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ERRATUM

Erratum

Risk of Sudden Cardiac Death and Preventive Measures in Athletes

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Abstract

Arrhythmias, which are fatal in some patients, can be triggered by sports in vulnerable people. It is estimated that 1:40,000–1:250,000 athletes will suffer a sudden cardiac death (SCD). However, female athletes appear to have some level of cardiac protection, since suffering from SCD considerably less than male athletes during sports. Athletes with underlying coronary, valvular or myocardial disease, as well as channelopathies, may be particularly prone to SCD from exercise- and sports-related physical activity. There are three main causes of SCD in young athletes: Sudden Arrhythmic Death Syndrome (56%), congenital anomalous coronary arteries (7%–14%), and hypertrophic cardiomyopathy (36%–48%). In the context of exercise, acute ischemia, myocardial infarction, and stroke risk are increased by catecholamine surge and exercise-induced stress. In middle-aged athletes, excessive cardiovascular activity is associated with a higher risk of mortality related to cardiovascular disease. It is possible to detect at-risk athletes by conducting cardiac screening, which involves a family history, physical examination, and a resting electrocardiogram. Consequently, efforts have been made to better understand the causes of SCD in athletes and to develop appropriate prevention methods.

Keywords: Athlete's heart, cardiac screening, cardiovascular abnormalities, sports, sudden cardiac death

INTRODUCTION

The sudden cardiac death (SCD) rate among athletes is considerably lower than that of the general population. The public's response to SCD occurring during a sports event raises questions about cardiovascular risks related to sports. In this paper, we examine the pathophysiology and etiology of SCD among athletes engaged in sports and exercise. Numerous studies have found that regular exercise lowers cardiovascular mortality, including SCD significantly compared with sedentary lifestyles.^[1,2] In contrast, exercise- and sports-related physical activity have been linked to SCD, particularly in athletes with underlying coronary, valvular, myocardial disease, and channelopathies. It appears that exercise may exacerbate predisposed individuals' tendency to develop malignant arrhythmias. There has been extensive research conducted by sports cardiologists worldwide to quantify the

incidence of SCD in athletes, identify risk factors, develop preparticipation screening tools, and formulate plans for on-field SCD management.^[3] The aim of this review is to inform the community about the current state of knowledge regarding athletes who are at risk of SCD.

EPIDEMIOLOGY OF SUDDEN CARDIAC DEATH IN ATHLETES

Across studies, the incidence of SCD in athletes ranges from 1:40,000 to 1:250,000, with this variance being driven by different methodologies, demographics, and sports disciplines.^[4] A 5-year prospective study found that 4.6 people/1 million had sports-related SCD, compared with 50–100 people per million in the general population.^[5] Sudden

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death is influenced by several factors, including an athlete's age, race, gender, ethnicity, training level, and type of sport. Over 80% of sports-related SCD deaths occurred in adults aged 35 and older due to atherosclerotic coronary artery disease (CAD).^[6] While preparing for any sporting event, the risk of sudden cardiac arrest (SCA) or SCD is approximately five-fold higher.^[7] A higher rate of adverse events is observed in occasional runners (1/7500–18000) than in marathon runners (1/50,000–200,000).^[8] Sports competition has been associated with SCD in vulnerable individuals who experience lethal arrhythmias. Unlike male athletes, female athletes appear to have some level of cardiovascular protection, since they typically do not die suddenly during sports. According to the data from the United States, black athletes are at a higher risk of SCD than white athletes.^[4,9] Corrado *et al.*,^[10] published one of the first large-scale studies of SCD in athletes in the Veneto area of Italy, which prospectively examined SCD events in a youth population (between 12 and 35 years of age), demonstrating an incidence rate equal to 1.0 in 100,000 people per year, including 2.3/100,000 among competitive athletes. The findings of Alattar *et al.*^[11] indicate that five (2.17%) Arab athletes had an SCD-related anomaly. Two of the athletes had Wolff-Parkinson-White (WPW) syndrome, one had Atrial Fibrillation, one had Long QT syndrome (LQTS), and one had arrhythmogenic right ventricular cardiomyopathy (ARVC). According to Riding *et al.*,^[12] 10 athletes (0.47%) have pathological substrate related to SCD. The hypertrophic cardiomyopathy (HCM) syndrome was detected in five black athletes and two Arab athletes, while the WPW syndrome was detected in three Arab athletes. Among younger athletes, more than half of all deaths result from nonmedical or traumatic causes. It is estimated that 0.2%–0.7% of young athletes develop cardiovascular disorders predisposing to SCD during sports. Sudden arrhythmic death syndrome-SADS (56%), HCM (36%–48%), and congenital anomalous coronary arteries originating from opposing sinuses (14%–17%) are the most common causes of SCD in athletes, while ARVC (4%–11%), myocarditis (6%–7%), and ion channelopathies (4%), are the least common. SADS is an unexplained or unexpected sudden death especially in young, despite a comprehensive autopsy and toxicological analysis. SADS may be caused by underlying primary electric disease.^[13] Atherosclerotic CAD is the cause of only 2%–3% of SCD in younger athletes^[7] [Figure 1].

ETIOLOGY

A physical exertion-induced SCD can be deadly despite its rarity. A significant percentage of these deaths, even among young, seemingly healthy individuals, is caused by undiagnosed cardiovascular disease. Recent studies found that around 65% of sudden deaths in student-athletes did not involve cardiovascular causes, but rather a suicide, trauma, or substance abuse. A substantial number of sudden deaths were caused by drowning and heat strokes.^[11] Tables 1 and 2 illustrate the pathological assessment and underlying conditions of SCD patients.^[7,14] More than three-quarters of nontraumatic sudden

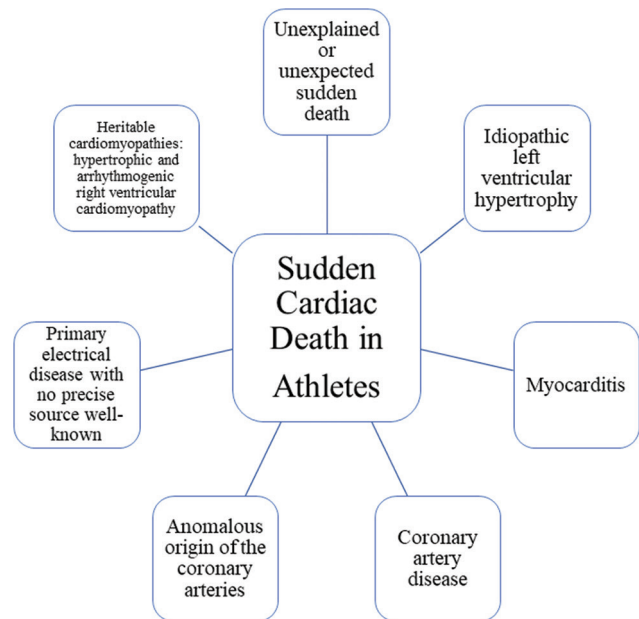


Figure 1: Sudden cardiac death in athletes

deaths in sports are caused by cardiovascular diseases. The cause of SCD in young athletes (<35 years old) can range from hereditary, congenital, or acquired structural and electrical problems. In the United States, SCD is most commonly caused by HCM, whereas in Italy, ARVC is commonly reported. Further causes of SCD include myocarditis, coronary artery abnormalities, valvular heart diseases, aortic dissection, commotio cordis, and inherited channelopathies such as WPW syndrome, LQTS, and Brugada syndrome. Children without obvious structural heart disease are also at risk of SCD, which occurs in as many as 12% of cases.^[12,15] It appears that these cases are associated with inherited arrhythmic substrates, and genetic testing of survivors of SCD might provide relevant results that explain the incident and may be valuable for family screening. Exercise-related SCD is also caused by drug use. For instance, cocaine and amphetamines can lead to myocardial infarction (MI), arrhythmias, myocarditis, and premature CAD. Chronic use of drugs can cause dilated cardiomyopathy, and performance-enhancing medications can have immediate negative effects on the cardiovascular system.^[16] Athletes who use anabolic drugs may be predisposed to hypertension, dyslipidemia, ventricular hypertrophy and fibrosis, and arrhythmias because of their ability to push themselves beyond their natural limits. Previously reported higher target hemoglobin levels with erythropoietin therapy are associated with an increased risk of MI or stroke^[17] [Table 3]. More than 85% of deaths among athletes over the age of 35 years are caused by atherosclerotic CAD^[18] [Figure 2]. In young athletes, congenital coronary artery abnormalities are a significant cause of death, particularly when they occur in the left coronary artery, which arises from the right sinus of the Valsalva and travels between the aorta and the pulmonary artery. It is possible for athletes to develop SCD due to mitral

Table 1: Pathological assessment of sudden cardiac death

Types	Subtype	Pathology	
Structural disorders	Cardiomyopathy	HCM	
		Idiopathic LVH	
		ARVC	
		IDC	
	Marfan	Aortic root dilatation/rupture/dissection	
		MVP	
	Valvular disease	Bicuspid aortic AS	
		Pulmonic stenosis	
	Disorders of coronary circulation	Congenital	ALCA from right sinus
			ARCA from left sinus
Acquired		Atherosclerosis	
Electrical disorders	Ion channelopathies	Long QT syndrome	
		WPW syndrome	
		Brugada syndrome	
		Short QT syndrome	
	VT	CPVT	
	Ventricular fibrillation	SADS	
	Acquired/ environmental	Sports injury	Commotio cordis
		Physical trauma	
Heat stroke		Ventricular fibrillation	
Infection		Subacute myocarditis	
	Performance-enhancing drugs	Myocardial infarction, ventricular arrhythmias	
	Hypothermia	Ventricular arrhythmias	

HCM: Hypertrophic cardiomyopathy, LVH: Ventricular hypertrophy, ARVC: Arrhythmic right ventricular cardiomyopathy, IDC: Implantable cardioverter defibrillator, MVP: Mitral valve prolapses, ALCA: Anomalous left coronary artery, ARCA: Anomalous right coronary artery, VT: Ventricular tachycardia, CPVT: Catecholaminergic polymorphic VT, SADS: Sudden Arrhythmic Death Syndrome, AR: Aortic regurgitation, MR: Mitral regurgitation, AS: Aortic stenosis, WPW: Wolff-Parkinson-White syndrome, QT: QT interval

valve prolapse, bicuspid aortic valves, and aortopathies. There is a 0.5%–4% frequency of myocarditis in the general population; however, it may contribute to up to 22% of SCD in those under 35 years old.^[19] Myocarditis produces myocardial necrosis and fibrosis, which increases the risk of SCD by predisposing to life-threatening ventricular arrhythmias, and physical activity increases this risk. It is possible that persistent scarring after the acute phase of myocarditis increases the risk of developing arrhythmias and SCD. There is evidence that more than 40% of SCD patients may have a healthy heart, according to a large autopsy investigation at an expert cardiac pathology center in the UK.^[5] There is a small possibility that some patients have inherited channelopathies, such as WPW syndrome. There is growing evidence that structurally normal hearts are more prevalent than cardiomyopathy, which has led to a significant paradigm shift regarding SCD's etiology.^[20] Several studies have shown that senior male athletes who have exercised vigorously for most of their lives may develop cardiovascular problems such as coronary artery calcification, atrial fibrillation, and myocardial fibrosis.^[21-23] It is believed

Table 2: Cardiovascular conditions associated with sudden cardiac death

Structurally abnormal heart	Structurally normal Heart
Congenital/genetic	
HCM	Congenital long QT syndrome
ARVC	CPVT
Dilated cardiomyopathy	WPW or another accessory pathway
Another cardiomyopathy (i.e., left ventricular noncompaction)	Brugada syndrome
Congenital anomalies of coronary origin and course	Other ion channelopathies
Aortopathy (i.e., Marfan syndrome and ascending aortic aneurysm/dissection)	
Valvular heart disease (i.e., congenital aortic stenosis, mitral valve prolapse)	
Acquired	
Atherosclerotic CAD	Commotio cordis
Kawasaki's disease	Acquired long QT (i.e., drug-induced)
Myocarditis	Other substance ingestion or environmental factors (i.e., hypo- or hyperthermia)

CAD: Coronary artery disease, ARVC: Arrhythmogenic right ventricular cardiomyopathy, HCM: Hypertrophic cardiomyopathy, VT: Ventricular tachycardia, CPVT: Catecholaminergic polymorphic VT, WPW: Wolff-Parkinson-White syndrome, QT: QT interval

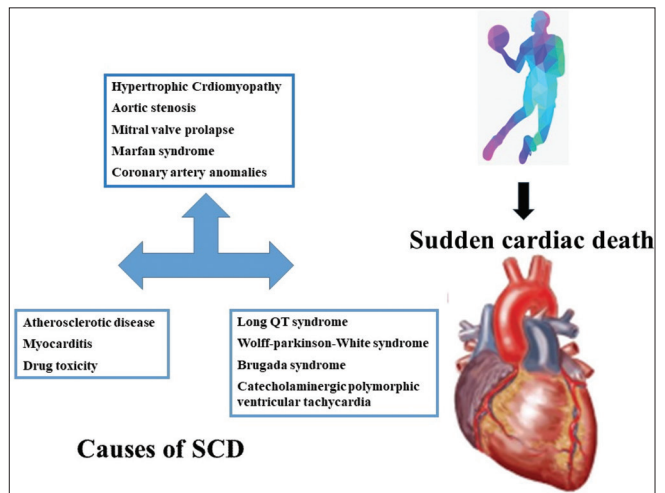


Figure 2: Sudden cardiac death causes

that these anomalies are probable consequences of exercise, and they were found in just a small proportion of female athletes. In spite of the fact that veteran male athletes had a higher frequency of coronary artery calcium than their sedentary counterparts, no differences were found between female athletes and controls. There has also been a report of myocardial fibrosis in experienced male athletes, but not in women. A recent study found that 17% of male triathletes exhibited late gadolinium enhancement in cardiac magnetic resonance but none of the female triathletes did.^[24] The RACE Paris registry showed that SCDs caused by CAD have an

acute thrombotic occlusion, while the RACER registry of 10 million runners showed that SCDs are caused by fixed coronary stenosis without thrombosis. Therefore, there are two plausible causes for the occurrence of ventricular tachyarrhythmias and cardiac arrests during sports activities. In this condition, coronary flow cannot be increased during exercise due to tachycardia reducing diastolic duration and exhausting the coronary vasodilatory reserve beyond stenosis. A sudden discontinuance of activity can aggravate ischemia, as it reduces venous return and lowers blood pressure in a vasodilated state, eventually leading to coronary hypoperfusion. Acute ischemia is exacerbated by electrolyte imbalance, heat stroke, and an excess of catecholamines in the blood. Eventually, this leads to malignant ventricular arrhythmias, which can occur during or soon after endurance exercise.^[25] The second explanation is acute plaque rupture during exercise, increased wall shear strain on the fragile plaque, along with catecholamine-induced coronary spasm and endothelial dysfunction, induces erosion of the thin fibrous cap, as well as intra-plaque hemorrhage and thrombosis.^[26]

RELATION BETWEEN EXERCISE, CARDIAC DISEASE, AND SUDDEN CARDIAC ARREST

In people with HCM, the balance between risk and benefit is unclear, with risks at extremely high levels of exercise.^[27,28] Researchers recently concluded that moderate-intensity exercise is safe and beneficial for people with HCM who are asymptomatic.^[29] With chronic diseases such as hypertension, a coronary disease with MI, and diabetes, regular exercise minimizes unfavorable cardiac remodeling. Heart failure, hypertension, and previous MI patients have been found to benefit from high-intensity interval training.^[30] Even high-intensity exercise poses virtually no risk to an athlete without predisposing factors or underlying cardiovascular disease. Sports and exercise offer a number of health benefits, including reduced mortality and morbidity risks as well as psychological benefits for the individual [Figure 3].^[31,32] In the absence of cardiac disease, long-term endurance athletes who run 15–30 h per week have an increased risk of developing lone paroxysmal atrial fibrillation. In a recent meta-analysis, athletes had a higher chance of developing lone paroxysmal atrial fibrillation than sedentary individuals. In contrast, athletes with atrial fibrillation were less likely to suffer a stroke than their age-matched peers.^[33,34] The higher risk can be attributed to increased myocardial oxygen demand and adrenergic output, which can lead to an arrhythmogenic condition or ischemia.^[35] The prevalence of cardiac anomalies requiring further testing in sports has been found to be between 2% and 4%, with clinically significant abnormalities occurring in about 0.3% of athletes. According to experts, many disorders that could cause SCA in athletes, such as inherited channelopathies, an abnormal origin of the coronary arteries, and premature CAD, would not be detected on a normal electrocardiogram (ECG). ECG of children and adolescents with cardiomyopathies shows that it is less sensitive than previously thought to identify

Table 3: Drugs and cardiovascular side effects

Drugs	Cardiovascular side effects
Anabolic agents	Dyslipidaemia Hypertension Pathological cardiac hypertrophy/cardiac fibrosis Arrhythmias
β2-adrenergic receptor antagonists (Clenbuterol)	Arrhythmias in animals
Selective estrogen receptor modulators (Tamoxifen)	Venous thrombosis Pulmonary embolism
Oxygen dissociation curve modulators	Cardiomyopathy
Hormone/metabolic modulators	Hypertension, hyper- or hypoglycaemia, dyslipidaemia
Oxygen-carrying modulators	Thromboembolic events Myocardial infarction Stroke Hypertension

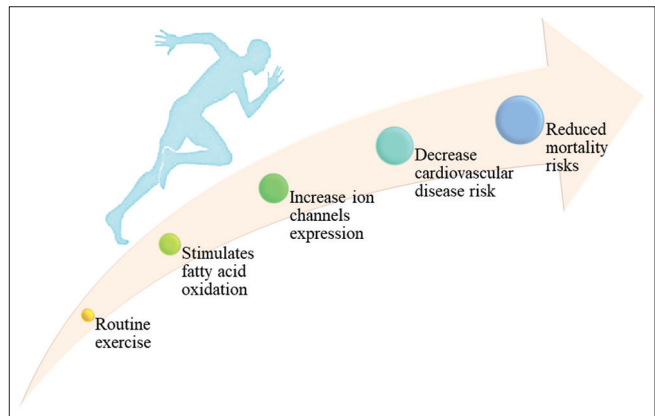


Figure 3: Cardiovascular benefits of regular exercise

cardiomyopathies.^[36] Typical abnormalities are found only in 25%–75% of adolescents with ARVC and in 50%–75% of asymptomatic young patients with HCM. A recent longitudinal study of top soccer players discovered that 6 of every 8 SCDs (6/100,000/year) occurred in athletes with a negative history, physical examination, and ECG.^[37]

HEARTS OF ATHLETES

The cardiovascular systems of athletes and the general population differ in terms of their functional and structural characteristics because of the type of exercise they engage in. Swimming and long-distance running belong to the endurance training category, while wrestling, weightlifting, and sports belong to the strength training category. Cardiovascular fitness affects the heart in a unique way for each athlete. As a result of exercise, around half of all athletes will show cardiac remodeling. Among the changes are increased cavity sizes on the ventricles and left atrium.^[38] In endurance athletes, the left ventricular (LV) chamber may expand significantly, resulting in a moderate increase in absolute LV wall thickness. Athletes with high levels of training are also more likely to develop

left atrial remodeling. During the acute phase of endurance exercise, oxygen consumption, cardiac output, stroke volume, and systolic blood pressure increase, while peripheral vascular resistance decreases. As a result of volume overload, endurance exercise leads to the dilation of the left ventricle, whereas resistance training leads to hypertrophy of the left ventricle. The risk of acute ischemia, MI, and SCD is higher during and up to 1 h after exercise when compared with sedentary hours. Compared to resting hours, exercise increases the risk of SCD by 8–16 times and MI by 6–10 times.^[39] As a result of regular and habitual physical activity, the greater relative risk associated with SCD, and acute MI is reduced.

SCREENING REQUIREMENT

In seemingly fit athletes, SCD usually occurs without warning symptoms or a history of heart disease. Sport-related sudden mortality can be reduced through preparticipation screening for silent cardiac conditions. The European Society of Cardiology (ESC), the American Heart Association (AHA), the International Olympic Committee (IOC), and the Federation Internationale de Football Association have endorsed preparticipation screening (PPS) cardiovascular for young athletes. It involves systematically evaluating athletes before competition to detect existing cardiac diseases that may put an athlete at risk for SCA, as well as other critical health issues. A screening program aims to detect athletes who are at high risk for sudden death and to restrict their participation in competitive or high-intensity activities to significantly reduce their risk. An examination and history of 14 points are part of the guidelines developed by the AHA for the PPS of competitive athletes.^[40] During a 25-year Italian preparticipation screening program, 0.2% of athletes had a disease that led to SCD based on their medical history, physical examination, 12-lead ECG, and restricted exercise testing. As a result of the screening process, the SCD rate dropped by 90% from 3.6/100,000 person-years to 0.4/100,000 person-years, with a false-positive rate of 7%.^[4]

PREVENTIVE MEASURES AND THE BEST APPROACH TO SCREEN ATHLETES IN A PRIMARY CARE SETTING

The assessment is primarily intended to improve athletes' health and safety. While preparticipation evaluations cannot prevent morbidity and death in sports, they can aid in the discovery of serious issues and the development of injury prevention strategies.^[20,41] All ages can benefit from sports and athletics, as it improves fitness, self-esteem, and coordination, and give athletes the opportunity for creative cooperation and competition. Any sport or level of competition will be open to athletes if their clearance status has been determined following appropriate tests, treatment, or rehabilitation. According to most guidelines, clinical history, physical examination, and ECG are the least expensive methods of preparticipation screening. In 2014, the AHA developed a 14-item cardiovascular screening checklist for congenital and hereditary heart disease in young

athletes.^[40] A pre-participation evaluation (PPE) aims to ensure the athlete's health and safety during training and competition. Physicians will use this information to make decisions about an athlete's physical activity. Any positive reaction on any of the 14 items may be deemed sufficient by the examiner to begin a detailed cardiovascular investigation that may include an ECG, echocardiography, or stress test. The Canadian Cardiovascular Society and Canadian Heart Rhythm Society recently published a joint position statement on cardiovascular screening of competitive athletes recommending measuring and comparing blood pressure in both arms, auscultating for heart murmurs, and examining for features of Marfan syndrome.^[42] Even though first affirmative responses on the PPE form are intended to be examined by a physician before an additional examination, Fudge *et al.*^[43] discovered that 46% of the first affirmative responses still needed further investigation after having been reviewed by the physician. ECG screening improves sensitivity by identifying athletes with hereditary ion channel disease including accessory pathways, as well as raising suspicions of athletes with cardiomyopathy. An ECG is considered to be more sensitive than a history and physical exam in detecting underlying cardiovascular abnormalities that may place athletes at risk for SCD.^[44] In a prospective study, resting ECGs have not been added to screening protocols. As of yet, there is no mandate regarding ECG screening for collegiate athletes in the US, although the ESC and IOC recommends its use, whereas the AHA recommends only a history and physical examination, primarily due to the cost and infrastructure concerns.^[3] Cardiopulmonary resuscitation (CPR) and rapid defibrillation double the survival rate of sports-related SCD.^[7,8,45] The first responders should be trained in recognizing symptoms, activating the emergency medical system, performing CPR, and using an automated external defibrillator (AED). Before 1995, one SCD per 55,000 finishers occurred in US Marathons, but after 1995, it decreased to one per 220,000 finishers due to emergency medical response services.^[46] An athlete experiencing cardiac arrest can be efficiently revived by performing rapid CPR and using an AED in time. In a study by Weisfeldt *et al.*,^[47] rapid use of an AED is associated with a higher chance of survival (odds ratio: 1.75; 95% confidence interval: 1.23–2.50; $P = 0.002$), with rates of survival to hospital discharge highest in recreational areas (49%). AED availability during a sporting event, education of trainers and bystanders, and systematic emergency response methods all contribute to high survival rates in settings with systematic emergency response methods and timely deployment of AEDs^[7,48–50] [Tables 4 and 5].

CONCLUSION

Sudden cardiac mortality among sportsmen is relatively rare. Globally, cardiomyopathy, hypertrophic, and ARVC are the most common causes. SCD in sports might be avoided and reduced if we understand the origins and processes of such incidents. The PPS of athletes should include a history, physical examination, and ECG to identify those at high risk for SCD.

Table 4: Preparticipation screening in competitive athletes

Screening	Details
History	Unexplained or exertional syncope, exertional chest pain, dyspnoea, palpitation
Family history	Family history of MI, SCD, and coronary risk factors Known h/o hypertrophic or dilated cardiomyopathy, long QT syndrome, CPVT, ARVC, Brugada, Marfan Syndrome
Examination	Blood pressure Heart murmur/cardiomegaly Marfanoid features Xanthelasma
ECG	Ischemia/infarction Chamber enlargement Long QT/WPW/ARVC/Brugada

ARVC: Arrhythmogenic right ventricular cardiomyopathy, VT: Ventricular tachycardia, CPVT: Catecholaminergic polymorphic VT, SCD: Sudden cardiac death, WPW: Wolff-Parkinson-White, ECG: Electrocardiogram, MI: Myocardial infarction, QT: QT interval

Table 5: Advantages and disadvantages of preparticipation sudden cardiac death screening

Advantages	Disadvantages
At-risk people can be identified and reduced risk of death	Costs
Ensure that the risk is extremely low if pathological report is normal	False-negative findings
Understand sudden cardiac death risk and sports-related cardiac structures and functions	Despite the lack of evidence supporting ECG's use in screening, it remains controversial

ECG: Electrocardiogram

As well as the role of paramedics/relevant stakeholders in aiding this process, appropriate PPS is essential to prevent SCD. There is a need for more research to develop solutions that can reduce the burden of SCD on this population.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Evaluation of Electrocardiographic Changes in Patients Under COVID-19 Treatment Regimes

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Abstract

Background and Aim: Awareness of electrocardiographic (ECG) changes is crucial in patients who receive coronavirus disease 2019 (COVID-19) treatment. In this study, we aimed to evaluate ECG parameters in patients under COVID-19 therapy and their relationship with the severity of lung involvement and the disease on the basis of thoracic computerized tomography (TCT) findings and laboratory parameters. **Materials and Methods:** Of 350 patients hospitalized due to COVID-19 between March 2020 and June 2020, 300 patients with available data were retrospectively analyzed. Blood analysis, electrocardiographic, and clinical findings were evaluated. Six-month follow-up data were also recorded. **Results:** The patients were categorized into two groups: survivor ($n = 206$, 68.7%, Group 1) and nonsurvivor patients ($n = 94$, 31.3%, Group 2). The mean total follow-up period was 125.39 ± 73.09 days. The mean age was similar in both groups. In multivariate regression analysis that aimed to predict COVID-19 disease severity, it was found that besides increased C-reactive protein and D-dimer levels, and $\geq 50\%$ lung involvement in TCT, which are well known as bad prognostic factors, the corrected QT interval duration (QTc) prolongation ≥ 60 milliseconds (msn) during hospitalization was associated with worse prognosis in COVID-19 patients during follow-up. **Conclusion:** Our study is the first study that demonstrated that the presence of ≥ 60 msn QTc prolongation during hospital stay was found to be the most valuable ECG parameter to predict the prognosis and had a significant association with $\geq 50\%$ lung involvement in TCT in patients under anti-COVID therapy. Close monitoring of this ECG parameter is important both in terms of treatment planning and interpretation of disease progression.

Keywords: COVID-19, electrocardiographic, mortality, myocardial injury, severity

INTRODUCTION

The world encountered a new virus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in 2019.^[1] The surface spike protein of SARS-CoV-2 binds to the human angiotensin-converting enzyme-2 (ACE2) receptor.^[2] ACE2 is expressed in the lungs, heart, intestinal epithelium, vascular endothelium, and kidneys, thereby providing a

mechanism for the multiorgan dysfunction that can be seen with SARS-CoV-2 infection.^[3] The clinical manifestation of SARS-CoV-2 is associated with ACE2R presence, so it is predominantly associated with respiratory system disease

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but can also affect the cardiovascular system as a result of multisystemic involvement. This new viral disease has been named as coronavirus disease-2019 (COVID-19).^[4]

Several studies have reported that elevated levels of cardiac markers such as cardiac troponin and electrocardiographic (ECG) or echocardiographic abnormalities can accompany other inflammatory markers depending on the disease severity.^[3,5] These effects may be an extension of systemic disease and hypoxia or could be associated with acute coronary syndrome and decompensated heart failure (HF).^[6] Cardiovascular effects have been reported to be present in 7.2% of all patients and 22% of the patients followed up in intensive care units.^[7] It has also been suggested that the medication used for COVID-19 treatment, including chloroquine, hydroxychloroquine, azithromycin, and lopinavir/ritonavir can cause ECG changes, especially QT or PR prolongation.^[8]

ECG is the first step test for the diagnosis of cardiac disorders. In patients with COVID-19 disease, the importance of ECG changes is still undefined.^[9,10] This study aimed to evaluate ECG parameters in patients under COVID-19 therapy and their relationship with the severity of lung involvement and the disease on the basis of thoracic computerized tomography (TCT) findings and laboratory parameters.

MATERIALS AND METHODS

Patient selection

A total of 350 patients who were hospitalized due to COVID-19 disease between March 2020 and June 2020 in our hospital were collected. All of the patients presented at the emergency department with respiratory symptoms, and TCT revealed findings compatible with COVID-19. Due to the absence of basal and follow-up medical records, 50 patients were excluded from the study. The remaining 300 patients who had been followed up for 6 months were retrospectively analyzed.

Data collection

After hospitalization, a standard clinical examination was performed. Blood tests were obtained for the evaluation of complete blood count-hemogram (CBC-Hg), creatinine, blood urea nitrogen, troponin I (TI), and C-reactive protein (CRP) levels. Furthermore, 12-lead ECG, heart rate (HR), PR-QRS-corrected QT interval duration (QTc) and the change in PR-QRS - QTc duration ([duration at control ECG]- [duration on admission ECG]) were calculated as milliseconds (msn). The presence of any ST segment change, left or right bundle block, was noted.

The QT duration was measured as the interval between the start of the Q wave and the end of the T wave, and corrected by HR as per the Bazett formula. The PR duration was measured as the interval between the start of the P wave and the end of the R wave. The QRS duration was measured as the interval from the start of the Q wave to the end of the S wave.

The presence of comorbidities (arterial hypertension [AHT], coronary arterial disease [CAD], chronic obstructive

pulmonary disease [COPD], diabetes mellitus [DM], HF, and chronic renal disease [CRD]) was recorded on the basis of documented medical history. AHT was defined as arterial pressure regulated with medication or diet, DM as blood glucose regulated with medication or diet, and CAD was defined when a history of >50% coronary lesion or acute coronary syndrome is present. HF was defined as left ventricular ejection fraction (LVEF) <50% on echocardiography. COPD was defined on the basis of a diagnosis made by a pulmonologist. CRD was defined as low glomerular filtration rate (GFR) for age.

The usage of hydroxychloroquine (HCQ) and macrolide was also noted, as they are known to cause QT prolongation associated with COVID-19 treatment.

The patients were evaluated by two-dimensional transthoracic echocardiography in case of any cardiac symptoms or elevated TI or significant ECG changes. All of these data were retrieved retrospectively from the hospital medical records.

The involvement of lung infiltration was defined on the basis of TCT findings (as $\geq 50\%$ or $< 50\%$). The incidence of in-hospital mortality, mortality during the follow-up period after discharge, and follow-up duration (period from admission to mortality or last outpatient clinic visit) were recorded retrospectively.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software version 21 (IBM, NY, USA). Data were presented as mean \pm standard deviation values for continuous variables and as number (*n*) and percentage (%) for categorical variables. Differences in proportions between groups were analyzed using the Chi-square test. The mean values of variables were compared using the Mann-Whitney *U*-test based on the distribution of continuous variables. Univariate and multivariate Cox regression analyses were used to define independent risk factors for mortality. Factors in univariate analyses with a $P < 0.1$ were included in the multivariate survival analyses according to certain risk factors and were evaluated using Kaplan-Meier analyses. In two-tailed tests, $P < 0.05$ were considered statistically significant.

Ethical statement

All procedures were performed with the informed consent of the patients. Approval for the study was granted by the Local Ethics Committee (Approval date 02.07.2020, number 786).

RESULTS

The study population ($n = 300$) was divided into two groups as survivor (Group 1; $n = 206$, 68.7%) and (Group 2; $n = 94$, 31.3%) groups. The mean total follow-up period for both groups was 125.39 ± 73.09 days and 31.33 ± 33.05 days for the nonsurvivor group. The results of this study showed that 206 (68.7%) patients were discharged uneventfully (survivor group). In our study, the median (interquartile range [IQ]) age of the patients was 62 (48–72) years in the survivors and 70 (61–80) years in the nonsurvivors ($P < 0.001$) [Table 1].

The presence of AHT, DM, CAD, HF, and gender distribution did not show any statistically significant difference between the two groups. The presence of CRD (patients with GFR <30), COPD, pulmonary infiltration, and the median age was statistically significant between the two groups [Table 1]. There was also no statistically significant difference regarding the use of hydroxychloroquine (Group 1: $n = 192$ (93%); Group 2: $n = 87$ (93%), $P = 0.603$) and macrolide (azithromycin) (Group 1: $n = 130$ (63%); Group 2: $n = 60$ (64%), $P = 0.815$) as QT-prolonging medications used in COVID-19 treatment [Table 1].

A statistically significant difference was detected between the two groups regarding mean LVEF, white blood cell (WBC), lymphocyte (LYM) count, hemoglobin (Hb), and platelet (PLT) counts, peak D-dimer values and peak TI [Table 2].

Table 1: Comparison of demographic and clinical features of the two groups

Variable	Survivors (Group 1), <i>n</i> (%)	Nonsurvivors (Group 2), <i>n</i> (%)	<i>P</i>
Female gender	82 (39.8)	42 (45)	0.426
Age (years), median (IQR)	62 (48-72)	70 (61-80)	<0.001
AHT	102 (49)	54 (57)	0.202
DM	54 (26)	32 (34)	0.164
CAD	54 (26)	31 (33)	0.228
HF	26 (13)	16 (17)	0.308
COPD	33 (16)	24 (25)	0.051
CRD (GFR <30 ml/min/1.73 m ²)	29 (14)	30 (32)	0.001
Presence of pulmonary infiltration	4 (2)	27 (29)	<0.001
Macrolide usage (azithromycin)	130 (63)	60 (64)	0.815
Hydroxychloroquine usage	192 (93)	87 (93)	0.603

GFR: Glomerular filtration rate, COPD: Chronic obstructive pulmonary disease, CRD: Chronic renal disease, AHT: Arterial hypertension, DM: Diabetes mellitus, CAD: Coronary arterial disease, HF: Heart failure, IQR: Interquartile range

Table 2: Comparison of laboratory features in the two groups

Variable	Median (IQR)		<i>P</i>
	Survivors (Group 1)	Non-survivors (Group 2)	
LVEF (%)	50 (35-60)	60 (40-60)	0.095
WBC (/L)	7495 (5412-9745)	11,980 (7795-16,860)	<0.001
NEU (/L)	4750 (3272-6680)	10,060 (6700-14,932)	<0.001
LYM (/L)	1495 (1060-2115)	910 (527-1335)	<0.001
Hb (g/dL)	12.5 (10.9-14.3)	10.8 (8.9-12)	<0.001
PLT ($\times 10^3$ /L)	227 (18-293.5)	241.5 (171-355)	0.440
CRP (mg/dL)	23 (6.7-69)	101 (38.5-178)	<0.001
PDD (mcg/L)	349 (177-937)	2558 (985-6253)	<0.001
Peak TI (ng/L)	0 (0-0)	0.34 (0-1.27)	<0.001

LVEF: Left ventricular ejection fraction, WBC: White blood cell, NEU: Neutrophil, LYM: Lymphocyte, Hb: Hemoglobin, PLT: Platelet, CRP: C-reactive protein, TI: Troponin I, PPD: Peak D-dimer, SD: Standard deviation, IQR: Interquartile range

The comparison of mean basal HR, PR, and QRS duration at hospital admission, control HR, control PR, control QTc duration, change in QTc duration, presence of ≥ 60 msn QTc prolongation, the presence of ST segment change during hospitalization also showed a significant difference between the groups [Table 3]. However, in our population, no arrhythmia associated with QT prolongation was detected in any patients.

The univariate analysis was performed to estimate prognosis due to COVID-19 pneumonia. The GFR <30, age >65 years, WBC ($10-20, 20-30, \geq 30 \times 10^3$ /L), neutrophil (NEU) ($\leq 1, > 5 \times 10^3$ /L), LYM ($\leq 1 \times 10^3$ /L); CRP (≥ 50 mg/dL), D-dimer (≥ 1000 mcg/L), TI (≥ 0.1 ng/mL); extension of lung infiltration $\geq 50\%$ in TCT, basal HR ≥ 100 /min during admission, control HR ≥ 100 /min; control QTc ≥ 500 ms; the presence of ≥ 60 ms QTc prolongation and presence of ST change during hospitalization found to be different between the groups. But on multivariate regression analysis, only NEU $> 5 \times 10^3$ /L, LYM $\leq 1 \times 10^3$ /L, CRP ≥ 50 mg/dL, D-dimer ≥ 1000 mcg/L, extension of lung infiltration $\geq 50\%$ in TCT, and presence of QTc prolongation ≥ 60 ms during hospitalization were found to be associated with worse prognosis [Table 4].

DISCUSSION

In this study, QTc prolongation ≥ 60 msn during hospitalization was found to be the most valuable ECG parameter in COVID-19 patients. This prolongation was not found to be associated with the usage of HCQ ($P = 0.603$) between the two groups.

Cardiac involvement in COVID-19 can be categorized into five types: (1) cardiac injury (mainly due to ischemia or myocarditis), (2) cardiac arrhythmia, (3) new-onset or worsening of heart failure, (4) thromboembolic disease, and (5) cardiac abnormalities induced by COVID-19 treatment.^[11] As a cost-effective tool, ECG is one of the best methods that determine cardiac involvement and the effects of medications in patients who suffer from COVID-19. Furthermore, it offers the possibility of remote evaluation.^[12] Current data regarding the evaluation of ECG changes during hospitalization in patients with COVID-19 are limited. In this study, ECG evaluation was made in 300 patients who were hospitalized due to COVID-19 pneumonia.

There are mainly four proposed mechanisms regarding cardiac involvement and ECG changes: (1) ACE2 is highly expressed in heart tissue, and therefore, SARS-CoV2 can cause direct cardiac damage, (2) Systemic hypoxemia due to COVID-19 may lead to myocardial injury, (3) Systemic inflammatory response may cause myocardial involvement, and (4) ECG changes may be associated with the side-effects of COVID-19 treatment (such as QT prolongation due to chloroquine and azithromycin).^[13] Cardiac involvement in patients with COVID-19 is reflected on ECG as QRS or ST segment changes, QT or PR prolongation, and atrial or ventricular arrhythmias. Furthermore, nonspecific ECG findings have been reported in

Table 3: Comparison of electrocardiogram parameters and changes in the two groups

Variable	Median (IQR)		P
	Survivors (Group 1)	Nonsurvivors (Group 2)	
Basal HR during admission (/mn)	85 (74-98)	96 (84-115)	<0.001
Basal QRS during admission (msn)	88 (80-98)	82 (76-98)	0.010
Basal QTc during admission (msn)	428 (409-450)	436 (415-455)	0.298
Control QRS during hospitalization (msn)	92 (82-100)	90 (78-110)	0.547
QTc during hospitalization (msn)	435 (415-457)	479 (452-499)	<0.001
QTc ≥500 msn during hospitalization, n (%)	10 (5)	23 (25)	<0.001
QRS duration change during hospitalization (msn)	2 (-2-6)	3 (-2-16)	0.051
QTc duration change during hospitalization (msn)	5 (-7-20)	40 (24-64)	<0.001
QTc longation ≥60 msn during hospitalization, n (%)	4 (2)	30 (32)	<0.001
Presence of ST segment change during hospitalization, n (%)	68 (33)	63 (67)	<0.001

ECG: Electrocardiogram, HR: Heart rate, PR: PR interval duration, QRS: QRS interval duration, QTc: Corrected QT interval duration, IQR: Interquartile range

Table 4: Comparison of independent predictors to estimate the mortality due to coronavirus disease 2019 pneumonia

Variable	Univariate analysis			Multivariate logistic regression analysis*				
	HR	95% CI	P	HR	95% CI	P		
COPD	1.562	0.982	2.485	0.06	1.758	0.726	4.256	0.211
GFR <30 ml/min/1.73 m ²	2.387	1.545	3.688	<0.001	1.593	0.678	3.744	0.285
Age >65 (years)	3.099	1.840	5.217	<0.001	1.859	0.824	4.193	0.135
LVEF <40%	1.949	0.643	5.908	0.24				
WBC (RR: <10×10 ³ /L)								
10-20×10 ³ /L	3.967	2.551	6.171	<0.001				
20-30×10 ³ /L	4.009	1.923	8.356	<0.001				
≥30×10 ³ /L	9.412	3.326	26.639	<0.001				
NEU (RR: 1-5×10 ³ /L)								
≤1×10 ³ /L	13.415	3.689	48.788	<0.001	1.562	0.160	15.256	0.701
>5×10 ³ /L	4.187	2.068	8.447	<0.001	3.105	1.247	7.731	0.015
LYM (RR: 1-3×10 ³ /L)								
≤1×10 ³ /L	3.494	2.304	5.297	<0.001	3.809	1.738	8.347	0.001
Hg change (for decrease of one unit) (g/dL)	1.002	0.999	1.004	0.25				
CRP 500 (mg/dL)	1.012	1.009	1.016	<0.001	1.009	1.004	1.015	0.002
D-dimer ≥1000 (mcg/L)	5.990	3.781	9.492	<0.001	3.384	1.557	7.352	0.002
TI ≥0.1 (ng/mL)	6.317	4.126	9.671	<0.001				
Extension of lung infiltration on TCT ≥50%	8.917	5.573	14.268	<0.001	9.699	2.658	35.383	0.001
Basal HR >100 (/min)	2.727	1.609	4.622	<0.001	1.153	0.467	2.847	0.757
Basal QRS ≥120 (msn)	0.827	0.383	1.787	0.63				
Control QTc ≥500 msn during hospitalization	3.467	2.161	5.565	<0.001				
Presence of ≥60 msn QTc prolongation	6.192	3.977	9.639	<0.001	12.360	4.238	36.042	<0.001
Presence of ST change	3.193	2.075	4.915	<0.001	0.984	0.439	2.204	0.969

*Therefore, due to the significant correlation between WBC and neutrophil values. Presence of QTc ≥60 msn prolongation during hospitalization and basal QTc ≥500 msn at admission. D-dimer and TI values, the variables of QTc ≥500 msn during hospitalization, TI and WBC levels were not put in the multivariate logistic regression model. HR: Heart rate, QRS: QRS interval duration, QTc: Corrected QT interval duration, GFR: Glomerular filtration rate, COPD: Chronic obstructive pulmonary disease, LVEF: Left ventricular ejection fraction, WBC: White blood cell, NEU: Neutrophil, LYM: Lymphocyte, CRP: C-reactive protein, TI: Troponin I, TCT: Thoracic computed tomography, CI: Confidence interval, HR: Hazard ratio, RR: Reference range, Hg: Hemogram

COVID-19 associated with hypoxia or inflammatory damage. In addition, tachycardia, which is defined as >90–100/bpm HR, has been associated with mortality and worsening of COVID-19.^[14] Consequently, ECG changes tend to be associated with worse prognosis in COVID-19 patients.

The mortality rate of the present study was similar to data reported by Huang *et al.*^[15] Consistent with previous studies, mortality was higher in older patients. This is probably because

the hospitalized population was predominantly composed of old patients with worse clinical conditions.^[4]

Various studies have shown that DM, AHT, CAD, obesity, CKD, and COPD are the most common comorbid diseases observed in COVID-19 patients and are known to be associated with worse COVID-19 outcomes.^[16-19] Consistent with previous studies, the most common comorbid diseases in the current study were AHT, DM, CAD, HF, and COPD, in decreasing

order [Table 1]. A statistically significant association was only determined between CRD and mortality ($P < 0.001$) [Table 1].

The major abnormal laboratory findings in cases with COVID-19 include elevated CRP, lymphopenia, leukopenia, and thrombocytopenia.^[20] Reade *et al.*^[21] reported that COVID-19 patients with low hemoglobin are associated with high mortality rates. Hence, several laboratory parameters, such as leukocytosis, elevated cardiac troponins as a marker of cardiac injury, thrombocytopenia, neutrophilia, lymphopenia, and high CRP levels, predict clinical worsening and poor survival in patients with COVID-19.^[14,22,23] Consistent with these data, the WBC, NEU, CRP, peak D-dimer, and peak TI levels were found to be significantly higher, and LYM, Hb, and PLT levels were found to be significantly lower in Group 2 compared to Group 1 in the current study [Table 2]. In the univariate analysis, TI level was found to have a statistically significant association with mortality, whereas LVEF values were similar between the two groups. This may indicate that early myocardial injury shown by significant TI increase could not be detected by LVEF [Table 4].

Li *et al.*^[24] showed a relationship between lesion extension in TCT scans and clinical deterioration of COVID-19. Consistent with this finding, the current study showed that $\geq 50\%$ lung infiltration in TCT scans was significantly associated with increased mortality [Table 4]. This variable has been considered valuable for the determination of the severity of pulmonary involvement and disease progression.

There are limited data regarding ECG changes and increased mortality. Wang *et al.*^[25] resented abnormal ECG in most of the COVID-19 patients and detected that ST-T change was the most important clinical evidence in the abnormal ECG. Pavri *et al.*^[26] showed that 50.7% of their COVID-19 patients

had PR interval change and increased HR. Angeli *et al.*^[9] declared that ST-T abnormality was present in 30% of the COVID-19 patients in their study. Santoro *et al.* reported QT prolongation in some of their COVID-19 population, and Jain *et al.*^[27,28] stated that QT prolongation can be caused by COVID-19 medications.

In light of these data, we aimed to determine the ECG parameters that could affect disease surveillance, such as the extension of lung involvement in TCT and laboratory parameters. In our study, tachycardia at admission, QRS duration change, ST segment changes, and QT duration prolongation showed a statistical significance on univariate analysis.

The current study showed that the presence of ≥ 60 msn QTc prolongation during hospitalization (HR = 12,360; 95% confidence interval [CI]: 4238–36,042; $P \leq 0.001$), extension of $\geq 50\%$ lung infiltration in TCT (HR = 9,699; 95% CI: 2658–35,383; $P = 0.001$), D-dimer ≥ 1000 mcg/L (HR = 3384, 95% CI: 1557–7352; $P = 0.002$), CRP ≥ 500 mg/dL (HR = 1009; 95% CI: 1004–1015; $P = 0.002$), LYM $\leq 1 \times 10^3$ /L (HR = 3809; 95% CI: 1738–8347; $P = 0.001$), NEU $> 5 \times 10^3$ /L (HR = 3105; 95% CI: 1247–7731; $P = 0.015$) were independent predictors for mortality in multivariate logistic regression analysis [Table 4 and Figure 1].

Study limitations

The main limitation of our study was that it was a retrospective and single-center study.

CONCLUSION

In conclusion, to the best of our knowledge, this is the first study that investigates the relationship between ECG changes

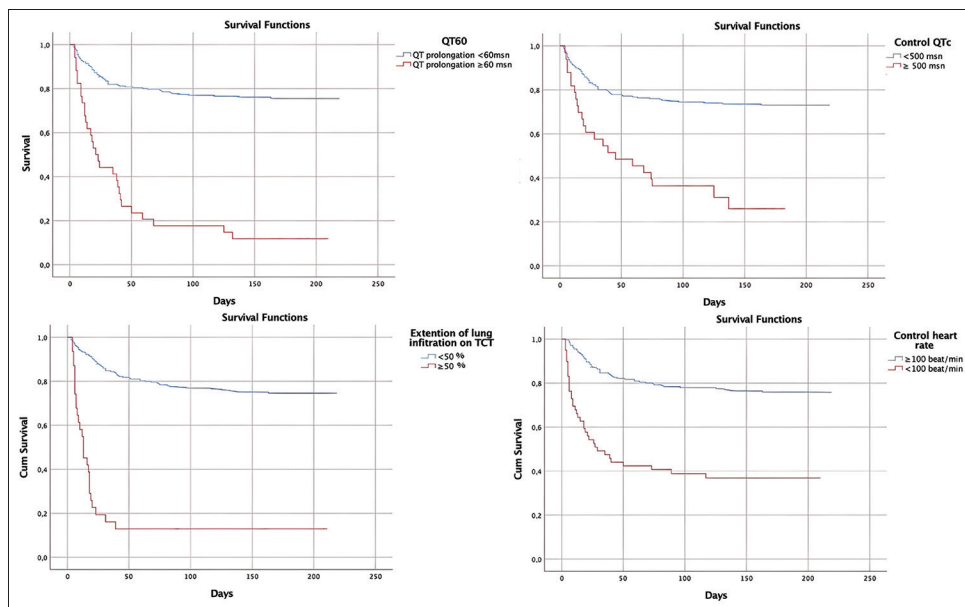


FIGURE 1: CONTROL QTc, QTc PROLONGATION, CONTROL HEART RATE, AND THORACIC COMPUTED TOMOGRAPHY FINDINGS ASSOCIATED WITH MORTALITY AND SURVIVAL. QTc: CORRECTED QT INTERVAL DURATION

and laboratory parameters and lung involvement severity in TCT in patients with COVID-19. We have shown that the presence of ≥ 60 msn QTc prolongation during hospitalization was the most valuable parameter to predict the prognosis and had a significant association with $\geq 50\%$ lung involvement in TCT in patients under anti-COVID-19 therapy. Therefore, close monitoring of ECG, especially QTc prolongation ≥ 60 msn during the hospital stay, is important both in terms of treatment planning and interpretation of disease progression.

Declaration of patient consent

All procedures are performed after the patients' verbal or written consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Outcomes of Aortic Balloon Valvuloplasty in Newborns: A Single-Centre Experience

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Abstract

Introduction: Critical or severe aortic stenosis in new-borns is a condition that requires rapid intervention. Aortic balloon valvuloplasty (ABV) is a method of choice that has been successfully performed since 1983. **Aims:** This study was conducted to explore the experiences of our centre. **Study Design:** The data of ABV performed on new-borns ($n = 52$) between 2007 and 2020 were retrospectively analysed to evaluate follow-up of the cases. **Materials and Methods:** Patients were divided into 4 groups according to procedural immediate results. **Results:** Left ventricular endocardial fibroelastosis and left ventricular systolic dysfunction were detected in 18 (34.6%) and 19 (36.5%) patients, respectively and there was a significant association between fibroelastosis and left ventricular dysfunction ($P < 0.05$). The preprocedural echocardiographic mean gradient was significantly lower in the unsuccessful group ($P < 0.41$). The mean hospital stay day was shorter in the group with optimal results without statistical significance ($P = 0.055$). Immediate inadequate results after the procedure were detected as a major risk for re-intervention. Re-intervention was required in one-fifth of the patients and the most common cause was aortic stenosis. The risk factors of mortality were found to be associated with the disease itself such as ventricular dysfunction, being critical aortic stenosis instead of procedural reasons. **Conclusion:** ABV is an effective method and as left ventricular dysfunction and critical aortic stenosis are risk factors of mortality, preprocedural evaluation, and quick intervention are essential.

Keywords: Aortic balloon valvuloplasty, critical aortic stenosis, new-borns

INTRODUCTION

Congenital valvular aortic stenosis constitutes 3%–6% of congenital heart diseases. It occurs more frequently in males than in females, by a ratio between 3:1 and 5:1. Of the patients, 15%–20% have accompanying patent ductus arteriosus, aortic coarctation, and ventricular septal defect.^[1]

Critical aortic stenosis is defined as the condition in which there is dependence on the ductus arteriosus for the adequate continuation of the systemic circulation and prevention of low cardiac output syndrome. In the case of critical aortic stenosis, prostaglandin E1 infusion therapy should be initiated

and palliative procedures should be performed as soon as possible.^[2]

Palliation strategies consisting of aortic balloon valvuloplasty (ABV) or surgical valvotomy are equally effective in terms of survival. However, percutaneous ABV has been preferred by many centres since it was first carried out in 1983. In this procedure, through stiff guide-wires, low-pressure balloon catheters with a width of a maximal 90% of the

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aortic annulus are inflated. Subsequently, hemodynamic, angiographic, and echocardiographic evaluations are performed to assess the immediate result of the procedure. If it is necessary, the procedure has to be repeated with bigger balloons.^[3] Determining factors of outcomes consist of aortic valve morphology, the severity of the stenosis, left ventricular structure and function, and the degree of regurgitation after valvuloplasty. The most common complication of the ABV is aortic regurgitation (AR) but a severe degree of regurgitation is rarely seen.^[4]

ABV or surgical valvotomy decision varies according to the experience and preference of the centres as both methods have a similar effect in decreasing the aortic valve gradient. There was no statistically significant difference between these two methods in terms of the need for re-intervention.^[5] Moreover, ABV procedure as a first-line palliative therapy has been shown to avoid or postpone aortic valve surgery.^[6] In our institution, we have preferred to perform ABV since 2007. The current study aims to evaluate postprocedural outcomes and long-term follow-up of the cases.

MATERIALS AND METHODS

In the current study, the medical records of new-borns with valvular aortic stenosis who were diagnosed in our hospital between 2007 and 2020 were retrospectively analysed ($n = 52$). Inclusion criteria comprised being younger than 1 month old and having critical or severe aortic valve stenosis. Those with additional congenital heart disease, except hemodynamically insignificant shunt lesions and patients who were not eligible for biventricular repair, were excluded.

The data were obtained from patients' medical history records including age, gender, weight, the use of prostaglandin infusion therapy before the procedure, the presence of inotropic therapy, preprocedural serum lactate level, preprocedural PH value, duration of the intubation, neonatal intensive care unit stay, the reason and time of the reintervention and the early and late complications of the ABV.

Echocardiographic evaluations were performed using Philips IE33 colour ultrasound systems (Philips, Bothell, Seattle, WA, USA) with S8-3, and S5-1 sector array transducers were used for TTE examination. The probes had a frequency of 3–8 MHz, and 1–5 MHz, respectively. Through the echocardiography, aortic valve peak and mean gradient, aortic annulus diameter, valve morphology, the left ventricular systolic functions, the presence of the fibroelastosis and/or the left ventricular hypertrophy and prepost procedural valves regurgitations were recorded. The aortic annulus diameter was measured by two-dimensional echocardiography in early systole and angiography in the left ventricular mid-systolic phase. Patients with an ejection fraction of <58% were determined to have left ventricular systolic dysfunction. Aortic valve regurgitation was graded using the standard methods according to the American Society of Echocardiography as none/trace (0), mild (1), moderate (2), or severe (3).^[7]

Ethical statement

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. This study has been approved by the TUEK department (Decision date: August 26, 2021 and decision number: 2021/8-1). We declare that informed consent from each patient was provided.

The procedure

Cardiac catheterization was performed in patients who had transthoracic echocardiographic continuous flow doppler average gradient of ≥ 50 mmHg in the aortic valve, ST-T wave change in patients with gradient <50 mmHg and presence of left ventricular systolic dysfunction. The access way of ABV was either the femoral artery or femoral vein in case of the presence of patent foramen ovale. Prophylactic heparin (50–100 units/kg (intravenous) was given to all patients who underwent femoral artery intervention during the procedure. Tyshak (NuMED) low-profile balloon was used in all patients. The balloon valvuloplasty procedure was initiated with a balloon/annulus diameter ratio of 0.8–0.9. If necessary, the procedure was continued with the balloon diameter/annulus diameter ratio of 1–1.2, considering the residual transvalvular gradient and the grade of AR. The valvular aortic gradient was measured as a peak and mean gradient by continuous flow Doppler echocardiography and systolic valvular gradient during catheterization.

The patients were divided into 4 groups according to postprocedural results including invasive aortic valvular gradient and the presence and degree of the AR. The groups were determined as follows: Group 1, Optimal: gradient <35 mmHg, and no AR. Group 2, Adequate with mild AR: gradient <35 mmHg and trivial or mild AR. Group 3, Adequate with prominent AR: gradient <35 mmHg and moderate to severe AR. Group 4, Inadequate: gradient >35 mmHg with or without AR. The success criteria for aortic valvuloplasty were determined to be present in groups 1 and 2, specifically postprocedural gradient below 35 mmHg and no prominent AR.

Heparin and tissue plasminogen activator were used in the treatment of patients in which disturbed circulation of the femoral artery by doppler ultrasonography were detected. The loading dose of heparin was 50 units/kg (intravenous), and the maintenance dose was 20 units/kg/h. The dosage range of the tissue plasminogen activator was between 0.1 and 0.5 mg/kg/h.

Early hospital mortality was specified at up to 72 h postprocedure, while total mortality at up to the time of discharge (range 2–43 day). Long-term mortality was defined as any time after discharge.

Statistical analysis

Statistical evaluations were made using the “IBM SPSS Statistics for Windows, version 19 (IBM Corp., Armonk, N.Y., USA)” program. Independent-samples *t*-tests were

used for the comparison of normally distributed numerical data, and the Chi-square test and Fisher's Exact Test were used for the analysis of categorical data. The Pearson test was used for the analysis of normally distributed numerical data and the Spearman test was used for those that did not show normal distribution. As descriptive statistics, the mean, standard deviation of continuous variables, and percentages of discontinuous variables were specified. The Kruskal-Wallis test was used to identify differences between groups. The Kaplan-Meier method was used to estimate freedom from each of the specified endpoints, stratified by age, over the available follow-up time. Binary logistic regression analysis was used to detect mortality-related factors. The statistical significance limit was accepted as $P < 0.05$.

RESULTS

According to demographic characteristics, 17.3% of the patients were female and 82.7% were male. The average age and body weight of the patients at the time of the catheterization were 14.4 ± 18.1 ; 3.254 ± 0.6 , respectively.

It was detected that 26.9% of the patients were intubated and 44, 3% were being given inotropic therapy and 28.8% of patients had acidosis before the procedure.

The mean of aortic valve maximal and average gradient were found 61.75 ± 18 and 34.3 ± 13.24 respectively in preprocedural echocardiographic evaluation. Aortic coarctation and aortic arch hypoplasia were seen in 17.4% and 3.8% of patients, respectively. Left ventricular endocardial fibroelastosis and left ventricular systolic dysfunction were detected in 18 (34.6%) and 19 (36.5%) patients, respectively. There was a significant association between fibroelastosis and left ventricular dysfunction ($P < 0.05$). While 8 (15, 4%) patients had mild preprocedural AR, moderate-severe AR was not detected in any of the patients. The preprocedural clinical and echocardiographic characteristics of the patients are given in Table 1.

Aortic valve morphology structure was shown normal only in 2 (3.8%) of the patients and dysplasia was seen in 21 (40.4%) of the patients. The most common aortic valve type was bicuspid. The types of overall aortic valves are shown in Figure 1.

The ABV success rate was 70%. Moderate to severe AR after the procedure was found in 8 (15.5%) of the patients. While

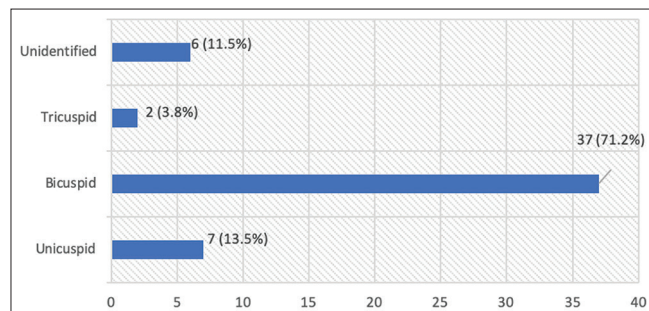


Figure 1: The type of aortic valve morphology (n, %)

7 (13.5%) of them belonged to group 3, 1 (2%) was in group 4. ABV results by groups are given in Table 2.

In the current study, we found no statistically significant differences in procedural results in terms of valve morphology and dysplasia, left ventricular dysfunction, fibroelastosis, and the need for invasive ventilation. Likewise, there was no association between the balloon-to-annulus ratio and the decrease in the gradient ($P > 0.05$). Additionally, the groups were compared according to the mean of age, weight, mechanical ventilation duration, the length of stay in the intensive care unit, echocardiographic aortic average and maximal gradient, echocardiographic aortic annulus Z score, ejection fraction levels, echocardiographic and angiographic balloon to annulus ratio, angiographic peak to peak gradient and preprocedural left ventricular pressure. It was demonstrated that there were no differences in terms of the parameters listed above except for the echocardiographic mean gradient. The preprocedural echocardiographic mean gradient was significantly lower in group 4 than in group 3 ($P < 0.41$). Moreover, although it was not statistically significant, it was

Table 1: Preprocedural demographic, clinical and echocardiographic characteristics of the patients

Characteristics	Results
Demographic and clinical findings	
Female/male, n (%)	9 (17.3)/43 (82.7)
Age at the time of the catheterization (days), mean±SD	14.4±18.1
Body weight (kg), mean±SD	3.254±0.6
Inotropic therapy, n (%)	23 (44.3)
Prostaglandin E 1 therapy, n (%)	15 (28.8)
Invasive ventilation, n (%)	14 (26.9)
Metabolic acidosis, n (%)	15 (28.8)
Systolic blood pressure (mmHg), mean±SD	68±12
Diastolic blood pressure (mmHg), mean±SD	41±8.9
Mean blood pressure (mmHg), mean±SD	51±10.7
Echocardiographic findings, mean±SD	
AoV maximal gradient (mmHg)	61.75±18
AoV average gradient (mmHg)	34.3±13.24
Aortic annulus diameter (mm)	5.92±1.03
Balloon-to-annulus ratio	1.01±0.15
Other heart diseases, n (%)	
Aortic coarctation	9 (17.4)
Aortic arch hypoplasia	2 (3.8)
Mitral valve stenosis	2 (3.8)
Left ventricular hypoplasia	2 (3.8)
Ventricular septal defect	4 (7.7)
Atrial septal defect	6 (11.6)
Endocardial fibroelastosis, n (%)	18 (34.6)
Left ventricular hypertrophy, n (%)	21 (40.4)
Left ventricular systolic dysfunction, n (%)	19 (36.5)
Mild AR, n (%)	8 (15.4)
Moderate-severe AR, n (%)	None
Ejection fraction, mean±SD	61.3±17.88
Fractional shortening, mean±SD	34.5±11.15

SD: Standard deviation, AR: Aortic regurgitation, AoV: Aortic valve

Table 2: Aortic balloon valvuloplasty results by groups

	Group 1	Group 2	Group 3	Group 4
n (%)	14 (26.9)	23 (44.2)	8 (15.4)	7 (13.5)
The mean of postprocedural invasive aortic gradient (mmHg)	22.14±9.69	19.96±8.99	25.63±10.48	38.0±1.67
Postprocedural AR, n (%)				
Trivial-mild	-	23 (44.2)	-	6
Moderate to severe	-	-	7 (13.5)	1 (2)
Total	52 (100)	52 (100)	52 (100)	52 (100)

AR: Aortic regurgitation

Table 3: Procedural details and outcomes of the study group

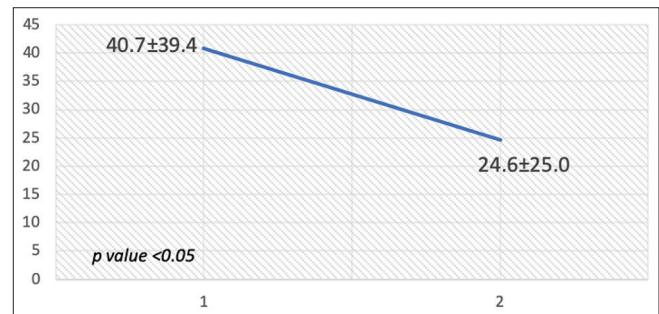
Characteristics	Results
Angiographic findings, mean±SD	
Preprocedural peak systolic gradient (mmHg)	68.57±20.52
Postprocedural peak systolic gradient (mmHg)	23.57±10.38
Aortic annulus diameter (mm)	6.7±0.97
Balloon diameter (mm)	5.9±0.97
Balloon to annulus ratio	0.84±0.11
The success of the procedure, n (%)	7 (13.5)
Re-intervention, n (%)	11 (21.2)
Mean re-intervention time (months), range	8.69±14.3 (0.3-46)
Mean follow-up time (years), range	5 (0.5-11.7)
Median intensive care length of stay (day), range	6 (2-43)
Peripheral arterial thrombosis, n (%)	9 (17.3)
Supraventricular tachycardia (adenosine responded), n (%)	1 (1.9)
AoV surgery types, n (%)	
AVR	1 (1.9)
AoV repair	2 (3.8)
Ross procedure	1 (1.9)
Sub-valvular resection	1 (1.9)
Mortality, n (%)	
Early hospital mortality	6 (11.5)
Total hospital mortality	11 (21.2)
Long-term mortality	0

SD: Standard deviation, AoV: Aortic valve, AVR: AoV replacement

seen that the mean length of stay in the intensive care unit was shorter in group 1 than in group 2 ($P = 0.055$).

The decrease in the patients' serum lactate level after the procedure as evidence of adequate perfusion was statistically significant ($P < 0.05$) [Figure 2]. The mean of neonatal intensive care unit stay was 9.5 ± 9.4 days and the intubation duration was 5.4 ± 6.3 h. Data related to procedure and follow-up are given in Table 2.

Re-intervention was required in 11 patients (21.2%) at follow-up. The mean of re-intervention time was 8.69 ± 14.3 months (range 0.3-46). The Kaplan-Meier estimates are shown in Figure 3. The re-intervention cause was aortic stenosis in 10 patients. The second ABV procedure was performed on all 11 patients as an interventional method. However, five of these patients (9.6%) required further surgical procedures. The types of surgery were as follows: one patient

**Figure 2:** The mean of the pre-and postprocedural serum lactate level (mg/dl)

underwent aortic valve replacement, 2 patients underwent aortic arch repair, one patient underwent Ross procedure, and one patient underwent sub-valvular resection for additional discrete membrane. The data relating to the procedures and follow-up are given in Table 3.

According to Cox regression analysis, the re-intervention rate was found to be associated with early results of ABV. Group 4 (inadequate results with the gradient >35 mmHg) was found to have a significantly high rate of re-intervention ($P = 0.045$) [Figure 4]. However, there was no association between valve morphology or dysplasia and the re-intervention rate.

Peripheral arterial thrombosis was seen in 9 (17.3%) of the patients in those who underwent arterial intervention. Furthermore, serious complications that occurred during hospitalization in the neonatal intensive care unit were as follows: 5 patients had initial renal failure followed by multi-organ failure, 3 had heart failure, 2 had a pulmonary haemorrhage, 1 had sepsis, 1 had thrombocytopenia and intracranial haemorrhage.

The early and total hospital mortality rate was 11.5 and 21.2%, respectively. We did not have long-term mortality. Left ventricular dysfunction, the presence of fibroelastosis, and critical aortic valve stenosis were risk factors for mortality [Table 4].

DISCUSSION

Critical congenital heart disease including critical aortic stenosis is the most common reason for acute cardiac failure in new-borns and is responsible for up to 25% of fatalities

of new-born infants.^[2] Approximately one-third of the aortic valve stenosis requiring intervention in the new-born period is critical aortic stenosis.^[4,5] In our study, the rate of 28.8%, or approximately one-third of the patients was corresponding to the definition of critical aortic stenosis similar to the literature.

When diagnosing valvular aortic stenosis by echocardiography, other accompanying lesions should be kept in mind such as aortic coarctation, aortic arch hypoplasia, mitral valve stenosis, and left ventricular hypoplasia. In accordance with the literature, the most common obstructive lesion associated with valvular aortic stenosis was aortic coarctation in the current study. Additionally, determining whether fibroelastosis is present or not is substantial because there was a significant association between fibroelastosis and left ventricular dysfunction ($P < 0.05$) similar to the literature.^[4,8,9]

In the current era, ABV is the method of choice for treating congenital valvular aortic stenosis by evolving with the development of new technologies and procedural techniques.^[6] Since the 1980s, the procedure's technical factors and associated outcomes have been studied and through them, balloon-to-aortic annulus ratio >1 , younger age, and unicuspid or thickened valve morphology were assigned as risk factors. Additionally,

new-borns who underwent ABV were found to have higher rates of complications and mortality.^[10-14]

The association between valve morphology and acute procedural outcomes has been extensively studied in medical research. It was postulated that the radial dilating force exerted by the inflation of the balloon usually tears the weakest part of the valve. While in the bicuspid aortic valve, the balloon dilatation tears the fused commissures with adequate relief of obstruction and some valvular regurgitation, in the unicuspid valve, balloon dilatation tends to split the leaflet opposite the patent commissure with only partial relief of obstruction and significant valvular regurgitation.^[1] However, studies have shown different results regarding this association. In a study, compared with other valve morphologies, patients with bicuspid aortic valves experienced diminished freedom from re-intervention, death, or transplant.^[11] Another study found no significant association between valve morphology and postprocedural diminished gradient, the presence and degree of AR, and the need for re-intervention.^[4] Vergnat *et al.*^[3] reported that valve morphology determined the need for reintervention and replacement in older children. In

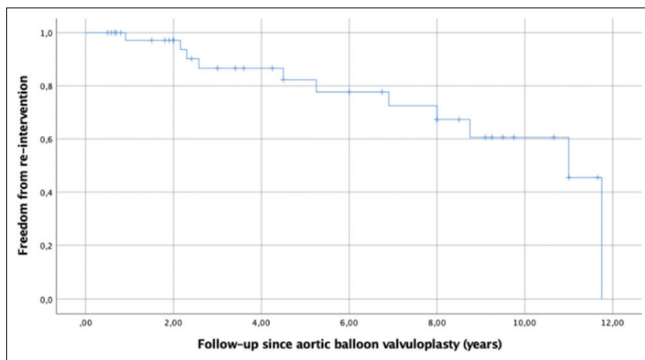


Figure 3: Kaplan Meier freedom from re-intervention is 73, 2% at 12 years after ABV. ABV: Aortic balloon valvuloplasty

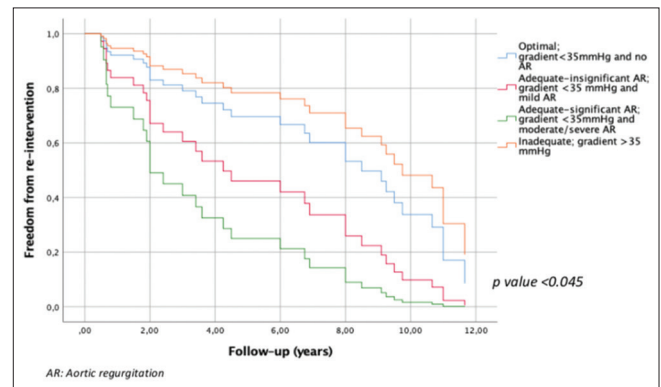


Figure 4: The re-intervention rate according to groups

Table 4: Logistic regression analysis of risk factors for mortality

	β	SE β	Wald's χ^2	df	P	e β (OR)
Age at the time of catheterization	-0.157	0.101	2.411	1	0.120	0.854
Weight at the time of catheterization	0.000	0.001	0.431	1	0.511	1000
Left ventricular dysfunction	3.571	1.115	10.265	1	0.001	35.556
Fibroelastosis	1.560	0.719	4.724	1	0.030	4.773
Dysplastic valve	0.069	0.669	0.011	1	0.918	1.071
Prostaglandin use (critical aortic stenosis)	3.268	0.898	13.242	1	0.000	26.250
Preprocedural echocardiographic AoV peak gradient	-0.002	0.019	0.013	1	0.908	0.998
Preprocedural echocardiographic AoV mean gradient	-0.024	0.028	0.707	1	0.401	0.976
Maximum balloon-to-aortic ratio	-0.521	0.407	1.636	1	0.201	0.594
Postprocedural immediate results, grouped						
Optimal	-0.642	0.808	0.631	1	0.427	0.526
Adequate-insignificant AR	-0.182	1.008	0.033	1	0.857	0.833
Adequate-significant AR	0.000	1.025	0.000	1	1.000	1.000
Inadequate	-0.916	0.592	2.399	1	0.121	0.400

AR: Aortic regurgitation, SE β : Standard error of β , OR: Odds ratio, AoV: Aortic valve

the current study, we did not demonstrate any association between valve morphology with neither postprocedural success rates nor re-intervention.

Angiography has been traditionally used for the measurement of the aortic valve annulus before the procedure. However, it should be kept in mind that angiographic methods may be more problematic than echocardiography due to possible overestimation. Therefore, using both echocardiographic and angiographic measurements of the aortic valve annulus is recommended. The balloon-to-aortic annulus ratio of >1.1 measured by echocardiography is associated with a greater proportion of significant AR development.^[14] In the current study, the echocardiographic mean balloon to-annulus ratio was detected at 1.01 ± 0.15 in line with the literature. Additionally, recent studies reported that balloon to aortic ratio was not associated with AR when considering the maximum ratio, similar to our study.^[4,15] We measured both echocardiographic and angiographic aortic annulus and did not exceed the maximum balloon aortic ratio.

The criteria for determining the success of the procedure differ in studies. Our success rate of the ABV was 71% and optimal, adequate, and inadequate results were 27%, 59%, and 14%, respectively. In a study conducted by Boe *et al.*^[6], patients were divided into 3 groups by ABV results; optimal; gradient <35 mmHg and no AR, adequate; gradient <35 mmHg and mild AR and inadequate; gradient >35 mmHg. According to this classification, the rate of optimal, adequate, and inadequate results were found 34.5%, 35.5%, and 30% respectively and the procedural success rate was reported as 70%. Varan *et al.*^[4] considered that moderate and less AR after ABV were successful and with reference to this the success rate was detected to be 90%. In the current study, there was only one case that had severe AR in the adequate-significant AR group. If the patients who belong in the inadequate group are excluded, the success rate can be considered 86%. Vergnat *et al.*^[3] defined the inadequate results as >50 mm Hg echocardiographic peak gradient and/or greater than mild regurgitation and their success rate was 80%. In another study conducted by Torres *et al.*^[16], it was demonstrated that acute procedural success of ABV was evenly distributed, with one-third optimal, one-third adequate, and one-third inadequate results.

In the current study, there were no factors affecting the procedural results. Similarly, Boe *et al.*^[6] reported that there were no significant factors associated with unsuccessful ABV in patients with critical aortic stenosis when compared to noncritical aortic stenosis patients. However, prior cardiac catheterization, preprocedural higher peak systolic gradient, preprocedural valve regurgitation, the number of balloon inflations, and trainee presence were found to be factors significantly associated with ineffective results in noncritical aortic stenosis. Varan *et al.*^[4] also detected that the annulus diameter, valve morphology, balloon/annulus diameter ratio, reduction in gradient with valvuloplasty procedure, and aortic

annulus Z-score were not significantly different between the procedure related to mild-to-moderate AR and severe AR patients. However, Reich *et al.*^[17] demonstrated that a functional bicuspid aortic valve was an independent risk factor for the appearance of AR after valvuloplasty. Since our study group was limited to babies under 2 months, it can be suggested that valve structure does not affect the success of the procedure so early. Furthermore, as seen in the studies above, the studies that found factors affecting the procedure were those with noncritical aortic stenosis.

We found that the preprocedural echocardiographic mean gradient was lower in group 4 than in group 3. As known, patients with left ventricular dysfunction cannot create an adequate aortic valve gradient. This difference between group 3 and group 4 was thought to be due to the increasing gradient because of the improvement in left ventricular contraction when the stenosis was resolved after the procedure.

The incidence of moderate and severe AR is reported in the literature as 2.2%–29%.^[8,11,16,18] Furthermore, it was determined that this complication was more frequent in the neonates after ABV.^[8] Our results were similar to the literature with a rate of 15%.

In our study, the median intensive care length of stay was 6 days (range 2–43). In other studies, it was reported that the median hospital stay was 2.5 days (range 0–70)^[3] and the mean 16.9 day.^[6] Differences between studies may be related to postprocedural care.

The risk factors for re-intervention have been discussed in a multitude of studies. In the current study, the re-intervention rate was detected to be 17, 3% and it is associated with immediate outcomes of the procedure. Singh^[11] reported that being under 3 months of age and having immediate postprocedural peak gradient >30 mmHg are considered predictors of restenosis. According to a study conducted by Sullivan PM *et al.*^[8], neonatal age, additional left heart lesions, and preintervention aortic valve gradient were not associated with the risk of aortic valve replacement. These variables are associated with the risk of left ventricular outflow tract re-intervention. In accordance with previous studies, severe AR and recurrent aortic valve stenosis were the most important reasons for late surgical intervention in our study.^[4,8]

In case of inadequate results, it can be difficult to decide whether to continue the procedure or not. Sullivan *et al.*^[8] reported that patients with moderate or severe acute AR and a residual aortic stenosis gradient <30 mmHg after valvuloplasty had an approximately three times greater risk of requiring aortic valve replacement compared to those patients with a residual aortic stenosis gradient ≥ 30 mmHg and mild or no AR. In addition, they all underwent aortic valve replacement at 15 years of follow-up while aortic valve replacement was not required in 52% of cases with high residual gradient and mild or no AR. Varan *et al.*^[4] detected that aortic valve replacement was done in 45% and 6.2% of patients with

residual gradient <45 mmHg with moderate-severe AR and ≥ 40 mmHg with mild or no AR respectively. We detected that one patient who had moderate AR underwent aortic valve replacement in the follow-up at 8, 8 years. However, a higher number of cases and longer follow-up periods are needed to better determine what the physicians should do.

According to the literature, ABV has a significant risk in terms of valve dysfunction and aortic valve replacement in the long-term.^[8,11] In a study conducted with new-borns, Sullivan *et al.*^[8] reported that aortic valve replacement was not required in 45% of the patients in the 15th year of follow-up after ABV. Maskatia *et al.*^[11] also reported that aortic valve replacement was not required in 70% and 61% of patients at 10 and 15 years of follow-up after ABV, respectively. In a study conducted by Soulatges *et al.*^[18], freedom from surgical intervention and transcatheter intervention were 72.9% and 54%, respectively in 37 new-borns at a mean follow-up of 11 years. Varan *et al.*^[4] detected that freedom from reintervention after valvuloplasty was 71.7% in the 1st year, 58.8% in the 3rd year, 53.1% in the 5th year, and 26.9% in the 10th year of follow-up. In our study freedom from re-intervention after valvuloplasty was 77.7% at a mean follow-up of 5 years.

We detected that our mean re-intervention time was 8.69 ± 14.3 months of age (range 0.3-46). In a study conducted by Varan *et al.*^[4], the mean re-intervention time was reported as 27.2 ± 45.8 months of age (range: 5 days-13 years).

Boe *et al.*^[6] reported that hospital mortality in critical aortic stenosis was 10%. Neonatal ABV mortality in an intermediate-term follow-up has been reported as 9.3% and 12% in other studies.^[1,4] There were no intraprocedural deaths in the current study, however, the hospital mortality was 21.2%. We noticed that most of the patients who did not survive (64%) were patients who had an ABV between the years 2007 and 2012 which may be due to the lack of experience and equipment or postprocedural care.

Mortality related to aortic stenosis for which ABV was performed is reported in critical aortic valve stenosis because of severe left ventricular systolic dysfunction and/or accompanying complex anomalies.^[19,20] Varan *et al.*^[4] reported left ventricular systolic dysfunction, borderline left ventricular structure, and endocardial fibroelastosis as important risk factors for mortality. In the current study, left ventricular dysfunction, the presence of fibroelastosis and critical aortic valve stenosis were detected as risk factors for mortality.

CONCLUSION

In a retrospective, single-centre study, our results indicate that ABV is an effective method in new-borns with severe or critical valvular aortic stenosis. Becoming aware of endocardial fibroelastosis in echocardiographic evaluation is important due to its association with left ventricular dysfunction. Inadequate results after the procedure are a major risk for re-intervention. Although AR was the most common

complication of the procedure, severe regurgitation was rarely seen. Left ventricular dysfunction and critical aortic stenosis were risk factors for mortality, therefore preprocedural accurate evaluation and rapid intervention are essential.

Study limitations

This study is a retrospective study. Therefore, there is limited available data.

We compared no surgical cases with the ABV procedure because in our clinic we generally opt for ABV in neonatal critical or severe aortic stenosis cases.

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Conflicts of interest

There are no conflicts of interest.

Declaration of patient consent

Written informed consent was obtained from the patients' legal guardians.

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Effectiveness of Statin Treatment in Reducing Red Cell Distribution Width and Mean Platelet Volume in Patients with Stable Coronary Artery Disease: A Retrospective Study

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Abstract

Objectives: Mean platelet volume (MPV) has been shown to be a predictor of platelet activation and plays a crucial role in the pathogenesis of atherosclerosis. Red cell distribution width (RDW) is a measure of the variability of erythrocyte volumes and might reflect underlying chronic inflammation. Both MPV and RDW are related to increased risk for cardiovascular disease. Since statins have pleiotropic effects, we aim to investigate the effect of statins on this possible hematologic markers of atherosclerotic risk in stable coronary artery disease (CAD). **Materials and Methods:** One hundred and twenty-one statin-naïve patients who had undergone coronary angiography for stable CAD between June 2012 and June 2013 were retrospectively enrolled in this study. Patients were treated with atorvastatin or rosuvastatin. The lipid profile and hematological parameters were measured at baseline and after statin treatment. **Results:** One hundred and twenty-one patients were included in the study. The mean age was 60.5 ± 9 years and 38% of patients were women. Out of 121 patients, 106 (87.6%) patients received atorvastatin therapy and 15 (12.4%) patients received rosuvastatin therapy. After a median follow-up period of 36 days, statin treatment markedly reduced low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and triglyceride (TG) levels ($P = 0.0001$, for all). For hematological parameters, only RDW significantly decreased after statin treatment ($P = 0.0001$). The Δ RDW were not associated with Δ LDL-C ($r = 0.03$; $P = 0.72$), Δ TG ($r = 0.06$; $P = 0.49$) and Δ TC levels ($r = 0.05$; $P = 0.55$). Statins had no effect on MPV levels ($P = 0.32$). **Conclusions:** Statin therapy significantly reduces the RDW levels in stable CAD irrespective of cholesterol levels, which might confirm the anti-inflammatory effect of statins. However, the association between decreased RDW levels and prognosis in stable CAD has to be established by multi-center, prospective studies in large populations.

Keywords: Hematological parameters, pleiotropic effects, statins

INTRODUCTION

Atherosclerotic cardiovascular diseases (CVD), including coronary artery disease (CAD), cerebrovascular disorders, aortic aneurysm, and peripheral artery disease, are the most important causes of mortality and morbidity worldwide.^[1] Increased serum levels of cholesterol, especially low-density lipoprotein cholesterol (LDL-C), is associated with the high risk of atherosclerotic CVD, and LDL-C reduction with statin treatment was linked to reduced risk of all-cause and

cardiovascular mortality both for primary and secondary prevention.^[2,3] It has been shown that the benefits of statins resulted from both LDL-C lowering effects and pleiotropic effects.^[4] Among many pleiotropic effects of statins, two of the most important ones are reducing platelet aggregation and the anti-inflammatory properties. It has been shown

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that there is a well-established positive correlation between hypercholesterolemia and the level of ADP-induced platelet adhesion, and statin therapy resulted in a significant decrease in ADP-induced platelet aggregation.^[5] It has also been demonstrated that statin treatment decreases reactive oxygen species generation and reduces the secretion of pro-inflammatory cytokines.^[6]

Mean platelet volume (MPV) is a simple estimate of platelet function and activation, and raised levels of MPV are correlated with increased thromboxane and beta-thromboglobulin secretion, procoagulant action, and expression of adhesion molecules.^[7]

Red cell distribution width (RDW) is a readily measured marker of the size variability of erythrocytes. The increase in RDW levels was linked to unfavorable serum lipid profile.^[8] In addition, RDW is associated with various inflammatory markers^[9-11] and it is assumed that chronic inflammation and oxidative stress have a pivotal role in atherosclerosis.^[12]

Thus, the aims of this study were to assess the effectiveness of statin treatment on serum lipid profiles, MPV, and RDW levels in statin-naive patients with stable CAD, the relationship between serum lipid sub-fractions and these hematological parameters, and finally, is there a correlation between the change in serum lipid profiles and the change in RDW and MPV levels.

MATERIALS AND METHODS

Study design and patient population

We retrospectively enrolled 121 consecutive patients who underwent coronary angiography with suspected CAD from June 2012 to June 2013. Patients having one or more major epicardial coronary artery stenosis of $\geq 50\%$, by visual estimation, and patients with medically treated stable CAD were included. Statin-naive patients with elevated levels of LDL-C ≥ 100 mg/dL were included in this study. We excluded patients with acute coronary syndromes, rheumatic valvular heart disease, anemia (Hemoglobin [Hb] < 12 mg/dL in women and Hb < 13 mg/dL in men), chronic renal disease (GFR < 60 mL/min), chronic liver disease, history of iron, Vitamin B12 and folate deficiency, supplementation of iron, folate or Vitamin B12, chronic obstructive pulmonary disease, hypothyroidism or hyperthyroidism, history of malignancy and normal coronary arteries.

Data collection

Medical history, medication use, smoking status, and anthropometric data were collected from institutional medical records retrospectively. Body mass index was counted as weight (kg) divided by the square of height (m^2). Systolic blood pressure (BP) ≥ 140 mmHg or diastolic BP ≥ 90 mmHg or the present use of BP-lowering medication is defined as hypertension. A fasting serum glucose ≥ 126 mg/dL or the present use of medication for diabetes is defined as diabetes mellitus. We specified 1-vessel, 2-vessel, and 3-vessel disease

according to the number of major epicardial coronary artery stenosis of $\geq 50\%$. Left ventricular ejection fraction (LVEF) was calculated from the apical 4- and 2-chamber imaging planes using the biplane method of disks using the Vivid 7 Dimension ultrasound system (GE Vingmed Ultra-sound, Horten, Norway).

Hematological and biochemical data were obtained from the results of preprocedural venous blood sample analysis retrospectively. Biochemical data were measured using an automated chemistry analyzer (Abbott Laboratories, Abbott Park, IL). Baseline fasting glucose, serum creatinine, total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) values were recorded. Hematological data were measured using EDTA tubes with Coulter LH Series hematology analyzer (Beckman Coulter, Inc., Hialeah, Florida). Since this study is retrospective, the time delay between sampling and data examination could not be rigidly controlled. Baseline hematologic parameters, including red blood cell, white blood cell and platelet count, Hb, RDW, and MPV were also recorded. The time between the coronary angiography and the first outpatient clinic visit is defined as the duration of the statin treatment. Hematological and biochemical data in the first outpatient clinic visit were also recorded for each patient.

Ethical statement

This study was approved by the local medical ethics committee (approval number 311, October 12, 2013) and was performed in accordance with the rights expressed in the Declaration of Helsinki.

Statistical analysis

A standard statistical software program (SPSS version 26; SPSS, Inc., Chicago, IL, USA) was used. The Kolmogorov-Smirnov test and histograms were used to check continuous variables for normality. The categorical variables were represented as numbers and percentages and continuous variables were represented as the means \pm standard deviations and median (interquartile range). Pre- and posttreatment levels were compared with Paired *t*-tests and Wilcoxon tests. The correlation between RDW and MPV levels with lipid parameters was determined with Spearman correlation analysis. Linear regression analysis was used to determine the relationships of RDW change (Δ RDW) with changes in other lipid parameters. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

The baseline clinical characteristics of all patients are presented in Table 1. The average age of these patients was 60.5 ± 9 years and consisted of 38% were women. The median duration of statin treatment was 36 days. All patients received statin therapy. In addition, 87.6% of patients received atorvastatin and 12.4% of patients received rosuvastatin therapy. Specifically, 41.3% of patients ($n = 50$) were hypertensive and 26.4% of patients ($n = 32$) had diabetes mellitus. The median LVEF of the patients was 60%.

As presented in Table 2, statin therapy significantly reduced TC ($P = 0.001$), LDL-C ($P = 0.0001$) and TG ($P = 0.0001$) levels. Moreover, statin therapy significantly lowered RDW ($P = 0.0001$), whereas no significant changes were observed for MPV ($P = 0.32$) and other hematological parameters. We found no correlation between RDW and serum cholesterol levels before (TC: $r = 0.15$, $P = 0.87$, LDL-C: $r = 0.57$, $P = 0.53$, HDL-C: $r = 0.75$, $P = 0.41$, TG: $r = -0.10$, $P = 0.29$) and after statin treatment (TC: $r = 0.04$, $P = 0.67$,

LDL-C: $r = 0.01$, $P = 0.88$, HDL-C: $r = 0.17$, $P = 0.07$, TG: $r = -0.09$, $P = 0.33$) [Table 3]. Furthermore, there was no significant correlation between Δ RDW and the change in each serum lipid parameter in linear regression analysis (Δ TC: $r = 0.05$, $P = 0.55$, Δ LDL-C: $r = 0.03$, $P = 0.72$, Δ HDL-C: $r = 0.03$, $P = 0.70$, Δ TG: $r = 0.06$, $P = 0.49$) [Figure 1].

DISCUSSION

Our study demonstrates that statin treatment significantly reduces serum lipid profile and RDW. Statin treatment had no effect on MPV levels. RDW levels are not correlated with serum lipid profiles at baseline and after treatment. Importantly, the magnitude of RDW decline is not associated with the change in serum lipid profiles.

The pleiotropic effects, including the anti-inflammatory effects of statin treatment, were demonstrated in many large randomized controlled trials. Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin was a primary prophylaxis trial between rosuvastatin and placebo. Rosuvastatin decreased LDL-C levels by 50%, high-sensitivity C-reactive protein (hs-CRP) levels by 37%, and the primary endpoint of acute myocardial infarction, ischemic stroke, arterial revascularization, hospitalization for unstable angina or mortality from cardiovascular causes by 44%.^[13] The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering was a secondary prophylaxis trial between atorvastatin 80 mg and placebo.^[14] Atorvastatin 80 mg/d reduced ischemic outcomes and significantly decreased hs-CRP levels by 83%.^[15] However, as there is a strong relationship between elevated serum lipid levels and CVD, it is particularly difficult to distinguish the LDL-C-lowering effect of statin treatment from their pleiotropic effects.^[16] As RDW serves as a useful parameter of chronic inflammation and oxidative stress, the effect of statin treatment on RDW levels might potentially explain the role of anti-inflammatory effects of statins in CAD population. In this study, we have noticed a significant reduction in RDW levels after statin treatment in stable CAD patients. This result of the present study is in accordance with a previous study that demonstrated a statistically significant association between decreasing RDW and statin use in a population with decompensated heart failure.^[17] In contrast to our findings, a few reports had showed no effect on RDW levels after atorvastatin treatment.^[18,19] This difference might be explained by the percentage of CAD patients in these studies. Kucera *et al.*^[18] recruited only %15 CAD patients, and Akın *et al.*^[19] conducted a primary prophylaxis trial. Since atherosclerosis is a low-grade inflammatory process^[12] and RDW is a well-documented marker of chronic inflammation, the magnitude of the decline in RDW levels in our study might have reached statistical significance. A further work with atorvastatin 10 mg/d in patients with hyperlipidemia and chronic cerebrovascular disease revealed a significant decrease in erythrocyte deformability in the treatment group, which also supports our findings.^[20]

Table 1: Baseline clinical characteristics

	All patients (n=121)
Age* (year)	60.5±9
BMI* (kg/m ²)	27.3±1.8
Women†	46 (38)
Duration of statin treatment (days)**	36 (32-52)
Hypertension†	50 (41.3)
Diabetes mellitus†	32 (26.4)
Medications	
Acetylsalicylic acid†	121 (100)
ACEI†	31 (25.6)
ARB†	19 (15.7)
Beta blocker†	45 (37.2)
Atorvastatin†	106 (87.6)
Rosuvastatin†	15 (12.4)
Incidence of coronary atherosclerosis	
1-vessel disease†	66 (54.5)
2-vessel disease†	44 (36.4)
3-vessel disease†	11 (9.1)
LVEF*** (%)	60 (55-60)

*Mean±SD, †n (%), **Median (IQR). SD: Standard deviation, IQR: Interquartile range, ACEI: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker, LVEF: Left ventricular ejection fraction, BMI: Body mass index

Table 2: Effects of statin treatment on laboratory data in all patients

	Baseline (n=121)	After treatment (n=121)	P
Serum glucose** (mg/dL)	103 (92-124)	105 (94-124)	0.12
BUN* (mg/dL)	37.1±10.8	36.1±11.1	0.22
Serum creatinine* (mg/dL)	0.89±0.18	0.92±0.19	0.08
TC* (mg/dL)	221±36	154±34	0.0001
HDL-C* (mg/dL)	46.5±14.4	44±11.5	0.027
LDL-C** (mg/dL)	141 (121-162)	78 (66-95)	0.0001
TG** (mg/dL)	141 (103-190)	116 (81-165)	0.0001
Red blood cell* (×10 ³ /mL)	5±0.4	5±0.3	0.92
White blood cell* (×10 ³ /mL)	7.7±1.8	7.8±2	0.21
Platelet** (×10 ³ /mL)	255 (227-305)	250 (215-307)	0.14
Hemoglobin** (g/L)	14.8 (13.7-15.7)	14.3 (13.3-15.3)	0.07
RDW** (%)	14 (13.6-14.5)	13.6 (13.2-14)	0.0001
MPV** (fL)	8.6 (8.3-9.2)	8.8 (8.3-9.2)	0.32

*Mean±SD, **Median (IQR). BUN: Blood urea nitrogen, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, RDW: Red cell distribution width, MPV: Mean platelet volume, TC: Total cholesterol, TG: Triglyceride, SD: Standard deviation, IQR: Interquartile range

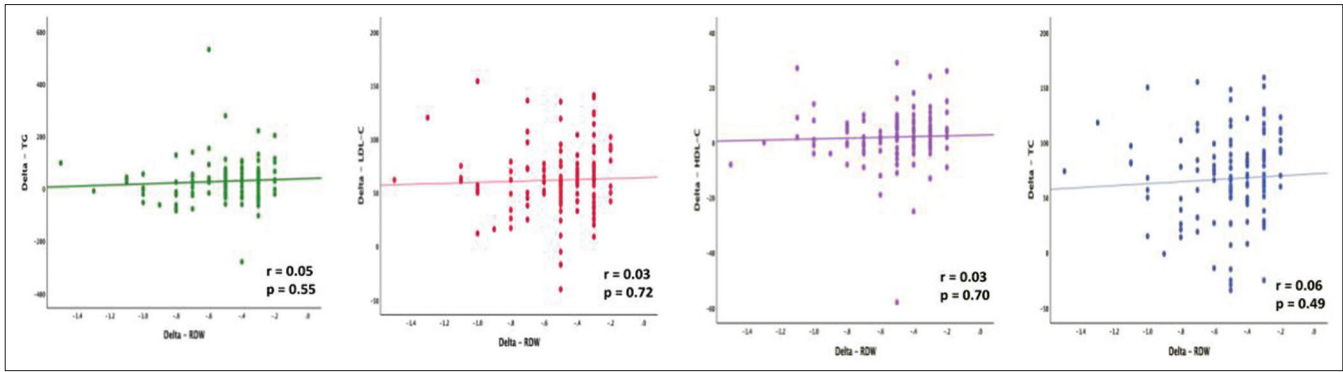


Figure 1: Correlations between Delta – RDW with Delta – total cholesterol, Delta – LDL-C, Delta HDL-C and Delta – triglyceride levels

Table 3: Correlation between plasma lipids and hematological parameters at baseline and after treatment

	Baseline				After treatment			
	RDW		MPV		RDW		MPV	
	r	P	r	P	r	P	r	P
TC	0.15	0.87	-0.04	0.65	0.04	0.67	-0.12	0.19
LDL-C	0.57	0.53	-0.16	0.86	0.01	0.88	-0.07	0.46
HDL-C	0.75	0.41	0.03	0.72	0.17	0.07	-0.09	0.33
TG	-0.10	0.29	-0.09	0.34	-0.09	0.33	0.02	0.84

TC: Total cholesterol, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, TG: Triglyceride

MPV reflects the size of the thrombocytes and is an easily measured marker of thrombocyte activity. Shattil *et al.*^[21] showed that in *ex vivo* enrichment of thrombocytes with cholesterol resulted in increased platelet activity. Up to date, numerous studies have described the potential effects of statin treatment on MPV levels; however, the results of these studies are controversial. Of these 10 studies, eight studies linked statin treatment to lower MPV, while two studies found no link.^[22] It is demonstrated that the type of anticoagulant used for the analysis of the components of blood, including thrombocytes, might affect the platelet count and MPV. McShine *et al.*^[23] showed that there was a substantial increase of MPV in the EDTA samples compared with citrated samples. In addition, it is demonstrated that MPV can be analyzed correctly by both EDTA and citrate if analysis be conducted within 1 h of sampling.^[24] In the present study, we used EDTA samples for blood count analysis. Although most studies that have shown the decrease in MPV levels after statin treatment do not clearly specify the time period of blood sample collection and examination, the hemogram analysis of the blood samples used in our research was conducted more than an hour after the blood sampling, which may have resulted in higher MPV values.

In this study, both MPV and RDW levels were analyzed in relation to the serum lipid profile at baseline and after statin treatment. The primary finding is neither MPV nor RDW correlated with plasma lipids. This finding is in contrast to that reported by Kucera *et al.*^[18] who showed a significant relationship between the hematological parameters and plasma

cholesterol levels, including HDL-C, TG, and small dense LDL-C. In their cohort, isolated hypercholesterolemia was found 52.5% of patients and combined hyperlipidemia in 47.5% of the patients. In addition, 15% of patients had CAD, and there were no diabetic patients. The imbalance between studied groups in baseline variables might influence the RDW and MPV levels which may explain discordant results.

To our knowledge, this is the first preliminary study suggesting that the decline in RDW levels after statin treatment is not associated with the change in serum lipid profiles. Further research is required to define the underlying pathophysiology and the association between RDW and statin treatment.

Study limitations

Our study has a few limitations. First, this is a retrospective study that reflects a single-center experience with a relatively small number of patients and a short median duration of statin treatment. Thus, large-scale and long follow-up studies are required to make further conclusions on the effect of statin treatment on RDW levels. Second, the time delay between blood sampling and data analysis for MPV might have affected our results. Furthermore, a major limitation of this study is that we did not have data on other inflammatory markers, such as hs-CRP, which might further support the anti-inflammatory effects of statin treatment. Finally, the statin dose was not determined in this study population.

CONCLUSIONS

Besides lipid-lowering effects, statin treatment significantly reduces RDW levels independent of serum cholesterol levels. The perception of the pleiotropic effects of statin treatment has provided a probability to examine and target other signaling pathways that may alter cardiovascular outcomes. Our study may serve as additional demonstrable evidence for the anti-inflammatory effects of statins. Further studies are required to clarify whether this decline is associated with better cardiovascular outcomes.

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Conflicts of interest

There are no conflicts of interest.

Declaration of patient consent

Written informed consent about the coronary angiography was obtained from all patients enrolled in this study.

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ERRATUM

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Bolus Versus Continuous Infusion of Nitroglycerin for the Treatment of Acute Hypertensive Heart Failure

The Ethics Committee Approval Form information of the article in the 1st issue of International Journal of the Cardiovascular Medicine has been updated due to the inaccuracy of the existing information.

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The Effect of COVID-19 Pandemic on Time in Therapeutic Range in Patients Using Warfarin

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Kind regards,

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