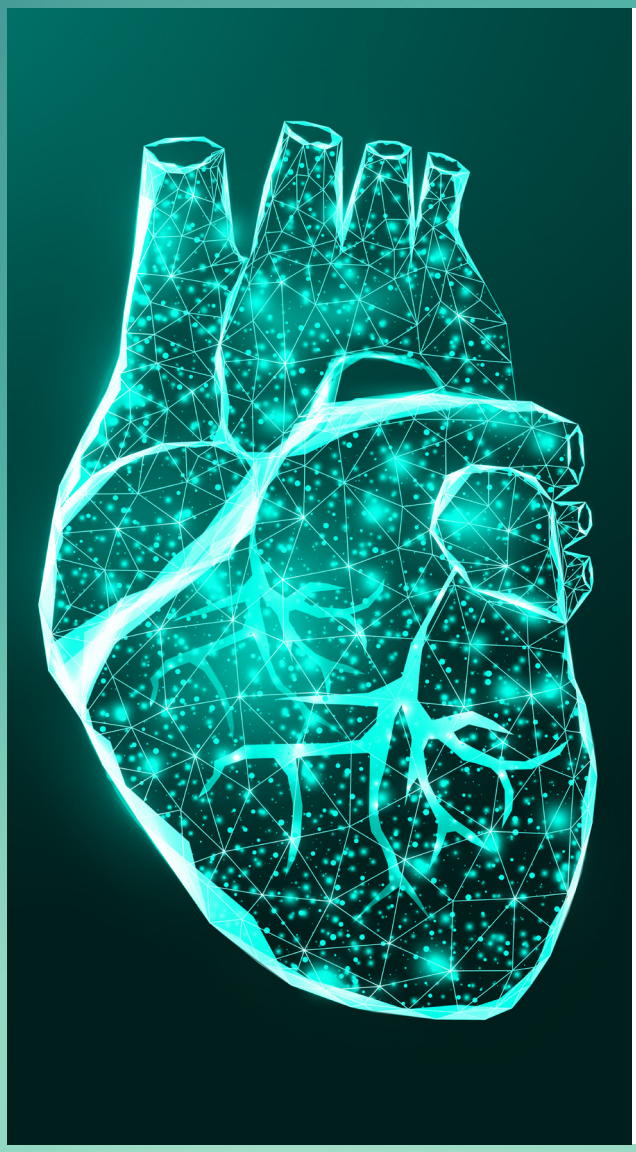
E-ISSN: 2405-819X

CARDIOVASCULAR ACADEMY SOCIETY

INTERNATIONAL JOURNAL OF THE CARDIOVASCULAR ACADEMY

OFFICIAL PUBLICATION OF THE CARDIOVASCULAR ACADEMY SOCIETY

VOLUME: 10 ISSUE: 3 SEPTEMBER 2024



galenos

INTERNATIONAL JOURNAL OF THE CARDIOVASCULAR ACADEMY

OFFICIAL PUBLICATION OF THE CARDIOVASCULAR ACADEMY SOCIETY

EDITORIAL BOARD

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Turkey
Phone: +90 (530) 177 30 97
E-mail: info@galenos.com.tr
yayin@galenos.com.tr
Web: www.galenos.com.tr
Publisher Certificate Number: 14521
Publication Date: September 2024
ISSN: 2405-8181 **E-ISSN:** 2405-819X
International scientific journal published quarterly.

INTERNATIONAL JOURNAL OF THE CARDIOVASCULAR ACADEMY

OFFICIAL PUBLICATION OF THE CARDIOVASCULAR ACADEMY SOCIETY

Please refer to the journal's webpage (**https://ijcva.org/**) for "Ethical Policy" and "Instructions to Authors".

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the ICMJE, COPE, WAME, CSE, NISO and EASE. The International Journal of the Cardiovascular Academy (ICJVA) is indexed in **Scopus, DOAJ, CNKI (China National Knowledge Infrastructure), EBSCO Central & Eastern European Academic Source, Hinari,** and **ProQuest**.

The journal is published online.

Owner: Ömer Kozan on behalf of the Cardiovascular Academy Society

Responsible Manager: Mehdi Zoghi

VOLUME: **10**
ISSUE: **3**
SEPTEMBER **2024**

INTERNATIONAL JOURNAL OF THE CARDIOVASCULAR ACADEMY

OFFICIAL PUBLICATION OF THE CARDIOVASCULAR ACADEMY SOCIETY

CONTENTS

RESEARCH ARTICLE

DOI: 10.4274/ijca.2024.00710
Int J Cardiovasc Acad 2024;10(3):45-52

Comparison of Clinical Characteristics, Risk Factors, and Risk Scores of Patients with and without Bleeding Episodes During Warfarin Treatment

Şaban Esen[1], Emre Özdemir[2], Tuncay Kiriş[2], Fatma Esin[2], Muhammet Mücahit Tiryaki[3]

[1]Clinic of Cardiology, Tunceli State Hospital, Tunceli, Turkey
[2]Department of Cardiology, Atatürk Training and Research Hospital, İzmir Katip Çelebi University, İzmir, Turkey
[3]Clinic of Cardiology, Muş State Hospital, Muş, Turkey

Abstract

Background and Aim: The annual risk of major bleeding due to anticoagulant use ranges from 2% to 5%, with 0.5% to 1% of these bleedings being fatal. The global usage of oral anticoagulants is 0.65%, with warfarin being the most commonly used oral anticoagulant agent. In our study, we aimed to determine the long-term bleeding risks of patients using warfarin in our clinic and to make treatment and risk factor adjustments according to this risk situation. We investigated the effectiveness of the most commonly used bleeding risk scores and their superiority over one another in this study.

Materials and Methods: This study included patients taking warfarin from January 2010 to January 1, 2022. Demographic data, laboratory parameters, known, and potential bleeding risk factors were recorded for all patients. Pre-treatment CHA_2DS_2-VASc, ATRIA, HAS-BLED, and ORBIT scores were calculated for all patients included in the study, along with their time in therapeutic range (TTR) values during follow-up. Patients were retrospectively monitored for bleeding events.

Results: In our study, we observed that anemia, chronic kidney failure, cancer, and mechanical valves were associated with an increased risk of bleeding compared with other risk factors. We found that among the risk scores assessed in patients, the HAS-BLED risk score more strongly predicted the risk of bleeding than the other risk scores. Additionally, we found that low TTR values were directly associated with bleeding.

Conclusion: Modifying identified risk factors in patients during the warfarin treatment process (such as anemia, chronic kidney failure, etc.) may reduce the risk of bleeding. Similarly, close monitoring of TTR, particularly in patients with high HAS-BLED and ORBIT risk scores assessed before treatment initiation, is considered a safe treatment approach to reduce the risk of bleeding.

Keywords: Warfarin, HAS-BLED, ORBIT, TTR, bleeding

INTRODUCTION

Anticoagulant therapy is performed with the aim of preventing thrombus formation in potential vascular structures or areas in the body that may block blood flow. Thrombus formation is a significant clinical condition that occurs in various medical and surgical conditions, such as atherosclerosis, atrial fibrillation (AF), and the presence of mechanical valves. Arterial and venous thromboses are major causes of mortality and morbidity. Arterial thromboses are the most common cause of myocardial infarctions, stroke, and extremity gangrene, whereas venous thromboses can lead to fatal pulmonary embolism (PE) and postphlebitic syndrome. Anticoagulant

To cite this article: Esen Ş, Özdemir E, Kiriş T, Esin F, Tiryaki MM. Comparison of Clinical Characteristics, Risk Factors, and Risk Scores of Patients with and without Bleeding Episodes during Warfarin Treatment. Int J Cardiovasc Acad. 2024;10(3):45-52

Address for Correspondence: MD Şaban Esen, Clinic of Cardiology, Tunceli State Hospital, Tunceli, Turkey
E-mail: saban___1064@hotmail.com
ORCID ID: orcid.org/0000-0001-5644-5787

Received: 18.05.2024
Revised: 17.07.2024
Accepted: 29.07.2024
Published Online: 18.09.2024

treatment prevents possible adverse clinical conditions by preventing thrombus formation. However, this also increases the risk of simultaneous bleeding. Most common indications for anticoagulation; acute myocardial infarction, left ventricular thrombus, AF, left ventricular aneurysm, prosthetic heart valve, venous thromboembolism (VTE), prophylaxis, etc.[1] The most commonly used anticoagulant drugs are; unfractionated heparin, low-molecular-weight heparin, bivalirudin, warfarin derivative warfarin, factor Xa inhibitors (apixaban, edoxaban rivaroxaban, fondaparinux), and direct thrombin inhibitors (dabigatran).[1] Warfarin may deplete functional vitamin K reserves and thus reduce thesynthesis of factors necessary for coagulation. In particular, the mechanical valve is the only oral anticoagulant agent that can be administered to moderate to severe mitral stenosis.

In patients receiving warfarin therapy for all indications, the annual risk of major bleeding is reported to be between 1-3%.[1] However, in studies involving patients receiving warfarin for AF, this risk is approximately 0.3-0.5%[2], and for VTE, the risk is found to be 1.3%.[2] In observational studies, it has been found that this ratecan reach up to 7% in patients taking warfarin who are not followed for study.

Some patients using anticoagulants with similar age and clinical characteristic experience bleeding, whereas others do not. Patients were investigated for known and possible additional risk factors that could explain the difference. Multiple risk scores are used to predict the risk of bleeding in patients taking warfarin. In our daily practice, we researched the HAS-BLED, ORBIT, and ATRIA risk scores because of their easy access to risk factors and straightforward calculation. We investigated the predictive values of these risk scores and compared their superiority to each other. The effect of time in therapeutic range (TTR) value on bleeding risk was also investigated.

MATERIALS AND METHODS

Our study comprised 500 patients who were prescribed warfarin for various reasons (AF, mechanical heart valve, DVT, pulmonary thromboembolism, etc.) and attended regular follow-up appointments at Atatürk Training and Research Hospital, İzmir Katip Çelebi University between 2000 and 2023.

The average age of the patients included in the study was 67.7 years, with 222 (44.4%) males and 278 (55.6%) females. The average follow-up period was 59.4 months (range: 35.9-94 months), with appointments scheduled for checkups every 3 months. In the retrospective follow-up, patients with bleeding were classified into three groups based on the TIMI bleeding criteria: major, minor, and minimal bleeding. Those with intracranial bleeding or a decrease in hemoglobin (Hgb) of 5 g/dL or more were included in the major bleeding group, those with a Hgb decrease of more than 3 g/dL were included in the minor bleeding group, and those with bleeding less than 3 g/dL were included in the minimal bleeding group. The total number of bleeding events was calculated as the sum of all bleeding events. Patients were divided into two groups: those with bleeding and those without bleeding. Patients in the two groups were compared according to risk factors known to increase the risk of bleeding, including anemia, coronary artery disease (CAD), peripheral artery disease, hypertension (HT), chronic kidney disease (CKD), malignancy, and mechanical valve replacement. Additionally, HAS-BLED, ORBIT, and ATRIA risk scores, which provide predictive values for bleeding risk in patients, were calculated. TTR was calculated for each patient to investigate the effect of effective international normalized ratio (INR) presence on bleeding risk. The left atrial (LA) diameter of each patient was measured at the beginning of follow-up. The ATRIA score is commonly used in clinical practice to predict the risk of stroke in patients with AF. In our study, we computed each patient's ATRIA risk score at the outset of the follow-up period to assess its predictive value in predicting bleeding.

TTR Calculation, Bleeding Risk Score Calculation, Bleeding Risk Factors

Patients should ideally maintain a TTR >70% to ensure effective anticoagulation therapy. TTR values below this threshold may indicate irregular treatment adherence, which can compromise the effectiveness of anticoagulation and increase the risk of adverse events, including bleeding complications.

This criterion ensures an adequate representation of the patient's anticoagulation status over time. Patients with fewer than four INR values measured within the specified intervals were excluded from the analysis due to insufficient data for accurate TTR calculation. Additionally, patients with intervals of >60 days between INR measurements were excluded. The diameter of the left atrium (LA) was also examined.

The file scanning included the history of our study and the collection of patient information for follow-up visits. The application file has been submitted to the local Ethics Committee of İzmir Katip Çelebi University for review. Ethics committee approval was granted with decision number 0301, dated 16.06.2022.

Statistical Analysis

Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS) for Windows version 26.0 (IBM SPSS Inc., Chicago, IL). Descriptive statistics were presented using mean and standard deviation (mean ± standard deviation) for normally distributed variables, whereas median and maximum-minimum values were used for non-normally distributed variables. Pearson's chi-square test and Fisher's exact test were employed to assess categorical variables. The normality of

continuous variables was assessed using visual (histogram) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). The t-test was used to compare normally distributed variables between the two groups, and the Mann-Whitney U test was used to compare non-normally distributed variables between the two groups. Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive value of bleeding risk scores. Bleeding risks were calculated according to the scores during follow-up using the Kaplan-Meier curve.

RESULTS

The study included 500 patients who were prescribed warfarin for various reasons (such as AF, mechanical heart valve, PE, etc.) and attended regular INR monitoring between 2000 and 2023. The average follow-up period was 59.4 months (range: 35.9-94 months), with appointments scheduled for checkups every 3 months. Patients included in the study were evaluated retrospectively. During the follow-up of the patients, bleeding events occurred in 196 (39.2%) patients, whereas no bleeding was detected in 304 (60.8%) patients. When examining patients who experienced bleeding, the findings based on the TIMI bleeding score were as follows: Seven patients experienced major bleeding, 90 patients experienced minor bleeding, and 97 patients experienced minimal bleeding. Additionally, 2 patients experienced both minor and minimal bleeding during follow-up period (Table 1). Mortality occurred in 99 patients (18%) during follow-up. When comparing the two groups, it was found statistically significant that the baseline Hgb values were lower in the bleeding group, whereas the creatinine values were higher. Furthermore, upon examining the left atrium diameter (LA), it was noted that the baseline left atrium diameter was larger in the bleeding group.

The study found that baseline Hgb levels were significantly lower in the group experiencing bleeding, whereas creatinine levels were higher in this group. Therefore, clinical characteristics such as anemia and CKD were identified as risk factors for bleeding in the present study. Baseline Hgb values were lower in the bleeding group than in the non-bleeding group (12.5±1.8 vs. 13.09±2.0, p=0.002). Additionally, creatinine levels were higher in the bleeding group than in the non-bleeding group (1.05±0.72 vs. 0.918±0.25, p=0.003).

Additionally, upon examining the LA diameter, it was observed that the baseline LA diameter was larger in the bleeding group. These findings suggest that increased LA size is a potential predictive factor for bleeding in these patients.

Table 2 presents the statistical analysis performed on these laboratory parameters.

Table 3 presents the statistical analysis of the effect of comorbid conditions on bleeding risk. There was nostatistically significant difference in the increased risk of bleeding between the groups in terms of comorbid conditions, such as CAD, HT, RDW, VTE, aortic valve replacement (AVR), AF, diabetes mellitus, peptic ulcer, cerebrovascular accident (CVA) stroke, or liver dysfunction. Although some of these risk factors have been shown to increase bleeding risk in previous studies, their ineffectiveness in our study could be due to the small number of patients and insufficient patient event records. Mitral valve replacement (MVR) was found to be associated with increased bleeding risk. Additionally, sex and age were found to have no effect on the increased risk of bleeding between groups.

After identifying the risk factors for bleeding in patients, we then examined the risk scores. The average ATRIA scores among the study participants were 3 (ranging from 1 to 6) in the nonbleeding group and 4 (ranging from 1 to 6) in the bleeding group. There was no statistically significant difference between the two groups (p=0.082). However, the HAS-BLED score was significantly higher in the bleeding group than in the non-bleeding group [3 (1-4) vs. 2 (1-3), p=0.001] (Figure 1). The ORBIT score was 0 (ranging from 0 to 2) in the non-bleeding group and 3 (ranging from 2 to 4) in the bleeding

Table 1: Patients' bleeding status and classification according to the TIMI bleeding score

Status	Bleeding (-)	Bleeding (+)			
		Classification according to the TIMI bleeding score			
Number of patients	n=304	Major bleeding	Minor bleeding	Minimal bleeding	Minor and minimal bleeding
		n=7	n=90	n=97	n=2

TIMI: Thrombolysis in myocardial infarction

Table 2: Laboratory data of the patients

Variables	Bleeding (-)	Bleeding (+)	p-value
Hemoglobin (g/dL)	13.09±2.0	12.5±1.8	0.002
Kreatinin (mg/dL)	0.918±0.25	1.05±0.72	0.003
LA, mm	43.2±8.3	46.2±7.8	0.001

LA: Left atrium

Table 3: Demographic characteristics of the patients

Variables	Bleeding (-) (n=304)	Bleeding (+) (n=196)	p-value
CAD, number (%)	68 (22%)	48 (26%)	0.321
PAD, number (%)	14 (4.5%)	2 (1.1%)	0.036
HT, number (%)	239 (47.9%)	158 (31.7%)	0.087
CKD, number (%)	9 (1.8%)	15 (3%)	0.002
MVR, number (%)	53 (17%)	48 (26%)	0.048
Cancer, number (%)	16 (5%)	22 (12%)	0.007
DM, number (%)	88 (17.6%)	56 (11.2)	0.386
SVO, number (%)	63 (20.1)	31 (16.6%)	0.326
Peptic ulcer, number (%)	0 (0%)	1 (0.5%)	0.195
Liver disease, number (%)	1 (0.3%)	3 (1.6%)	0.117
AF valvular, number (%)	65 (20.8%)	49 (26.2%)	0.161
AF non- valvular, number (%)	168 (53.7)	93 (49.7%)	0.393
AVR, number (%)	51 (16.3%)	36 (19.3%)	0.408
VTE, number (%)	25 (8.1%)	13 (7)	0.641
ASA, number (%)	13 (4.2%)	14 (7.5%)	0.115
Klopidogrel, number (%)	2 (0.6%)	4 (2.2%)	0.136
Prasugrel	0	0	-
Tikagrelor, number (%)	1 (0.3%)	0 (0)	0.439
Statin, number (%)	50 (16%)	36 (19.4%)	0.342
PPI, number (%)	9 (2.9%)	2 (1.1%)	0.178
NSAI, number (%)	0	0	
New SVO, number (%)	15 (4.9%)	15 (8.1%)	0.155
Gender, men/women, number	139/172	104/83	0.946
Age	67.2±12.2	68.6±12.5	0.216
HD	0 (0%)	3 (1.6%)	0.002

CAD: Coronary artery disease, PAD: Peripheral arterial disease, HT: Hypertension, CKD: Chronic kidney disease, MVR: Mitral valve replacement, DM: Diabetes mellitus, SVO: Cerebrovascular event, AF: Atrial fibrillation, AVR: Aortic valve replacement, VTE: Venous thromboembolism, ASA: Acetylsalicylic acid, PPI: Proton pump inhibitor, NSAI: Nonsteroidal anti-inflammatory drug, HD: Hemodialisis

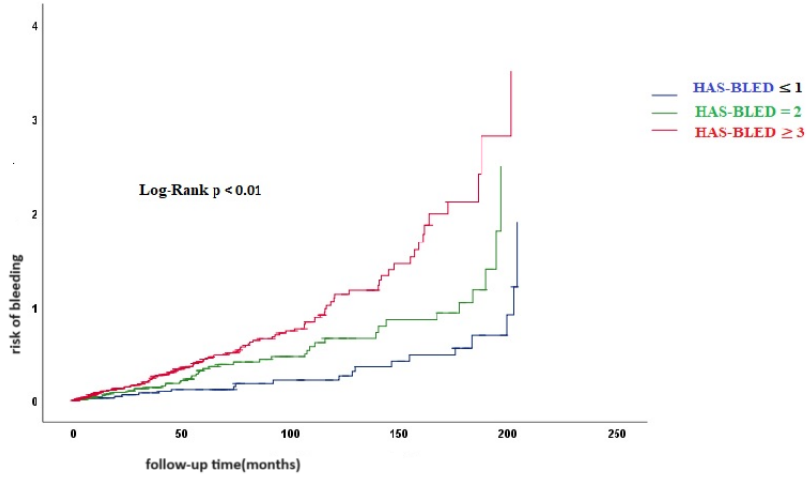


Figure 1: Bleeding risk according to HAS-BLED score

group. There was a statistically significant association between a high ORBIT score and the risk of bleeding (p=0.001) (Figure 2). The HAS-BLED score of the patients included in the study was significantly higher in the group with bleeding compared with the group without bleeding [3 (1-4) vs. 2 (1-3), p=0.001]. Figure 3 presents the ROC curve for bleeding risk.

In our study, the mean TTR value in the nonbleeding group was 80.4±11.2, whereas it was calculated as 47.5±12.5 in the bleeding group. A low TTR value was found to be significantly associated with an increased risk of bleeding (p=0.001) (Table 4).

In the multivariate analysis, HAS-BLED, ORBIT, mechanical valve replacement, TTR, cancer, and left atrium diameter (LA) were identified as independent predictors of bleeding (Table 5).

DISCUSSION

Despite having similar characteristics and risk factors, some patients experience bleeding, whereas others do not. Therefore, in this study, we investigated potential additional risk factors in addition to known risk factors. We found that known risk factors, such as anemia and elevated creatinine levels, were associated with increased bleeding risk. MVR is also associated with increased bleeding risk. However, other known risk factors like CAD, AVR, CVA (stroke), PTE (PE), antiplatelet use and HT were not found to be associated with increased bleeding risk in our study. Some of these risk factors have been shown to increase bleeding risk in previous studies; however, their ineffectiveness in our study could be attributed to the small number of patients included and the inadequacy of follow-up and event records.

The left atrium collects blood during systole and supports the filling of the left ventricle during diastole, playing a crucial physiological role. Given these functions, it provides important prognostic information about cardiac physiology, cardiac health, and adverse cardiovascular events (CVE). Increased LA diameter occurs as a result of atrial remodeling and can be associated with increased left ventricular filling pressure (left ventricular diastolic dysfunction), increased volume load, or valvular heart disease. In our study group, we investigated the potential for increased LA size to increase bleeding risk and its predictive value for possible bleeding events. We observed that an increase in LA diameter assessed echocardiographically was associated with increased bleeding risk in our study.

Additionally, we evaluated the effectiveness of bleeding risk scores and compared their performance. Our findings indicate that the HAS-BLED risk score outperforms the other predictors

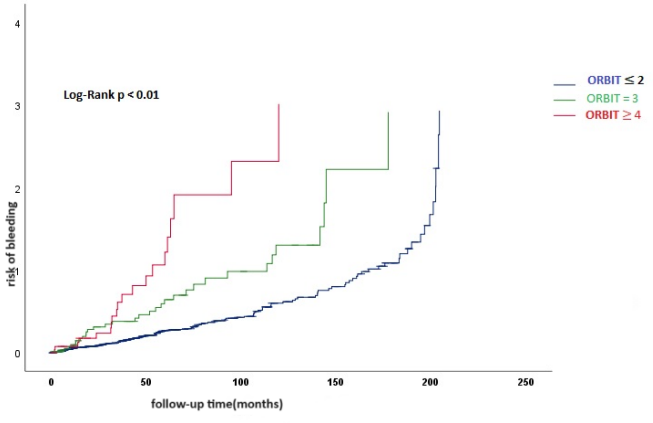


Figure 2: Bleeding risk according to ORBIT score

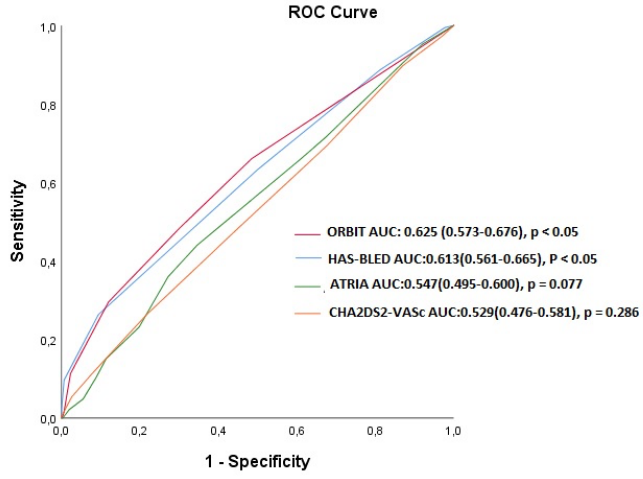


Figure 3: Receiver operating characteristic (ROC) curve for bleeding risk

Table 4: Bleeding risk scores of patients

Variables	Bleeding (-) (n=304)	Bleeding (+) (n=196)	p-value
TTR	80.4±11.2	47.5±12.5	0.001
HAS-BLED score	2 (1-3)	3 (1-4)	0.001
ATRIA score	3 (1-6)	4 (1-6)	0.082
ORBIT score	0 (0-2)	3 (2-4)	0.001
CHADVASC score	3 (2-4)	3 (2-5)	0.536

TTR: Therapeutic range time

Table 5: Multivariate analysis of bleeding risk

Variables	Multivariate analysis	p-value
Cancer	3.117 (1.228-7.268)	0.007
MVR	1.746 (1.024-2.978)	0.041
LA size (mm)	1.039 (1.009-1.071)	0.011
ORBIT score	1.347 (1.127-1.610)	0.001
TTR	0.982 (0.972-0.993)	0.002
HAS-BLED score	1.422 (1.115-1.815)	0.005

LA: Left atrium, TTR: Therapeutic range time, MVR: Mitral valve replacement

of bleeding risk. Furthermore, we demonstrated a direct association between low TTR and bleeding in patients.

In 2012, a study was published involving 965 patients[3] patients was associated with an increased risk of bleeding during follow-up. It was determined that a high HAS-BLED score was highly predictive of bleeding. Additionally, the current study revealed that a high HAS-BLED score was predictive of CVE and all-cause mortality. In our study, the average HAS-BLED score in the bleeding group was 3 (ranging from 1 to 4), whereas in the group it was calculated as 2 (ranging from 1 to 3). The difference in scores between the two groups was statistically significant. Our findings align with those of the aforementioned study, indicating that an increase in the HAS-BLED score is associated with a higher bleeding risk, thus confirming its important predictive value.

Similar to our study, a meta-analysis involving 8097 patients was published in 2017. In the analysis, patients were classified into low (0-2 points), medium (3 points), and high (4-7 points) risk categories based on ORBIT score. It was observed that the bleeding risk of patients in these groups increased by 1.21, 1.44, and 1.73 times, respectively. High ORBIT scores in patients taking anticoagulants were found to significantly increase the risk of bleeding, demonstrating statistical significance.[4]

In a study conducted in 2016 on 2293 patients, the HAS-BLED, ATRIA, and ORBIT risk scores were compared to predict bleeding risk. Each score was calculated for each patient, and the statistical significance was evaluated. Patients with HAS-BLED scores ≥3 were found to have a 1.85-fold increased risk of bleeding and a 2.4-fold increased risk of major bleeding. For patients with ATRIA scores ≥4, the increase in bleeding risk was not statistically significant; however, the risk of major bleeding alone increased by 2.4 times. Similarly, in patients with ORBIT scores ≥3, there was no statistically significant increase in bleeding risk, but the risk of major bleeding alone increased by 2.9 times. All three scores were found to be statistically significant in determining major bleeding risk; however, the HAS-BLED score demonstrated a higher predictive value for bleeding risk than the other two scores.[5] Likewise, our study also showed that the HAS-BLED risk score had the highest predictive value.

A study conducted in 2013 involved 937 patients and investigated the effectiveness of ATRIA and HAS-BLED risk scores.[6] In the study, 49% of patients were male and 51% were female, with an average age of 76. The mean HAS-BLED score of these patients was 2 (ranging from 2 to 3), and 35% had a HAS-BLED score ≥3. The mean ATRIA score was 3, and 16% of the patients had a score ≥5. Patients were followed for an average of 952 days, during which an increased risk of bleeding was detected in patients with a HAS-BLED score ≥3. Similarly, although an ATRIA score of 5 or above increases the risk of major bleeding, its effectiveness in predicting bleeding was found to be insufficient. Similar to the results of the previous study, in this study, the scores of the patients in the group with bleeding and the group without bleeding were compared. Accordingly, bleeding rates were increased in the group with a high HAS-BLED score. Similar to our study, the ATRIA risk score was found to be unsuccessful in predicting bleeding.

In a study involving 2233 patients, the predictive value of TTR values for risks such as bleeding, CVA/transient ischemic attack (TIA), and death was investigated.[7] The average age of the patients was 68.4 years, and the average follow-up period was 30 months (ranging from 12 to 36 months). The average number of INR tests performed on patients was 9 (ranging from 5 to 13).

Although it is recommended that the TTR value be >70%, ineffective TTR was not detected in this study. Ineffective TTR was defined as <65%. Additionally, for sensitivity analysis, TTR values were divided into 3 groups. Patients with TTR <45.1% were classified into group 1, those with TTR ranging from 45.1% to 66.8% were classified into group 2, and those with values >66.8% were classified into group 3. Patients with TTR <65% were at increased risk of bleeding, stroke, and death. Moreover, as the subgroups moved from group 3 to group 1, the risk of bleeding, death, and cerebrovascular events increased.

Similar to our study, low TTR treatment was associated with irregularity and increased the risk of bleeding. Studies on bleeding risk factors generally indicate that factors such as cancer, anemia, mechanical valve implantation, elevated creatinine levels, and LA dilation tend to increase the risk of bleeding. The presence of these factors together may indicate an even higher risk of bleeding.

Between 2007 and 2016, a study was conducted involving 6445 patients taking warfarin or NOAC, and it was published in 2020 to investigate the effect of LA enlargement on bleeding and CVA.[8] The group taking warfarin comprised 46.9% of the patients, whereas the group receiving NOAC comprised 48.2%. In this study, the average left atrium diameter was 47 mm. The current study found that the use of NOACs in patients with LA dilatation reduced the risk of cerebrovascular disease.

However, no difference was found between warfarin and NOAC in terms of bleeding risk in these patients. The current study found that LA enlargement was associated with overall bleeding.

Between 2004 and 2016, a study investigated the effect of warfarin use on increased bleeding risk in patients undergoing mitral valve repair. Of the patients, 754 were receiving vitamin K antagonists (VKA), while 1462 were not. The two groups were compared in terms of bleeding events. In the VKA group, the

risk of major bleeding events related to any cause significantly increased during the 180-day follow-up period (VKA: 8.58% vs. non-VKA: 4.21%; risk ratio, 2.09; p<0.001).[9]

A study conducted between 2008 and 2011, involving 546 patients, aimed to determine whether mechanical valve replacement increased the risk of bleeding. Patients were prospectively followed for the risk of major bleeding, thromboembolism, and death. Among the participants, 398 patients underwent AVR, 122 patients underwent MVR, and 26 underwent both AVR and MVR. In terms of thromboembolism risk, the ratios were 1.8/100 and 2.2/100 in the AVR group and 2.2/100 in the MVR group, indicating a higher risk in the MVR group. Regarding bleeding risk, there was a 4.4% increase in the AVR group and a 4.6% increase in the MVR group. A similar increase in bleeding risk was found in both groups.[10] In our study, 48 patients (26%) who underwent MVR therapy experienced bleeding, while 53 patients (17%) did not.

The presence of MVR was associated with a statistically significant increase in the risk of bleeding. In our study, we did not observe an increased risk of bleeding in the AVR group. This finding could be attributed to the small sample size and inadequate event recording and follow-up. Another possible reason could be the lower target INR range in AVR patients compared to MVR patients.

In 2021, a study involving 1512 patients investigated the impact of anemia on bleeding risk. The average Hgb level among the patients was 13.2±1.8 g/dL, and 518 patients were considered to have anemia (Hgb <11 g/dL). Patients were followed-up for an average of 25.8±10.5 months. The study reported rates of 2.9% for ischemic stroke/TIA, 4.9% for major bleeding, 1.8% for CVE, and 9.2% for mortality. A statistical analysis revealed a significant association between anemia and an increased risk of major bleeding.[11]

In a study involving 578 patients, the effect of renal failure on bleeding risk among patients receiving warfarin was investigated. Particularly in patients with moderate-to-severe renal failure, the study found a lower required dose of warfarin and a lower achievement rate of the target INR. Compared with the other groups, patients with severe renal failure were found to have a major bleeding risk twice as high. Compared with the normal patient population, initiating lower starting doses of warfarin and closely monitoring INR may be beneficial in patients with moderate to severe renal failure to reduce potential side effects.[12]

Study Limitations

Increasing the number of patients in the study enhances its representativeness of the population. Consequently, more accurate and reliable data are obtained, which allows better interpretation. In our study, the

the major bleeding risk scores. However, by expanding the number of risk scores (e.g., GARFIELD-AF, etc.), the risk score with the highest predictive value can be determined, which evaluation of each patient before treatment in daily practice. Despite screening more than 5,000 retrospective cases of warfarin use in the study, many patients were not included due to a lack of regular INR monitoring, follow-up from a single center, and inadequate record-keeping.

CONCLUSION

The TTR value calculated in patients is predictive of bleeding risk. Informing and raising awareness among patients with ineffective TTR values and ensuring more frequent INR monitoring for these patients are crucial for achieving effective TTR and consequently reducing the risk of bleeding. This approach is particularly important for patients with a history of previous bleeding events.

Since our study revealed that HAS-BLED and ORBIT risk scores, in particular, have predictive value for bleeding risk, assessing these scores before initiating warfarin treatment can provide insights into the risk of bleeding. Patients with high scores should be monitored for bleeding events. Modifying factors that increase the risk of bleeding in these patients (such as HT, anemia, etc.), and if necessary, considering alternative treatments (such as NOACs) may be warranted.

In this study, we demonstrated that the LA diameter value exhibits predictive value similar to risk scores in forecasting bleeding. Consequently, it can be regarded as a standalone parameter similar to HAS-BLED or ORBIT risk scores for assessing bleeding risk. The advantage of the proposed score lies in its easy accessibility and simple measurability for each patient.

In our study, 22 of the patients with cancer (12%) experienced bleeding, whereas 16 (5%) did not. A statistically significant increase in bleeding risk was associated with the presence of cancer (p=0.007). Chemotherapeutic drugs administered to patients with cancer receiving warfarin therapy may affect their blood INR levels, either increasing or decreasing them. Additionally, interruptions in warfarin therapy due to necessary treatments can hinder the achievement of effective TTR, thereby increasing the risk of bleeding.

Close monitoring of INR levels and achieving the effective TTR value (TTR >70%) in patients with high HAS-BLED and ORBIT risk scores, which are assessed before initiating warfarin treatment, are essential to prevent potential major bleeding events in these patients.

Shortening the intervals between INR checks, closely adjusting doses, and considering alternative medications for patients taking concomitant drugs that may affect warfarin levels can help achieve and maintain the target TTR.

Ethics

Ethics Committee Approval: The application file has been submitted to the local Ethics Committee of İzmir Katip Çelebi University for review. Ethics committee approval was granted with decision number 0301, dated 16.06.2022.

Informed Consent: Retrospective study.

Authorship Contributions

Concept: E.Ö., Design: Ş.E., E.Ö., T.K., Data Collection or Processing: Ş.E., T.K., F.E., M.M.T., Analysis or Interpretation: Ş.E., E.Ö., T.K., F.E., M.M.T., Literature Search: Ş.E., T.K., F.E., M.M.T., Writing: Ş.E., E.Ö., M.M.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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

REFERENCES

1. Gomes T, Mamdani MM, Holbrook AM, Paterson JM, Hellings C, Juurlink DN. Rates of hemorrhage during warfarin therapy for atrial fibrillation. CMAJ. 2013;185:E121-7.
2. Shoeb M, Fang MC. Assessing bleeding risk in patients taking anticoagulants. J Thromb Thrombolysis. 2013;35:312-9.
3. Gallego P, Roldán V, Torregrosa JM, Gálvez J, Valdés M, Vicente V, *et al*. Relation of the HAS-BLED bleeding risk score to major bleeding, cardiovascular events, and mortality in anticoagulated patients with atrial fibrillation. Circ Arrhythm Electrophysiol. 2012;5:312-8.
4. Wang C, Yu Y, Zhu W, Yu J, Lip GYH, Hong K. Comparing the ORBIT and HAS-BLED bleeding risk scores in anticoagulated atrial fibrillation patients: a systematic review and meta-analysis. Oncotarget. 2017;8:109703-11.
5. Senoo K, Proietti M, Lane DA, Lip GY. Evaluation of the HAS-BLED, ATRIA, and ORBIT Bleeding Risk Scores in Patients with Atrial Fibrillation Taking Warfarin. Am J Med. 2016;129:600-7.
6. Roldán V, Marín F, Fernández H, Manzano-Fernandez S, Gallego P, Valdés M, *et al*. Predictive value of the HAS-BLED and ATRIA bleeding scores for the risk of serious bleeding in a "real-world" population with atrial fibrillation receiving anticoagulant therapy. Chest. 2013;143:179-84.
7. Krittayaphong R, Chantrarat T, Rojjarekampai R, Jittham P, Sairat P, Lip GYH. Poor Time in Therapeutic Range Control is Associated with Adverse Clinical Outcomes in Patients with Non-Valvular Atrial Fibrillation: A Report from the Nationwide COOL-AF Registry. J Clin Med. 2020;9:1698.
8. Wu VC, Wang CL, Gan ST, Wu M, Chen SW, Kuo CF, *et al*. Efficacy and safety of NOAC versus warfarin in AF patients with left atrial enlargement. PLoS One. 2020;15:e0243866.
9. Brown CR, Sperry AE, Cohen WG, Han JJ, Khurshan F, Groeneveld P, *et al*. Risk of Stroke and Major Bleeding With Vitamin K Antagonist Use After Mitral Valve Repair. Ann Thorac Surg. 2023;115:957-64.
10. Labaf A, Grzymala-Lubanski B, Stagmo M, Lövdahl S, Wieloch M, Själander A, *et al*. Thromboembolism, major bleeding and mortality in patients with mechanical heart valves- a population-based cohort study. Thromb Res. 2014;134:354-9.
11. Krittayaphong R, Pumprueg S, Thongsri T, Wiwatworapan W, Choochunklin T, Kaewkumdee P, *et al*. Impact of anemia on clinical outcomes of patients with atrial fibrillation: The COOL-AF registry. Clin Cardiol. 2021;44:415-23.
12. Limdi NA, Beasley TM, Baird MF, Goldstein JA, McGwin G, Arnett DK, *et al*. Kidney function influences warfarin responsiveness and hemorrhagic complications. J Am Soc Nephrol. 2009;20:912-21.

RESEARCH ARTICLE

DOI: 10.4274/ijca.2024.41861
Int J Cardiovasc Acad 2024;10(3):53-59

Comparison of Outcomes between Early and Late Presentation of ST-elevation Myocardial Infarction in Patients with Cardiogenic Shock

Nagarathna Shenoy, Tom Devasia

Department of Cardiology, Kasturba Medical College, Manipal, India

Abstract

Background and Aim: Cardiogenic shock (CS) arising from ST-elevation myocardial infarction (STEMI) is associated with high mortality. This study aimed to evaluate the clinical characteristics and outcomes of early versus late-present patients with CS complicated with STEMI.

Materials and Methods: This prospective observational study enrolled 92 patients with STEMI and CS from September 2020 to December 2021. Patients were divided into two groups based on the time from symptom onset to hospitalization: early (<24 hours, n=48) and late (≥24 hours, n=44). Demographic data, clinical characteristics, management strategies, and outcomes were compared between the two groups. The Society of Cardiovascular Angiography and Intervention was used to predict mortality between the groups. After one month of discharge outcomes like death, stroke, and non-fatal myocardial infarction were reported.

Results: Most patients were male (70.7%) with a mean age of 63.4±10.9 years. Late presenters were more likely to have lower socioeconomic status and reside in rural areas. The late presentation group had a higher proportion of patients in advanced societies of cardiovascular angiography and intervention stages (D and E) compared with the early group. Late presenters had significantly higher rates of acute kidney injury (72.7% vs. 41.7%, p=0.003) and major adverse cardiovascular events (81.8% vs. 45.8%, p<0.001) at discharge, driven primarily by increased mortality, although the gap in mortality rates narrowed by one month.

Conclusion: Early presentation of STEMI complicated by CS is associated with improved outcomes. Late presenters experienced higher rates of complications and mortality.

Keywords: Management, mortality, myocardial infarction, shock, cardiogenic, ST elevation myocardial infarction

INTRODUCTION

Cardiogenic shock (CS), a severe and life-threatening complication, can stem from various cardiac conditions like fulminant myocarditis, heart failure and cardiomyopathy.[1] CS is a serious complication arising from ST-elevation myocardial infarction (STEMI), occurring in 3-13% of patients. Despite advances in early revascularization techniques and intensive care management, CS remains the primary driver of death rates in STEMI patients.[2] A study by Bagai et al.[3] indicated that patients who experienced CS after an acute myocardial infarction (AMI) had a higher rate of in-hospital mortality compared to patients without CS. The timing of presentation following the onset of symptoms plays a crucial role in determining the prognosis of STEMI complicated by CS. It is crucial to quickly identify CS caused by STEMI to ensure patient survival.[4] It is challenging to classify patients with CS based on the risk or stage of the disease for better management and

To cite this article: Shenoy N, Devasia T. Comparison of Outcomes between Early and Late Presentation of ST-elevation Myocardial Infarction in Patients with Cardiogenic Shock. Int J Cardiovasc Acad. 2024;10(3):53-59

Address for Correspondence: Asst. Prof. Nagarathna Shenoy, Department of Cardiology, Kasturba Medical College, Manipal, India
E-mail: nagarathna.nayak@manipal.edu
ORCID ID: orcid.org/0009-0008-0788-7085

Received: 06.06.2024
Revised: 13.08.2024
Accepted: 19.08.2024
Published Online: 18.09.2024

outcomes because they often arrive at the hospital at different stages of the condition.[5] In response to this challenge, the Society of Cardiovascular Angiography and Intervention (SCAI) introduced a novel classification system for CS. This system categorizes patients into five distinct groups with the aim of improving patient management and research outcomes.[6]

In western countries, prompt reperfusion therapy has reduced the time to hospital arrival in STEMI patients. However, limited resources and delayed presentation remain a challenge for developing countries.[7-10] Bridging this gap requires insights into the clinical characteristics and outcomes of early and late presenters. Therefore, our study aimed to evaluate patients with STEMI associated with CS at a tertiary care center. By comparing early and late presenters, we sought to enhance our understanding of disease progression.

MATERIALS AND METHODS

Study Design and Population

This prospective, observational study was conducted from September 2020 to December 2021 at tertiary institutions. The study protocol was approved by the Kasturba Medical College and Kasturba Hospital Institutional Ethics Committee (approval number: 381/2020, date: 10.07.2020) and was registered with the clinical trial registry of India (CTRI/2020/10/028222).

Patients aged 18 years or older who presented to the emergency room with chest pain and were diagnosed with STEMI and CS were included in the study. Exclusion criteria comprised shock unrelated to STEMI, cardiac arrest before hospitalization, pregnancy, terminal illness, advanced malignancy, and inability to document the time of symptom onset. Written informed consent was obtained from all enrolled patients. A total of 92 patients were enrolled and divided into two groups based on the time from symptom onset to hospitalization: 48 patients were early presenters (hospitalized in <24 hours of symptom onset) and 44 patients were late presenters (hospitalized ≥24 hours of symptom onset).

CS was defined as a systolic blood pressure <90 mmHg for at least 30 min or the need for supportive measures to maintain a systolic blood pressure ≥90 mmHg despite adequate filling pressures and signs of end-organ hypoperfusion.

Data Collection

A thorough set of data was collected, including age, gender, social habits, socioeconomic status, area of residence, comorbidities, and family history. The rhythm patterns and blood vessel involvement were evaluated using electrocardiography (ECG) and echocardiography. Patients were managed using emergency medication and different revascularization techniques like cardiopulmonary resuscitation in triage, mechanical ventilation, like coronary artery bypass grafting (CABG), and intra-aortic balloon pump (IABP). Major adverse cardiac events (MACE), considered as a composite of non-fatal MI, stroke, and death, were reported during discharge and at 1-month follow-up.

According to the consensus statement, patients were categorized into one of the five classes outlined in the SCAI classification system for CS; Class A: patients at risk of developing CS, Class B: patients showing early signs of CS, Class C: patients with classic CS, Class D: patients whose condition is deteriorating, and Class E: patients in a critical state.[6]

Management Strategy

The treatment approach involved initial stabilization using inotrope, mechanical ventilation, and/or IABP, followed by revascularization before discharge. The treating physician had discretion over specific treatment choices, including inotropic drug selection, IABP use, and timing of revascularization. Revascularization decisions were influenced by factors such as time from symptom onset, ongoing pain or electrical instability, hemodynamic status, end-organ failure, myocardial viability in the infarct-related artery, presence of mechanical complications, and patient consent. Antiplatelet therapy included aspirin, clopidogrel, ticagrelor, and GP IIb/IIIa inhibitors. Two physicians blinded to patient outcomes analyzed each patient's angiographic profile. Significant stenosis was defined as >70% in the left anterior descending (LAD), right coronary, and left circumflex arteries and >50% in the left main coronary artery. Patients were monitored throughout their hospital stay. The median time to appropriate care was 18 hours in the present study.

Statistical Analysis

Data were analyzed using SPSS version 20. Categorical variables are reported as proportions, and continuous variables are reported as mean ± standard deviation. The chi-square test and Student's t-test were employed for the statistical analysis of categorial and continuous variables, respectively. Statistical significance was defined as a *P*-value of 0.05.

RESULTS

The study involved a total of 92 patients, with 48 and 44 patients in the early presentation group (<24 hours) and 44 patients in the late presentation group (≥24 hours). Most patients were male (70.7%) and the average age was 63.4±10.9 years. There was a significant difference in socioeconomic status between the early and late groups, with more patients from the upper middle class in the early group (50.0%) and more patients from the lower class in the late group (40.9%). Similarly, there was a significant difference in terms of area of residence,

with a higher proportion of rural patients in the late group (54.5%) than in the early group (20.8%). Almost all patients (98.9%) presented with chest pain, whereas fewer patients experienced breathlessness (30.4%) and giddiness/syncope (13.0%). Comorbidities such as dyslipidemia, diabetes mellitus, hypertension, thyroid disorders, stroke, and peripheral arterial disease were prevalent in both groups. Regarding mentation, a significant difference was observed between the early and late groups, with more patients being disoriented (70.5%) in the late group than in the early group (18.8%). Table 1 presents the baseline demographic and clinical characteristics of early and late presenters of STEMI complicated with CS.

Among overall patients, the mean left ventricular ejection fraction (LVEF) was 36.9%. In the early group, 19 (39.6%) patients had right ventricular infarction, whereas 14 (31.8%) patients in the late group suffered from the same condition. In terms of MI types, anterior wall MI was the most common, affecting 55.4% of all patients. It was more prevalent in the late group (65.9%) than in the early group (45.8%). Inferior wall MI was the second most common presentation, occurring in 33.7% of all patients, with a higher frequency in the early group (39.6%) than in the late group (27.3%). The percentage of patients who received mechanical ventilation support was higher in the early (43.8%) and late (88.6%) groups than in other revascularization techniques like CABG and IABP, which was statistically significant. The median lactate level was 40.2 mg/dL, and the median troponin T level upon arrival was 0.92 ng/mL. The serum creatinine level was elevated at 2.16 mg/dL at the time of discharge in all patients. The SCAI classification of CS showed that the late group had a higher percentage of patients in stage D (45.5%) and stage E (31.8%) compared with the early group (stage D: 33.3%, stage E: 18.8%). There were no patients from the study falling under stages A and B of the SCAI classification for CS. Tables 2 and 3 present the anthropometric, laboratory investigations, and management of early vs late presenters of STEMI complicated with CS. The median time to symptom onset for appropriate care was 18 h in the present study.

Table 1: Baseline demographics and clinical characteristics of early and late presenters of cardiogenic shock complicating STEMI

Variables	Total (n=92 patients)	Early (<24 hours) (n=48 patients)	Late (≥24 hours) (n=44 patients)	*P*-value
Male, n (%)	65 (70.7)	37 (77.1)	28 (63.6)	0.176
Age, years	63.4±10.9	63.9±10.5	62.7±11.5	0.620
Social habits				
Smoker, n (%)	36 (39.1)	18 (37.5)	18 (40.9)	0.831
Alcoholic, n (%)	13 (14.1)	7 (14.6)	6 (13.6)	1.000
Tobacco chewing frequency, n (%)	17 (18.5)	5 (10.4)	12 (27.3)	0.057
Socioeconomic status				
Lower, n (%)	24 (26.1)	6 (12.5)	18 (40.9)	<0.001
Upper lower, n (%)	22 (23.9)	9 (18.8)	13 (29.5)	
Lower middle, n (%)	17 (18.5)	9 (18.8)	8 (18.2)	
Upper middle, n (%)	29 (31.5)	24 (50.0)	5 (11.4)	
Area of living				
Rural, n (%)	34 (37.0)	10 (20.8)	24 (54.5)	0.003
Semiurban, n (%)	36 (39.1)	23 (47.9)	13 (29.5)	
Urban, n (%)	22 (23.9)	15 (31.3)	7 (15.9)	
Comorbidities				
Dyslipidemia, n (%)	10 (10.9)	6 (12.5)	4 (9.1)	0.742
Diabetes mellitus, n (%)	51 (55.4)	29 (60.4)	22 (50.0)	0.402
Hypertension, n (%)	50 (54.3)	25 (52.1)	25 (52.1)	0.680
Thyroid disorders, n (%)	7 (7.6)	1 (2.1)	6 (13.6)	0.051
Stroke, n (%)	4 (4.3)	2 (4.2)	2 (4.5)	1.000
Peripheral arterial disease, n (%)	3 (3.3)	0 (0.0)	3 (6.8)	0.105
Family history, n (%)	8 (8.7)	5 (10.4)	3 (6.8)	0.716

STEMI: ST-elevation myocardial infarction

Table 2: Anthropometric and laboratory investigations of early and late presenters of cardiogenic shock that complicate STEMI

Variables	Total (n=92 patients)	Early (<24 hours) (n=48 patients)	Late (≥24 hours) (n=44 patients)	*P*-value
ECG rhythmic presentations				
Sinus rhythm, n (%)	66 (73.8)	30 (62.5)	36 (81.8)	0.129
Atrial fibrillation, n (%)	9 (9.8)	6 (12.5)	3 (6.8)	
Heart blocks, n (%)	17 (18.5)	12 (25.0)	5 (11.4)	
MI				
Inferior posterior wall MI, n (%)	10 (10.9)	7 (14.6)	3 (6.8)	0.137
Anterior wall MI, n (%)	51 (55.4)	22 (45.8)	29 (65.9)	0.137
Inferior wall MI, n (%)	31 (33.7)	19 (39.6)	12 (27.3)	0.137
Right ventricular infarction, n (%)	33 (35.9)	19 (39.6)	14 (31.8)	0.516
SCAI stages of cardiogenic shock				
Stage C, n (%)	33 (35.9)	23 (47.9)	10 (22.7)	0.39
Stage D, n (%)	36 (39.1)	16 (33.3)	20 (45.5)	
Stage E, n (%)	23 (25.0)	9 (18.8)	14 (31.8)	
Coronary angiographic findings				
Vessel involvement				
Single vessel disease, n (%)	27 (29.3)	17 (35.4)	10 (22.7)	0.006
Double vessel disease, n (%)	22 (23.9)	14 (29.2)	8 (18.2)	
Multivessel disease, n (%)	34 (36.9)	17 (35.4)	17 (38.8)	
Culprit vessel				
Right coronary artery, n (%)	34 (36.9)	25 (52.1)	9 (19.7)	<0.001
Left anterior descending artery, n (%)	58 (63.0)	33 (68.7)	25 (56.8)	0.122
Left circumflex artery, n (%)	15 (16.3)	13 (26.6)	2 (4.5)	0.039

STEMI: ST-elevation myocardial infarction, MI: Myocardial infarction, ECG: Electrocardiogram, SCAI: Society for cardiovascular angiography and intervention

Table 3: Management of early and late presenters of cardiogenic shock that complicates STEMI

Variables	Total (n=92 patients)	Early (<24 hours) (n=48 patients)	Late (≥24 hours) (n=44 patients)	*P*-value
Emergency management				
Noradrenaline, n (%)	67 (72.8)	43 (89.6)	24 (54.5)	<0.001
Noradrenaline and adrenaline, n (%)	25 (26.2)	5 (10.4)	20 (45.5)	
Oral medication				
Aspirin, n (%)	92 (100)	48 (100)	44 (100)	0.944
Ticagrelor, n (%)	79 (85.9)	45 (93.8)	34 (77.3)	0.035
Clopidogrel, n (%)	13 (14.1)	2 (4.2)	11 (25)	0.006
GP IIb/IIa inhibitors, n (%)	14 (15.2)	11 (22.9)	3 (6.8)	0.042
Revascularization				
Cardiopulmonary resuscitation during triage, n (%)	30 (32.6)	5 (10.4)	25 (56.8)	<0.001
Mechanical ventilation support, n (%)	60 (65.2)	21 (43.8)	39 (88.6)	<0.001
IABP, n (%)	38 (41.3)	17 (35.4)	21 (47.7)	0.291
CABG, n (%)	9 (9.8)	3 (6.3)	6 (13.6)	0.302
PCI, n (%)	83 (91.2)	45 (93.7)	38 (86.4)	0.206

STEMI: ST-elevation myocardial infarction, CABG: Coronary artery bypass graft surgery, IABP: Intra-aortic balloon pump, PCI: Percutaneous coronary intervention

The clinical outcomes of early and late CS patients with STEMI are described in Table 4. Late presentation was associated with significantly higher rates of acute kidney injury (n=32, 72.7%) and in-hospital MACE (n=36, 81.8%), driven primarily by increased in-hospital mortality (n=34, 77.3%) followed by stroke (n=2, 4.5%), although by one month the gap in mortality rates between the two groups had narrowed. Mortality one month after discharge was (2.1%) and in late group (4.5%).

DISCUSSION

CS is the primary cause of mortality among patients hospitalized with AMI. Although a paucity of studies have investigated the timing of CS during AMI hospitalization, none have examined the changing trends in the extent of CS based on the timing of its occurrence. The present study data for patients with early and late presentation of STEMI associated with CS are consistent with the findings from previous studies, which demonstrated a decline in the incidence of adverse outcomes in patients with AMI complicated by CS over time, attributable to earlier hospital presentation.[11,12]

Advanced age, hypertension, diabetes, and smoking are strong predictors of in-hospital mortality among patients who develop CS after AMI and require immediate management.[13] Singh et al.[14] in their study also found a positive association between these factors and higher mortality rates. Nguyen et al.[15] found that older age, presence of diabetes, and presentation with STEMI increased the likelihood of developing complication. However, the present study did not reveal a significant difference in the prevalence of diabetes, hypertension, and smoking between early and late presenters.

In the present study, the mean LVEF was 36.9%, and the early group had a greater number of patients (n=19) with right ventricular infarction. On the other hand, anterior MI was more prevalent among patients in the late group (65.9%) than in the early group. Additionally, both groups exhibited a greater number of patients with multivessel coronary artery disease involvement. Similarly, a study comparing the incidence and outcomes of CS in anterior versus inferior STEMI found that anterior STEMI was more frequently complicated by CS and associated with higher in-hospital mortality.[16] Left ventricular dysfunction is implicated in most CS cases associated with STEMI, and ECG findings are often consistent with recent total occlusion of the LAD artery. The SHOCK trial investigators observed that the predominant cause of CS was left ventricular failure, accounting for 78.5% of all cases assessed in the study.[17]

The SCAI classification system for CS aimed to establish a standardized assessment of disease severity in affected patients, thereby enabling the evaluation of mortality risk associated with varying degrees of the condition.[6] The SCAI classification effectively separated patients with CS into distinct risk categories when applied to an unbiased clinical cohort in the study.[5] Jentzer et al.[18] applied the SCAI CS classification to an unselected cohort of patients and found that it was independently associated with in-hospital mortality. In our study, we observed that most patients in the late group were classified into SCAI stage D (45.5%) and stage E (31.8%). When relating these stages to mortality outcomes, patients in the late group experienced higher in-hospital mortality rates (77.3%) compared with the early group (16.7%), suggesting that advanced SCAI stages correlate with increased mortality risk.

Management and Outcomes

The American Heart Association recommends a stepwise treatment strategy for patients with CS associated with STEMI, beginning with the administration of vasoactive medications followed by the insertion of percutaneous mechanical circulatory support devices if vasoactive medications fail to improve hemodynamic.[19,20] The practice guidelines from both the American and European medical authorities indicate that the use of IABP can be considered a potential intervention. Its purpose is to reduce the afterload

Table 4: Outcomes of early and late presenters of cardiogenic shock that complicate STEMI

Variables	Total (n=92 patients)	Early (<24 hours) (n=48 patients)	Late (≥24 hours) (n=44 patients)	*P*-value
In-hospital AKI, n (%)	50 (54.3)	18 (37.5)	32 (72.7)	0.001
In-hospital MACE				
In- hospital non-fatal MI, n (%)	1 (1.1)	1 (2.1)	0 (0.0)	1.000
In-hospital stroke, n (%)	3 (3.3)	1 (2.1)	2 (4.5)	0.605
In-hospital mortality, n (%)	42 (45.6)	8 (16.7)	34 (77.3)	<0.001
MACE 1 month after discharge				
Nonfatal MI, n (%)	2 (2.2)	2 (5.0)	0 (0.0)	1.000
Stroke, n (%)	1 (1.1)	0 (0.0)	1 (2.3)	1.000
Death by number (%)	3 (3.3)	1 (2.1)	2 (4.5)	0.387

STEMI: ST-elevation myocardial infarction, AKI: Acute kidney injury, MACE: Major adverse cardiac events, MI: Myocardial infarction

on the left ventricle and attempt to stabilize the hemodynamic conditions in patients experiencing mechanical complications arising from AMI.[20,21] IABP may provide a mortality benefit for patients experiencing rapidly decompensating and severe CS.[4] Earlier research has proposed that the downward trajectory of mortality rates among patients with CS arising from AMI can be primarily ascribed to the prompt use of balloon pump devices and the administration of evidence-backed pharmacological interventions.[15] In our study, a higher number of patients in the late group underwent IABP (47.7%), CABG (13.6%), mechanical ventilation (88.6%), and cardiopulmonary resuscitations (56.8%). Whereas 93.7% underwent percutaneous coronary intervention in the early group. Despite the extensive efforts to develop and implement novel therapeutic approaches for CS in the context of AMI, the prognosis for patients afflicted with this condition has remained largely unchanged, with a staggering mortality rate where one out of every two patients succumbs to the condition.[22] A study by Hashmi et al.[13] observed a high frequency (44.73%) of in-hospital mortality among patients who developed CS after AMI. Despite adhering to the guidelines for management and having similar frequencies of factors affecting the condition in both groups, the mortality rate was higher among the late group. These findings underscore the importance of early hospital presentation to improve outcomes.

Study Limitations

This study has several limitations that should be considered. This was a single-center study with a relatively small sample size, which may limit the generalizability of the findings to a wider population. The follow-up period of 1 month may have been insufficient to capture long-term outcomes and the potential impact of late presentation on long-term prognosis. Therefore, larger multi-center studies with longer follow-up periods are warranted to validate the findings and explore the long-term implications of delayed presentation on outcomes and quality of life.

CONCLUSION

The current study underscores the critical importance of early presentation in STEMI complicated by CS. Late presenters experienced significantly worse outcomes, including higher rates of acute kidney injury, MACE, and in-hospital mortality. Socioeconomic factors and rural residence were associated with delayed presentation, highlighting the need for targeted interventions to improve healthcare access and awareness.

Ethics

Ethics Committee Approval: The study protocol was approved by the Kasturba Medical College and Kasturba Hospital Institutional Ethics Committee (approval number: 381/2020, date: 10.07.2020).

Informed Consent: Written informed consent was obtained from all enrolled patients.

Authorship Contributions

Surgical and Medical Practices: N.S., T.D., Concept: N.S., T.D., Design: T.D., Data Collection or Processing: N.S., Analysis or Interpretation: N.S., T.D., Literature Search: N.S., T.D., Writing: N.S., T.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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

REFERENCES

1. Alpert JS, Becker RC. Cardiogenic shock: elements of etiology, diagnosis, and therapy. Clin Cardiol. 1993;16:182-90.
2. Vrints CJ. Update on the management of cardiogenic shock complicating acute myocardial infarction. SAGE Publications Sage UK: London, England: 2020, p. 99-101.
3. Bagai A, Chen AY, Wang TY, Alexander KP, Thomas L, Ohman EM, *et al*. Long-term outcomes among older patients with non-ST-segment elevation myocardial infarction complicated by cardiogenic shock. Am Heart J. 2013;166:298-305.
4. Chang L, Yeh R. Evaluation and management of ST-elevation myocardial infarction and shock. Eur Cardiol. 2014;9:88-91.
5. Schrage B, Dabboura S, Yan I, Hilal R, Neumann JT, Sörensen NA, *et al*. Application of the SCAI classification in a cohort of patients with cardiogenic shock. Catheter Cardiovasc Interv. 2020;96:213-9.
6. Baran DA, Grines CL, Bailey S, Burkhoff D, Hall SA, Henry TD, *et al*. SCAI clinical expert consensus statement on the classification of cardiogenic shock: This document was endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the Society of Critical Care Medicine (SCCM), and the Society of Thoracic Surgeons (STS) in April 2019. Catheter Cardiovasc Interv. 2019;94:29-37.
7. Newby LK, Rutsch WR, Califf RM, Simoons ML, Aylward PE, Armstrong PW, *et al*. Time from symptom onset to treatment and outcomes after thrombolytic therapy. GUSTO-1 Investigators. J Am Coll Cardiol. 1996;27:1646-55.
8. Berger PB, Ellis SG, Holmes DR Jr, Granger CB, Criger DA, Betriu A, *et al*. Relationship between delay in performing direct coronary angioplasty and early clinical outcome in patients with acute myocardial infarction: results from the global use of strategies to open occluded arteries in Acute Coronary Syndromes (GUSTO-IIb) trial. Circulation. 1999;100:14-20.
9. Goldberg RJ, Spencer FA, Fox KA, Brieger D, Steg PG, Gurfinkel E, et al. Prehospital Delay in Patients With Acute Coronary Syndromes (from the Global Registry of Acute Coronary Events [GRACE]). Am J Cardiol. 2009;103:598-603.
10. Welsh RC, Chang W, Goldstein P, Adgey J, Granger CB, Verheugt FW, *et al*. Time to treatment and the impact of a physician on prehospital management of acute ST elevation myocardial infarction: insights from the ASSENT-3 PLUS trial. Heart. 2005;91:1400-6.
11. Jeger RV, Radovanovic D, Hunziker PR, Pfisterer ME, Stauffer JC, Erne P, *et al*. Ten-year trends in the incidence and treatment of cardiogenic shock. Ann Intern Med. 2008;149:618-26.
12. Awad HH, Anderson FA Jr, Gore JM, Goodman SG, Goldberg RJ. Cardiogenic shock complicating acute coronary syndromes: insights from the Global Registry of Acute Coronary Events. Am Heart J. 2012;163:963-71.

13. Hashmi KA, Abbas K, Hashmi AA, Irfan M, Edhi MM, Ali N, *et al*. In-hospital mortality of patients with cardiogenic shock after acute myocardial infarction; impact of early revascularization. BMC Res Notes. 2018;11:721.

14. Singh M, White J, Hasdai D, Hodgson PK, Berger PB, Topol EJ, *et al*. Long-term outcome and its predictors among patients with ST-segment elevation myocardial infarction complicated by shock: insights from the GUSTO-I trial. J Am Coll Cardiol. 2007;50:1752-8.

15. Nguyen HL, Yarzebski J, Lessard D, Gore JM, McManus DD, Goldberg RJ. Ten-Year (2001-2011) Trends in the Incidence Rates and Short-Term Outcomes of Early Versus Late Onset Cardiogenic Shock After Hospitalization for Acute Myocardial Infarction. J Am Heart Assoc. 2017;6:e005566.

16. Gupta T, Weinreich M, Kolte D, Khera S, Villablanca PA, Bortnick AE, *et al*. Comparison of incidence and outcomes of cardiogenic shock complicating posterior (inferior) versus anterior ST-elevation myocardial infarction. Am J Cardiol. 2020;125:1013-9.

17. Hochman JS, Buller CE, Sleeper LA, Boland J, Dzavik V, Sanborn TA, *et al*. Cardiogenic shock complicating acute myocardial infarction--etiologies, management and outcome: a report from the SHOCK Trial Registry. J Am Coll Cardiol. 2000;36(3 Suppl A):1063-70.

18. Jentzer JC, van Diepen S, Barsness GW, Henry TD, Menon V, Rihal CS, *et al*. Cardiogenic shock classification to predict mortality in the cardiac intensive care unit. J Am Coll Cardiol. 2019;74:2117-28.

19. Henry TD, Tomey MI, Tamis-Holland JE, Thiele H, Rao SV, Menon V, *et al*. Invasive Management of Acute Myocardial Infarction Complicated by Cardiogenic Shock: A Scientific Statement From the American Heart Association. Circulation. 2021;143:815-29.

20. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, *et al*. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;61:485-510.

21. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, *et al*. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021;42:1289-367. Erratum in: Eur Heart J. 2024 Feb 1;45(5):404-5.

22. Muzafarova T, Motovska Z. Laboratory predictors of prognosis in cardiogenic shock complicating acute myocardial infarction. Biomedicines. 2022;10:1328.

DOI: 10.4274/ijca.2024.92485
Int J Cardiovasc Acad 2024;10(3):60-61

Can Geographical and Socioeconomic Status be the Best Prognostic Indicators of Cardiogenic Shock in the Modern Era of PCI?

Beytullah Çakal

Department of Cardiology, İstanbul Medipol University Faculty of Medicine, İstanbul, Turkey

Keywords: Cardiogenic shock, heart failure, intensive care, myocardial infarction

Dear Editor,

The incidence of cardiogenic shock (CS) is about 5-10% of the cases complicated by acute myocardial infarction (AMI).[1] Regrettably, despite increased rates of early revascularization, improvement in mechanical support devices (MCS), and adjunctive pharmacotherapies, mortality still remains high at about 50% at first month.[2] The devastating effect of shock in terms of major cardiovascular effect (MACE) among surviving patients after hospitalization declines slightly by the time, with similar mortality rates beyond one year compared with the non-shock group.[3] Therefore, new adjunctive strategies to reduce the occurrence and burden of CS to prevent and overcome this complication should be designed and implemented.

In this issue of the Journal, Shenoy et al.[4] provided data from a tertiary care center regarding MACE rates among early and late presenters with CS and emphasized socioeconomic disparities and the effects of rurality as important factors for MACE rates. They collected 92 patients with AMI complicated by CS and divided them into two groups according to the timing of presentation: early presenters (<24 hours, n=48) and late presenters >24 hours). The main finding was that late presenters with CS had a higher risk of in-hospital MACE (2.1% vs. 4.5%), primarily driven by increased in-hospital mortality and acute kidney injury (37.5% vs. 72.4%), whereas the gap in mortality tended to narrow at the first month follow-up. After considering the social determinants of presentation timing, lack of healthcare access for rural residents and low socioeconomic status (SES) were associated with a higher risk of developing late presentation.

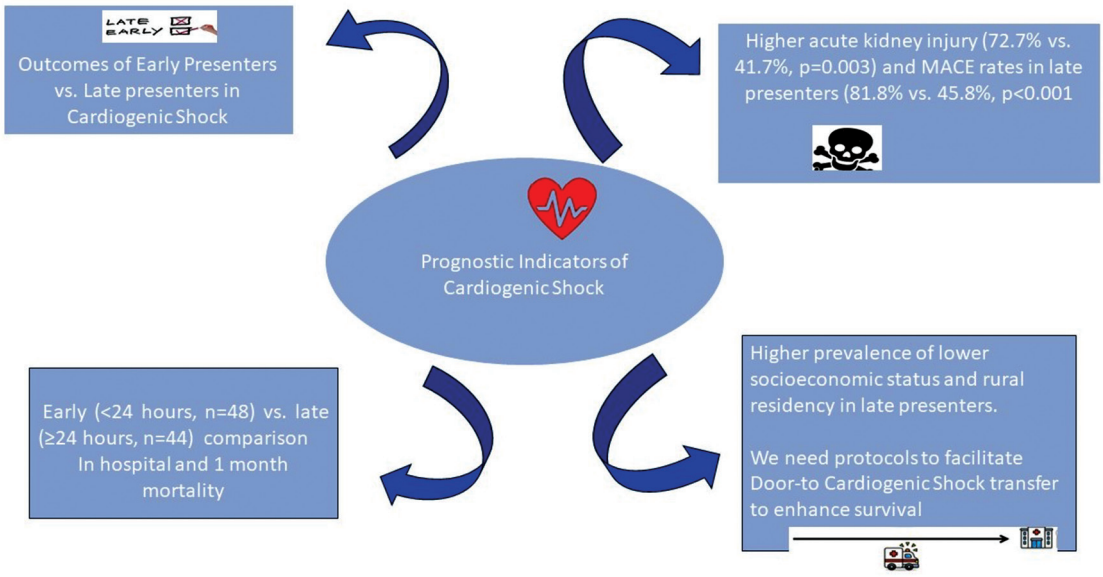
The exceptionally high mortality rates in myocardial infarction patients experiencing CS highlight the shortcomings of conventional therapies. This should motivate us to investigate potentially adjustable factors that could enhance outcomes. Short-term acute mechanical circulatory support should be implemented when urgent hemodynamic compromise occurs in appropriately selected patients, as per the 2022 AHA (Class IIa, Level of evidence B-NR) and the 2021 ESC (IIa, C) recommendations. Crucially, there is no evidence to favor one MCS over another, and device selection varies by country and local expertise. Only IABP was used as the MCS in this study. Using other MCS devices, such as VA-ECMO or Impella, or combining them in these patients could also enhance survival, but future larger multicenter studies are required as well.

Recent data highlight the crucial necessity for timely implementation of MCS, especially in cases of MI-related CS, and this study makes a valuable contribution to the field.[5]

To cite this article: Beytullah Çakal. Can Geographical and Socioeconomic Status be the Best Prognostic Indicators of Cardiogenic Shock in the Modern Era of PCI? Int J Cardiovasc Acad. 2024;10(3):60-61

Address for Correspondence: Beytullah Çakal, Department of Cardiology, İstanbul Medipol University Faculty of Medicine, İstanbul, Turkey
E-mail: bcakal@hotmail.com
ORCID ID: orcid.org/0000-0003-0230-6575

Received: 03.09.2024
Revised: 06.09.2024
Accepted: 09.09.2024
Published Online: 18.09.2024



Graphical abstract of the present study

The authors found that patients with CS living in rural areas had significantly higher in-hospital mortality and adverse cardiovascular outcomes. Although there have been many innovations in percutaneous coronary interventions over the years and technological advancements are continually being sought, mortality rates have changed only slightly. Thus, this study is important in demonstrating that efforts to improve patients' access to health care services could significantly reduce mortality in the management of CS. Few studies have highlighted this issue. Recently, Naumann et al.[6] compared 30-day mortality in a large patient cohort (1720 CS patients) during on-hour and off-hours admission and found increased mortality during off-hours due to delays (41% vs. 48%).[6]

Previously, data from high-income countries have indicated that patients with AMI from lower SES backgrounds tend to experience longer reperfusion times.[7] Additionally, patients from lower SES areas are less frequently admitted to centers of excellence for cardiovascular care, thereby leading to a lower usage of MCS devices. Findings of this study are in line with data from high-income countries.

These findings highlight the necessity of recognizing this vulnerable patient group and underscore the importance of implementing policies that address specialized multidisciplinary teams with extensive expertise in managing patients with CS.

Ethics

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

REFERENCES

1. Anderson ML, Peterson ED, Peng SA, Wang TY, Ohman EM, Bhatt DL, *et al.* Differences in the profile, treatment, and prognosis of patients with cardiogenic shock by myocardial infarction classification: A report from NCDR. Circ Cardiovasc Qual Outcomes. 2013;6:708-15.
2. Arrigo M, Price S, Baran DA, Pöss J, Aissaoui N, Bayes-Genis A, *et al.* Optimising clinical trials in acute myocardial infarction complicated by cardiogenic shock: a statement from the 2020 Critical Care Clinical Trialists Workshop. Lancet Respir Med. 2021;9:1192-202.
3. Singh M, White J, Hasdai D, Hodgson PK, Berger PB, Topol EJ, *et al.* Long-term outcome and its predictors among patients with ST-segment elevation myocardial infarction complicated by shock: insights from the GUSTO-I trial. J Am Coll Cardiol. 2007;50:1752-8.
4. Shenoy N, Devasia T. Comparison of Outcomes between Early and Late Presentation of ST-elevation Myocardial Infarction in Patients with Cardiogenic Shock. Int J Cardiovasc Acad. 2024;10:53-9.
5. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. 2022;24:4-131.
6. Naumann D, Fischer J, Gmeiner J, Lüsebrink E, Beer BN, Grieger M, *et al.* The association of off-hour vs. on-hour intensive care unit admission time with mortality in patients with cardiogenic shock: a retrospective multi-centre analysis. Eur Heart J Acute Cardiovasc Care. 2024;13:347-53.
7. Bergström G, Redfors B, Angerås O, Dworeck C, Shao Y, Haraldsson I, *et al.* Low socioeconomic status of a patient's residential area is associated with worse prognosis after acute myocardial infarction in Sweden. Int J Cardiol. 2015;182:141-7.

RESEARCH ARTICLE

DOI: 10.4274/ijca.2024.85856
Int J Cardiovasc Acad 2024;10(3):62-69

Assessment of Endothelial Dysfunction in T2DM: A Doppler Ultrasound Study Correlated with CRP Levels, Glycemic Control, and BMI

Surya Prakash Sabapathi[1], Karthikeyan Selvaraj[2], Amirtha Ganesh Balasubramaniyan[3]

[1]Department of Cardiology, Panimalar Medical College Hospital and Research Institute, Chennai, India
[2]Department of Cardiology, Mahatma Gandhi Medical College and research Institute, Puducherry, India
[3]Department of Cardiology, All India Institute of Medical Sciences, Mangalagiri, India

Abstract

Background and Aim: Endothelial dysfunction is a crucial precursor to atherosclerosis and cardiovascular complications, particularly prevalent in individuals with type 2 diabetes mellitus (T2DM). This study aimed to assess endothelial impairment in T2DM using flow-mediated dilatation (FMD) and to determine its correlation with body mass index (BMI), duration of diabetes, C-reactive protein (CRP) levels, and glycemic control.

Materials and Methods: A total of 100 T2DM patients aged thirty to sixty participated. Doppler ultrasonography was used to measure brachial artery FMD, while blood samples were used to assess glycosylated hemoglobin A1c (HbA1c) and CRP levels. Correlations were evaluated using the Pearson correlation coefficient.

Result: The duration of diabetes r value is negative 0.866, p-value less than 0.001, CRP levels as "r value" is negative 0.724, "*P*-value" less than 0.001, and HbA1c levels "r value" is negative 0.722, "*P*-value" less than 0.001 were observed to have negative relationships with FMD. Additionally, there was a significant association r value was negative 0.342, "*P*-value" less than 0.001 between BMI and FMD. These results were corroborated by subgroup analyses, which highlighted the intricacy of "endothelial dysfunction" in T2DM and the significance of comprehensively addressing several risk variables. This study elucidates the intricate interplay of metabolic, inflammatory, and vascular factors contributing to "endothelial dysfunction" in T2DM patients. Elevated HbA1c and CRP levels, prolonged diabetes duration, and high BMI were linked to impaired endothelial function, underscoring the importance of holistic risk factor management.

Conclusion: For patients with T2DM, maintaining endothelial function and reducing cardiovascular risk require comprehensive treatment plans that target inflammation, obesity, and glycaemic management. Timely intervention and vigilant monitoring of risk factors are crucial to prevent vascular complications in high-risk populations.

Keywords: Endothelial dysfunction, cardiovascular risk, glucose regulation, flow-mediated dilatation, T2DM, CRP

To cite this article: Sabapathi SP, Selvaraj K, Balasubramaniyan AG. Assessment of Endothelial Dysfunction in T2DM: A Doppler Ultrasound Study Correlated with CRP Levels, Glycemic Control, and BMI. Int J Cardiovasc Acad. 2024;10(3):62-69

Address for Correspondence: Surya Prakash Sabapathi, Department of Cardiology, Panimalar Medical College Hospital and Research Institute, Chennai, India
E-mail: dr.suriya01@gmail.com
ORCID ID: orcid.org/0000-0002-0095-0853

Received: 18.06.2024
Revised: 29.08.2024
Accepted: 03.09.2024
Published Online: 18.09.2024

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a widespread health issue characterized by insulin resistance, elevated blood sugar levels, and increased susceptibility to cardiovascular issues.[1] "Endothelial dysfunction" is a notable risk factor for atherosclerosis and cardiovascular disease among the various complications associated with T2DM. The equilibrium between vasodilation and vasoconstriction is crucial, and when "endothelial dysfunction" occurs, characterized by reduced vascular endothelial cell function, it disrupts this balance, leading to vascular damage and organ dysfunction.[2] Understanding the mechanisms and implications of "endothelial dysfunction" in T2DM is imperative for devising effective preventive and therapeutic strategies to mitigate cardiovascular risk in this population.

One layer of endothelial cells that lines the inside of blood arteries is called the vascular endothelium, and it is essential for preserving vascular homeostasis. Through the production of numerous vasoactive chemicals, including as nitric oxide (NO), prostacyclin, and endothelin-1, endothelial cells control vascular tone, inflammation, thrombosis, and angiogenesis. NO exhibits the most potent vasodilatory properties by enhancing leukocyte adherence and platelet aggregation while simultaneously relaxing vascular smooth muscle cells.[3] "Endothelial dysfunction" in the context of T2DM leads to a reduction in the availability of NO and an increase in the synthesis of endothelium-derived molecules that promote vasoconstriction.[4]

One of the main characteristics of T2DM is elevated blood glucose, which is important in the development of "endothelial dysfunction". Extended exposure to elevated glucose concentrations triggers a sequence of metabolic and biochemical alterations in endothelial cells, culminating in compromised endothelial performance.[5] High blood sugar causes oxidative stress, inflammation, and advanced glycation end products , all of which worsen vascular damage and impede endothelial cell function.[6] Consequently, individuals with T2DM exhibit increased susceptibility to "endothelial dysfunction", predisposing them to accelerated atherosclerosis and cardiovascular events.

The assessment of endothelial function is a valuable tool for evaluating cardiovascular risk and disease progression in T2DM.[7] To evaluate endothelial function, Doppler ultrasonography is commonly used to quantify flow-mediated dilation (FMD) in the brachial artery. This non-invasive technique determines the artery's ability to expand in response to heightened blood flow, primarily induced by the endothelial cells' release of NO.[8,9] Impaired FMD reflects "endothelial dysfunction" and predicts adverse cardiovascular outcomes in T2DM.

Circulating biomarkers provide insights into the underlying causes of "endothelial dysfunction" in diabetes mellitus second type, complementing the information obtained from FMD. C-reactive protein (CRP), an acute-phase reactant and indicator of systemic inflammation, correlates with endothelial activation and dysfunction.[10] Elevated CRP levels in patients with T2DM indicate increased cardiovascular risk and reflect the inflammatory milieu conducive to "endothelial dysfunction".[11] Thus, correlating CRP levels with FMD offers a comprehensive assessment of the inflammatory component of "endothelial dysfunction" in T2DM.

Moreover, glycemic control, as reflected by glycosylated hemoglobin A1c (HbA1c) levels, plays a pivotal role in modulating endothelial function in T2DM. Prolonged hyperglycemia exacerbates endothelial damage, impairs NO bioavailability and promoting atherosclerosis. Consequently, optimizing glycemic control represents a cornerstone in the management of T2DM to mitigate "endothelial dysfunction" and reduce cardiovascular risk.

Considering these factors, the purpose of this study was to evaluate "endothelial dysfunction" using Doppler ultrasonography for FMD of the brachial artery in patients with T2DM. Evaluation and comparison of the degree of "endothelial dysfunction" will be conducted with systemic inflammation, as indicated by CRP levels, and glycemic management, as indicated by HbA1c levels. Furthermore, the relationships between diabetes length, body mass index (BMI), and the degree of "endothelial dysfunction" will be investigated in this study. In order to improve understanding of cardiovascular pathogenesis and direct targeted therapeutic approaches to reduce morbidity and mortality in this at-risk population, this study aimed to shed light on the intricate interactions between inflammatory, vascular, and metabolic factors that contribute to "endothelial dysfunction" in second type diabetes.

MATERIALS AND METHODS

Study Design

To gain insight into "endothelial dysfunction" among individuals with second type diabetes mellitus, this study adopted an observational methodology. Conducted jointly by the Institute of "Internal Medicine and the Institute of Diabetology", affiliated with Madras Medical College and Rajiv Gandhi Government General Hospital in Chennai, the research spans a duration of six months.

Sample Size and Selection Criteria

A total of 100 patients who met specific inclusion and exclusion criteria were enrolled in the study. The inclusion criteria were individuals aged between 30 and 60 years with a confirmed

diagnosis of T2DM. The exclusion criteria include individuals aged over 60 years, those with type 1 diabetes mellitus, pregnant women, critically ill patients, current smokers, and individuals with systemic hypertension or dyslipidemia under treatment.

Data Collection

Before being included in the study, participants must submit a comprehensive history taking, clinical assessment, and informed consent. Serum CRP and HbA1c levels, which are biomarkers of systemic inflammation and glycemic control, are assessed using blood samples.

Assessment of Endothelial Function

The procedure involves placing a pneumatic cuff on the forearm distal to the image site and inflating it to a suprasystolic pressure for 5 min. Upon deflation, shear stress causes the release of vasodilators like NO, which diffuses into the vascular smooth muscles, causing relaxation and vasodilatation. The change in brachial artery diameter from baseline to its maximum increase was used to calculate FMD, expressed as a percentage. However, for accurate data comparison between centers, standardization of this method is crucial.

There are five critical elements in FMD methodology that require standardization. The position of the probe is essential, with the cuff placed distal to it. The shear stress induced by cuff occlusion should last for 5 min to optimize reactive hyperemia. High-quality stereotactic images should be captured using a stereotactic apparatus. Environmental factors such as room temperature, time of day, and consumption of fatty foods or caffeine must be controlled. Additionally, reactive hyperemic stimuli, including cuff position, shear stress duration, and ischemia, should be standardized. Physiological variables like arterial stiffness, flow pattern, and blood viscosity should also be considered for consistency across studies (Figure 1).

Statistical Analysis

The demographic details and laboratory results of the participants were compiled using descriptive statistics. The association between FMD, CRP levels, HbA1c levels, illness duration, and BMI was evaluated using Pearson correlation analysis. Multivariate regression analysis can be used to account for possible confounders. "$P < 0.05$ is the threshold for statistical significance". The Institutional Ethics Committee of Madras Medical Collage approved the study protocol (study no: 07032016, date: 22.03.2016). Every participant provided informed consent, and study-wide participant data confidentiality was maintained.

RESULTS

This study assessed endothelial dysfunction in patients with T2DM using FMD and analyzed its correlation with various parameters, such as CRP levels, HbA1c, and BMI. The results of the present study provide significant insights into the relationship between endothelial function and these parameters.

The analysis of FMD in relation to age groups in Table 1 and Graph 1. demonstrated a clear pattern: younger individuals (31-40 years) exhibited a higher prevalence of FMD greater

Table 1: Distribution of age, HBA1c, CRP, BMI, and duration of DM based on FMD

Age wise distribution of flow-mediated diatation				
FMD group	**31-40 years**	**41-50 years**	**51-60 years**	**Total**
<5	0	10	32	42
	0.00%	31.20%	80.00%	42.00%
>5	28	22	8	58
	100.00%	68.80%	20.00%	58.00%
Total	28	32	40	100
	100.00%	100.00%	100.00%	100.00%
FMD with HBA1c				
HBA1c_group	**>5**	**<5**	**Total**	
<6.5	16	0	16	
	100.00%	0.00%	16.00%	
>6.5	42	42	84	
	50.00%	50.00%	84.00%	
Total	58	42	100	
	58.00%	42.00%	100.00%	
FMD with CRP levels				
FMD_group	**CRP group <5**	**CRP group >5**	**Total**	
>5	32	26	58	
	100.00%	38.20%	58.00%	
<5	0	42	42	
	0.00%	61.80%	42.00%	
Total	32	68	100	
	100.00%	100.00%	100.00%	
FMD with BMI				
FMD group	**<19**	**19-25**	**Above 25**	**Total**
>5	4	34	20	58
	100.00%	70.80%	41.70%	58.00%
<5	0	14	28	42
	0.00%	29.20%	58.30%	42.00%
Total	4	48	48	100
	100.00%	100.00%	100.00%	100.00%

FMD: Flow-mediated dilatation, BMI: Body mass index, HbA1c: Hemoglobin A1c, CRP: C-reactive protein, DM: Diabetes mellitus

than 5, with 100% of them falling into this category. In contrast, the prevalence of FMD >5 decreased notably with age, as evidenced by only 31.2% in the 41-50 years group and 20% in the 51-60 years group. This decline suggests that endothelial function deteriorates with advancing age, as indicated by the lower percentage of individuals with better FMD in the older age brackets.

In Table 2 and Graph 2, a strong correlation was observed between FMD and HbA1c levels. Patients with HbA1c levels >6.5% had a 50% prevalence of FMD >5, whereas none of the patients with HbA1c levels 6.5% exhibited FMD >5. This finding underscores the impact of poor glycemic control on endothelial function, indicating that higher HbA1c levels are associated with impaired endothelial performance.

The correlation between FMD and CRP levels also revealed significant findings. Patients with CRP levels exceeding 5 mg/L had an FMD >5 in only 38.2% of cases, whereas those with CRP levels below 5 mg/L had an FMD >5 in all cases. This suggests that elevated CRP levels, which are indicative of increased inflammation, are associated with reduced endothelial function.

BMI's relationship with FMD showed that a higher BMI was linked to poorer endothelial function. Specifically, individuals with a BMI >25 had only a 41.7% prevalence of FMD >5 compared with 70.8% in those with a BMI between 19-25 and 100% in those with a BMI 19. These data highlight the detrimental effect of high BMI on endothelial health.

Correlation analysis across the entire study cohort revealed strong negative correlations between FMD and HbA1c ($r = -0.724$, $P < 0.001$) and CRP ($r = -0.866$, $P < 0.001$), and a moderate negative correlation with BMI ($r = -0.342$, $P < 0.001$). These results indicate that worsening glycemic control, inflammation, and BMI are associated with impaired endothelial function.

Further analysis of the subgroups in Table 3 and Graph C, Table 4 and Graph D provides additional insights. In Group I, which consisted of patients with T2DM without other comorbidities, FMD showed very strong negative correlations with CRP levels ($r = -0.803$, $P < 0.001$) and duration of diabetes ($r = -0.802$, $P < 0.001$). However, HbA1c had a less pronounced correlation ($r = -0.397$, $P < 0.004$). Conversely, in Group II, which included patients with T2DM and other comorbidities, CRP levels ($r = -0.850$, $P < 0.001$) and duration of diabetes ($r = -0.767$, $P < 0.001$) showed strong negative correlations with FMD, while HbA1c had a similar strong correlation ($r = -0.759$, $P < 0.001$). BMI also demonstrated a moderate correlation ($r = -0.343$, $P = 0.015$) in this group.

In conclusion, the present study highlights a significant association between endothelial dysfunction and poor glycemic control, elevated inflammation, and high BMI in patients with T2DM. These findings suggest that addressing these factors could potentially improve endothelial function and overall vascular health in this population.

DISCUSSION

The results of this study provide valuable insights into the relationship between endothelial dysfunction and various factors in T2DM patients, with a focus on FMD and its correlation with HbA1c, CRP levels, and BMI.

Our findings indicate a notable decline in endothelial function with advancing age. Younger individuals (31-40 years) showed a significantly higher prevalence of FMD greater than 5 compared to older age groups. This decline is consistent with the existing literature on age-related endothelial dysfunction, possibly due to increased oxidative stress and reduced NO bioavailability. The deterioration of endothelial function in older adults is well documented and likely to be intensified in the context of T2DM.

Table 2: Correlation analysis of FMD and related variables

Variable	Pearson correlation	*P*-value	n
FMD	-0.722	<0.001	100
HBA1c	-0.724	<0.001	100
CRP	-0.866	<0.001	100
BMI	-0.342	<0.001	100

FMD: Flow-mediated dilatation, BMI: Body mass index, HbA1c: Hemoglobin A1c, CRP: C-reactive protein

Table 3: Correlation analysis of FMD and related variables in group I type 2 diabetes mellitus patients without other comorbidities

Variable	Pearson correlation	*P*-value	n
FMD	-0.927	<0.001	50
CRP	-0.803	<0.001	50
Duration	-0.802	<0.001	50
HbA1c	-0.397	<0.004	50

FMD: Flow-mediated dilatation, BMI: Body mass index, HbA1c: Hemoglobin A1c, CRP: C-reactive protein, DM: Diabetes mellitus

Table 4: Correlation analysis of FMD and related variables among patients with group II type 2 diabetes mellitus and other comorbidities

Variable	Pearson correlation	*P*-value	n
CRP	-0.850	<0.001	50
Duration	-0.767	<0.001	50
HbA1C	-0.759	<0.001	50
BMI	-0.343	0.015	50

FMD: Flow-mediated dilatation, BMI: Body mass index, HbA1c: Hemoglobin A1c, CRP: C-reactive protein, DM: Diabetes mellitus

The strong negative correlation between HbA1c levels and FMD underscores the impact of poor glycemic control on endothelial health. Patients with higher HbA1c levels, which are indicative of chronic hyperglycemia, showed markedly reduced endothelial function. This finding is consistent with previous studies that established a link between high HbA1c and endothelial dysfunction in patients with diabetes. Chronic elevated blood glucose levels contribute to endothelial damage through several mechanisms, including the formation of advanced glycation end products and increased oxidative stress, which impair endothelial NO production and function.

Similarly, the significant negative correlation between CRP levels and FMD highlights the role of inflammation in endothelial dysfunction. Elevated CRP levels, a marker of systemic inflammation, were associated with reduced FMD. This finding corroborates the hypothesis that inflammatory processes contribute to endothelial impairment in diabetes. CRP-induced endothelial dysfunction is thought to result from inflammatory cytokines that adversely affect endothelial cell function and promote atherogenesis.

The relationship between BMI and FMD suggests that obesity further exacerbates endothelial dysfunction. Higher BMI values were associated with poorer endothelial function, consistent with existing research that links obesity to endothelial impairment. Excess adiposity contributes to endothelial dysfunction through various mechanisms, including increased production of inflammatory cytokines, elevated oxidative

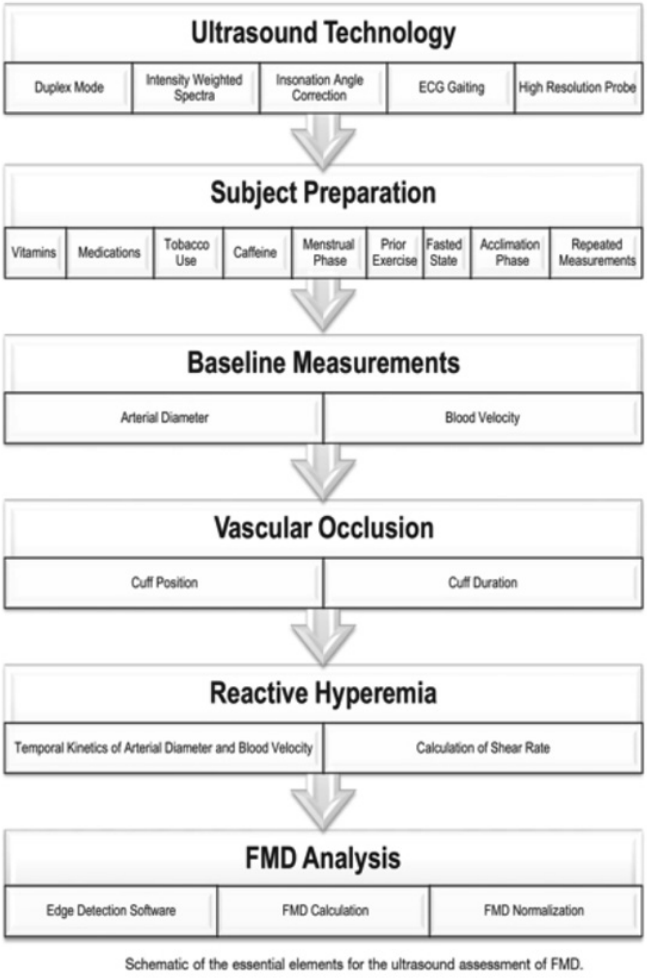
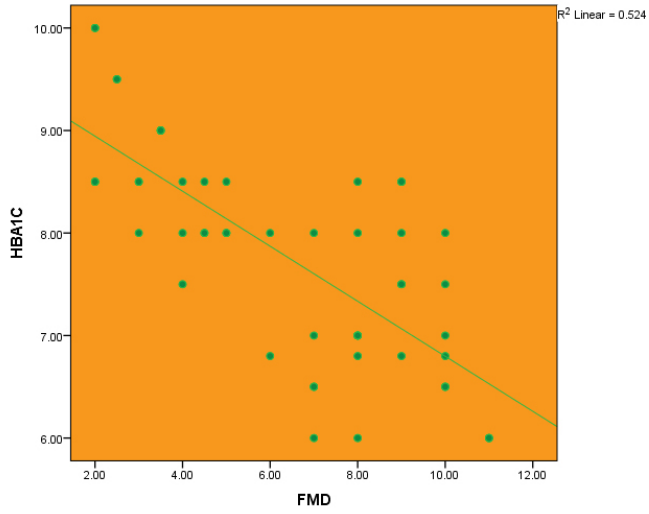


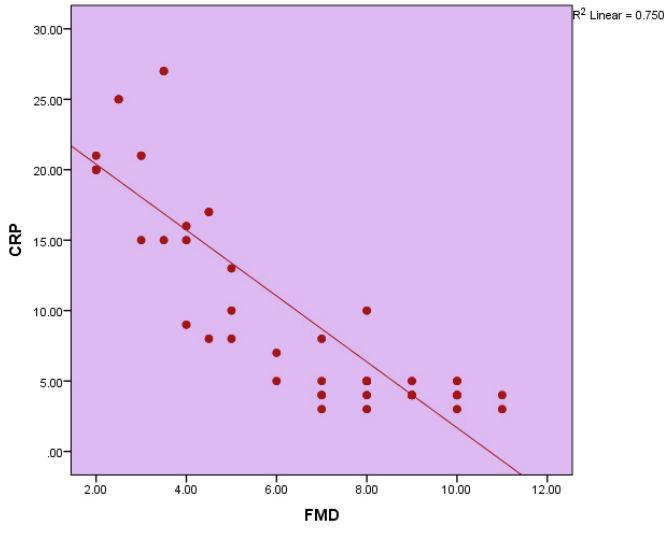
Figure 1: Essential elements for USG assessment of FMD

USG: Ultrasonography, FMD: Flow-mediated dilatation



Graph 1: The following diagram shows the correlation between FMD and HbA1c in 100 subjects

FMD: Flow-mediated dilatation, HbA1c: Hemoglobin A1c

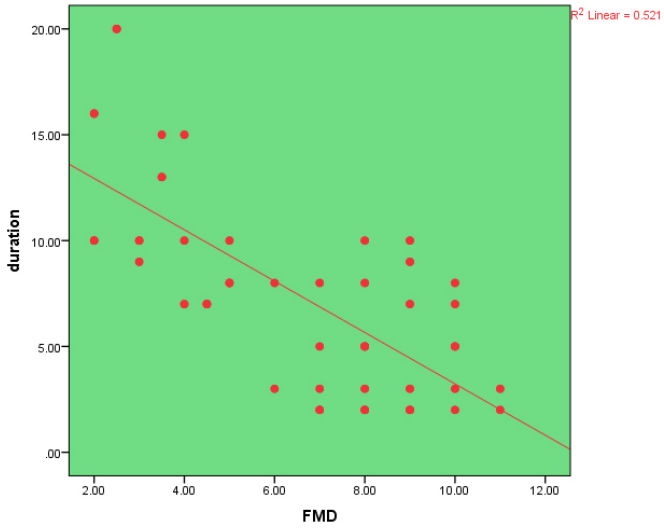


Graph 2: The following diagram shows the correlation between FMD and CRP in 100 subjects

FMD: Flow-mediated dilatation, CRP: C-reactive protein

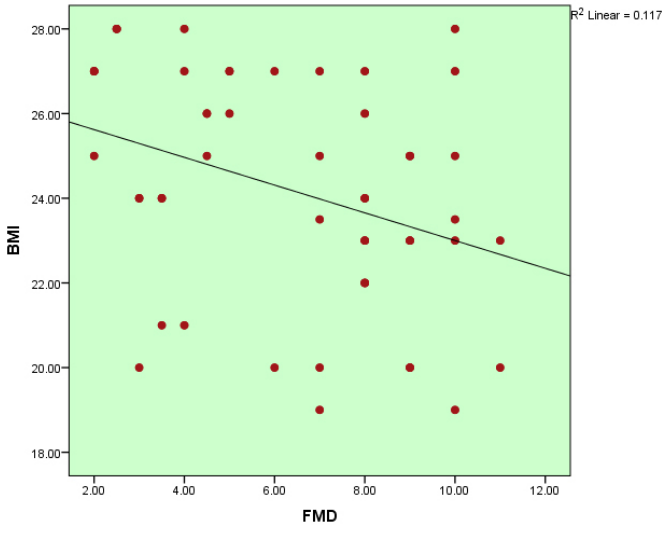
stress, and altered metabolic pathways. The findings indicate that managing BMI could be a crucial factor in improving endothelial function in patients with T2DM.

Subgroup analyses reveal additional nuances. In patients with T2DM without other comorbidities (Group I), FMD showed a strong negative correlation with CRP levels and diabetes duration. This suggests that systemic inflammation and longer duration of diabetes can significantly affect endothelial function. In contrast, patients with T2DM and other comorbidities (Group II) showed strong correlations between FMD and both CRP levels and HbA1c, with BMI also showing a moderate correlation. The presence of additional comorbidities can compound the effects of poor glycemic control and inflammation on endothelial function.



Graph 3: The following diagram shows the correlation between FMD and the duration of diabetes in the 100 subjects included in the study

FMD: Flow-mediated dilatation



Graph 4: The following diagram shows the correlation between FMD and BMI in 100 subjects

FMD: Flow-mediated dilatation, BMI: Body mass index

Overall, our study highlights the multifaceted nature of endothelial dysfunction in T2DM. The interplay between glycemic control, inflammation, and obesity underscores the need for comprehensive management strategies targeting these factors. Effective control of blood glucose levels, systemic inflammation reduction, and weight management are crucial for improving endothelial function and reducing cardiovascular risk in patients with T2DM. Future research should explore interventions targeting these factors to further elucidate their impact on endothelial health and overall cardiovascular outcomes in patients with diabetes.

The study "Association of Endocan, ischemia-modified albumin (IMA), and high-sensitivity CRP (hsCRP) Levels With Endothelial Dysfunction" in T2DM demonstrates the strong relationship that exists between "endothelial dysfunction" in T2DM and biomarkers, such as endocan, IMA, and hsCRP. T2DM patients with "endothelial dysfunction" showed higher levels of endocan, hsCRP, and IMA than those without, suggesting that these variables may operate as separate risk factors for vascular impairment in this group.[12]

The research titled "Association of Endocan, IMA, and hsCRP Levels With Endothelial Dysfunction" in T2DM demonstrated a strong correlation between biomarkers, such as endocan, IMA, and hsCRP, and "endothelial dysfunction" in individuals with T2DM. Elevated levels of endocan, hsCRP, and IMA were observed in T2DM patients with "endothelial dysfunction" compared with those without, suggesting that these biomarkers may serve as independent indicators of vascular impairment in this population.[13]

In contrast, the study "endothelial dysfunction" and platelet hyperactivity in T2DM; molecular insights and therapeutic strategies highlights the role of inflammation, insulin resistance, and hyperglycemia in promoting atherosclerotic vascular complications and offers molecular insights into the pathogenesis of these conditions in T2DM.[14]

Moreover, the article "Resistin levels and inflammatory and endothelial dysfunction" markers in obese postmenopausal women with T2DM clarifies the relationships between resistin levels and "endothelial dysfunction" and inflammatory markers in obese postmenopausal women with T2DM. A greater risk of coronary heart disease was shown to be independently

correlated with elevated resistin levels, highlighting resistin's potential as a biomarker for cardiovascular risk assessment in this group.[15]

Additionally, there is a correlation between resistin levels and markers of inflammation and endothelial dysfunction in obese postmenopausal women with T2DM. This was clarified in the paper "Resistin levels and inflammatory and endothelial dysfunction" in obese postmenopausal women with T2DM. Elevated resistin levels were independently linked with an increased risk of coronary heart disease, suggesting the potential of resistin as a biomarker for cardiovascular risk assessment in this population.[16]

Adiponectin, CRP, and endothelial function were evaluated in "Type II diabetic and non-diabetic individuals" after "acute myocardial infarction (AMI)" in the research "Persistent endothelial dysfunction" is related to elevated CRP levels in patients with type II diabetes after AMI. Patients with T2DM were shown to have persistent endothelium-dependent dysfunction and inflammatory activity, which may have an impact on their lower risk of coronary artery disease.[17]

In the article "T2DM mellitus worsens arterial stiffness in hypertensive patients through endothelial dysfunction", researchers looked at the relationship between arterial stiffness and endothelial function in hypertensive patients with and without T2DM. Results showed that T2DM, especially in hypertensive individuals with diabetes mellitus, increased arterial stiffness by exacerbating "endothelial dysfunction", as seen by higher pulse wave velocity and reduced FMD.[18]

All the factors considered advance our comprehension of the multifactorial nature of "endothelial dysfunction" in T2DM and underscore the importance of identifying biomarkers for risk assessment and therapeutic targeting in this population.

Study Limitations

As a cross-sectional study, data are captured at a single point in time, which prevents the establishment of causal relationships between endothelial dysfunction and the various metabolic, inflammatory, and anthropometric factors examined.

There may be unmeasured confounding variables that influence endothelial function in T2DM, such as lifestyle factors (diet, physical activity), medication adherence, and other comorbid conditions, which were not accounted for in the analysis.

Doppler ultrasonography is a widely accepted non-invasive method for assessing endothelial function, but it may be subject to operator variability and technical limitations.

CONCLUSION

This study sheds light on the intricate connection between "endothelial dysfunction" and various vascular, inflammatory, and metabolic factors in individuals diagnosed with T2DM. The observation of noteworthy associations between FMD and variables such as glycemic management, CRP levels, diabetes duration, and BMI underscores the complex characteristics of diabetic vasculopathy. Optimizing glycemic control, attenuating inflammation, addressing obesity, and promoting cardiovascular health are critical strategies to mitigate cardiovascular risk in individuals with T2DM. These findings emphasize the importance of comprehensive risk factor management for preventing vascular complications and underscore the need for targeted interventions aimed at preserving endothelial function and improving vascular outcomes in high-risk populations.

Acknowledgment

We extend our appreciation to all healthcare professionals involved in diagnosing and managing patients included in this study.

REFERENCES

1. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, *et al*. Pathophysiology of Type 2 Diabetes Mellitus. Int J Mol Sci. 2020;21:6275.
2. Sandoo A, van Zanten JJ, Metsios GS, Carroll D, Kitas GD. The endothelium and its role in regulating vascular tone. Open Cardiovasc Med J. 2010;4:302-12.
3. Rajendran P, Rengarajan T, Thangavel J, Nishigaki Y, Sakthisekaran D, Sethi G, *et al*. The vascular endothelium and human diseases. Int J Biol Sci. 2013;9:1057-69.
4. Dhananjayan R, Koundinya KS, Malati T, Kutala VK. Endothelial Dysfunction in Type 2 Diabetes Mellitus. Indian J Clin Biochem. 2016;31:372-9.
5. Funk SD, Yurdagul A Jr, Orr AW. Hyperglycemia and endothelial dysfunction in atherosclerosis: lessons from type 1 diabetes. Int J Vasc Med. 2012;2012:569654.
6. Yamagishi SI, Matsui T. Role of Hyperglycemia-Induced Advanced Glycation End Product (AGE) Accumulation in Atherosclerosis. Ann Vasc Dis. 2018;11:253-8.
7. Flammer AJ, Anderson T, Celermajer DS, Creager MA, Deanfield J, Ganz P, *et al*. The assessment of endothelial function: from research into clinical practice. Circulation. 2012;126:753-67.
8. Thijssen DH, Black MA, Pyke KE, Padilla J, Atkinson G, Harris RA, *et al*. Assessment of flow-mediated dilation in humans: a methodological and physiological guideline. Am J Physiol Heart Circ Physiol. 2011;300:2-12.
9. Harris RA, Nishiyama SK, Wray DW, Richardson RS. Ultrasound assessment of flow-mediated dilation. Hypertension. 2010;55:1075-85.
10. Stanimirovic J, Radovanovic J, Banjac K, Obradovic M, Essack M, Zafirovic S, *et al*. Role of C-Reactive Protein in Diabetic Inflammation. Mediators Inflamm. 2022;2022:3706508.
11. Mugabo Y, Li L, Renier G. The connection between C-reactive protein (CRP) and diabetic vasculopathy. Focus on preclinical findings. Curr Diabetes Rev. 2010;6:27-34.

12. Balamir I, Ates I, Topcuoglu C, Turhan T. Association of Endocan, Ischemia-Modified Albumin, and hsCRP Levels With Endothelial Dysfunction in Type 2 Diabetes Mellitus. Angiology. 2018;69:609-16.

13. Ahmed TM, Nassar M, Mohamed HAA, Elhadidy KE, Farhan HM, El Basset ASA, *et al*. Evaluation of serum levels of Irisin as a marker of endothelial dysfunction in patients with type 2 diabetes mellitus. Endocrinol Diabetes Metab. 2023;6:403.

14. Kaur R, Kaur M, Singh J. Endothelial dysfunction and platelet hyperactivity in type 2 diabetes mellitus: molecular insights and therapeutic strategies. Cardiovasc Diabetol. 2018;17:121.

15. Giandalia A, Alibrandi A, Giorgianni L, Lo Piano F, Consolo F, Longo Elia G, *et al*. Resistin levels and inflammatory and endothelial dysfunction markers in obese postmenopausal women with type 2 diabetes mellitus. Diabetol Metab Syndr. 2021;13:98.

16. Hayashi M, Morioka T, Hatamori M, Kakutani Y, Yamazaki Y, Kurajoh M, *et al*. Plasma omentin levels are associated with vascular endothelial function in patients with type 2 diabetes at elevated cardiovascular risk. Diabetes Res Clin Pract. 2019;148:160-8.

17. Nyström T, Nygren A, Sjöholm A. Persistent endothelial dysfunction is related to elevated C-reactive protein (CRP) levels in Type II diabetic patients after acute myocardial infarction. Clin Sci (Lond). 2005;108:121-8.

18. Bruno RM, Penno G, Daniele G, Pucci L, Lucchesi D, Stea F, *et al*. Type 2 diabetes mellitus worsens arterial stiffness in hypertensive patients through endothelial dysfunction. Diabetologia. 2012;55:1847-55.

RESEARCH ARTICLE

DOI: 10.4274/ijca.2024.80775
Int J Cardiovasc Acad 2024;10(3):70-78

Association between Heart Rate and Global Left Ventricular Longitudinal Strain and Left Atrium Structural and Functional Changes in Hypertensive Patients with Normal Left Ventricular Ejection Fraction (A Speckle Tracking Study)

Murat Gökhan Yerlikaya[1], Ender Emre[1], Ahmet Özderya[1], Faruk Kara[1], Gülay Uzun[1], Hüseyin Karal[1], Turhan Turan[1], Ozan Tezen[2], Kaan Hancı[3], Ezgi Kalaycıoğlu[1], Mustafa Çetin[4]

[1]Clinic of Cardiology, Ahi Evren Chest and Cardiovascular Surgery Training and Research Hospital, Trabzon, Turkey
[2]Department of Cardiology, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, İstanbul, Turkey
[3]Clinic of Cardiology, Akçaabat Haçkalı Baba State Hospital, Trabzon, Turkey
[4]Department of Cardiology, Recep Tayyip Erdoğan University Faculty of Medicine, Rize, Turkey

Abstract

Background and Aim: The structure and function of the left heart cavity have important prognostic value in heart diseases, and heart rate (HR) control is an important treatment goal. In this study, we investigated the effects of HR on left heart structure and function in hypertensive patients with normal left ventricular (LV) systolic function.

Materials and Methods: This was a single-center, prospective, observational (case-control) study. A total of 153 patients were included in the study. Patients were divided into two groups according to their HR (70 beats/min and below and above 70 beats/min). LV and atrial strain analyses were performed during echocardiographic evaluation.

Results: Patients with a resting HR of 70 beats/min or less were included in group 1 (64.2±4.5) and patients with a resting HR above 70 beats/min were included in group 2 (79.1±6.8). There is a significant difference between group 1 and group 2 in left atrial maximum volume (60.8±15.5 mL vs. 52.9±16.3 mL $P = 0.007$), left atrial minimum volume (28.8±9.5 vs. 22.6±7.9 $P < 0.001$), left atrial emptying fraction (52.8±8.5% vs. 56.1±8.5% $P = 0.035$), left atrial expansion index (1.19±0.44 vs. 1.36±0.47 $P = 0.044$), pLASRcd (-1.3±0.38 vs. -1.5±0.61 $P = 0.031$), and global longitudinal strain (-19.3±3 vs. -18.2±2.7 $P = 0.07$). In the multivariable regression analysis, beta-bloker [odds ratio (OR): 0.291, 95% confidence interval (CI) 0.105-0.810, $P = 0.018$], mean high diastolic blood pressure (OR: 1.054, 95% CI 1.009-1.101, $P = 0.018$), left atrial minimum volume (OR: 0.870, 95% Cl 0.809-0.938, $P < 0.001$), S' (OR: 10.6, 95% CI 1.1-104, $P = 0.041$), left atrial expansion index (OR: 0.870, 95% CI 0.809-0.930, $P < 0.033$) were determined as independent predictors of high resting HR.

Conclusion: HR control is an important goal in patients with hypertension who have preserved LV systolic function. Mortality and morbidity can also be improved by HR control.

Keywords: Heart rate, hypertension, strain, preserved left ventricular systolic function

To cite this article: Yerlikaya MG, Emre E, Özderya A, Kara F, Uzun G, Karal H, Turan T, Tezen O, Hancı K, Kalaycıoğlu E, Çetin M. Association between Heart Rate and Global Left Ventricular Longitudinal Strain and Left Atrium Structural and Functional Changes in Hypertensive Patients with Normal Left Ventricular Ejection Fraction (A Speckle Tracking Study). Int J Cardiovasc Acad. 2024;10(3):70-78

Address for Correspondence: Ender Emre, Clinic of Cardiology, Ahi Evren Chest and Cardiovascular Surgery Training and Research Hospital, Trabzon, Turkey
E-mail: dr.enderemre@hotmail.com
ORCID ID: orcid.org/0000-0003-0002-7660

Received: 02.05.2024
Revised: 11.09.2024
Accepted: 13.09.2024
Published Online: 18.09.2024

INTRODUCTION

Hypertension is an important risk factor with a high prevalence worldwide, and its role in adverse cardiovascular (CV) events is well known. The damage caused by hypertension to the heart can be detected by echocardiography.[1] Impaired left ventricular (LV) systolic function is an important independent predictor of adverse CV events, such as heart failure and CV death.[2] In patients with long-standing hypertension, impaired LV function, LV hypertrophy, and myocardial fibrosis are markers of end-organ damage.

The heart rate (HR) is an important and easily observable indicator that does not require advanced technical equipment. High HR is associated with increased CV events in the general human population and individuals with CV risk factors.[3] In the Framingham Study, HR was found to be associated with mortality in men and women who are patients with hypertension.[4] Therefore, it is important to quantify the potential risks associated with the resting HR of patients. In this context, the resting HR and its structural and functional effects on the heart should be well defined.

Speckle tracking echocardiography has emerged as a non-invasive and sensitive method for detecting early regional and global myocardial dysfunction that is undetectable by conventional two-dimensional (2D) echocardiographic imaging in both symptomatic and asymptomatic patients with CV disease (CVD). Subclinical systolic dysfunction can be detected using global longitudinal strain (GLS), which is beyond conventional echocardiographic evaluation.[5]

The left atrium (LA) has an important role in the regulation of LV filling and has been identified as an important biomarker of CVD and adverse CV outcomes.[6] The role of LA function as a biomarker is increasingly being evaluated, both alone and in conjunction with the LA dimension. Strain parameters, which are less dependent on the load than the traditional parameters of LA structure and function, are becoming increasingly important.[7]

In this study, we aimed to reveal the relationship between the HR of patients with hypertension with preserved ejection fraction (EF), who are at risk of adverse CV events, and subclinical LV dysfunction and LA function with strain, which is a sensitive method for demonstrating subclinical dysfunction. We believe that determining the safest target HR in this risky patient group will contribute to preventing adverse CV events.

MATERIALS AND METHODS

Participants and Data

This single-center, prospective, observational (case-control) study. A total of 325 patients who were admitted to the cardiology outpatient department of our hospital with a diagnosis of hypertension between January 2019 and February 2019 were included in the study. We planned to invite patients for echocardiography evaluation between April 15, 2022, and May 15, 2022. Informed consent was obtained from all patients. The study design was approved by the University of Health Sciences Türkiye, Trabzon Kanuni Training and Research Hospital's Ethics Committee in accordance with good clinical practice, and the study was conducted in accordance with the Declaration of Helsinki (decision no.: 2022/26, date: 11.04.2022).

The exclusion criteria of our study; previously known CVD history (coronary artery disease, peripheral artery disease, arrhythmia, moderate and advanced valvular disease), clinically diagnosed heart dysfunction (EF <50%), oncology disease, advanced kidney, and liver failure. Patients were analyzed according to the exclusion criteria. One hundred fifty-three patients who met all the criteria were included in the study, and the demographic data of these patients were recorded.

The body mass index (BMI) is defined as the body mass divided by the square of the body height and is expressed in units of kg/m^2. Smoking was defined as "current smokers" and "non-smokers". Drugs used by patients receiving hypertension treatment were determined by categorizing them into groups. Patients with glucose levels of 126 mg/dL or above and who were on medication for diabetes mellitus (DM) were classified as diabetic. Patients with total cholesterol levels of 200 mg/dL or higher and who were on medication for hypercholesterolemia were classified as hypercholesterolemic patients.

Laboratory and Echocardiographic Evaluations

Blood tests were performed using venous blood. As routine tests in the cardiology outpatient department; complete blood count (BC-5800 automatic hematology analyzer, Mindray Medical electronics Co. Shenzhen, China), fasting blood glucose level, kidney function test, lipid panel, and C-reactive protein (CRP) (AU680 Clinical Chemistry Analyzer System; Beckman Colter K.K.) were assessed. The glomerular filtration rate was calculated using the Cockcroft-Gault formula. Total cholesterol, low-density-lipoprotein, high-density-lipoprotein, and triglyceride levels were studied as lipid panels.

Echocardiographic studies, including two-dimensional, M-mode, pulsed Doppler, and pulsed tissue Doppler imaging (TDI) examinations, were performed using an echocardiography machine (VIVID S-5 General Electric Medical System Vingmed Ultrasound AS, Horten, Norway) equipped with a 3.6- MHz transducer and TDI. Parasternal and apical (standard 2- and 4-chamber images were taken with a 5.1-MHz sector transducer. LVEF was calculated using Simpson's method. The LV end-diastolic septal and posterior wall thicknesses

were calculated using the M-mode in the parasternal long-axis view. Early and late mitral filling flow were recorded by Doppler echocardiography. The systolic, early diastolic, and late diastolic tissue velocity waves obtained from the annulus were recorded by TDI. The isovolumetric relaxation time and E-wave deceleration time were also measured by Doppler echocardiography.

LA volumes were calculated using the formula of 0.85x(A1XA2/L), where A1 is the planimeter LA area in the apical 4-chamber view, A2 is the planimeter LA area in the apical 2-chamber view, and L is the LA long-axis length determined as the distance of the perpendicular line measured from the middle of the plane of the mitral annulus to the superior aspect of the LA. With measurements taken at the end of ventricular systole, just before mitral valve opening, LA maximum volume; at the end of ventricular diastole when the mitral valve was closed, the minimum LA volume was calculated. Using these parameters, the LA emptying volume (LAV_{max}-LAV_{min}), LA emptying fraction [(LAV_{max}-LAV_{min})/LAV_{max}], and LA expansion index [(LAV_{max}-LAV_{min})/LAV_{min}] were calculated.

Transthoracic images were processed to assess left atrial and ventricular deformation through speckle-tracking imaging using 2D strain software (EchoPAC 108.1.12, General Electric Medical Systems, Horten, Norway, featuring software for speckle-tracking of the left ventricle) by two cardiologists who were blinded. LA and LV endocardial boundaries were selected with automatic contour tracking and optimized using manual adjustment as needed. LV-GLS analysis was calculated by taking apical 4-chamber, apical 3-chamber, and apical 2-chamber images. LA-GLS analysis was calculated using apical 4 and apical 2 chamber images. The strain and strain rates were calculated and recorded separately during ventricular systole, early peak diastole, and atrial systole.

Strain echocardiography parameters were named as follows;

LASr: Strain during reservoir phase, LAScd: Strain during conduit phase, LASct: Strain during contraction phase, pLASRr: Peak strain rate during reservoir phase, pLASRcd: Peak strain rate during conduit phase, pLASRct: Peak strain rate during contraction phase, GLSLV: Left ventricul global longitudinal strain rate.

Heart Rate and Blood Pressure Measurements

In general, guidelines recommend a HR below 70 beats/min for patients with heart failure and coronary artery disease. For this reason, we used 70 beats/min as the cut-off value for the study. Rest electrocardiography (ECG) was performed on the patients in the supine position. ECG parameters were evaluated using a 0.01 mm graduated ruler. The mean HR was calculated by measuring 3 different RR intervals. The resting HR was set at 70 beats/min. People with a resting HR above 70 beats/min were categorized as group 2 (n=89), and people with a resting HR of 70 beats/min and below were categorized as group 1 (n=64). Blood pressure measurements were obtained separately with an office and 24-hour blood pressure holter. A 24-hour ambulatory blood pressure monitoring was performed using an Agilis-CDABPM (ELA Medical, France, 2002) device, a non-invasive ambulatory blood pressure monitoring instrument. Blood pressure was measured at 15 minute intervals during the day and at 30 minute intervals during the night. Among all the readings, ≥80% was considered valid.

Statistical Analysis

SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Kolmogorov-Smirnov and homogeneity of variance tests were performed to examine the normal distribution of the data. The independent samples t-test was used for a two-group comparison of normally distributed variables, and variables were expressed as mean standard deviation. The Mann-Whitney U test was used for two-group comparisons of variables that did not show normal distribution, and variables were expressed as median, minimum, and maximum values. Categorical variables were compared using the chi-square test, and the number was presented as a percentage. All variables were evaluated by univariate regression analysis. Independent variables that were statistically significant in the univariate analysis were carried out in the multivariate analysis. The predictors were determined using a multivariate logistic regression test. $P < 0.05$ was considered statistically significant.

RESULTS

One hundred fifty-three patients were included in the study. Patients with a resting HR of 70 beats/min and below were named group 1 (n=64). Patients with a resting HR above 70 beats/min were named group 2 (n=89). Average age is 72.8 years. The demographic characteristics of the individuals included in the study, drug treatments they used, blood pressure monitoring, and blood parameters are presented in Table 1. A significant difference was detected between the two groups in age ($P < 0.001$), DM ($P = 0.034$), mean diastolic blood pressure (DBP) ($P = 0.004$), beta-blocker (BB) use ($P = 0.036$), oral antidiabetic use ($P = 0.039$), and statin use ($P = 0.004$). There was no statistical difference between the BMI indexes of the patients in both groups. However, the average BMI of the patients in both groups was >30; thus, they were determined as preobese and 1st degree obese. There was no statistical difference in the hemoglobin, CRP, triglyceride, high-density lipoprotein, low-density lipoprotein (LDL), total cholesterol, estimated glomerular filtration rate, creatinine, fasting blood sugar, insulin, oral hypoglycemic agents, diuretics, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor,

angiotensin II receptor blockers, use, average office systolic blood pressure (SBP), oficce DBP, smoking, hyperlipidemia, and sex. Routine echocardiographic data of the patients are shown in Table 2, and strain echocardiographic data are given in Table 3. Evaluation of echocardiographic data showed that LAV_{max} (60.8±15.5 mL vs. 52.9±16.3 mL $P = 0.007$), LAV_{min} (28.8±9.5 mL vs. 22.6±7.9 mL $P < 0.001$), left atrium empty fraction (LAEF) (52.8±8.5% vs. 56.1±8.5, $P = 0.035$), left atrium expansion index (LAEI) (1.19±0.44 vs. 1.36±0.47, $P = 0.044$), pLASRcd (-1.3±0.38 vs. -1.5±0.61, $P = 0.031$) were significantly different between group 1 and group 2, respectively. There was no statistical difference between other parameters.

In the univariable regression analysis, age ($P < 0.001$), DM (0.049), using BB (0.049), using statin ($P = 0.005$), mean diastolic blood pressure ($P = 0.005$), LAV_{max} ($P = 0.009$), LAV_{min} ($P = 0.001$), S' ($P = 0.018$), LAEF ($P = 0.038$), LAEI ($P = 0.048$), and pLASRcd ($P = 0.04$) were associated with a higher resting HR. In the multivariable regression analysis, BB (OR: 0.291, 95% CI 0.105-0.810, $P = 0.018$), mean diastolic blood pressure (OR: 1.054, 95% CI 1.009-1.101, $P = 0.018$), LAV_{min} (OR: 0.870, 95% CI 0.809-0.938, $P < 0.001$), Sm (OR: 10.6, 95% CI 1.1-104, $P = 0.041$), LAEI (OR: 0.870, 95% CI 0.809-0.930, $P = 0.033$) were determined as independent predictors of high resting HR. Data are presented in Table 4.

DISCUSSION

As a result of this study, we found that, in hypertensive patients with preserved LV function, LAV_{min}, LAEI, BB use, mean diastolic blood pressure, and LV-S' were associated with HR, independent of other factors.

Table 1: Demographics and laboratory data

Variables	Group 1 (n=64)	Group 2 (n=89)	*P*-value
Heart rate (beats/min)	64.2±4.5	79.1±6.8	<0.001
Age (years)	57.06±9.4	51.1±9.2	<0.001
Sex (male, %)	29 (45.3)	40 (44.9)	0.547
BMI (kg/m^2)	31.3±4.6	32.6±4.9	0.121
Diabetes mellitus (%)	44 (68.8)	47 (52.8)	0.034
Hyperlipidemia (%)	47 (73.4)	54 (62.1)	0.098
Smoke (%)	9 (14.1)	21 (24.1)	0.091
Office SBP (mmHg)	152.1±13.2	149.9±16.6	0.379
Oficce DBP (mmHg)	92.1±9.3	94.5±11.5	0.173
Average SBP (mmHg)	140.7±15	143.4±15.5	0.313
Average DBP (mmHg)	81.5±12.5	87.9±13.2	0.004
Beta blocker (%)	24 (37.5)	20 (22.7)	0.036
ACEI (%)	25 (39.7)	31 (35.2)	0.348
ARB (%)	24 (37.5)	29 (33)	0.341
Diuretic (%)	27 (42.2)	31 (35.2)	0.241
Calcium channel blockers (%)	20 (31.2)	18 (20.7)	0.099
Oral hypoglycemic agents (%)	42 (65.6)	44 (50)	0.039
Insulin (%)	2 (3.1)	10 (11.4)	0.056
Fasting blood glucose (mg/dL)	128.8±50.2	129.6±54.4	0.928
Statin (%)	26 (40.6)	17 (19.3)	0.004
Creatinine (mg/dL)	0.8±0.16	0.78±0.17	0.464
eGFR	85.6±19	88.3±14.4	0.489
Total cholesterol (mg/dL)	197.1±44.2	210±41.1	0.055
LDL-C (mg/dL)	128.3±35	136±34	0.144
HDL-C (mg/dL)	45.9±9.6	47.2±12.9	0.501
Triglyceride (mg/dL)	170.6±93	169.4±83	0.934
C-reactive protein (mg/dL)	0.25 (0.11-0.47)	0.32 (0.15-0.60)	0.127
Hemoglobin (mg/dL)	13.5±1.2	13.8±1.5	0.225

BMI: Body mass ındex, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin II receptor blockers, eGFR: Estimated glomerular filtration rate, LDL-C: Low-density lipoprotein-cholesterol, HDL-C: High-density lipoprotein-cholesterol

Cardiac remodeling in hypertension involves an imbalance in the production of collagen types 1 and 3, which carry the main stress in the extracellular matrix.[8] Increased stress, particularly in the subendocardial region causes heterogeneous myocardial fibrosis to form and enlarge. This irregular collagen production and myocardial fibrosis are associated with decreased GLS and cause early deterioration of systolic function in hypertensive patients.[9] Hypertension is also associated with morphological and functional abnormalities in LA. LA size increase and tissue Doppler LA strain fluctuations are common findings in strain imaging in hypertensive patients.[10]

In the literature, HR was associated with survival in both healthy individuals and individuals with different underlying CVDs. A high HR can cause poor outcomes by affecting the CV system in many ways (ventricular workload, myocardial oxygen consumption, endothelial stress, increase in aortic/arterial stiffness, and decrease in myocardial oxygen delivery). Therefore, treatment approaches aim to decrease the HR and increase survival.[11]

Sardana et al.[12] showed in their study that BB use among hypertensive individuals without heart failure was significantly associated with deterioration in LA reservoir, conduit, and contraction function, which is consistent with the findings of the present study. However, the negative effects of high diastolic blood pressure and DM on LA strain parameters are known.[13] In our study, BB use and DM incidence were higher in group 1; diastolic blood pressure elevation was higher in group 2. Therefore, it cannot be clearly said that the data we obtained

Table 2: General echocardiography data

Variable	Group 1 (n=64)	Group 2 (n=89)	*P*-value
LVEF (%)	60.4±7.1	61.7±5.9	0.223
IVS (mm)	12.1±1.7	11.8±2	0.378
PW (mm)	11.4±1.6	11.1±1.8	0.196
LAV_{max} (mL)	60.8±15.5	52.9±16.3	0.007
LAV_{min} (mL)	28.8±9.5	22.6±7.9	<0.001
E (cm/s)	74.9±16.2	71.9±19.2	0.323
A (cm/s)	85.2±19.7	84.9±20.1	0.933
EDT (ms)	207.8±53	197±45	0.228
S' (cm/s)	8.8±2	9.6±2.1	0.015
E' (cm/s)	10.2±3.7	10.5±5	0.640
A' (cm/s)	12±3.4	12±3.5	0.958
IVRT (ms)	66.1±24	70±26	0.336
E/A	0.9±0.29	0.88±0.27	0.366
E/E'	5.62±4.29	4.38±3.92	0.073
LAEV (mL)	31.7±9.06	28.7±8.7	0.081
LAEF (%)	52.8±8.5	56.1±8.5	0.035
LAEI	1.19±0.44	1.36±0.47	0.044

LVEF: Left ventricular ejection fraction, IVS: Interventricular septum, PW: Posterior wall, LAV: Left atrial volume, EDT: E-wave deceleration time, E': Early diastolic tissue velocity, S': Systolic tissue velocity, A': Late diastolic tissue velocity, IVRT: Isovolumic relaxation time, LAEV: Left atrium empty volume, LAEF: Left atrium empty fraction, LAEI: Left atrium expansion index

Table 3: Strain echocardiography data

Variable	Group 1 (n=64)	Group 2 (n=89)	*P*-value
LASr, %	35.1±9.9	34.9±7.4	0.972
LAScd, %	-17.1±4.7	-18.01±4.3	0.914
LASct, %	-17.9±4.7	-18.01±4.3	0.979
pLASRr	1.3±0.34	1.54±0.42	0.056
pLASRcd	-1.3±0.38	-1.5±0.61	0.031
pLASRct	-2.3±0.64	-2.43±0.55	0.315
GLSLV, %	-19.3±3	-18.2±2.7	0.071

LASr: Strain during reservoir phase, LAScd: Strain during conduit phase, LASct: Strain during contraction phase, pLASRr: Peak strain rate during reservoir phase, pLASRcd: Peak strain rate during conduit phase, pLASRct: Peak strain rate during contraction phase, GLSLV: Left ventricul global longitudinal strain

Table 4: Multivariate regression analysis of factors predicting heart rate differences

	Univariate			Multivariate		
Variable	**OR**	**CI 95%**	***P*-value**	**OR**	**CI 95%**	***P*-value**
Age (years)	0.939	0.898-0.969	<0.001			
Diabetes mellitus	0.509	0.260-0.997	0.049			
Beta blocker	0.490	0.241-0.997	0.049	0.291	0.105-0.810	0.018
OHA	0.524	0.270-1.017	0.056			
Statin	0.350	0.169-0.724	0.005			
Average DBP	1.040	1.012-1.069	0.005	1.054	1.009-1.101	0.018
LAV_{max}	0.970	0.949-0.992	0.009			
LAV_{min}	0.922	0.881-0.966	0.001	0.870	0.809-0.938	<0.001
S'	7.496	1.417-39.65	0.018	10.6	1.1-104	0.041
LAEF	1.050	1.003-1.099	0.038			
LAEI	2.399	1.008-5.712	0.048	0.870	0.809-0.930	0.033
pLASRcd	3.113	1.056-9.179	0.040			
Costant			0.030	7.905		

OHA: Oral hypoglycemic agents, DBP: Diastolic blood pressure, LAV: Left atrial volume, S': Systolic tissue velocity, LAEF: Left atrial emptying fraction, LAEI: Left atrial expansion index, pLASRcd: Peak strain rate during the conduit phase, OR: Odds ratio, CI: Confidence interval

are related to a single variable. However, the use of BBs plays a significant role in positively affecting strain parameters by reducing HR.

When the baseline characteristics of the groups were examined in our study, it is noteworthy that DM and age parameters, which are the most important risk factors in determining CV risk score, were higher in the group with low HRs. DM and age are the most important risk factors in many CV risk-scoring systems. In a meta-analysis by Al Saikhan et al.[14], GLS was defined as a prognostic marker for CV mortality and morbidity, and its worsening was defined as a conventional risk factor. Risk factors affecting GLS, such as aging, hypertension, and CVD, are common features of longitudinal population-based elderly samples. Even if the LVEF is normal in elderly patients, GLS changes with the effect of these risks factors.[15,16] In the study by Enomoto et al.[17], there was no difference between the age and HR groups. Strain values were found to be better in the control group without DM and hypertension than in the group with hypertension only. Although the strain value of the group with only DM tended to be better than that of the group with both DM and hypertension, this difference did not show statistical significance.[17] In a study by Kraigher-Krainer et al.[18], high HR was found to negatively affect GLS. In our study, parallel to the aforementioned result, despite DM and advanced age, which adversely affect GLS, the GLS value in the group with a low HR tended to be better than that in the group with a high HR (-19.3±3 vs. -18.2±2.7 $P = 0.07$). The reason for this may be that the BB group was chosen as an additional drug in the possible long-term follow-up of hypertension (37.5% vs. 22.7% $P = 0.036$). When evaluated together with the results of our study, HR should also be considered when reaching the target blood pressure for the treatment of hypertension, with or without DM. For this purpose, the BB and non-dihydropyridine CCB groups should also be considered in our minds, especially in drug selection in patients with advancing age.

The LA plays an important role in the regulation of LV filling and contributes to one-third of the cardiac output.[19] LA has also been identified as an important biomarker of CVD-associated adverse outcomes.[6,20] Although LA size was previously used as a biomarker, LA function is increasingly being evaluated along with it.[21] Strain parameters are relatively independent of coupling effects and are less load dependent than conventional parameters of the LA function.[7] Poor LA strain is associated with advanced age, high frequency of atrial fibrillation, left ventricle hypertrophy, poor left and right ventricular systolic function, and poor left and right ventricular diastolic function.[22] However, the relationship between HR and LA strain parameters was not directly demonstrated. In our study, the reason for the poor left atrial size and strain values in the group with low HR may be explained by the direct effects of advanced age and DM, as well as the direct effects of its negative effects on diastolic dysfunction. There are many studies supporting this situation. There are only few studies showing the relationship between age and LA strain and strain rate. In the study of Boyd et al.[23], which had results consistent with our study, it has been shown that LA systolic strain and strain rates decrease significantly with aging. DM affects LA enlargement and dysfunction independently of other risk factors. In many studies, it has been shown that LA reservoir and conduit function is impaired in diabetic patients.[24] In the study by Kadappu et al.[25], 73 patients with type 2 DM

were compared with the control group according to age and gender. In the diabetes group, hypertension and the LA volume index were increased independent of the effect of diastolic dysfunction. LA global strain value was found to be decreased in the diabetes group compared with the control group, and this effect did not change in the increased diastolic dysfunction group.[25] These findings were also confirmed by Muranaka et al.[26] in which strain evaluation of LV and LA functions in patients with diabetes was performed. In our study, results consistent with the literature were obtained, and the pLASRcd value in the first group was found to be lower than that in the second group (-1.3±0.38 vs. -1.5±0.61 $P = 0.031$), whereas the pLASRr value tended to be lower in the first group (-1.3±0.34 vs. -1.5±0.42 $P = 0.056$). In our study, it was observed that low HR cannot prevent the negative changes in LA structure and function that develop with the effects of DM and age.

LV diastolic dysfunction occurs as a result of hypertension. Changes in the size and function of the LA are associated with the severity of LV diastolic dysfunction.[27] In addition to hypertension, obesity, female sex, DM, and age factors also affect LV diastolic dysfunction. In our study, the LA size function and LV diastolic status were consistent with the literature. Diastolic parameters in the first group tended to be worse than those in the second group (E/Em, 5.62±4.29 vs. 4.38±3.92, $P = 0.073$), LA dimensions increased (LAV_{max}, 60.8±15.5 vs. 52.9±16.3, $P = 0.007$, LAV_{min}, 28.8±9.5 vs. 22.6±7.9, $P < 0.001$) and worsening of functions was detected (LAEF, 52.8±8.5 vs. 56.1±8.5, $P = 0.035$, LAEI, 1.19±0.44 vs. 1.36±0.47, $P = 0.044$). In the study of Salako et al.[28], it was shown that there was no improvement in cardiac structural changes despite antihypertensive treatment. Similarly, a study by Chen et al.[27] showed that LA dimensions did not regress to normal levels by keeping blood pressure within normal limits with anti-hypertensive treatment. In our study, it was observed that the positive effect of HR on LV GLS was not apparent in LA strain parameters (pLASRr, 1.3±0.34 vs. 1.54±0.42, $P = 0.056$, pLASRcd, -1.3±0.38 vs. -1.5±0.61, $P = 0.031$, GLSLV, -19.3±3 vs. -18.2±2.7, $P = 0.071$). Therefore, with opportunistic blood pressure measurements and detection of hypertension at an early stage, adverse events can be prevented or delayed with the use of different targets, such as GLS.

Many studies have shown the effects of HR control and strain values on mortality and morbidity.[29] Here, we aimed to evaluate the relationship between HR control and strain. Our study did not include mortality or morbidity data.

Statin use and presence of DM were associated with a lower HR in the univariate analysis, but were not found to be independent predictive factors in the multivariate analysis. The association between statin use and DM and low HR may be related to BB use in group 1 rather than the effect of statin use and DM itself. Therefore, statin use and DM can be considered confounding factors. The reason why statin use was higher in group 1 was that the LDL level required to start statin medication in patients with DM was lower.

Some studies have shown that patients with isolated systolic hypertension are less sensitive to h HR-lowering drugs. There are even studies showing that BBs, which are drugs that reduce HR, increase SBP.[30]

Beta blocker use was significantly more frequent in group 1 than in group 2. However, the use of all antihypertensive drugs was proportionally higher in group 1. Why diastolic blood pressure in group 1 is lower than in group 2. This may be due to the collective effect of all these medications. Although there was a statistical difference in diastolic blood pressure between the 2 groups, it was not thought to be a parameter that would affect the main purpose of our study since it was in the normal and high-normal categories.

In the multivariate analysis, although there was no difference between the groups in LA strain values; LAEI and LAV_{min}, which showed structural and functional changes, differed in favor of the group with high HR. This condition, as mentioned before, was caused by poor LV diastolic function caused by DM and aging, as well as their independent negative effects. In particular, in the early period, aiming to control the HR along with the blood pressure target may have a positive effect on the functional and structural changes in LA. Preventing or reversing structural and functional deterioration in LA can also prevent atrial arrhythmia that may occur in the future and possible cerebrovascular stroke.

Study Limitations

The single-center nature of the study and the limited number of patients are our primary limitations. The other limitations are the lack of randomization and long-term follow-up. More reliable results can be obtained using multicenter studies with larger patient populations.

CONCLUSION

There are no known medical treatments that affect mortality in heart failure patients with preserved LV systolic function. Some drugs are partially effective against morbidity. As observed in our patient groups with preserved LV systolic function, it is necessary to reveal systolic and diastolic parameters, the status of LA structure, and functions to determine the appropriate intervention. It was observed that diastolic dysfunction cannot be corrected with HR control, and LA structure function cannot be positively affected by HR control. However, it is important that the LV GLS value, which affects mortality and morbidity, improves with HR control. HR control is an important goal in hypertension patients with preserved LV systolic function.

With the positive effect of HR control on GLS, mortality and morbidity can also be improved.

Ethics

Ethics Committee Approval: The study design was approved by the University of Health Sciences Türkiye, Trabzon Kanuni Training and Research Hospital's Ethics Committee in accordance with good clinical practice, and the study was conducted in accordance with the Declaration of Helsinki (decision no.: 2022/26, date: 11.04.2022).

Informed Consent: Informed consent was obtained from all patients.

Authorship Contributions

Surgical and Medical Practices: M.G.Y., A.Ö., F.K., G.U., H.K., E.K., Concept: M.G.Y., E.E., E.K., Design: M.G.Y., E.E., E.K., Data Collection or Processing: M.G.Y., A.Ö., F.K., G.U., H.K., Analysis or Interpretation: T.T., E.K., M.Ç., Literature Search: M.G.Y., E.E., K.H., Writing: M.G.Y., E.E., O.T., E.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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

REFERENCES

1. Santos ABS, Foppa M, Bertoluci C, Branchi TV, Fuchs SC, Fuchs FD. Stage I hypertension is associated with impaired systolic function by strain imaging compared with prehypertension: A report from the prever study. J Clin Hypertens (Greenwich). 2019;21:1705-10.
2. Shah AM, Claggett B, Sweitzer NK, Shah SJ, Anand IS, Liu L, *et al.* Prognostic Importance of Impaired Systolic Function in Heart Failure With Preserved Ejection Fraction and the Impact of Spironolactone. Circulation. 2015;132:402-14.
3. Oba Y, Hoshide S, Kabutoya T, Kario K. Increased Resting Heart Rate on Electrocardiogram Relative to In-office Pulse Rate Indicates Cardiac Overload: The J-HOP Study. Am J Hypertens. 2018;31:1106-12.
4. Gillman MW, Kannel WB, Belanger A, D'Agostino RB. Influence of heart rate on mortality among persons with hypertension: the Framingham Study. Am Heart J. 1993;125:1148-54.
5. Alsharari R, Oxborough D, Lip GYH, Shantsila A. Myocardial Strain Imaging in Resistant Hypertension. Curr Hypertens Rep. 2021;23:24.
6. Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, *et al.* Left atrial size: physiologic determinants and clinical applications. J Am Coll Cardiol. 2006;47:2357-63.
7. Marwick TH. Measurement of strain and strain rate by echocardiography: ready for prime time? J Am Coll Cardiol. 2006;47:1313-27.
8. Shahbaz AU, Sun Y, Bhattacharya SK, Ahokas RA, Gerling IC, McGee JE, *et al.* Fibrosis in hypertensive heart disease: molecular pathways and cardioprotective strategies. J Hypertens. 2010;28(Suppl 1):25-32.
9. Kang SJ, Lim HS, Choi BJ, Choi SY, Hwang GS, Yoon MH, *et al.* Longitudinal strain and torsion assessed by two-dimensional speckle tracking correlate with the serum level of tissue inhibitor of matrix metalloproteinase-1, a marker of myocardial fibrosis, in patients with hypertension. J Am Soc Echocardiogr. 2008;21:907-11.
10. Gupta S, Matulevicius SA, Ayers CR, Berry JD, Patel PC, Markham DW, *et al.* Left atrial structure and function and clinical outcomes in the general population. Eur Heart J. 2013;34:278-85.
11. Boudoulas KD, Borer JS, Boudoulas H. Heart Rate, Life Expectancy and the Cardiovascular System: Therapeutic Considerations. Cardiology. 2015;132:199-212.
12. Sardana M, Syed AA, Hashmath Z, Phan TS, Koppula MR, Kewan U, *et al.* Beta-Blocker Use Is Associated With Impaired Left Atrial Function in Hypertension. J Am Heart Assoc. 2017;6:e005163.
13. Atas H, Kepez A, Atas DB, Kanar BG, Dervisova R, Kivrak T, *et al.* K. Effects of diabetes mellitus on left atrial volume and functions in normotensive patients without symptomatic cardiovascular disease. J Diabetes Complications. 2014;28:858-62.
14. Al Saikhan L, Park C, Hardy R, Hughes A. Prognostic implications of left ventricular strain by speckle-tracking echocardiography in the general population: a meta-analysis. Vasc Health Risk Manag. 2019;15:229-51.
15. Modin D, Biering-Sørensen SR, Mogelvang R, Landler N, Jensen JS, Biering-Sørensen T. Prognostic Value of Echocardiography in Hypertensive Versus Nonhypertensive Participants From the General Population. Hypertension. 2018;71:742-51.
16. Russo C, Jin Z, Elkind MS, Rundek T, Homma S, Sacco RL, *et al.* Prevalence and prognostic value of subclinical left ventricular systolic dysfunction by global longitudinal strain in a community-based cohort. Eur J Heart Fail. 2014;16:1301-9.
17. Enomoto M, Ishizu T, Seo Y, Yamamoto M, Suzuki H, Shimano H, *et al.* Subendocardial Systolic Dysfunction in Asymptomatic Normotensive Diabetic Patients. Circ J. 2015;79:1749-55.
18. Kraigher-Krainer E, Shah AM, Gupta DK, Santos A, Claggett B, Pieske B. *et al.* Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. J Am Coll Cardiol. 2014;63:447-56.
19. Matsuda Y, Toma Y, Ogawa H, Matsuzaki M, Katayama K, Fujii T, *et al.* Importance of left atrial function in patients with myocardial infarction. Circulation. 1983;67:566-71.
20. Tsang TS, Barnes ME, Gersh BJ, Takemoto Y, Rosales AG, Bailey KR, *et al.* Prediction of risk for first age-related cardiovascular events in an elderly population: the incremental value of echocardiography. J Am Coll Cardiol. 2003;42:1199-205.
21. Vieira MJ, Teixeira R, Gonçalves L, Gersh BJ. Left atrial mechanics: echocardiographic assessment and clinical implications. J Am Soc Echocardiogr. 2014;27:463-78.
22. Buggey J, Hoit BD. Left atrial strain: measurement and clinical application. Curr Opin Cardiol. 2018;33:479-85.
23. Boyd AC, Richards DA, Marwick T, Thomas L. Atrial strain rate is a sensitive measure of alterations in atrial phasic function in healthy ageing. Heart. 2011;97:1513-9.
24. Gan GCH, Ferkh A, Boyd A, Thomas L. Left atrial function: evaluation by strain analysis. Cardiovasc Diagn Ther. 2018;8:29-46.
25. Kadappu KK, Boyd A, Eshoo S, Haluska B, Yeo AE, Marwick TH, *et al.* Changes in left atrial volume in diabetes mellitus: more than diastolic dysfunction? Eur Heart J Cardiovasc Imaging. 2012;13:1016-23.
26. Muranaka A, Yuda S, Tsuchihashi K, Hashimoto A, Nakata T, Miura T, *et al.* Quantitative assessment of left ventricular and left atrial functions by strain rate imaging in diabetic patients with and without hypertension. Echocardiography. 2009;26:262-71.
27. Chen Y, Sato H, Watanabe N, Adachi T, Kodani N, Sato M, *et al.* Factors influencing left atrial volume in treated hypertension. J Cardiol. 2012;60:133-8.

28. Salako BL, Ogah OS, Adebiyi AA, Oladapo OO, Aje A, Adebayo AK, *et al*. Blood pressure control and left ventricular hypertrophy in hypertensive Nigerians. Ann Afr Med. 2009;8:156-62.

29. Peverill RE, Cheng K, Cameron J, Donelan L, Mottram PM. Relationships of global longitudinal strain with s`, long-axis systolic excursion, left ventricular length and heart rate. PLoS One. 2020;15:e0235791.

30. Goldberger JJ, Jacobson JT. Relationship of blood pressure to heart rate in isolated systolic hypertension. J Investig Med. 2011;59:1228-32.

CASE REPORT

DOI: 10.4274/ijca.2024.25743
Int J Cardiovasc Acad 2024;10(3):79-81

Dilated Cardiomyopathy in Pregnancy: A Review of ACEI Exposure and Fetal Risks

Nergiz Aydın[1], Hakan Akıllı[2], Yakup Alsancak[2], Sefa Tatar[2]

[1]Safranbolu State Hospital, Clinic of Cardiology, Karabük, Turkey
[2]Necmettin Erbakan University Faculty of Medicine, Department of Cardiology, Konya, Turkey

Abstract

Dilated cardiomyopathy (DCM) is a rare disease that can lead to serious cardiac complications, especially during pregnancy. In this study, a case of DCM in an advanced pregnancy with no known history of the disease resulting in spontaneous delivery is presented. Pregnancy in patients with DCM may have adverse outcomes because of increased cardiac output and plasma volume. This case demonstrates that pregnancy carries serious risks, particularly in patients with an ejection fraction <40%. The fetotoxic effects of angiotensin-converting enzyme inhibitors use during pregnancy are emphasized, and the importance of a multidisciplinary approach is highlighted.

Keywords: Dilated cardiomyopathy, pregnancy, angiotensin receptor blocker, premature birth, Down syndrome

INTRODUCTION

Dilated cardiomyopathy (DCM) is characterized by enlarged left ventricle and systolic dysfunction. The approximately 50% increase in plasma volume and cardiac output during pregnancy and the ability to adapt to these dynamic changes are of great clinical importance, particularly in pregnant women with reduced cardiac function. The occurrence of DCM during pregnancy or worsening of preexisting DCM during pregnancy pose a high risk to the mother and fetus. Management of DCM during pregnancy requires great care to protect maternal and fetal health. However, some drugs used during pregnancy may have teratogenic and fetotoxic effects on the fetus. Angiotensin-converting enzyme inhibitors (ACEIs) are commonly used as first-line therapy for DCM, but the fetal toxicity of ACEIs is well known. In this case report, we present a case of DCM treated with ACEIs throughout pregnancy and postpartum follow-up.

CASE REPORT

A 38-year-old female patient with no known medical history and two previous pregnancies was admitted with shortness of breath and orthopnea. Echocardiography revealed an ejection fraction (EF) of 30% and severe functional mitral regurgitation. There was no history of peripartum cardiomyopathy after previous deliveries. Electrocardiography revealed sinus rhythm and tachycardia (Figure 1). Cardiomegaly and pleural effusion, more prominent in the right hemithorax, were observed in the thorax computed tomography scan to exclude additional lung parenchymal pathologies that could explain the current clinical presentation (Figure 2). After patient decompensation was achieved, coronary angiography was performed to exclude ischemic cardiomyopathy, and normal coronary anatomy was observed. She was hospitalized twice with decompensation 5 and 3 months after her first admission. The patient, who did not come for routine checkups in the following period, was

To cite this article: Aydın N, Akıllı H, Alsancak Y, Tatar S. Dilated Cardiomyopathy in Pregnancy: A Review of ACEI Exposure and Fetal Risks. Int J Cardiovasc Acad. 2024;10(3):79-81

Address for Correspondence: Nergiz Aydın, Safranbolu State Hospital, Clinic of Cardiology, Karabük, Turkey
E-mail: nrgz.ydn@hotmail.com
ORCID ID: orcid.org/0000-0003-3155-4076

Received: 28.07.2024
Revised: 06.09.2024
Accepted: 09.09.2024
Published Online: 18.09.2024

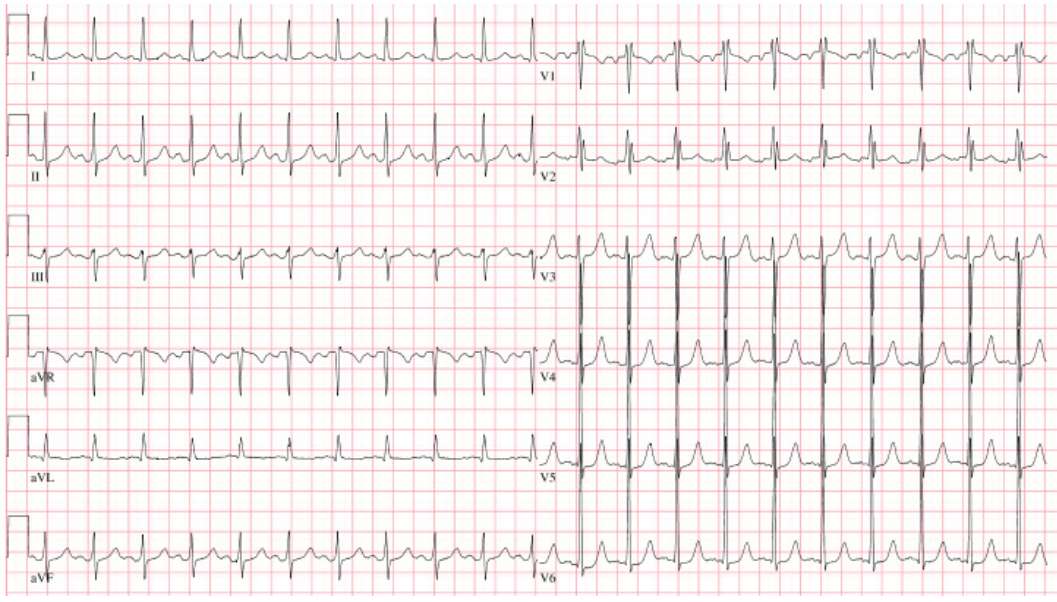


Figure 1. ECG at admission
ECG: Electrocardiogram

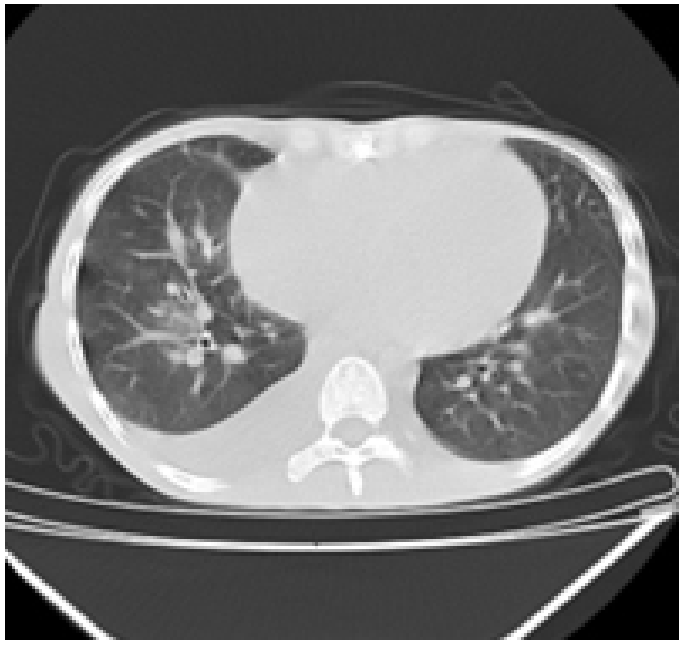


Figure 2. Thoracic CT scan at the time of initial presentation
CT: Computed tomography

admitted to the hospital after a spontaneous birth at home 1 year after his last hospitalization. At the patient's last hospital admission before pregnancy, the pro-BNP level was 6106 ng/L, NYHA 2-3. In the anamnesis, it was learned that the patient was unaware of her pregnancy, did not go to the gynecology and cardiology clinic for a check-up during the pregnancy, and continued to take the medications she had used before pregnancy, ramipril 5 mg, metaprolol 200 mg and furosemide 40 mg, throughout the pregnancy. No pathological findings were observed after birth. In the evaluation performed by the pediatric clinic, it was found that the premature baby was born with Down syndrome, but there was no additional pathology. The patient, for whom cardiac treatment was rearranged, was discharged with recommendations. Two months after discharge, he was hospitalized again due to decompensation. The patient, who did not adequately respond to diuretics and developed increased of, acute renal failure, and sepsis during follow-up, died. Informed consent was obtained from the patient's family for the publication of this case report and any accompanying images.

DISCUSSION

Increased cardiac output and plasma volume due to pregnancy may lead to adverse outcomes in patients with DCM. The clinical consequences of DCM in pregnancy depend on pre-pregnancy cardiac health. It has been shown to be associated with poor outcomes, particularly in patients with EF <40%.[1] Patients with EF >30% tolerated pregnancy well, but the rate of preterm birth was higher. Peripartum cardiovascular events occurred more frequently in patients with high pre-pregnancy BNP levels, advanced diastolic dysfunction, and NYHA 2.[2] ACEIs used as first-line therapy in patients with DCM are contraindicated due to the risks of teratogenicity, fetal renal failure, and neonatal death. Diuretics and selective beta-blockers, such as metoprolol, are relatively safe. Captopril, enalapril, and lisinopril have

been shown to cross the human placenta in pharmacologically significant amounts.[3] Similar results are likely to be observed in other groups of ACEIs. Once in the fetus, most ACEIs are excreted in active forms by the kidneys in urine and may reenter the circulation via the swallowed amniotic fluid.[4] In an animal study conducted with rats and rabbits, the incidence of major malformations was not increased in offspring administered ACEI during organogenesis, whereas decreased uteroplacental flow, low birth weight, hypotension, premature birth, and fetal death were observed.[5] It is known that, unlike exposure to ACEIs in the first trimester, exposure in the second and third trimesters is fetotoxic and may lead to anuria associated with oligohydramnios, limb contractures, craniofacial deformities, and pulmonary hypoplasia.[4] Intrauterine growth retardation, prematurity, patent ductus arteriosus, severe neonatal hypotension, neonatal anuria, and neonatal or fetal death are expected outcomes in this patient group.[6] There is no scientific evidence showing that the use of ACEIs increases the risk of Down syndrome. It is believed that Down syndrome detected in the fetus in this case most likely occurred coincidentally. The commonly known fetotoxic effects of ACEI were not observed in our patient. It has been shown that the risk of malformations in live births is not significantly increased after exposure to ACE inhibitors/ARBs in early pregnancy.[7] This may be due to the patient not using her medications regularly or to the complete discontinuation of ACE inhibitors in advanced pregnancy due to hypotension that occurs during pregnancy. Another issue affecting the prognosis of patients with DCM is social and environmental factors. DCM is associated with high post-discharge mortality, especially in patients from low-income areas with high income inequality.[8] Low education level and socioeconomic status are associated with an increased incidence of sudden cardiac death.[9] The sociocultural level of the patient is of great importance, especially in DCM patients with low education levels, to maintain regular follow-ups, ensure patient compliance with treatment, and provide pre-pregnancy counseling and close management of prenatal care in cases such as possible pregnancies requiring medication revision. Disciplined management with obstetricians, cardiologists, and anesthesia during the birth and postpartum periods is important for achieving optimum outcomes.

CONCLUSION

DCM increases the risk of mortality and morbidity, along with physiological changes during pregnancy. It is important to provide counseling with a multidisciplinary team before pregnancy, during pregnancy, and during the postpartum period to share pregnancy-related risks and make necessary medical treatment revisions. However, to manage this process optimally, patient cooperation and compliance are very important.

Ethics

Informed Consent: Informed consent was obtained from the patient's family for the publication of this case report and any accompanying images.

Authorship Contributions

Surgical and Medical Practices: H.A., Y.A., Concept: N.A., S.T., Design: N.A., H.A., Y.A., S.T., Data Collection or Processing: N.A., Analysis or Interpretation: H.A., Y.A., S.T., Literature Search: H.A., Y.A., S.T., Writing: N.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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

REFERENCES

1. Gevaert S, De Pauw M, Tromp F, Ascoop AK, Roelens K, De Backer J. Treatment of pre-existing cardiomyopathy during pregnancy. Acta Cardiol. 2014;69:193-6.
2. Yokouchi-Konishi T, Kamiya CA, Shionoiri T, Nakanishi A, Iwanaga N, Izumi C, *et al.* Pregnancy outcomes in women with dilated cardiomyopathy: peripartum cardiovascular events predict post delivery prognosis. J Cardiol. 2021;77:217-23.
3. Reisenberger K, Egarter C, Sternberger B, Eckenberger P, Eberle E, Weissenbacher ER. Placental passage of angiotensin-converting enzyme inhibitors. Am J Obstet Gynecol. 1996;174:1450-5.
4. Ratnapalan S, Koren G. Taking ACE inhibitors during pregnancy. Is it safe? Can Fam Physician. 2002;48:1047-9.
5. Mastrobattista JM. Angiotensin converting enzyme inhibitors in pregnancy. Semin Perinatol. 1997;21:134-34.
6. Barr M Jr. Teratogen update: angiotensin-converting enzyme inhibitors. Teratology. 1994;50:399-409.
7. Moretti ME, Caprara D, Drehuta I, Yeung E, Cheung S, Federico L, *et al.* The fetal safety of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers. Obstet Gynecol Int. 2012;2012:658310.
8. Amiya E. Social Inequalities in Non-ischemic Cardiomyopathies. Front Cardiovasc Med. 2022;9:831918.
9. Nichol G, Thomas E, Callaway CW, Hedges J, Powell JL, Aufderheide TP, *et al.* Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA. 2008;300:1423-31.