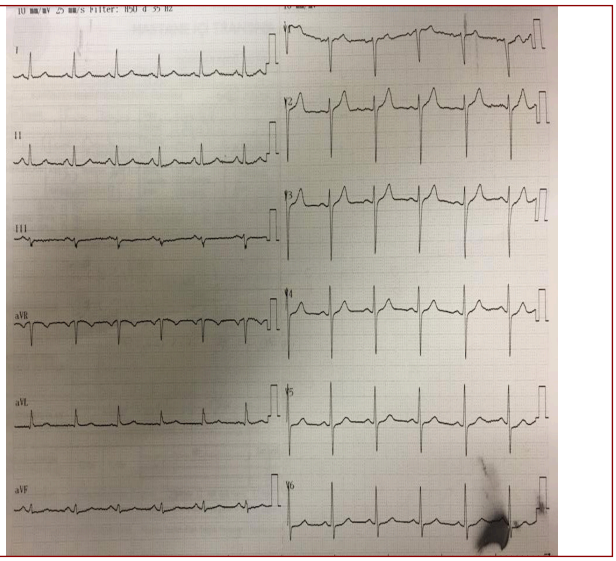

Figure 2. 12-lead electrocardiography of the patient consistent with sinus rhythm simultaneous with the termination of migraine headache after benzodiazepine treatment.

DISCUSSION

We present the case of a young patient with simultaneous acute migraine headache and AF attack and successful treatment of both conditions simultaneously with iv administration of BZD. To our knowledge, this is the first case in the literature demonstrating beneficial effect of BZD in acute migraine headache and accompanying AF. Although there is a close association between migraine and AF, pathophysiological mechanisms and clinical significance of this relationship are not entirely known.4 In addition, there are relatively few reports documenting the occurrence of AF during migraine headache.[2,5]

Besides being a significant cause of debilitating symptoms and disability especially among young individuals, migraine headache is also linked with ischemic vascular pathologies including stroke and coronary heart disease. It is primarily defined as a neurological disease with various symptoms and manifestations affecting the peripheral organs associated with gastrointestinal system, central nervous system, heart, and circulation. Nausea, vomiting, diarrhea, anorexia, pallor, flushing, piloerection, diaphoresis and mood disturbances are the main symptoms accompanying migraine headache and autonomic dysfunction, which occurs as a result of an imbalance between the sympathetic and parasympathetic system, underlies the pathogenesis of the disease and the occurrence of these symptoms.[1,7] For instance, sympathetic hyperactivation and a concomitant decrease in parasympathetic functions were demonstrated previously in migraineurs.[8] In a similar manner, sympathetic system activation during migraine attack may be the underlying mechanism triggering AF in our patient. However, iv administration of metoprolol, an agent that inhibits the sympathetic nervous system activation centrally, did not terminate the attacks. Furthermore, it is not possible to directly conclude that AF is secondary to migraine headache in this patient although syncope episode occurred after the initiation of headache. Nonetheless, concurrent termination of headache and AF highlights a robust pathophysiological connection between acute migraine headache and AF attack in this patient.

AF is the most common arrythmia all over the world and associated with excess risk of morbidity and mortality. Stroke is the most devastating complication of AF, and its frequency also increases in migraine patients. Alterations in the functioning of autonomic nervous system is known to play role in the pathophysiology of AF akin to the migraine.[7] Increasing line of evidence suggests that atrial repolarization abnormalities contribute to the initiation and maintenance of AF in migraineurs.[3,7] Moreover, atrial conduction abnormalities and diastolic dysfunction, which are contributors of AF development, were shown in migraineurs in previous transthoracic echocardiography studies.[9,10] Furthermore, presence of diastolic dysfunction was linked with a long migraine history.[10] When it comes to our patient, there was a slightly increased left atrium diameter that could make the patient prone to AF development. Otherwise, he had no history and/or signs of vascular disease, hypertension, diabetes mellitus, stroke, and heart failure. Accordingly, the patient was not anticoagulated and was planned to be followed up with beta blocker treatment. Subsequent examinations including stress test and ambulatory rhythm monitoring were planned to be performed during outpatient visits according to the clinical status and complaints of the patient.

BZDs modulate the effect of inhibitory neurotransmitter GABA through GABA-A receptors in the central nervous

system. In general, GABA plays an inhibitory role in the brain by reducing neuronal excitability and transmission. This inhibitory activity underpins anxiolytic, anticonvulsant, sedative-hypnotic and muscle relaxant effects from a clinical perspective.[6] In our case, we decided to use BZD in order to relief the patients' anxiety and agitation, but BZD did not only improve anxiety but also terminated AF and migraine headache simultaneously. In their case series, Kahn et al. demonstrated that clonazepam, which is a highly potent BZD, improved AF episodes in some patients suffering from panic disorder.[11] To our knowledge, concurrent improvement in AF and migraine attack has not been demonstrated in the literature hitherto.

It is reasonable to ask how BZD administration achieved this therapeutic effect. Neurobiological mechanisms and pathways of this effect might be multifactorial and complex. Basically, relief of anxiety and agitation might have alleviated the attacks through GABAergic stimulation subsequently inhibiting sympathetic nervous system activity. For example, according to a recent clinical study GABA containing tea significantly decreased immediate stress score and improved heart rate variability among university students.[12] In a similar manner, central GABA-A receptor activation were shown to decrease blood pressure and heart rate in an animal model study.[13] On the contrary, microinjections of GABA or its receptor agonist into the intermediate nucleus tractus solitarii of anaesthetized animals produced hypertension and tachycardia according to a previous study.[14] When it comes to effects of BZDs in migraine, treatment with short-acting BZDs but not long-acting ones was associated with migraine occurrence through one year follow-up period.[15] On the other hand, beneficial effects of lorazepam, a subtype of BZD, was shown to be beneficial in alleviating the symptoms of acute migraine headache.[16]

CONCLUSION

It is not logical to conclude that BZDs can be used in the treatment of AF and/or migraine headache in the light of this case report. However, this mutual effect deserves to be investigated in future studies and might open a new avenue in pharmaceutical investigations of both diseases. In conclusion, simultaneous initiation of acute migraine headache and AF attack and concurrent termination of both conditions after BZD therapy is an interesting situation that needs to be investigated in well-designed preclinical and clinical studies. Close follow-up of this patient might give important clues about the pathophysiology of migraine and AF.

ETHICAL DECLARATIONS

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Intravascular ultrasound application in the evaluation of left main coronary artery lesions

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ABSTRACT

Although atherosclerotic left main coronary artery stenosis (LMCA) has a low rate in the coronary angiography series, they have significant cardiovascular mortality and morbidity rates because their disease affects a significant proportion of the myocardium. Therefore, in severe cases (≥50% stenosis of the LMCA), coronary artery bypass grafting is the revascularization of choice. However, assessing LMCA disease severity involves anatomical and technical challenges. Coronary intravascular ultrasound may help to overcome these difficulties. In this article, we report a 73-year-old case of LMCA disease that was considered to be severe by visual assessment of coronary angiography, and surgical intervention was abandoned because of a minimal lumen area of more than 6 mm2 when IVUS was performed.

Keywords: Left main coronary artery, intravascular ultrasound, coronary artery disease

INTRODUCTION

Atherosclerotic left main coronary artery (LMCA) stenosis account for approximately 4% of all coronary angiograms.[1] The significance of LMCA disease is that almost 70% of the entire myocardium is at risk and is associated with a significantly higher risk of cardiovascular morbidity and mortality than disease of other coronary artery branches.[2] Current clinical practice guidelines recommend revascularization in patients with ≥50% stenosis of the LMCA.[3] Given the significant mortality and morbidity advantage, revascularization has traditionally been considered the gold standard for CABG.[4] Angiographical evaluation of the LMCA can be challenging. Some anatomic and congenital variations and some difficulties of the standard coronary angiography technique make this evaluation even more challenging.[5] In this article, we report a case in which the LMCA was judged to be non-critical by coronary intravascular ultrasound (IVUS) reassessment, although it appeared serious on coronary angiography.

CASE

A 73-year-old male patient was admitted to the cardiology outpatient clinic of another hospital with complaints of chest pain and shortness of breath and underwent coronary angiography. After evaluation, a coronary artery bypass grafting (CABG) operation was recommended, and the patient was referred to cardiovascular surgery. However, the patient refused to undergo surgery and applied to our hospital's cardiology outpatient clinic for re-evaluation. When the patient's coronary angiography CD was re-evaluated, LMCA stenosis was evaluated as suspicious in terms of severity, and it was decided to perform IVUS.

He had known coronary artery disease, hypertension, and diabetes mellitus, and continued to smoke. On examination, the general condition was good, and the cardiovascular system examination revealed S1, S2, with no additional sounds or murmurs. Respiratory sounds were normal, blood pressure was 135/92, and pulse rate was 88 beats/minute. Electrocardiography showed a normal sinus rhythm, and no evidence of ischemia was observed (**Figure 1**). Laboratory findings were normal, and troponin was not elevated (**Table**).

The patient was taken to the angiography laboratory for IVUS, and the procedure was performed using the transfemoral approach technique. A 7F diagnostic catheter was inserted into the LMCA. Visual assessment of the control coronary angiography revealed 60-70% restenosis of the LMCA, 70% in-stent restenosis after LAD D1, CX with diffuse disease, and RCA with plaque (**Figures 2, 3, and 4**). To evaluate the LMCA, a 0.14 mm guidewire was sent into the LAD lumen, and an IVUS catheter was advanced. The IVUS catheter was brought to the coaxial line, and LMCA images were obtained. Images were obtained from the distal, mid, and osteal sections of the LMCA, and measurements were made. The diameters of the LMCA were measured as distal 12.71 mm^2, mid 15.44 mm^2, and osteal 15.44 mm^2 (**Figures 5, 6, and 7**). The CABG operation was abandoned, and percutaneous transluminal coronary angioplasty (PTCA) was successfully performed on the lesion after LAD D1, and the patient was discharged from the cardiology service after adjusting his medical treatment.

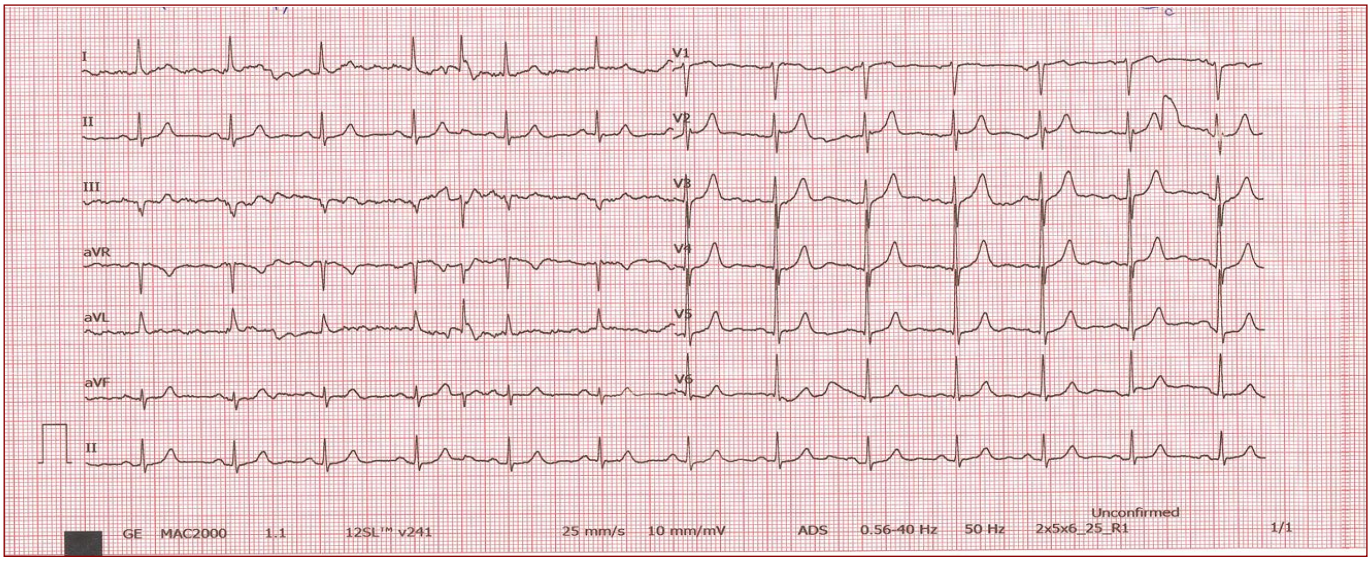

Figure 1. Initial electrocardiographic image of the patient on admission to the cardiology service

Table. Laboratory findings of LMCA case	
Glucose (mg/dl)	132 (70-110)
Creatinine (mg/dl)	0.9 (0.8-1)
AST (U/L)	21 (0-40)
ALT (U/L)	25(0-41)
Total cholesterol (mg/dl)	204 (0-200)
High density lipoprotein cholesterol (mg/dl)	42 (30-60)
Low density lipoprotein cholesterol (mg/dl)	142 (0-130)
Triglyceride (mg/dl)	112 (0-150)
Hemoglobin (mg/dL)	14.3 (13-17)
Platelets (10^3/ µL)	233 (150-450)
WBC (10^3/ µL) Troponin (µg/l)	8.1 (4.5-10) 13 (0-14)

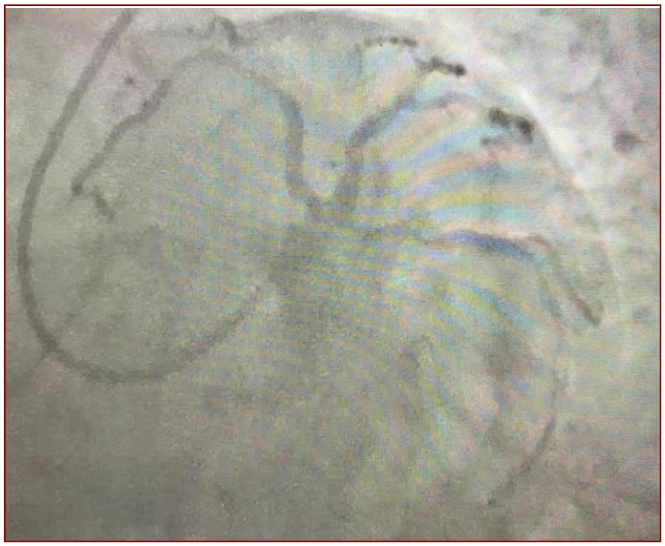

Figure 3. Angiographic image of the LMCA from the left-caudal angle

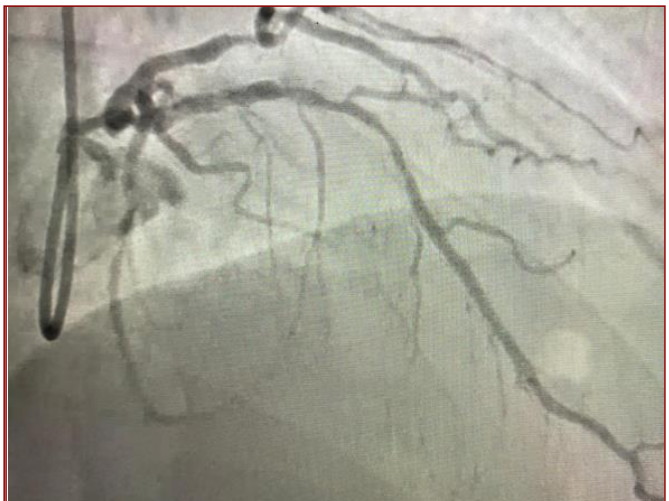

Figure 2. Angiographic image of the LMCA from the right-cranial angle

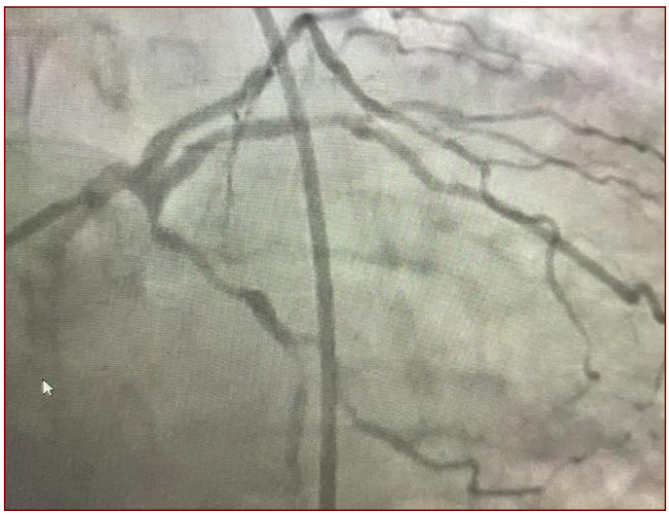

Figure 4. Angiographic image of the LMCA from the right-caudal angle

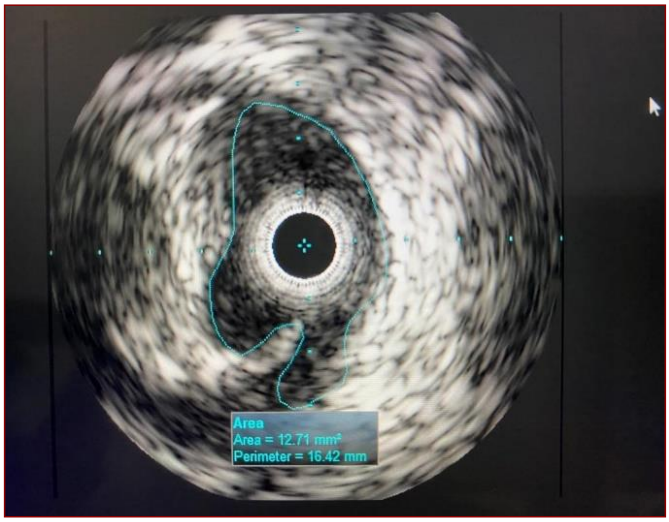

Figure 5. IVUS appearance and diameter measurement of the distal LMCA

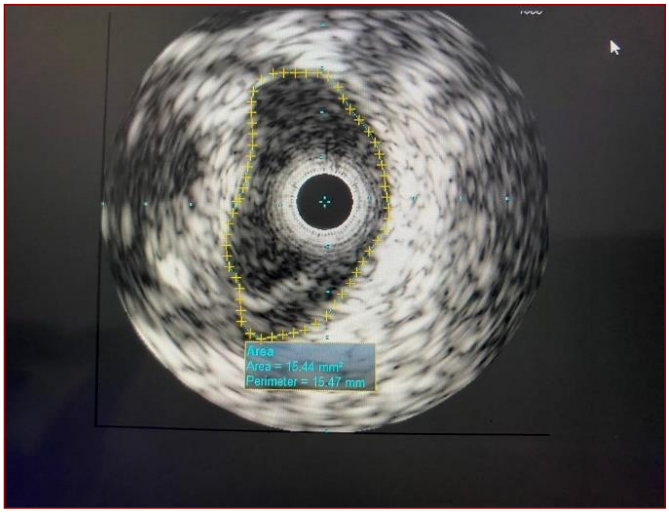

Figure 6. IVUS appearance and diameter measurement of the mid LMCA

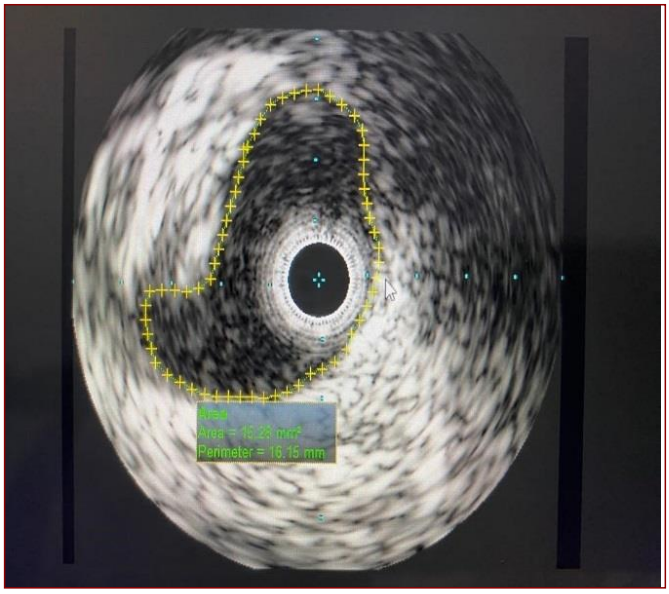

Figure 7. IVUS visualization and diameter measurement of the proximal LMCA

DISCUSSION

This article emphasizes the importance of visual assessment and re-evaluation with an imaging modality, such as IVUS in patients with LMCA, before making the decision to perform CABG.

Standard coronary angiography has been and continues to be indispensable in the evaluation of the coronary tree, including the LMCA. Until recently, LMCA interventions with PTCA were recommended in isolated cases, such as patients who were hemodynamically unstable and/or at high risk for CABG operations.4 Recent data have shown that, in some cases, PTCA may be as safe as CABG for LMCA interventions.[6-8] In particular, it showed that CABG and PTCA had similar outcomes at 1 and 5 years in patients with low or intermediate SYNTAX scores.[9]

Angiographic evaluation of the LMCA can be challenging. LMCA disease is particularly difficult to accurately assess on angiography, as the arterial segment is usually short, calcified, and often has disease involving the bifurcation. Not surprisingly, the significance of angiographically assessed stenosis at this particular location is observer-dependent, and reproducibility of results is low even among experienced clinicians.[10] Given the critical importance of the LMCA for coronary circulation and thus its high prognostic value, accurate lesion assessment is crucial in guiding clinical management.

IVUS was first used to evaluate LMCA lesions in the 1990s.[11] It provides precise and detailed information on atherosclerotic burden, plaque extension and plaque morphology from the aorto-ostial junction to the distal segment and ostia of both the left anterior descending and left circumflex arteries. This information, together with other clinical data, can provide guidance on the need for revascularization or deferral based on a minimal lumen area. IVUS may also be a useful tool to plan PCI strategy and optimize outcomes in terms of stent size, lesion extent, stent apposition, dilation, and detection of edge dissection.[5]

Several studies have proposed a wide range of MLA cut-off values (between 4.5 and 7.5 mm^2) to guide medical therapy versus revascularization, especially in LMCA lesions, based on the ability to significantly correlate with an FFR <0.8. The MLA cut-off of 6 mm^2 was frequently used as the standard for deferring revascularization, as it was validated in the prospective multicenter (LITRO) study.[5] The studies emphasize that an IVUS-defined MLA cutoff of >6 mm^2 appears to be a safe deferral threshold for revascularization in Western and Asian populations. A meta-analysis of 10 non-IVUS studies found that IVUS-guided PCI to the LMCA significantly reduced all-cause mortality by 40% and cardiac death by 53%, as well as the risk of stent thrombosis and target organ revascularization.[12]

CONCLUSION

IVUS is helpful in assessing the severity of the LMCA lesion, overcoming many limitations of angiography in this anatomic segment. It should not be overlooked that patients with LMCA stenosis should be evaluated with IVUS before deciding on CABG.

ETHICAL DECLARATIONS

Informed Consent: All patients signed and free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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