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International Journal of the Cardiovascular Academy

October-December 2019 Volume 5 Issue 4

CONTENTS

ORIGINAL ARTICLES

Comparative Assessment of Left Ventricular Function after Coronary Artery Bypass Grafting and Percutaneous Coronary Intervention to LAD by Speckle Tracking Echocardiography Study

Mahmoud S. Abd El Moneum, Eman Saeed Elkeshk, Khaled Emad El-Din El-Rabbat, Adem M. Ahmed 109

Transesophageal Echocardiography and Scopy Co-guided Percutaneous Mitral Balloon Valvuloplasty Procedure: Experience of a Tertiary Health Center with a Literature Review

Emre Ozdemir, Sadik Volkan Emren, Nihan Kahya Eren, Cem Nazli, Mehmet Tokaç 116

Admission Plasma Glucose and Maternal Prognostic Factors in Preeclampsia

Ozgur Kirbas, Ebru Hacer Biberoglu, Nuri Danisman 121

Correlation of B-type Natriuretic Peptide with Severity of Coronary Artery Disease Assessed by SYNTAX Score II in ST Elevation Acute Coronary Syndrome Patients

Onur Tasar, Gonenc Kocabay, Metin Cagdas, Yavuz Karabag 129

Heart Disease: Lifestyle, Knowledge, and Perception among Young Nigerian Adults

Ejiroghene Martha Umuerri 134

Accelerated Dobutamine Stress Echocardiography Protocol versus the Standard One in the Assessment of Coronary Artery Disease

Ahmed Bendary, Hani Alkhazragy, Alshaymaa Sabry, Mohamed Osama, Khalid Elrabbat 141

Coronary Artery Dominance and Atrial Fibrillation Recurrence after Cryoballoon Pulmonary Vein Isolation

Ahmet Korkmaz, Ilyas Emre Yakıcı, Bekir Demirtaş, Funda Başyigit, Havva Tugba Gursoy, Emrullah Kızıltunc, Ender Ornek, Ozgul Ucar Elalmis, Mehmet Ileri, Umit Güray 146

Diagnostic Modality for Evaluation of Right Ventricle in Chronic Thromboembolic Pulmonary Hypertension Patients

Mustafa Oguz, Tarik Kivrak, Murat Sunbul, Fuad Dede, Bedrettin Yildizeli, Bulent Mutlu 152

Is Vitamin D Level Elevated in Patients on Statin Treatment?

Gulcin Sahingoz Erdal, Nihan Turhan Caglar, Dilay Karabulut, Nursel Kocamaz, Nilgun Isiksacan 159

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Original Article

Comparative Assessment of Left Ventricular Function after Coronary Artery Bypass Grafting and Percutaneous Coronary Intervention to LAD by Speckle Tracking Echocardiography Study

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Abstract

Background: Speckle-tracking echocardiography (STE) is a noninvasive imaging technique that analyzes global and regional myocardial function. **Aims:** This study aims to compare the assessment of the left ventricular (LV) function after percutaneous coronary intervention (PCI). **Settings and Design:** One hundred patients presented to the catheterization laboratory and cardiothoracic operating room in Benha University Hospital and Kasr Al–Ainy University Hospital for PCI and coronary artery bypass grafting (CABG) to left anterior descending artery (LAD). **Patients and Methods:** This study enrolled 100 patients. They were divided into two groups: Group I: 50 patients with PCI to LAD and Group II: 50 patients with CABG to LAD. Echocardiography (conventional echocardiography and two-dimensional STE) was performed for all patients 24 h before and 1 month after the procedures. **Statistical Analysis Used:** Data management and statistical analysis were done using SPSS version 25. **Results:** There were significant increases in global circumferential strain (GCS) after CABG surgery with mean value of −17.8 before the procedure and −23.8 after it while there were no significant increases in global longitudinal strain (GLS) after the same procedure with mean value of −17.5 before the procedure and −18.1 after it. There were significant increases in GLS with mean value of −17.0 before PCI and −21.2 after it, and there were significant increases in GCS with mean value of −17.1 before PCI and −25.4 after it with improvement in myocardial function after this procedure. GLS and GCS were significantly higher in patients with PCI than patients with CABG with $P < 0.001$. **Conclusions:** GLS and GCS are more effective than the parameters of standard echocardiography such as the LV end-diastolic volume, LV end-systolic volume, wall motion score index, and ejection fraction for evaluating LV function after PCI and CABG surgery. GLS and GCS are significantly higher in patients with PCI than patients with CABG surgery to LAD.

Keywords: Coronary artery bypass grafting surgery, echocardiography, global circumferential strain, global longitudinal strain, speckle tracing

Introduction

Coronary artery disease (CAD) includes a wide spectrum of heart diseases which have the highest mortality in the world.[1] Acute myocardial infarction (MI) is a leading cause of morbidity and mortality worldwide. It occurs when irreversible myocardial cell damage or death occurs.[2]

The management of patients with CADs consists of several approaches, including medical management, percutaneous

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coronary intervention (PCI), and coronary artery bypass grafting (CABG).[3] The use of PCI to manage CAD has expanded significantly during the past three decades.[4]

This has resulted in a reduction in mortality rate caused by early and late complications of CAD; however, even successful percutaneous intervention with complete reperfusion to the left anterior descending artery (LAD) does not exclude the risk of left ventricular (LV) remodeling. CABG surgery has been accepted as an effective therapeutic strategy for CAD.[5]

CABG does not only improve clinical symptoms but also reduces the risk of sudden cardiac death. It can also increase myocardial function and enhance exercise tolerance.[6] Elderly patients frequently receive CABG; however, they are at high risk because of age-related impairment of organ function and poor surgical tolerance; thus, it is important to accurately evaluate postoperative changes in myocardial function with various parameters.[7]

The assessment of the potential benefits of intervention for managing ischemic CAD must include the baseline LV function.[8]

The assessment of cardiac function by measuring LV ejection fraction (EF) using echocardiography is the most common method in the daily clinical practice. However, this technique has limitations related with its intra- and inter-observer variability, affected by preload conditions, does not correlate with symptoms and its detection of subtle changes in myocardial function is low.[9]

Despite studies evaluating various clinical factors and routine echocardiographic parameters predisposing to LV failure as a complication to CAD, there are still some gaps, and some of the diagnostic parameters failed to identify patients with LV failure after reperfusion.[10]

Speckle-tracking echocardiography (STE) is a noninvasive imaging technique that analyzes global and regional myocardial function; STE can overcome some of these limitations. LV global circumferential strain (GCS) (LVGCS) seems to be the most sensitive method to detect myocardial dysfunction and has promise for future applications,[11] LV global longitudinal strain (GLS) (LVGLS) has been found to be a better parameter to assess LV function than EF.[12]

Aim of the work

The aim of this study was to compare the assessment of LV function after PCI and CABG to LAD by STE.

Patients and Methods

The study was conducted on 100 patients who presented to catheterization laboratory and operating room in Benha University Hospital for PCI and CABG to LAD from July 1, 2018, to April 30, 2019 with STE done 24 h before and 1 month after the procedures.

This study enrolled 100 patients. They were divided into two groups, Group I: 50 patients who had PCI to LAD and Group II: 50 patients who had CABG to LAD.

The patients in this study were divided into 49 patients with ST-elevation MI (STEMI), 36 patients with non-STEMI, and 15 patients with unstable angina without significant difference between the two groups [Table 1].

The patients were at low risk according to The Global Registry of Acute Coronary Events score.

The patients referred to the hospital 48 h before elective PCI and CABG surgery, the study was done 24 h before the interventions.

The patients had a history of chest pain before the hospital admission with the following angiographic findings of other epicardial vessels without significant difference between the two groups [Table 2].

Inclusion criteria included patients with LAD lesion proven by previous diagnostic coronary angiography with 50 patients who had PCI to LAD and 50 patients who had CABG to LAD.

Exclusion criteria included patient's refusal, heart muscle disease (severe heart failure and cardiomyopathy). Severe valvular disease, severe myocarditis, significant arrhythmia, previous pacemaker implantation, very poor image quality and uncompleted reperfusion therapy, and patient critical circumflex stenosis.

All patients included in the study were subjected to:

- Informed consent
- Full history taking
- General and local examination of the heart
- 12 lead electrocardiography (ECG)
- Routine laboratory tests including complete blood count, liver functions, renal functions, and virology
- Echocardiography (conventional echocardiography and STE) was performed 24 h before and 1 month after the procedures.

Conventional echocardiography

Standard views were used to get images for the LAD territory including:

Parasternal long- and short-axis views at the level of papillary muscle and apical four- and two-chamber views

Table 1: Patient population

	Group I	Group II
Patients with STEMI	20	29
Patients with NSTEMI	22	14
Patients with unstable angina	8	7

STEMI: ST-segment elevation myocardial infarction, NSTEMI: Non-STEMI

Table 2: Population according to coronary angiography

Coronary angiography	Group I	Group II
LCX lesion	25	21
RCA lesion	12	15
LCX and RCA	13	14

LCX: Left circumflex artery, RCA: Right coronary artery

to study the different echocardiographic parameters such as LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), wall motion score index (WMSI), and EF (EF = (SV/EDV) *100) to compare between the two groups.

Two-dimensional speckle tracking echocardiography

It is a new technique used for qualification of LV deformation such as GLS and GCS.

GLS is a useful parameter that expresses longitudinal contraction of the myocardium, in adults, GLS <−16% is considered abnormal, GLS >−18% is considered normal, and GLS −16%–−18% is considered borderline.[13]

GCS is used to describe the reduction in the circumference of the LV cavity. Its normal value in adults is ranging from −20% to −27%.

Coronary angiography: Was done to all patients?

All the echocardiographic studies including offline analysis were done by one competent consultant, and the type of the device used was Vivid 7.

In short-axis views of STE, the circumferential deformation was measured, while the apical views were used to assess longitudinal function. There were no major adverse cardiovascular event during this study.

Statistical analysis

Data collected throughout history, basic clinical examination, laboratory investigations, and outcome measures were coded; entered; and analyzed using Microsoft Excel software. Data were then imported into the Statistical Package for the Social Sciences (SPSS version 20.0, IBM Company, Armonk, New York, USA) software for analysis. According to the type of data qualitative represent as number and percentage, quantitative continues group represented by mean ± standard deviation, the following tests were used to test differences for significance. Differences of paired variable were calculated by Mac Namer test, while differences between two groups were calculated by paired t-test. $P < 0.05$ were considered significant.

Results

Study population

All 100 patients in the two groups consisted of 50 males and 50 females with the mean age 55 ± 4 in Group I and 57 ± 5 in Group II with 43 patients having diabetes, 63 having hypertension, 57 smokers, 40 having a positive family history, and 41 having dyslipidemia [Table 3 and Figure 1].

Vital signs

There were no significant differences in pre- and post-procedural systolic blood pressure (SBP) in both groups. *P* values were 0.491 and 0.828, respectively.

SBP % change showed no significant difference between both groups ($P = 0.787$).

Table 3: General characteristics in both groups

	Group I ($n=50$)	Group II ($n=50$)	*P*
Age (years), mean±SD	55±4	57±5	0.141
Gender			
Males	32 (64.0)	28 (56.0)	0.414
Females	18 (36.0)	22 (44.0)	
Diabetes	20 (40.0)	23 (46.0)	0.545
Hypertension	31 (62.0)	32 (64.0)	0.836
Smoking	33 (66.0)	24 (48.0)	0.069
Family history	23 (46.0)	17 (34.0)	0.221
Dyslipidemia	17 (34.0)	24 (48.0)	0.155

Independent *t*-test was used for age. Chi-square test was used for categorical data. SD: Standard deviation

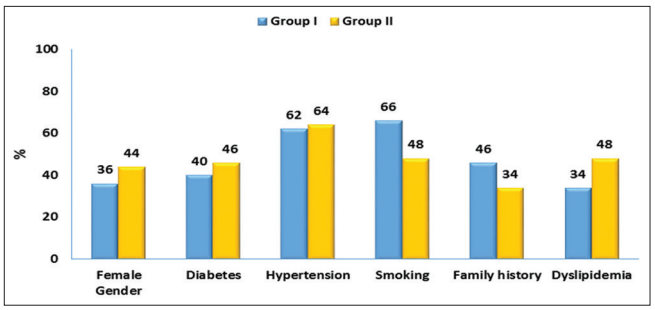


Figure 1: General characteristics in both groups

There were no significant differences in pre- and post-procedural diastolic blood pressure (DBP) in both groups. *P* values were 0.468 and 0.326, respectively.

DBP % change showed no significant difference between both groups ($P = 0.207$).

There were no significant differences in pre- and post-procedural heart rate (HR) in both groups. *P* values were 0.935 and 0.664, respectively.

HR % change showed no significant difference between both groups ($P = 0.824$) [Table 4 and Figure 2].

There were no significant differences between both groups as regards all ECG changes [Table 5 and Figure 3].

Echocardiography

Conventional echocardiography

The parameters used in conventional echocardiography are LVEDV, LVESV, WMSI, and EF.

There were no significant differences in pre- and post-procedural as regards LVEDV, LVESV, WMSI, and EF in both groups [Table 6 and Figure 4].

Two-dimensional speckle tracking echocardiography

- There were no significant differences in preprocedural GLS between both groups
- Mean postprocedural GLS was significantly higher in Group I compared to Group II
- Median GLS% change was significantly higher in Group I compared to Group II

Table 4: Systolic, diastolic blood pressure and heart rate in both groups

	Group I (n=50)	Group II (n=50)	P
SBP			
Pre, mean±SD	132±24	129±21	0.491
Post, mean±SD	127±16	128±11	0.828
Percentage change, median (range)	0 (−22.2-20)	−6.5 (−17.6-30)	0.787
DBP			
Pre, mean±SD	86±12	84±13	0.468
Post, mean±SD	82±10	81±7	0.326
Percentage change, median (range)	0 (−22.2-16.7)	−10.0 (−20-41.7)	0.207
HR			
Pre, mean±SD	80±12	80±12	0.935
Post, mean±SD	79±9	80±8	0.664
Percentage change, median (range)	0 (−17.6-23.1)	0 (−22.2-23.1)	0.824

Independent *t*-test was used. Mann-Whitney U-test was used for % change. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, SD: Standard deviation

Table 5: Electrocardiography findings in both groups

ECG	Group I (n=50), n (%)	Group II (n=50), n (%)
Normal	8 (16.0)	7 (14.0)
ST depression, T-wave inversion	22 (44.0)	14 (28.0)
ST elevation in anterolateral leads	20 (40.0)	29 (58.0)

Chi-square test was used. ECG: Electrocardiography

- There were no significant differences in preprocedural GCS between both groups
- Mean postprocedural GCS was significantly higher in Group I compared to Group II
- Median GCS % change was significantly higher in Group I compared to Group II [Table 7 and Figure 5].

Coronary angiography

There were no significant differences between both groups as regards segments of LAD affected (P = 0.204) [Table 8].

Discussion

This study enrolled 100 patients divided into two groups. Group I: 50 patients with PCI to LAD and Group II: 50 patients with CABG to LAD. The aim of this study was to compare the LV function after PCI and CABG to LAD by STE. We revealed that GCS is better than GLS shortly after CABG surgery due to the arrangement of the longitudinal muscle fibers in the LV and the locations of the myocardial regions affected by CAD. Increase in GLS and GCS in patients after PCI with improvement in myocardial function after this procedure. Both GLS and GCS are significantly higher in patients with PCI than patients with CABG surgery to LAD.

In this study, we found that there were no significant differences in terms of age with P = 0.141, gender with P = 0.414 and risk factors including smoking, hypertension, diabetes mellitus, dyslipidemia, and family history of coronary heart disease between two groups. This was concordant with D'Andrea *et al*.

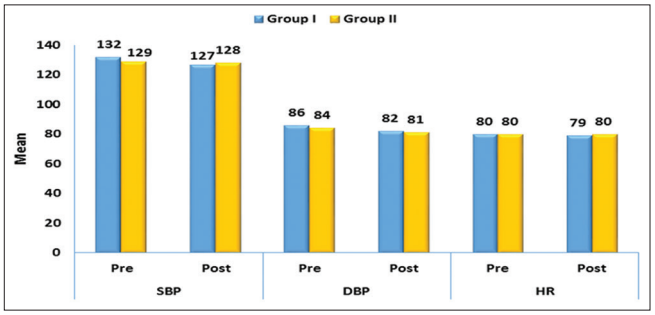


Figure 2: Systolic, diastolic blood pressure, and heart rate in both groups

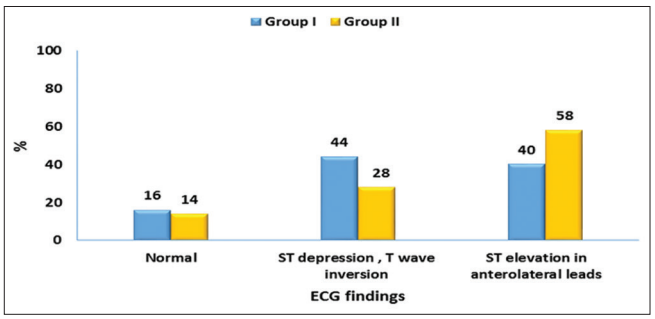


Figure 3: Electrocardiography findings in both groups

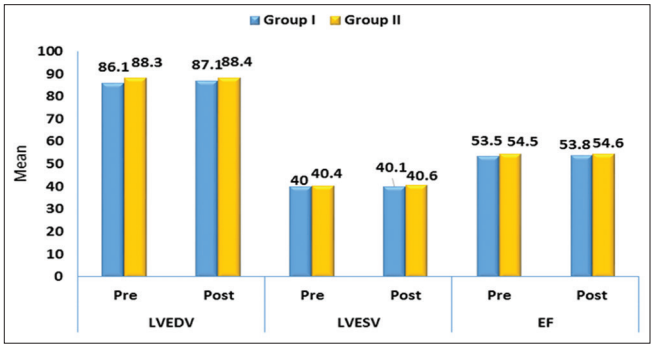


Figure 4: ECHO parameters in both groups

who examined 70 patients with non-ST-segment EMI.[14] This was discordant with Bochenek *et al*. who examined 66 patients

Table 6: ECHO parameters in both groups

	Group I (*n*=50)	Group II (*n*=50)	*P*
LVEDV			
Pre, mean±SD	86.1±14.4	88.3±14.8	0.463
Post, mean±SD	87.1±15.5	88.4±14.9	0.673
Percentage change, median (range)	0.3 (−15.5-55.1)	0 (−3.3-4.7)	0.064
LVESV			
Pre, mean±SD	40.0±8.5	40.4±8.9	0.812
Post, mean±SD	40.1±8.2	40.6±8.8	0.782
Percentage change, median (range)	0 (−17.1-31.1)	0 (−1.7-21.4)	0.556
EF			
Pre, mean±SD	53.5±4.8	54.5±4.5	0.290
Post, mean±SD	53.8±4.5	54.6±4.1	0.400
Percentage change, median (range)	0.6 (−5.5-4.4)	0 (−2.6-2.9)	0.061
WMSI			
Pre, mean±SD	1.2±0.09	1.17±0.11	0.137
Post, mean±SD	1.14±0.11	1.12±0.11	0.267
Percentage change, median (range)	−8.3 (−23.1-18.2)	0 (−28.6-9.1)	0.238

Independent *t*-test was used. Mann-Whitney U-test was used for % change. LVEDV: Left ventricular end-diastolic volume, LVESV: Left ventricular end systolic volume, EF: Ejection fraction, WMSI: Wall motion score index, SD: Standard deviation

Table 7: Global longitudinal strain and global circumferential strain in both groups

	Group I (*n*=50)	Group II (*n*=50)	*P*
GLS			
Pre, mean±SD	−17.0±1.7	−17.5±1.7	0.142
Post, mean±SD	−21.2±6.5	−18.1±1.9	0.001
Percentage change, median (range)	31.3 (9.8-62.9)	3.1 (−7.7-12.4)	<0.001
GCS			
Pre, mean±SD	−17.1±2.4	−17.8±2.3	0.124
Post, mean±SD	−25.4±1.9	−23.8±2.1	<0.001
Percentage change, median (range)	46.7 (32.1-100)	33.9 (8.9-76.7)	<0.001

Independent *t*-test was used. Mann-Whitney U-test was used for % change. GLS: Global longitudinal strain, GCS: Global circumferential strain, SD: Standard deviation

Table 8: Left anterior descending segment affected in both groups

Coronary angiography	Group I (*n*=50), *n* (%)	Group II (*n*=50), *n* (%)	*P*
Distal	18	15	0.204
Mid	28	26	
Proximal	4	9	

Chi-square test was used

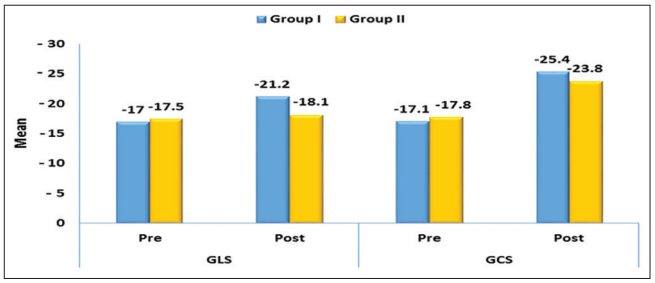


Figure 5: Global longitudinal strain and global circumferential strain in both groups

with first STEMI 48 h before and 3 months after primary PCI to evaluate myocardial function.[15]

This study demonstrated that there were no significant differences in both SBP and DBP in pre- and post-procedural in the two groups; the *P* value for SBP was 0.491 and 0.828 in both groups, respectively, while the *P* value for DBP in both groups was 0.468 and 0.326, respectively. There were no significant differences in pre- and post-procedural HR in both groups; the *P* value was 0.935 and 0.664 in the two groups, respectively. In this study, there were no significant differences in ECG in both groups with *P* = 0.174.

This was concordant with, Lacalzada *et al*. who found that there were no significant differences as regarding the vital signs.[16]

While GLS mostly reflects subendocardial ischemia, GCS reflects mid-wall ischemia, it is normal that the GLS values are lower than the GCS values and if the subendocardium is affected as in ischemia the GLS will be more affected than the GCS, the normal values of GLS are −16%–−18% while the normal values of GCS are −20%–−27%. In our study, after CABG, the GLS takes more time to recover while the

GCS showed an immediate increase due to the arrangement of muscle fibers.

In this study, we used conventional echocardiography parameters such as LVEDV, LVESV, EF, and WMSI in the both two groups preprocedural and postprocedural.

This study demonstrated that there were no significant differences in LVEDV, LVESV, WMSI, and EF in the both two groups pre- and post-procedural. This finding could have been due to the fact that these parameters are not direct measurements of myocardial function since they are affected by the loading conditions as preload and afterload.

This was in concordance with Gasior *et al*. who found that there were no significant changes in these parameters;[17] and this was concordant with Shehata who investigated 50 patients with anterior STEMI and found that there were no significant changes in these parameters.[18]

This was discordant with Cong *et al*. who found that echocardiographic parameters such as WMSI were higher in patients with LV remodeling than patients with normal left ventricle after interventions.[19]

Two-dimensional STE was used to obtain GLS and GCS in the two groups, preprocedural and postprocedural to compare the LV function in the two groups.

This study demonstrated that there were significant increases in GCS after CABG while there was no significant increase in GLS after the same procedure, this may be related to the arrangement of muscle fibers and the subendocardial ischemia.

This was concordant with Chan *et al*. who found that there were increases in GCS while there were delays in GLS in patients who undergo CABG due to the ischemia of longitudinal muscle fibers.[20]

This was discordant with Park *et al*. who investigated 24 patients with STEMI 24 h before, 48 h, 1 month, 3 months after the procedure and found that there were significant increases in GLS.[21]

This study demonstrated that there were significant increases in GLS and GCS in patients after PCI with improvement in myocardial function after this procedure.

This was concordant with Paul and George who found that GLS and GCS were excellent predictors of LV function after primary PCI in patients with acute STEMI.[22]

This study demonstrated that both GLS and GCS were significantly higher in patients with PCI than in patients with CABG. This was concordant with Chan *et al*.[20]

After all, STE is recommended to be used in the assessment of LV function after PCI and CABG surgery to LAD to detect the subtle changes after these procedures.

A larger number of studies and longer follow-up period are required to confirm the results and recommendations concerning the assessment of LV function after PCI and CABG surgery in patients with LAD lesion.

Conclusions

The parameters of STE-GLS and GCS are more effective than the parameters of standard echocardiography such as the LVEDV, LVESV, WMSI, and EF for evaluating myocardial improvements after PCI and CABG surgery. GCS is better than GLS shortly after CABG surgery because of the arrangement of the longitudinal muscle fibers in the LV and the locations of the myocardial regions affected by CAD. Increase in GLS and GCS in patients after PCI with improvement in myocardial function after this procedure. Both GLS and GCS are significantly higher in patients with PCI than patients with CABG surgery to LAD.

Recommendations

STE is recommended to assess the LV function after PCI and CABG surgery to LAD.

Study limitations

Some images are suboptimal – small sample size – limited duration of the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Transesophageal Echocardiography and Scopy Co-guided Percutaneous Mitral Balloon Valvuloplasty Procedure: Experience of a Tertiary Health Center with a Literature Review

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Abstract

Objective: Rheumatic valvular heart disease (RVHD) is an important health problem in Turkey, as in all developing countries. There is no exact prevalence data for RVHD in Turkey. But according to the Jones criteria, Turkey has a moderate risk for acute rheumatic fever (ARF). Patients with recurrent bouts of ARF resulting in carditis can progress to RVHD. The aim of this study was to evaluate percutaneous mitral balloon valvuloplasty (PMBV) procedures and compared the findings with the literature. **Materials and Methods:** PMBV procedure indication was determined according to the guidelines and heart team consensus. Echocardiography was evaluated prior to PBMV in all patients. The study included a total of 131 patients who underwent PMBV in the cardiology clinic of our hospital in the period 2007–2017. All PBMV procedures were performed under intraprocedural transesophageal echocardiography (TEE) guidance in addition to fluoroscopy with general anesthesia. **Results:** The patients comprised 83% female and 17% male with a mean age of 41.2 ± 10.1 years. Mean ejection fraction was 60.3% ± 3.1%, mean left atrium diameter was 46.7 ± 5.3 mm, and mean Wilkins score was 8.7 ± 1. After procedure with there was no mortality. There was statistically significant increase on mitral valve area and statistically significant decrease on pulmonary arterial pressure and statistically significant decrease on transmitral gradient. **Conclusion:** This is one of the few studies worldwide to have detected the safety and efficacy of PBMV with TEE and scopy coguidance. It is the first such study in Turkey. In accordance with the literature, the procedures performed with TEE and fluoroscopy co-guidance in our clinic have increased the safety of the procedure and decreased complication rates.

Keywords: Balloon valvuloplasty, echocardiography, fluoroscopy, mitral valve stenosis, rheumatic heart disease

Introduction

Rheumatic valvular heart disease (RVHD), which is a major cardiac health problem in Turkey, is also a common problem in developing countries. It is related to an exaggerated immune response due to cross-reactivity between Group-A beta-hemolytic streptococcus antigen and the valve tissue.[1] There is no precise data on the prevalence of RVHD in Turkey. Patients with recurrent attacks of acute rheumatic fever (ARF) resulting in carditis which can develop into RVHD. According to the Jones criteria, Turkey has a moderate risk for ARF in the general population.[1] Severe mitral stenosis (MS) is the major cause of clinical worsening and limitation in the functional capacity of patients with RVHD. Since the first description

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of the valvuloplasty procedure in 1984, percutaneous mitral balloon valvuloplasty (PMBV) has been the primary procedural decision in many patients with MS.[2] Although it entails mortal risks, which diminish with the increasing experience of the practitioner and the proper patient selection; PMBV is an effective method in the short and long term.[3] To reduce complications in our clinic, the PMBV procedure is performed under transesophageal echocardiography (TEE) and general anesthesia. The aim of this study was to evaluate the PMBV procedures applied in our clinic between 2008 and 2017 and to compare the results with the literature.

Materials and Methods

Patients who underwent PMBV were retrospectively identified. The PMBV procedure indication was determined according to the guidelines[4] and heart team (cardiologists, cardiac surgeons, and anesthetists) consensus. The demographic characteristics, before-after procedural echocardiography results, and rates of complications of the patients were retrospectively evaluated. Transthoracic echocardiography (TTE) was evaluated before the PBMV procedure in all patients. The echocardiographic parameters used were mitral valve area (echocardiographic mitral valve area was calculated using pressure half-time and the planimetric method, with the smallest value of these two accepted), transmitral gradients, Wilkins' Score, left atrial appendage, and mitral insufficiency severity. Patients with a Wilkins Score ≥11, >2° mitral insufficiency and thrombus in the left atrium, were excluded from the study. The echocardiographic and clinical evaluations were performed at 24 h and at the end of the postprocedural 1st month. A total of 131 patients were identified who underwent PMBV in the cardiology clinic of our hospital between 2007 and 2017. All procedures were applied after obtaining the patient's written and verbal consent. All PBMV procedures were performed under intraprocedural TEE guidance in addition to fluoroscopy with general anesthesia. Intraprocedural TEE was used as ultrasonographic guidance during the transseptal puncture (TSP) procedure by visualization of the tenting of the interatrial septum before pushing the needle for TSP [Figure 1]. All TSP procedures were performed with a Mullin sheath and Brockenbrough needle. After a successful TSP procedure, PMBV was performed with an Inoue balloon. The appropriate opening of the Inoue balloon can be monitored under TEE and if necessary, under fluoroscopy [Figure 2].

Intraprocedural TEE was also used to confirm the balloon position across from the mitral valve leaflets and to avoid damaging the subvalvular apparatus and for the early determination of postprocedural complications.

After the procedure, mitral regurgitation, valvular area, and transmitral gradient can be measured easily with TEE, so that mitral balloon valvuloplasty can be performed repeatedly during the same session if the result of the operation is suboptimal or insufficient [Figure 3].

TTE was performed at 24 h after the procedure before patients were discharged.

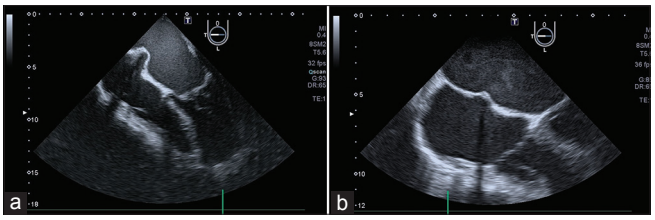


Figure 1: With the guidance of transesophageal echocardiography(TEE), transseptal puncture can be performed with confidence of detection of septal tenting on different degrees' view of TEE (a-b)

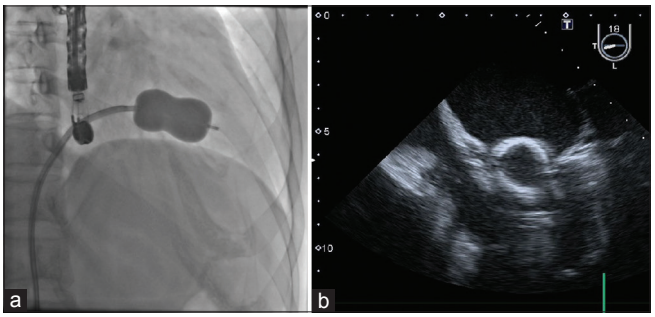


Figure 2: The appropriate opening of the Inoue balloon can be monitored under transesophageal echocardiography (a) and if necessary, under fluoroscopy (b)

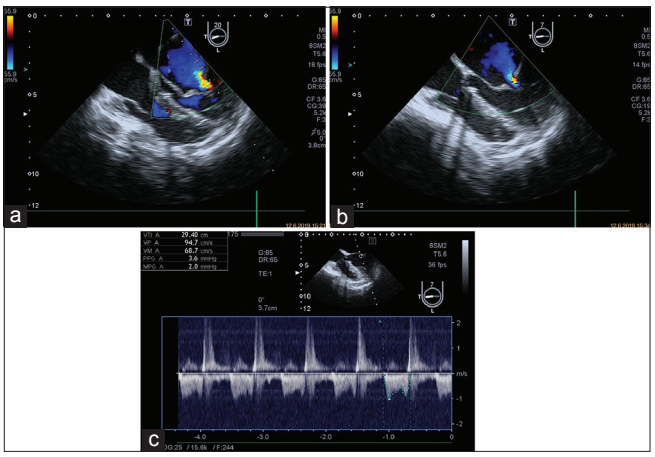


Figure 3: After the procedure, the mitral regurgitation (a-b), valvular area, and transmitral gradient (c) can be measured easily with transesophageal echocardiography, and if necessary procedure can repeat in same session

The postprocedural echocardiographic measurements in this study were accepted as the echocardiographic evaluation based on the 1-month findings.

Approval for this study was granted by the non-Interventional Clinical Research Ethics Committee of our hospital (decision no: 72, dated: 06.02.19).

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS version 17 software (SPSS Inc., Chicago, IL, USA). Categorical variables were stated as a number of patients and percentage and continuous variables as mean ± standard deviation values. Conformity of the data to normal distribution

was assessed with visual (histogram and probability graphs) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk test). Comparisons of categorical variables between groups were evaluated with the Chi-square test. Pre- and post-procedure values were compared using the paired-samples *t*-test. A value of $P < 0.05$ was accepted as statistically significant.

Results

The patients comprised 110 (83%) females and 21 (17%) males, with a mean age of 41.2 ± 10.1 years. Two patients were pregnant. The mean ejection fraction was 60.3% ± 3.1%, mean left atrium diameter was 46.7 ± 5.3 mm. The mean Wilkins score was 8.7 ± 1 [Table 1]. The mitral valve area was measured as 1.12 ± 0.19 cm^2, before the procedure and 1.9 ± 0.26 cm^2 after the procedure ($P < 0.001$) [Graph 1a and Table 2]. The mitral peak gradient was measured as 22.3 ± 6.5 mmHg before the procedure and 11.6 ± 3.3 mmHg after the procedure ($P < 0.001$) [Graph 1b and Table 2]. The mean gradient was measured as 12.1 ± 4.2 mmHg before the procedure and 4.9 ± 1.6 mmHg after the procedure ($P < 0.001$) [Graph 2a and Table 2]. Mean systolic pulmonary arterial pressure was 42.4 ± 15.2 mmHg before the procedure and 26.9 ± 8.1 mmHg after the procedure ($P < 0.001$) [Graph 2b and Table 2]. Severe mitral insufficiency was seen in 6 patients (4.5%), three of which were due to chordae rupture and underwent urgent surgical mitral valve replacement (SMVR), and the other three were due to partial chordae rupture and were followed up medically. During the medical follow-up, one of these cases underwent elective SMVR. Cardiac tamponade was seen in one patient (1%) [Table 3] and was treated with percutaneous pericardiocentesis, and the patient was discharged from the hospital after PBMV. Moderate mitral insufficiency was seen in 7 patients (5.3%). The procedure was unsuccessful in 2 (1.5%) patients with mitral valve area remaining <1.5 cm^2 after PMBV [Table 3] and those patients who underwent elective SMVR. No mortality occurred in any patient.

Discussion

Until the first description of PMBV by Inoue *et al*.[2] in 1984, the preferred treatment option for patients with severe MS was surgical mitral commissurotomy. After the Inoue technique was introduced, PBMV became an appropriate procedure for patients with MVA <1.5 cm², moderate-severe MS with symptoms NYHA class ≥2, and for those with moderate-severe MS with new-onset atrial fibrillation and significant pulmonary hypertension (resting >50 mmHg, with exercise >60 mmHg).[4] In 1990, the Wilkin score was described as a prediction of the success of PBMV in rheumatic mitral valve stenosis. The Wilkin score four components (1-leaflet mobility; 2-leaflet thickness; 3-subvalvular thickening; and 4-leaflet calcification) are individually scored from 1 to 4 points.[5] If the score is ≤8, then a favorable outcome is mostly predicted with PBMV. If the score is >8, with moderate-severe mitral insufficiency in the presence of an atrial thrombus, then SMVR is recommended.

Kronzon *et al*.[6] reported the safety of TEE-guided PBMV, and Goldstein *et al*.[7] used intraprocedural TEE for the PBMV procedure in 93 patients. Vilacosta *et al*.,[8] Ramondo *et al*.,[9] and Park *et al*.[10] also reported shorter fluoroscopy time and procedure time with the use of intraprocedural TEE. As the current study was a retrospective cohort, fluoroscopy and procedure time could not be evaluated. However, as general anesthesia was used in the current study cases, procedure time was no shorter than that of the PMBV cases with fluoroscopy guidance only.

The National Heart, Lung, and Blood Institute classified complications related to mitral balloon valvuloplasty as important and unimportant. Important complications of the procedure are death, shock, the development of severe mitral insufficiency, systemic embolism, cardiac tamponade, urgent surgery requirement, and acute myocardium infarction. Unimportant complications include vasovagal reaction, arrhythmia requiring treatment, and iatrogenic atrium septum defect. The prevalence of all of these complications has been reported to be approximately 12%.[11] The total complication rate of the current study was 5.3%, which is lower than the above-reported values.

PMBV-related mortality has been shown to be 0%–3% in most studies, with causes of death reported as cardiac tamponade

Table 1: General characteristics and basal echocardiographic findings of patients

Age (years)	41.2±10.1
Gender, *n* (%)	
Female	110 (83)
Ejection fraction (%)	60.3±3.1
Left atrium (mm)	46.7±5.3
Wilkins score	8.7±1

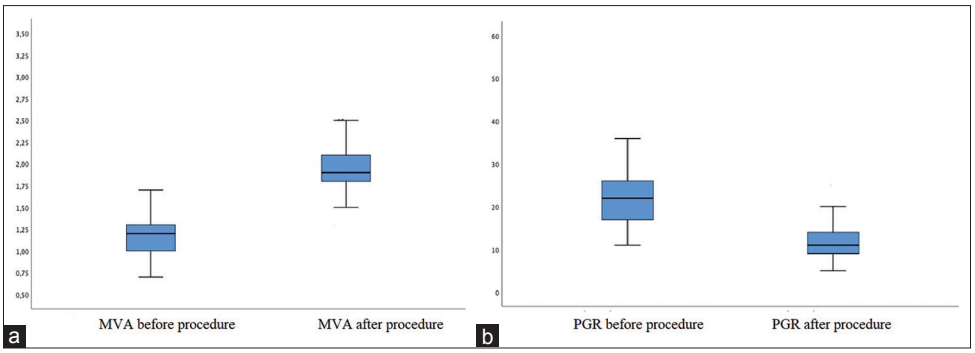
Table 2: Echocardiographic changes before and after the procedure

	Before procedure	After procedure	*P*
MVA (cm^2)	1.12±0.19	1.9±0.26	<0.001
Peak gradient (mmHg)	22.3±6.5	11.6±3.3	<0.001
Mean gradient (mmHg)	12.1±4.2	4.9±1.6	<0.001
SPAP (mmHg)	42.4±15.2	26.9±8.1	<0.001

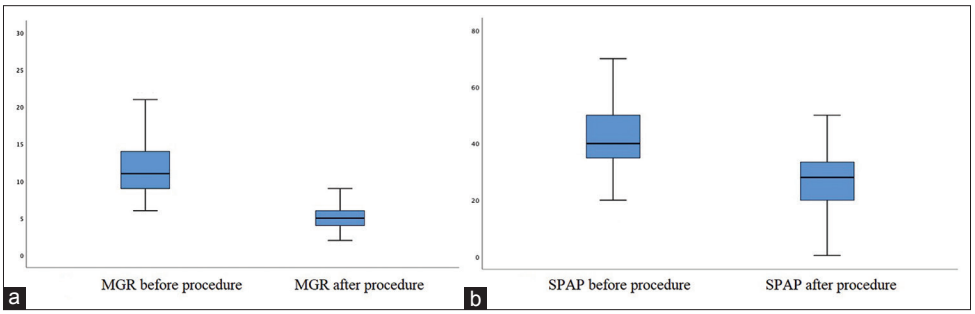
MVA: Mitral valve area, SPAP: Systolic pulmonary arterial pressure

Table 3: Important and unimportant complications of the procedure

Total complications, *n* (%)	7 (5.3)
Severe mitral insufficiency, *n* (%)	6 (4.5)
Cardiac tamponade, *n* (%)	1 (1)
Moderate mitral insufficiency, *n* (%)	7 (5.3)
Failed procedure, *n* (%)	2 (1.5)



Graph 1: (a) Mitral valve area (MVA) distribution as cm^2, and (b) peak transmitral gradient (PGR) distribution as mmHg before and after the percutaneous mitral balloon valvuloplasty procedure



Graph 2: (a) Mean transmitral gradient (MGR) distribution as mmHg, and (b) systolic pulmonary arterial pressure (sPAP) distribution as mmHg before and after the percutaneous mitral balloon valvuloplasty procedure

and the development of severe mitral insufficiency.[12] In the current study, no mortality occurred in any patient.

Hemopericardium, seen at the rate of 1%–3%, is one of the most important causes of death and is often associated with TSP or myocardial injury.[12] In the current study, cardiac tamponade occurred in 1 patient (1%) and was treated with percutaneous pericardiocentesis.

Severe mitral regurgitation has been reported in 1.4%–9.4% of patients with PMBV,[13] and 1.3%–3.2% of severe mitral insufficiency require urgent SMVR.[14] In the current study, severe mitral insufficiency was seen in 4.5% of patients. Half of these cases (n:3) were due to chordae rupture and underwent urgent SMVR, while the other three were due to partial chordae rupture and they were followed up medically. During the medical follow-up, one of these patients underwent elective SMVR. Therefore, when compared with the findings in literature, the TEE and fluoroscopy co-guided PMBV procedures of the current study had low hemodynamically significant severe mitral insufficiency rates.

During TSP, TEE can visualize the position of the Mullins sheath and the Brockenbrough needle on the interatrial septum, and this makes the procedure safer. In the current study, with good procedural success rates, the mitral valve area increases, mitral peak gradient, mean gradient, and systolic pulmonary arterial pressure decreases were statistically significant with a value of $P < 0.001$. Moreover, complication rates were lower (total complication rate of 5.3%) and there was no mortality.

Conclusion

As our knowledge this study is one of the few studies from the worldwide and the first study from the Turkey, which have researched the safety and efficacy of PBMV with TEE and fluoroscopy co-guidance. Fluoroscopy and TEE-guided PMBV are safer with lower complication rates. However, this was a retrospective study, with some limitations regarding missing data such as fluoroscopy time.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Admission Plasma Glucose and Maternal Prognostic Factors in Preeclampsia

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Abstract

Aims: We aimed to investigate if admission plasma glucose (PG) level was a significant and independent risk factor for the patients' length of stay at the intensive care unit (ICU), as the primary outcome parameter, and also for the maternal and fetal complications, as the secondary outcome parameters, among a group of nondiabetic pregnant women with severe preeclampsia. **Materials and Methods:** In this prospective case–control study including 63 pregnant women, admission PG, glycosylated hemoglobin, neutrophil–lymphocyte ratio, platelet count, liver enzymes, and other laboratory parameters and clinical characteristics including length of stay at the hospital, maternal, and fetal complications were investigated. **Results:** Admission PG levels were found to be significantly elevated in preeclamptic women with poor outcome. Furthermore, platelet count, fibrinogen, alanine aminotransferase, and aspartate aminotransferase values were significantly associated with the length of stay at ICU. **Conclusion:** We claimed that hyperglycemia was an acute reaction, reflecting the severity of preeclampsia and PG levels to be added to the routine high-risk pregnancy panel on initial presentation to the hospital.

Keywords: Eclampsia, fibrinogen, glycosylated hemoglobin, hellp syndrome, intensive care unit, neutrophil, platelet

Introduction

Prior studies have suggested that stress-induced metabolic response to homeostatic threats leads to hyperglycemia as a consequence of enhanced glucose production, diminished insulin synthesis, and insulin resistance in peripheral tissues.[1] While sustained hyperglycemia may induce substrate mobilization, leading to abnormalities in defence mechanisms and organ functions, acute hyperglycemia, contrarily, may be beneficial to the stressed organism.[2] Although some have claimed that increased glucose on admission is a predictor of adverse outcomes such as mortality,[3] morbidity, length of hospital stay and infections in emergencies like myocardial infarction,[4-6] stroke,[7,8] and in other acute conditions including trauma,[9] others have suggested that lower glucose level on admission may be associated with worse outcomes[10,11] after an acute event, such as myocardial infarction.

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Maternal hyperglycemia during pregnancy has also been correlated with increased risk of maternal complications, including pregnancy-induced hypertension and preeclampsia, and fetal complications such as intrauterine fetal demise, congenital anomalies, neonatal hypoglycemia, and hyperbilirubinemia.[12] Despite clinical data demonstrating the impact of admission glucose on the outcome in different clinical situations, definitions of hyperglycemia are inconsistent, ranging from 6 to 8 mmol/L (110–145 mg/dL) for nondiabetic patients and up to 11 mmol/L (200 mg/dL) for diabetic patients.[5]

The American Diabetes Association (ADA) has defined gestational diabetes mellitus (GDM) as glucose intolerance

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with onset during pregnancy.[13] The hyperglycemia and adverse pregnancy outcome study[14] and the task force of the International Association of Diabetes and Pregnancy Study Groups, recommend that the diagnosis of GDM be made, when one or more of the following criteria are met: fasting plasma glucose (PG) 5.1–6.9 mmol/l (92–125 mg/dl); 1-h PG ≥10.0 mmol/l (180 mg/dl) following a 75 g oral glucose load; 2-h PG 8.5–11.0 mmol/l (153–199 mg/dl) following a 75 g oral glucose load,[15] instead of current ADA recommendations[16] of at least 2 of the following tresholds are met or exceeded: fasting 95 mg/dL, 1-h 180 mg/dL, or 2 h 155 mg/dL. Glycosylated hemoglobin (HbA1c) reflects antecedent glycometabolic state and is minimally affected by stress during acute emergencies;[13] the relationship between HbA1c and the short-term prognosis in acute obstetric complications has not been well defined.

Recently, neutrophil count and neutrophil–lymphocyte ratio (NLR) are being investigated as potential prognostic biomarkers in critically ill patients. Data are lacking in preeclampsia and in other pregnancy complications.

Our primary aim in this study, for the first time in the literature, was to investigate if admission PG level was a significant and independent risk factor for the patients' length of stay at the intensive care unit (ICU), as the primary outcome parameter, and also for the maternal and fetal complications, as the secondary outcome parameters, among a group of pregnant women with severe preeclampsia. Therefore, we also studied HbA1c, NLR, platelet count, liver enzymes and other laboratory parameters, clinical characteristics, like length of stay at the hospital, overall and after being discharged from the ICU, cesarean section rate, and birth weight.

Materials and Methods

Sixty-three nulliparous pregnant women with severe preeclampsia were recruited consecutively for this prospective case–control study between February 2014 and August 2014 at the high-risk pregnancy unit at Zekai Tahir Burak Women's Health Care, Education And Research Hospital, Ankara, Turkey. The study was approved by the institutional review board of the hospital. The universal principles of Declaration of Helsinki were applied.

Diagnosis of preeclampsia is based on systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg measured while resting for two 4-h intervals after the 20th gestational week, as well as proteinuria of 300 mg/dL detected in a 24-h urine sample, or in the absence of proteinuria, hypertension together with evidence of systemic disease including thrombocytopenia, increased levels of liver transaminases, renal failure, pulmonary edema, and visual or cerebral disturbances.[17] The diagnosis of severe preeclampsia was based on the presence of any of the following criteria: systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg on two separate measurements performed at 6-h intervals at the least, increased serum creatinine (>1.1 mg/dL), headache, visual impairment, epigastric pain or pain in the right upper quadrant, elevated hepatic enzymes (to twice normal concentration), thrombocytopenia (platelet <100,000/mm^3), or pulmonary edema.[18]

Women with preexisting or a history of medical conditions, including chronic hypertension, prediabetes, diabetes mellitus – fasting PG ≥7.0 mmol/l (126 mg/dl), 2-h PG ≥11.1 mmol/l (200 mg/dl) following a 75 g oral glucose load, random PG ≥11.1 mmol/l (200 mg/dl), HbA1c >5.7% (5.7%–6.4% prediabetes, ≥6.5% diabetes)[16] or other cardiovascular, endocrinological, urogenital, gastrointestinal, autoimmune or oncological disease thrombophilia, multiple gestation or trophoblastic disease, women who use medications that may interfere with blood glucose, such as glucocorticoids, who has pregestatioanal obesity (body mass index [BMI], BMI >30), and smokers, were excluded.

The clinical data (age, BMI, body temperature, systolic and diastolic blood pressure, gestational age, length of hospital, ICU, post-ICU stay, birthweight, maternal, and fetal complications) and the blood samples were collected prospectively, but laboratory workup and data evaluation were achieved retrospectively, without any intervention. During hospital admission, blood samples were obtained from the antecubital vein early in the morning, following 8 h of fasting, and PG, HbA1c, complete blood count, NLR, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactic acid dehydrogenase (LDH), international normalized ratio (INR), and fibrinogen assessments were carried out at the central laboratories of Zekai Tahir Burak Women's Hospital, Ankara. Subsequently, all of the severe preeclamptic women followed up with an institutional standard protocol which was compatible with the one defined previously.[19]

The statistical analysis was conducted with the Statistical Package for the Social Sciences v 11.5 for Windows (Chicago, IL, USA). Data were summarized as mean ± standard deviation (SD) and median (range). Student's *t*-test or Mann–Whitney U-test was used for group comparisons depending on distributions. Correlations were assessed using Pearson or Spearman correlation analysis. A two-sided $P < 0.05$ was considered to be statistically significant. Continuous variables were examined using oneway ANOVA or Kruskal–Wallis tests if data were not normally distributed. The statistical test and correlation coefficient were chosen according to whether the data distribution was normal or not. Multivariate regression analysis and backward stepwise elimination were used for calculating variable dependent length of ICU stay. We utilized the Kolmogorov–Smirnov test to show that our sample came from a normally distributed population.

Results

In the study, 63 pregnant women with severe preeclampsia were hospitalized and treated at the ICU. As shown in Table 1, they were all young (27.41 years), overweight (28.74 kg/m^2) by World Health Organization criteria, stage 2 hypertensive (160.96/102.20 mmHg) by the American Heart

Table 1: Clinical and laboratory characteristics of pregnant women with preeclampsia (*n*=63)

Parameter	Results
Age (year), mean±SD	27.41±4.14
BMI (kg/m^2), mean±SD	28.74±2.00
Systolic BP (mmHg), mean±SD	160.96±12.78
Diastolic BP (mmHg), mean±SD	102.20±11.10
Gestational age (weeks), mean±SD	31.60±3.97
Admission fasting glucose (mg/dL), mean±SD	100.88±30.52
Discharge fasting glucose (mg/dL), mean±SD	87.61±15.95
Fasting glucose difference* (mg/dL), mean±SD	13.26±31.72
HbA1c, mean±SD	4.71±0.37
Hb (%), mean±SD	13.06±1.69
Hematocrit (%), mean±SD	38.67±4.66
Platelet (µL), mean±SD	17,5873.01±78,084.42
N (µL), mean±SD	9.75±3.86
L (µL), mean±SD	2.22±0.81
N/L ratio, mean±SD	5.25±4.32
INR, mean±SD	0.89±0.08
Fibrinogen (mg/dL), mean±SD	393.58±134.97
Newborn weight (g), mean±SD	1600.63±760.07
Hospital stay (day), mean±SD	5.63±2.73
ICU stay (day), mean±SD	2.16±1.57
Post-ICU stay (day), mean±SD	3.47±2.13
LDH (U/L), median (range)	522.00 (178.00-2913.00)
ALT (U/L), median (range)	23.00 (4.00-1822.00)
AST (U/L), median (range)	29.00 (12.00-2166.00)

*Significant (two-tailed) *P* 0.002. ICU: Intensive care unit, BMI: Body mass index, HbA1c: Glycosylated hemoglobin, SD: Standard deviation, LDH: Lactic acid dehydrogenase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, INR: International normalized ratio, N/L ratio: Neutrophil/lymphocyte ratio, BP: Blood pressure

Association criteria, all in the third trimester (31.6 weeks). Mean birth weight was 1600.63 ± 760.07 g. Forty-eight out of 63 fetuses (76.2%) were defined to have intrauterine growth retardation. Although there was no maternal mortality, perinatal mortaliy rate was 28.6% (18 of 45). While the patients stayed at the hospital on average for 5.6 days, 2.6 days of it was at ICU.

Laboratory characteristics (mean ± SD) of the cases by glucose status are presented in Table 2.

Table 3 summarizes the clinical and laboratory characteristics by length of stay ≤2 versus >2 days at ICU. As shown in Table 3, the longer the duration of patients' ICU stay, the higher their fasting PG, neutrophil count, NLR, LDH, ALT, and AST values and the lower the platelet count and fibrinogen levels were, among pregnant women with severe preeclampsia.

Hyperglycemia was found to be correlated with the development of hemolysis, elevated liver enzymes, low platelet count syndrome (HELLP) syndrome (*P* = 0.019), eclampsia (*P* = 0.017), and disseminated intravascular coagulation (DIC) (*P* = 0.017), as demonstrated in Table 4.

Contrarily, only women with HELLP syndrome stayed significantly longer (*P* = 0.001) at the ICU (>2 days) [Table 5].

Table 2: Laboratory characteristics among pregnant women with preeclampsia by glucose status

Parameter	PG (mg/dL)	Results
HbA1c, mean±SD	≤92	4.70±0.37
	>92	4.71±0.38
Hb (%), mean±SD	≤92	12.87±1.40
	>92	13.30±1.97
Hematocrit (%), mean±SD	≤92	38.45±4.10
	>92	38.94±5.31
Platelet (µL), mean±SD	≤92	19,2558.82±68,948.02
	>92	15,6310.34±84,638.77
N (µL), mean±SD	≤92	8.85±3.16
	>92	10.81±4.37
L (µL), mean±SD	≤92	2.33±0.83
	>92	2.10±0.77
N/L ratio, mean±SD	≤92	4.55±4.67
	>92	6.07±3.78
INR, mean±SD	≤92	0.89±0.06
	>92	0.90±0.09
Fibrinogen (mg/dL), mean±SD	≤92	403.76±111.69
	>92	381.65±159.26
Intensive care (day), mean±SD	≤92	2.00±1.27
	>92	2.34±1.87
Hospital (day), mean±SD	≤92	4.70±1.85
	>92	6.72±3.19
Newborn weight (g), mean±SD	≤92	1658.82±634.15
	>92	1532.41±892.37
LDH (U/L), median (range)	≤92	535.00 (178-2799)
	>92	492.00 (206-2913)
ALT (U/L), median (range)	≤92	20.50 (6-1822)
	>92	60.00 (4-1502)
AST (U/L), median (range)	≤92	26.50 (12-2166)
	>92	40.00 (12-849)

HbA1c: Glycosylated hemoglobin, SD: Standard deviation, N/L ratio: Neutrophil/lymphocyte ratio, INR: International normalized ratio, LDH: Lactic acid dehydrogenase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, PG: Plasma glucose

Length of ICU stay and birth weight were studied with regard to admission PG, and only a significant correlation was found between birth weight below 1800 g and hyperglycemia (*P* = 0.035) [Table 6].

Tables 7 and 8 presented data regarding perinatal complications and Table 9 regarding birth weight status, when PG and HbA1c levels were considered as reference points. While hyperglycemia was found to have a significant correlation with the development of HELLP syndrome (*P* = 0.007), eclampsia (*P* = 0.027), and renal failure (*P* = 0.000), HbA1c was not correlated with any one of the complications. Contrarily, the mean HbA1c values were lower in women who delivered fetuses weighing below 1800 g when compared with the ones ≥1800 g (*P* = 0.003).

HbA1c had a positive correlation with platelet count and birth weight and a negative correlation with Hb and hematocrit levels [Table 10]. NLR was positively correlated with PG levels, and length of ICU and hospital stay [Table 11].

Mean PG, neutrophil, NLR, LDH, AST, and ALT values determined the length of patients' stay at ICU [Table 12].

Finally, in Table 13, platelet count was negatively correlated with PG, Hb, hematocrit, and diastolic blood pressure and was positively correlated with HbA1c. Moreover, neutrophil count and INR were inversely correlated with gestational week($r = -0.309$, $P = 0.014$) and fibrinogen levels ($r = -0.504$, $P = 0.001$), respectively.

Table 3: Comparison of clinical and laboratory characteristics among pregnant women with preeclampsia by length of stay at intensive care unit

Parameter	ICU day	Results
Admission fasting glucose (mg/dL), mean±SD	≤2	96.57±22.49
	>2	113.56±45.50
HbA1c, mean±SD	≤2	4.75±0.35
	>2	4.58±0.43
Hb (%), mean±SD	≤2	12.87±1.61
	>2	13.63±1.83
Hematocrit (%), mean±SD	≤2	38.28±4.42
	>2	39.83±5.30
Platelet (µL), mean±SD	≤2	19,4319.14±72,847.69
	>2	12,1687.50±68,771.81
N (µL), mean±SD	≤2	9.24±3.67
	>2	11.25±4.14
L (µL), mean±SD	≤2	2.21±0.81
	>2	2.27±0.84
N/L ratio, mean±SD	≤2	4.67±2.52
	>2	6.95±7.32
INR, mean±SD	≤2	0.89±0.07
	>2	0.91±0.09
Fibrinogen (mg/dL), mean±SD	≤2	415.55±111.80
	>2	329.06±176.11
LDH (U/L), median (range)	≤2	479.00 (178-2913)
	>2	740.50 (359-2799)
ALT (U/L), median (range)	≤2	19.00 (6-1502)
	>2	71.00 (4-1822)
AST (U/L), median (range)	≤2	25.00 (12-849)
	>2	61.50 (12-2166)

ICU: Intensive care unit, HbA1c: Glycosylated hemoglobin, SD: Standard deviation, N/L ratio: Neutrophil/lymphocyte ratio, INR: International normalized ratio, LDH: Lactic acid dehydrogenase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

A multivariate analysis showed that admission PG ($P = 0.001$), also platelet count ($P = 0.045$), fibrinogen ($P = 0.001$), AST ($P = 0.041$), and ALT ($P = 0.035$) were still significantly associated with the length of stay at ICU, even after all associated risk factors were entered into the logistic regression model.

On multivariate analysis, admission PG over 92 mg/dL remained a significant predictor of HELLP syndrome (odds ratio [OR] = 3.79 95% confidence interval [CI]: 1.20–11.92), of eclampsia (OR = 1.20 95% CI: 1.023–1.42), of DIC (OR = 1.20 95% CI: 1.02–1.42), and of birth weight below 1800 g (OR = 3.143 95% CI: 1.063–9.293). Among newborns with birth weight ≥1800 g, OR of maternal admission PG being measured more than 92 mg/dL was decreased (OR = 0.659 95% CI: 0.445–0.977). Contrarily, among newborns with birth weight below 1800 g, relative risk of mothers having admission PG above 92 mg/dL was higher (OR = 2.071 95% CI: 1.001–9.293). The relative risk of staying at ICU more than 2 days was significantly increased only in the presence of HELLP syndrome (OR = 7.03 95% CI: 2.02–24.46).

Discussion

Preeclampsia is considered primarily to be a vascular disorder, associated with an ischemic placenta, endothelial cell dysfunction,[20] intravascular inflammation,[21] and activation of the hemostatic system.[22] The clinical manifestations of preeclampsia result from the involvement of multiple organs, including the kidneys, liver, brain, heart, lung, and pancreas.[23]

Diabetes mellitus[24] and even lesser degrees of glucose intolerance have also been shown to be associated with adverse maternal and perinatal outcomes.[25,26] Even in the absence of prediabetes and diabetes, maternal hyperglycemia and insulin resistance as a stress-induced metabolic response during pregnancy have been shown to be correlated with increased risk of maternal and fetal complications.[12] This contradicts the evidence which supports the opinion that stress hyperglycemia may be protective against homeostatic threats, allowing the host to survive during periods of severe stress.[26] Indeed, it has been demonstrated that critically ill adults with stress

Table 4: Comparison of demographic characteristics among pregnant women with preeclampsia by elevated glucose status

PG	HELLP		Eclampsia		Renal failure		Ablatio placenta		DIC		IUGR		Perinatal mortality	
	+	−	+	−	+	−	+	−	+	−	+	−	+	−
≤92														
n	6	28	0	34	0	34	1	33	0	34	26	8	7	27
Percentage	31.6	63.6	0.0	58.6	0.0	55.7	25.0	55.9	0	58.6	54.2	53.3	38.9	60.0
>92														
n	13	16	5	24	2	27	3	26	5	24	22	7	11	18
Percentage	68.4	36.4	100	41.4	100	44.3	75.0	44.1	100	41.4	45.8	46.7	61.1	40.0
Total#	19	44	5	58	2	61	4	59	5	58	48	15	18	45
P	0.019*		0.017**		0.20**		0.32**		0.017**		0.955*		0.12*	

*Pearson χ^2, **Fisher's exact test. DIC: Disseminated intravascular coagulation, HELLP: Hemolysis, elevated liver enzymes, low platelet count syndrome, IUGR: Intrauterine growth retardation, PG: Plasma glucose

Table 5: Comparison of perinatal complications among pregnant women with preeclampsia by length of stay at intensive care unit

Length of ICU stay	HELLP		Eclampsia		Renal failure		Ablatio placenta		DIC		IUGR		Perinatal mortality	
	+	−	+	−	+	−	+	−	+	−	+	−	+	−
≤2														
n	9	38	3	44	0	47	3	44	2	45	38	9	12	35
Percentage	47.4	86.4	60.0	75.9	0.0	77.0	75.0	74.6	40.0	77.6	79.2	60.0	66.7	77.8
>2														
n	10	6	2	14	2	14	1	15	3	13	10	6	6	10
Percentage	52.6	13.6	40.0	24.1	100	23.0	25.0	25.4	60.0	22.4	20.8	40.0	33.3	22.2
Total[#]	19	44	5	58	2	61	4	59	5	58	48	15	18	45
P	0.001*		0.59**		0.06**		0.01**		0.09**		0.13*		0.36*	

*Pearson χ^2; **Fisher's exact test. DIC: Disseminated intravascular coagulation, HELLP: Hemolysis, elevated liver enzymes, low platelet count syndrome, ICU: Intensive care unit, IUGR: Intrauterine growth restriction

Table 6: Comparison of length of stay at intensive care unit and birth weight by degree of glycemia

PG	ICU day		Newborn weight	
	>2	≤2	≥1800	<1800
≤92				
n	9	25	17	17
Percentage	56.2	53.2	70.9	43.6
>92				
n	7	22	7	22
Percentage	43.8	46.8	29.2	56.4
Total	16	47	24	39
P	0.83*		0.035*	

*Pearson χ^2. PG: Plasma glucose, ICU: Intensive care unit

hyperglycemia have a significantly lower mortality than those with normal blood glucose levels.[27]

The stress response is mediated by the hypothalamic–pituitary–adrenal axis.[28] This stimulus leads to activation of adrenal glands through sympathetic ganglions, thereby release of catecholamines,[29] which together with cortisol, glucagon, and growth hormon stimulate hepatic gluconeogenesis and glycogenolysis.[30] This process further contributes hyperglycemia through activated hepatic gluconeogenesis, also together with pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin (IL)-1 and IL-6[31] and adipokines[32] released from adipocytes, inhibits glucose uptake in peripheral tissues,[31] eventually leading to peripheral insulin resistance.

In the light of all these scientific but contradictory information, we decided to investigate, for the first time to our knowledge, the possible relationship between the admission PG levels with maternal and fetal complications among a group of pregnant women with severe preeclampsia who were being treated at the ICU.

In this study, we demonstrated that elevated admission PG (>92 mg/dL) is encountered in 46% of our study population and is significantly associated with several complications related to preeclampsia, such as HELLP syndrome, eclampsia, and DIC defect.

PG levels were significantly and positively correlated with neutrophil count, NLR, ALT, and AST levels, also but inversely, with platelet count. Clinically, there was a significant correlation between PG and the overall length of stay at the ICU and at the hospital.

As defined in the material and methods section, women with admission HbA1c levels above 5.7 were excluded, to rule out prediabetes and diabetes mellitus. Mean HbA1c levels were indifferent between women with high and normal admission PG levels (4.71 vs. 4.70) and also between women who stayed at the ICU more than 2 days and 2 days or less (4.58 vs. 4.75). In the present study, mean HbA1c levels were significantly lower only in women who delivered babies less than 1800 g when compared with the ones who delivered heavier babies (4.60 vs. 4.89, $P = 0.003$). Overall, HbA1c values showed significant correlation positively with platelet count and birth weight and negatively with Hb and hematocrit values. Based on our data, we confirmed that HbA1c levels were minimally affected by stress, at least in pregnancy complications such as severe preeclampsia.

Platelet count was found to be one of the prognostic markers in this study. Mean platelet count was significantly lower among women with high admission PG level and who were kept in ICU longer than 2 days, in comparison to those with normal PG level and who were kept in ICU for 2 days or less (156,319 vs. 192,558 and 121,687 vs. 194,319, respectively). Mean platelet values were conversely correlated with HbA1c and inversely correlated with PG, Hb, hematocrit, and diastolic blood pressure. In regard to ICU stay, the laboratory parameters which showed significant and direct correlation were PG, neutrophil, NLR, LDH, AST, and ALT values.

Neutrophils are the most abundant leukocytes in human circulation, also the first ones recruited to the inflammatory site to eliminate the pathogens. Hyperactivated neutrophils, in situations like burn shock or traumatic injury, contribute to oxidative tissue damage and eventual organ failure.[33,34] Hyperglycemia induces neutrophil dysfunction proportionally with its extent[35] through myeloperoxidase biochemical

Table 7: Comparison of perinatal complications among pregnant women with preeclampsia by elevated glucose and glycosylated hemoglobin status

	HELLP		Eclampsia		Renal failure		Ablatio placenta	
	n	Mean±SD	*n*	Mean±SD	*n*	Mean±SD	*n*	Mean±SD
PG								
+	19	116.52±40.13	5	166.00±46.95	2	186.00±57.98	4	96.50±21.82
−	44	94.13±22.68	58	95.27±21.32	61	98.09±25.64	59	101.18±31.14
P	0.007		0.027		0.001		0.76	
HbA1c								
+	19	4.67±0.36	5	4.86±0.18	2	4.50±0.84	4	4.65±0.63
−	44	4.73±0.38	58	4.70±0.38	61	4.72±0.36	59	4.71±0.36
P	0.606		0.372		0.421		0.75	

PG: Plasma glucose, HbA1c: Glycosylated hemoglobin, SD: Standard deviation, HELLP: Hemolysis, Elevated liver enzymes, low platelet count syndrome, PG+: Admission glucose level is high, PG-: Admission glucose level is normal

Table 8: Comparison of perinatal complications among pregnant women with preeclampsia by elevated glucose and glycosylated hemoglobin status

	DIC		IUGR		Perinatal mortality	
	n	Mean±SD	*n*	Mean±SD	*n*	Mean±SD
PG						
+	5	130.60±57.48	48	103.12±31.66	18	103.72±27.85
−	58	98.32±26.41	15	93.73±26.25	45	99.75±31.76
P	0.279		0.302		0.645	
HbA1c						
+	5	4.74±0.33	48	4.72±0.38	18	4.57±0.41
−	58	4.71±0.38	15	4.68±0.35	45	4.77±0.35
P	0.87		0.754		0.060	

PG: Plasma glucose, DIC: Disseminated intravascular coagulation, IUGR: Intrauterine growth restriction, SD: Standard deviation, HbA1c: Glycosylated hemoglobin, PG+: Admission glucose level is high, PG-: Admission glucose level is normal

Table 9: Comparison of glucose and glycosylated hemoglobin values among pregnant women with preeclampsia by the birth weight status

Birth weight (g)	PG		HbA1c	
	n	Mean±SD	*n*	Mean±SD
≥1800	24	95.33±30.71	24	4.89±0.30
<1800	39	104.30±30.29	39	4.60±0.37
P	0.260		0.003	

PG: Plasma glucose, SD: Standard deviation, HbA1c: Glycosylated hemoglobin

Table 10: Correlation of glycosylated hemoglobin values with other laboratory characteristics and birth weight

HbA1c	Platelet	Hb	Hematocrit	Birth weight
r	0.251*	−0.278*	−0.268*	0.307*
P	0.047	0.027	0.034	0.015

*Pearson. HbA1c: Glycosylated hemoglobin

pathway, reduces neutrophil degranulation, and exaggerates coagulation in healthy controls who were exposed to glucose infusion and endotoxin.[36]

Lately, neutrophil biology is being investigated as potential biomarkers by which to predict the outcome of critically ill, hospitalized patients. Accordingly, the blood NLR has been identified as a potentially useful marker of clinical outcome in disease states with an inflammatory component. Its association with a poor outcome in patients with cardiovascular diseases, malignancies, cystic fibrosis, and familial mediterranean fever,[37,38] and also in patients with obstetric complications such as preeclampsia, preterm delivery, miscarriage, and intrahepatic cholestasis[39-43] have been reported previously. In the present study, both neutrophil count and NLR were elevated in women with PG above 92 mg/dL in comparison to those with normal PG levels (10.81 vs. 8.85/μL and 6.07 vs. 4.55, respectively). Likewise, women who stayed at ICU more than 2 days revealed higher NLR, when compared with those who stayed shorter (11.25 vs. 9.24/μL and 6.95 vs. 4.67, respectively). NLR was found to be positively correlated with admission PG ($P = 0.026$), duration of stay at ICU ($P = 0.015$), and at the hospital ($P = 0.031$). Finally, admission PG, platelet count, fibrinogen, AST, and ALT values were still significantly associated with the length of stay at ICU.

Conclusion

It has been debated whether increased glucose is a direct mediator of adverse outcomes or just a marker of severe disease conditions. Since hyperglycemia improved immediately following delivery, we claim that hyperglycemia is an acute reaction, a reflection of disease severity rather than the consequence of a preexisting metabolic disorder.

We confirmed that admission PG was a significant and independent marker. The simple and inexpensive characteristic of the test, also availability of results soon after admission, provides important prognostic information and permits early risk stratification and decision-making in clinical management of women with severe preeclampsia. Therefore, we suggest PG levels to be added to the routine high-risk pregnancy panel on initial presentation to the hospital. In selecting pregnant

Table 11: Correlation of neutrophil lymphocyte ratio with other laboratory characteristics and length of hospital/ intensive care unit stay

N/L ratio	PG	N	L	ICU day	Hospital day
r	0.280**	0.727*	−0.565*	0.305**	0.272**
P	0.026	0.000	0.000	0.015	0.031

*Pearson, **Spearman's. N/L ratio: Neutrophil/lymphocyte ratio, ICU: Intensive care unit, PG: Plasma glucose

Table 12: Correlation of length of hospital/intensive care unit stay with other laboratory characteristics

ICU day	PG	*n*	N/L ratio	LDH	AST	ALT
r	0.506*	0.327*	0.305**	201.0[u]	221.0[u]	210.0[u]
P	0.000	0.009	0.015	0.006	0.014	0.009

*Pearson, **Spearman's, [u]Mann-Whitney U-Test. ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, N/L ratio: Neutrophil/lymphocyte ratio, ICU: Intensive care unit, PG: Plasma glucose

Table 13: Correlation of platelet count with other laboratory characteristics and length of hospital/intensive care unit stay

Platelet	PG	Hb A1c	Hb	Hematocrit	Diastolic BP
r	−0.360*	0.251*	−0.427*	−0.361*	−0.317*
P	0.004	0.047	0.000	0.004	0.011

*Pearson. BP: Blood pressure, PG: Plasma glucose, Hb A1c: Glycosylated hemoglobin

women to be managed at the ICU, admission PG cutoff level of 92 mg/dL can be used. HbA1c measurement, on the other hand, was not demonstrated to be a determinant of acute hyperglycemia. Although NLR was significantly correlated with PG, it was not found to be an independent parameter. For that reason, we suggest that in addition of this laboratory test as a marker it would not contribute to the clinical management.

There are potential limitations in this study that should be acknowledged. First, our study population was considerably small, especially when women with particular complications associated with preeclampsia are considered. Furthermore, there is no direct evidence supporting the relationship between acute hyperglycaemia and stress. As we did not measure stress response hormones or insulin resistance through insulin and glucose measurements, it was not possible for us to specifically identify which mechanism might be more responsible for the hyperglycemia. Further large, prospective, comparative studies are urgently needed.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Correlation of B-type Natriuretic Peptide with Severity of Coronary Artery Disease Assessed by SYNTAX Score II in ST Elevation Acute Coronary Syndrome Patients

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Abstract

Background: We aimed to evaluate the role of B-type natriuretic peptide (BNP) in assessing severity of coronary artery disease by SYNTAX score (SS) II in a prospective study among ST elevation acute coronary syndrome (ACS) patients. **Methods:** One thousand and six patients with ST elevation myocardial infarction (STEMI) who admitted for primary percutaneous intervention were included. The patients were divided into two groups according to SS II values (≤32 and >32). The independent predictors of high SS II were investigated, and the best cutoff value of BNP, high-sensitivity C-reactive protein (hs-CRP), peak troponin I, and hemoglobin level in predicting high SS II was determined. **Results:** There was a positive correlation between BNP, white blood cell, hs-CRP, fasting blood glucose, peak troponin I, and SS I. SS II and hemoglobin were negative, but other parameters were positively correlated. High SS II group independent predictors of hypertension, diabetes mellitus, smoking, multivessel disease, high Killip class, BNP, peak troponin I, hemoglobin, and hs-CRP levels were found in STEMI patients. The value of BNP >87.15 pg/ml with 59% sensitivity and 77% specificity (area under the curve [AUC]: 0.722 [95% confidence interval [CI]: 0.689–0.756], $P < 0.001$), hs-CRP >10.85 mg/dl with 64% sensitivity and 64% specificity (AUC: 0.685 [95% CI: 0.65–0.72], $P < 0.001$), peak troponin I >77.83 ng/mL with 68% sensitivity and 63% specificity (AUC: 0.704 [95% CI 0.67–0.738], $P < 0.001$), and hemoglobin >16.75 g/dL with 4% sensitivity and 97% specificity (AUC: 0.345 [95% CI: 0.309–0.382] $P < 0.001$) independently predicted high SS II group. **Conclusion:** Serum BNP level was independently associated with the severity of coronary atherosclerosis in patients with ACS together with multivessel disease, left ventricular ejection fraction, hs-CRP, and troponin. Therefore, BNP assessment gives additional prognostic information for early risk stratification of patients with ACS.

Keywords: Acute coronary syndrome, B-type natriuretic peptide, coronary artery disease

Introduction

The SYNTAX score (SS) is an angiographic scoring system based on the severity and complexity of coronary lesions.[1,2] To overcome the pitfalls of a system score based on coronary angiograms, seven clinical parameters, namely age, creatinine clearance (CrCl), left ventricular ejection fraction (LVEF), presence of unprotected left main, peripheral vascular disease (PVD), female sex, and chronic obstructive pulmonary disease (COPD), have been added to SS to obtain SS II.[3]

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Cardiovascular biomarkers, such as B-type natriuretic peptide (BNP), high-sensitivity C-reactive protein (hs-CRP), and troponin I, have been suggested to relate to coronary artery disease (CAD) severity.[4] Furthermore, BNP has been used as a marker for prognosis in patients with acute coronary syndrome (ACS).[5-7] Although several studies in ACS patients demonstrated an association between increased BNP levels and poor clinical outcome,[5,6] it is not known if there is a relation between the quantity of BNP levels and the severity of CAD assessed by SS II.

We aimed to evaluate the role of BNP in assessing severity of CAD by SS II in a prospective study among ST elevation ACS patients.

Methods

This was a single-center study that was screened 1214 patients with ST elevation myocardial infarction (STEMI) who admitted for primary percutaneous intervention between January 2015 and March 2018. Exclusion criteria were previous myocardial infarction history, systemic inflammatory disease, hepatic disease, malignant disease, renal failure, and previous coronary artery bypass grafting. Finally, 1006 patients were included in the study. The research protocol was approved by our institution's ethics committee. All patients gave written inform consent. Clinical data, including sex, age, cardiovascular risk factors, medications, coronary angiogram, medical history, transthoracic echocardiography, and biochemical parameters, were collected. STEMI was defined as a presentation with acute chest pain, or suffocating shortness of breath, together with persistent ST-segment elevation >1 mm in 2 or more adjacent leads, or with a new or presumed new left bundle branch block or right bundle branch block on electrocardiography.[8] Hypertension (HT) was defined as repeated systemic blood pressure measurements exceeding 140/90 mmHg or treatment with antihypertensive drugs for a known diagnosis of HT. Diabetes mellitus (DM) was diagnosed by fasting blood glucose ≥126 mg/dL, blood glucose >200 mg/dL at any time, or a history of DM, including those treated with diet, oral medications, or insulin. Hypercholesterolemia was defined as a baseline cholesterol level >200 mg/dL and/or a low-density lipoprotein cholesterol level >130 mg/dL or previously diagnosed and treated hypercholesterolemia. Active smokers were those with regular smoking in the previous 6 months.

Baseline BNP, hs-CRP, and other routine blood tests were measured at admission. The BNP levels were measured by the enzyme immunoassay kit, based on standards and which ELISA technology (Biomedica Medizinprodukte GmbH, Wien, Divischgasse) (normal <100 pg/ml). hs-CRP, lipid profile, and peak cardiac enzyme levels were also obtained from all patients. Emergent coronary angiography was performed by the Judkins technique (Siemens Axiom Artis zee 2010; Siemens Healthcare, Erlangen, Germany). Percutaneous coronary intervention (PCI) procedures were performed using standard techniques. The type of stents (bare metal or drug eluting) using the thrombectomy and balloon was also left to the operator's discretion. All patients were treated with aspirin, clopidogrel or ticagrelor, and unfractionated heparin with the recommended doses after hospital admission. During and after the procedures, the use of glycoprotein 2b/3a inhibitors was at the operator's choice. At the hospital, medical treatments of patients were performed according to international guidelines.[8] At the admission, standard two-dimensional transthoracic echocardiography was performed for all patients (S5; GE Medical System, Horten, Norway). LVEF was measured by the Simpson method. The SS I and SS II were calculated according to baseline coronary angiography in all patients by two trained interventional cardiologists who were blinded to the patients' laboratory and clinical data. The SS I was determined for all coronary lesions with >50% diameter stenosis in a vessel >1.5 mm, based on the SYNTAX and SS II calculator (www.syntaxscore.com). PVD was defined as aorta or arteries other than coronaries, with exercise-related claudication, or revascularization surgery, or reduced or absent pulsation measured by duplex ultrasonography, or angiographic stenosis of more than 50% in case of severe symptoms. COPD was defined as the long-term use of a chronic bronchodilator or steroids for lung disease. CrCl was defined by the Cockcroft–Gault formula, expressed in ml/min. The patients were divided into two groups according to SS II values (≤32 and >32). All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients provided written informed consent.

Statistical analysis

Data were analyzed using the SPSS 17.0 version (SPSS Inc., Chicago, Illinois, USA). Normality of the data was determined using the Kolmogorov–Smirnov test. The continuous variables with a normal distribution are presented as mean ± standard deviation values, while those without a normal distribution are presented as median and interquartile range values. Frequency distribution was calculated for the categorical variables (numbers and percentages [%]). The continuous variables of the two groups were compared using the Student's *t*-test or the Mann–Whitney U-test. Categorical data were compared using the Chi-square test or Fisher's exact test. Correlations between different variables were assessed by Pearson's correlation test for continuous variables and Spearman test for noncontinuous variables. Multivariate logistic regression analyses were performed to identify the independent predictors of high SS II, using variables that showed statistically significant association with them in the univariate analyses. Receiver operating characteristic curve analysis was used to determine the best cutoff value of BNP, hs-CRP, peak troponin I, and hemoglobin level in predicting high SS II.

Results

We included 1006 patients (mean age: 57.0 ± 13.0 years; 80% were male) who were diagnosed with STEMI and performed coronary angiography in our clinic. The ischemia-related artery was left anterior descending in 545 patients, right coronary artery in 336 patients, and circumflex artery in 112 patients. Multivessel disease was present in 432 patients. The SS II values of the patients ranged from 13.40 to 80.45, and the median value was 30.5. Patients were divided into two groups according to SS II values. The mean SS I and SS II values of the high SS II group were 18.0 ± 5.0 and 42.9 ± 10.3, respectively, whereas the mean SS and SS II values of the low SS II group were 15.4 ± 3.7 and 22.7 ± 4.6, respectively. The comparison of baseline clinical and laboratory parameters of patients is shown in Table 1. Patients in the high SS II group were older, more diabetic, more hypertensive, more PVD, more smokers, and a higher Killip class than the patients in the lower SS II group. In patients with high SS II group, the use of angiotensin-converting enzyme inhibitors, beta-blocker, and statin was higher, whereas the use of aspirin was similar in both the groups. Higher white blood cell (WBC), fasting blood glucose, peak troponin I, hs-CRP, BNP, lower hemoglobin, and glomerular filtration rate values were present in the high SS II group. Multivessel disease and left main coronary artery involvement were more frequent in the SS II high group, whereas the mean ejection fraction (EF) value in the SS II high group was lower.

When all patients were evaluated, there was a positive correlation between BNP, WBC count, hs-CRP, fasting blood glucose, peak troponin I, and SS I, whereas there was no correlation between hemoglobin and SS. SS II and hemoglobin were negative; on the other hand, other parameters were positively correlated. Patients were divided into the following three groups according to LVEF to reduce the effect of EF on BNP: EF low group with <40%, EF middle range group between 40% and 49%, and high EF group with ≥50%. In the restructured correlation analysis, it was observed that SS I and BNP were positively correlated outside the middle range group, and BNP and SS II were well correlated in all the EF groups. Relation between SS I and SS II with BNP, WBC count, hemoglobin, hs-CRP, fasting blood glucose, and peak troponin I is shown in Table 2.

In multivariate logistic regression analysis, high SS II group independent predictors of HT, DM, smoking, multivessel disease, high Killip class frequency, BNP, peak troponin I, hemoglobin, and hs-CRP levels were found in STEMI patients. Table 3 shows the independent predictors of the high SS II group.

The value of BNP >87.15 pg/ml independently predicted high SS II group with 59% sensitivity and 77% specificity

Table 1: Baseline characteristics

	All patients	SS II ≤32	SS II >32	*P*
Age of patient	57.0±13.0	50.8±9.9	63.4±11.7	<0.001
Gender of patient (male)	846.0 (80.0)	477.0 (96.4)	325.0 (63.6)	<0.001
Presence of diabetes	254.0 (24.0)	41.0 (8.3)	206.0 (40.3)	<0.001
Presence of hypertension	474.0 (44.8)	159.0 (32.1)	299.0 (58.5)	<0.001
Presence of COPD	47.0 (4.4)	12.0 (2.4)	35.0 (6.8)	<0.001
Presence of peripheral arterial disease	186.0 (17.6)	13.0 (2.6)	167.0 (32.7)	<0.001
Presence of dyslipidemia	425.0 (40.2)	216.0 (43.6)	196.0 (38.4)	0.089
Family history of CAD	230.0 (21.8)	117.0 (23.6)	107.0 (20.9)	0.304
History of smoking	556.0 (52.6)	330.0 (66.7)	203.0 (39.7)	<0.001
Beta-blocker use	86.0 (8.1)	30.0 (6.1)	55.0 (10.8)	0.007
Statin use	197.0 (18.6)	81.0 (16.4)	111.0 (21.7)	0.031
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use	231.0 (21.9)	67.0 (13.5)	156.0 (30.5)	<0.001
Previous medication aspirin use	26.0 (2.5)	12.0 (2.4)	13.0 (2.5)	0.903
Killip class>1 on admission (%)	218.0 (20.6)	53.0 (10.7)	158.0 (30.9)	<0.001
WBC count (/1000)	12.4±4.0	11.8±3.3	13.0±4.6	<0.001
Hemoglobin (g/dL)	13.6±1.9	14.1±1.5	13.1±2.1	<0.001
CRP (mg/dl)	10.8 (5.9-18.3)	7.7 (4.8-13.5)	14.0 (7.7-24.5)	<0.001
Estimated glomerular filtration rate (ml/min/1.73m^2)	85.7±26.5	98.3±20.6	72.8 (26.0)	<0.001
Fasting blood glucose on admission (mg/dL)	128.0 (105.0-172.0)	116.0 (100.0-134.0)	148.0 (118.0-216.0)	<0.001
Peak troponin I (ng/mL)	84.4 (38.8-187.0)	54.4 (21.7-117.7)	121.0 (56.0-237.3)	<0.001
BNP (pg/mL)	72.5 (38.0-135.0)	51.2 (29.4-87.0)	97.1 (56.0-211.0)	<0.001
LVEF (%)	46.4±8.7	50.6±6.4	42.4±8.7	<0.001
Left main CAD presence	15.0 (1.4)	3.0 (0.6)	12.0 (2.3)	0.023
Multivessel disease presence	431.0 (40.8)	153.0 (30.9)	256.0 (50.1)	<0.001
Baseline SS	16.7±4.6	15.4±3.7	18.0±5.0	<0.001
Baseline SS II	33.0±12.9	22.7±4.6	42.9±10.3	<0.001

COPD: Chronic obstructive pulmonary disease, SS: SYNTAX score, CAD: Coronary artery disease, WBC: White blood cell, CRP: C-reactive protein, LVEF: Left ventricular ejection fraction, BNP: B-type natriuretic peptide

Table 2: Relation between SYNTAX score I and SYNTAX score II with B-type natriuretic peptide, white blood cell count, high-sensitivity C-reactive protein, fasting blood glucose, and peak troponin I

	Total				EF <40 (*n*=293)				40 ≤ EF ≤ 50 (*n*=391)				EF >50 (*n*=322)			
	Bazal SS		Bazal SS II		Bazal SS		Bazal SS II		Bazal SS		Bazal SS II		Bazal SS		Bazal SS II	
	Correlation coefficient	*P*	Correlation coefficient	*P*	Correlation coefficient	*P*	Correlation coefficient	*P*	Correlation coefficient	*P*	Correlation coefficient	*P*	Correlation coefficient	*P*	Correlation coefficient	*P*
BNP (pg/mL)	0.311	<0.001	0.486	<0.001	0.262	<0.001	0.358	<0.001	0.101	0.047	0.292	<0.001	0.258	<0.000	0.369	<0.001
WBC count (/1000)	0.189	<0.001	0.221	<0.001	0.111	0.057	0.120	0.040	0.158	0.002	0.074	0.146	−0.021	0.711	−0.159	0.004
Hemoglobin (g/dL)	−0.035	0.253	−0.328	<0.001	0.038	0.514	−0.290	<0.001	0.078	0.123	−0.401	<0.001	−0.177	<0.001	−0.488	<0.001
CRP (mg/dl)	0.257	<0.001	0.403	<0.001	0.162	0.009	0.273	<0.001	0.108	0.048	0.128	0.018	0.086	0.150	0.085	0.155
Fasting blood glucose on admission (mg/dL)	0.125	<0.001	0.443	<0.001	0.158	0.007	0.493	<0.001	−0.015	0.769	0.304	<0.001	0.021	0.713	0.409	<0.001
Peak troponin I (ng/mL)	0.365	<0.001	0.456	<0.001	0.195	<0.001	0.225	<0.001	0.228	<0.001	0.103	0.043	0.108	0.052	0.044	0.436

CRP: C-reactive protein, EF: Ejection fraction, SS: SYNTAX score, BNP: B-type natriuretic peptide, WBC: White blood cell

Table 3: Independent predictors of high SYNTAX score II group

	P	OR	95% CI for Exp(*B*)	
			Lower	Upper
Presence of diabetes	<0.001	6.789	4.333	10.638
Presence of hypertension	<0.001	2.108	1.476	3.011
History of smoking	<0.001	0.534	0.372	0.766
Killip class >1 on admission (%)	<0.001	2.260	1.393	3.667
Hemoglobin (g/dL)	<0.001	0.766	0.689	0.851
hs-CRP (mg/dl)	<0.001	1.036	1.018	1.054
Peak troponin I (ng/mL)	<0.001	1.005	1.003	1.007
Multivessel disease	<0.001	1.970	1.378	2.816
BNP (pg/mL)	<0.001	1.004	1.002	1.006

OR: Odds ratio, CI: Confidence interval, hs-CRP: High-sensitivity C-reactive protein, BNP: B-type natriuretic peptide

(AUC: 0.722 [95% CI: 0.689–0.756], $P < 0.001$); hs-CRP > 10.85 mg/dl independently predicted high SS II group with 64% sensitivity and 64% specificity (AUC: 0.685 [95% CI: 0.65–0.72]) $P < 0.001$); peak troponin I >77.83 ng/mL independently predicted high SS II group with 68% sensitivity and 63% specificity (AUC: 0.704 [95% CI: 0.67–0.738] $P < 0.001$); and hemoglobin > 16.75 independently predicted high SS II group with 4% sensitivity and 97% specificity (AUC: 0.345 [95% CI: 0.309–0.382] $P < 0.001$).

Discussion

The main finding of this study is that BNP and hs-CRP levels are related to the severity of coronary atherosclerosis assessed by SS II: patients with multivessel disease showed higher BNP levels, and BNP threshold of 88 pg/ml is able to predict the extension and severity of coronary disease with 77% specificity. As far as we know, this article is the first in the literature that evaluates the relation between CAD severity by SS II and biomarker levels (BNP, hs-CRP, and troponin I).

SS I is an important tool that can help clinicians to establish the optimal revascularization approach in patients with CAD. SS II combines the anatomical-based SS with the clinical baseline variables. Seven clinical parameters (age, creatinine clearance, LVEF, presence of unprotected left main, PVD, female sex, and COPD) have been added to SS to obtain SS II.[3] A recent article published by Salvatore *et al*.[3] reported that SS II might present a useful tool to predict the risk of adverse clinical events in patients with ACS and severe CAD undergoing PCI.

Previously, it has been showed that BNP provides predictive information on ACS, and it is related to the severity of CAD in patients with ACS.[9,10] Palazzuoli *et al*.[5] demonstrated that circulating BNP levels are elevated in ACS with diffuse coronary involvement and associated with multivessel disease and the extension of coronary disease. In addition, BNP could be indicators for multivessel disease, poor thrombolysis in myocardial infarction flow, and CAD extension. Although our results are in accordance with their study, we used SS II

system as a different tool to assess the coronary artery severity. Besides the different scoring system, they found that BNP higher than 80 pg/ml, which is lower than our findings, appears able to predict the extension of coronary disease. To calculate SS II, the anatomical SS is combined with age, CrCl, LVEF, and COPD, all of which affect the BNP levels. According to the current study, this new value should be used with SS II scoring system.

Hs-CRP levels on admission are associated with short- and long-term mortality in patients with ACS.[11] Karadeniz *et al*.[12] found that serum hs-CRP levels could predict the severity and complexity of coronary atherosclerosis together with multivessel disease, LVEF, and troponin levels. Nevertheless, they used the SS I to assess the severity of atherosclerosis, and the cutoff point of 5.77 was found as an independent predictor of a high SS I in patients with ACS.

In addition, we investigated the relationship between SS II and clinical and laboratory variables by multiple regression analyses. We found that BNP, hs-CRP, peak troponin I levels as well as diabetes, smoking, and multivessel disease were independent predictors for the high SS II group.

Limitations

Long term follow up could not be possible because this is a cross sectional study. Although it is a single-center study, we recruited a large sample size.

Conclusion

Serum BNP level was independently associated with the severity of coronary atherosclerosis in patients with ACS together with multivessel disease, LVEF, hs-CRP, and troponin. To our knowledge, this is the first study to demonstrate that BNP is an independent predictor of SS II in patients with ACS. Therefore, BNP assessment gives additional prognostic information for early risk stratification of patients with ACS.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Heart Disease: Lifestyle, Knowledge, and Perception among Young Nigerian Adults

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Abstract

Background: The proliferation of heart-unhealthy lifestyles may in part be responsible for the unabated scourge from heart disease. Assessments of knowledge and perception are key factors in curbing lifestyle-related diseases. **Aims:** The aim of the study is to determine the prevalence of heart-unhealthy lifestyles and its association with knowledge and perception of heart disease among young adults in Delta State, Nigeria. **Settings and Design:** A cross-sectional observational study conducted in Oghara, Nigeria. **Materials and Methods:** Three hundred healthy adults aged 18–35 years were recruited using the multistage sampling technique. The study instrument was a modified structured interviewer-administered questionnaire. Ethical approval was obtained before conducting the survey. **Statistical Analysis Used:** Obtained data were summarized and analyzed using SPSS version 22.0 software. **Results:** The response rate was 98% (294/300): 103 males and 191 females. The mean and median age of the respondents was 27 years. Majority of the respondents had at least 6 years of formal education. Heart-unhealthy lifestyles were prevalent: lack of exercise (71.4%), inadequate fruit intake (46.9%), alcohol consumption (26.5%), and tobacco smoking (19%). The mean knowledge score for heart disease was 39.49%. Using a score of 50% as the benchmark for good knowledge, 59% of the respondents had poor knowledge. Majority of the respondents did not perceive that they were at risk of heart disease. **Conclusion:** Heart-unhealthy lifestyles are common among young Nigerian adults. Knowledge of and self-perceived susceptibility to heart disease were poor in this study. There is a need for increased and refocused heart-health education at all ecological levels from early on in life.

Keywords: Health belief model, heart unhealthy lifestyle, knowledge, young adults

Introduction

The challenges from cardiovascular disease (CVD) are of foremost public health concern worldwide, more so in low- and middle-income countries. Nigeria, a lower-middle-income country, with a population of over 180 million persons as of 2016 had a proportional mortality of 11% accrued to CVD.[1] A number of risk factors have been associated with the development of heart disease, some of which are lifestyle related (behavioral). The World Health Organization (WHO) has identified cigarette smoking, physical inactivity, harmful use of alcohol, and consumption of unhealthy diet as some heart-unhealthy behaviors.[2] Several factors including rapid urbanization with increasing adoption of heart-unhealthy lifestyle, poor health-seeking behaviors, and a dearth in policy initiatives (and implementation) promoting healthy living may contribute to the growing burden of CVD in these resource-limited countries.[2,3]

Technological advancement, one of the feats of globalization, inadvertently plays a critical role in influencing lifestyle choices that support physical inactivity. Aside from supporting a sedentary lifestyle, glamorous and enticing adverts on television (TV) and other media can negatively influence young adults to indulge in social habits such as smoking and alcohol consumption. Previous studies have reported unhealthy lifestyles such as cigarette smoking, harmful use of alcohol,

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and other psychoactive substances as seen more frequently among young adults compared to middle-aged and elderly persons.[4] Furthermore, over the years, there is a paradigm shift in food culture. At present, young people commonly choose fast-foods and unhealthy snacks that are loaded with trans fat and salt over healthy foods such as fruits and vegetables.[5]

Not surprisingly, therefore, in a review of the global CVD burden, it was observed that the burden borne by young people showed an increasing trend. Similarly, in another review, young adults in Sub-Saharan Africa had a high prevalence of cardiovascular risk factors attributable to the cumulative effects of heart-unhealthy lifestyle compared to other regions of the world.[3] Young adults in the Federal Republic of Nigeria are those aged between 18 and 35 years.[6] However, the mean ages of the study population in many CVD-related epidemiological studies in Nigeria were over 35 years.[7,8] Thus, the heart health of young adult Nigerians living in Nigeria can be described as largely understudied.

To curb the CVD scourge, the role of prevention, early detection, and treatment cannot be undermined. Adoption of heart-healthy lifestyle is a vital preventive strategy. Lack of knowledge and wrong perception of the relationship between heart-unhealthy behaviors and the occurrence of heart disease are two significant factors that can frustrate efforts at CVD prevention. The knowledge and perception of heart-unhealthy behaviors using the Health belief model (HBM) as conceptual framework among young Nigerian adults is generally lacking in the existing literature. The aim of this survey, therefore, is to determine the prevalence of heart-unhealthy lifestyles and the knowledge and perception of heart disease among young adults in Delta State, Nigeria.

Materials and Methods

Study location

The study location was Oghara, Delta State, South-South Nigeria. Oghara is a semi-urban agrarian town. It is also the administrative headquarters of Ethiope West Local Government Area (LGA), 1 of the 25 LGAs in Delta State. Each LGAs consist of wards with a different number of communities/settlements. Oghara has five wards with a total population of 159,385.

Study design

The study design was cross-sectional and observational.

Study population

In Nigeria, young adults are persons aged between 18 and 35 years.[6] To be included in this study, the potential study participant must be a healthy young adult who had resided in Oghara for at least 1 year and is willing to participate in the study voluntarily. Young adults who were visitors to or had lived less than a year in Oghara, and those who did not consent to take part in the study were excluded from the study.

The study population was recruited using a multistage sampling technique. First, the study location was selected by nonprobability convenience sampling. Following which, Ogharaefe-1, one of the five wards in Oghara, was selected by balloting, a simple random sampling technique. After that, a simple random sampling technique by balloting was again used to select streets from a sampling frame containing the list of all the streets in Ogharaefe-1 ward. Each selected street was regarded as a cluster. Finally, the study population who satisfied the inclusion criteria were recruited from households within the clusters until the sample size was reached.

Sample size determination

The minimum sample size for this study was calculated using the Cochrane formula.[9] Assuming a confidence level of 95% and level of precision of 5% (0.05), the proportion of adults with hypertension in Oghara as 21%,[7] and a nonresponse rate of 10%, the minimum sample size was 280.

Data collection

Data were obtained from the study participants using a pretested interviewer-administered questionnaire adapted from previously validated questionnaires. Questions relating to lifestyle, knowledge, and perception were adapted from the WHO STEPwise questionnaire,[10] the Heart Disease Knowledge Questionnaire,[11] and the HBM,[12] respectively.

Heart-unhealthy lifestyles

Four domains were assessed: tobacco smoking, physical inactivity, alcohol consumption, and unhealthy diet.

Ever smoked respondents are those that admitted having ever smoked tobacco, even if it were experimental puff(s), while current smokers were those who reported smoking within 1 month preceding the survey.

Knowledge of heart disease

Twenty items tested knowledge of heart disease, 11of which were correct. A correctly identified item was scored as 1, while an incorrectly identified item attracted a score of 0. Respondents that indicated "not sure" or "I don't know" were also scored 0. Items unattended to by respondents were left out during the analysis. To determine the overall knowledge score, the sum of the correctly answered questions was computed and converted into percentages for each respondent. Respondents who scored 50% and above have good knowledge, while those with scores of <50% have poor knowledge.

Perception of heart disease and heart-healthy lifestyle

The HBM was used to assess respondents' perception of the susceptibility to and the seriousness of heart disease and stroke. The reliability and internal consistency of the questions on perception were tested using Cronbach's alpha (α). Values >0.7 was regarded as acceptable interrelatedness, while $\alpha \leq 0.7$ may indicate poor interrelatedness, a small number, or heterogenicity of questions. Responses were ranked with a five-point Likert scale from strongly agree to strongly disagree.

Data analysis

Obtained data were checked for correctness, coded, and analyzed with the Statistical Product and Service Solutions

version 22.0 software (IBM SPSS Inc. Chicago, Illinois, USA). The study population was summarized using frequencies, percentages, proportions, and 95% confidence interval (CI). The associations between the level of knowledge of heart disease and sociodemographic data and lifestyle-related cardiovascular risk factors were tested using Chi-square analysis. Statistical significance was established if $P < 0.05$.

Ethical consideration

A full committee ethical approval with number HREC/PAN/2017/066/0266 was obtained on December 7, 2017, from the Health Research Ethics Committees of Delta State University Teaching Hospital, Oghara, before the commencement of the survey. The University of Roehampton (Online) also provided an expedited ethics review approval prior to the survey. Written informed consent was obtained from the eligible study participants, and the conduct of the survey was guided by the tenets of the Helsinki declaration.

Results

Data collection was done between February 2018 and March 2018. Of the 300 questionnaires distributed, 98% were analyzed, as six had insufficient data.

Sociodemographic profile

The mean and median age of the study population was 27.01 (95% CI: 26.39–27.63) and 27.0 years, respectively. About two-thirds of the study population were female. Half were single, and more than 90% had received at least 6 years of formal education [Table 1].

Self-reported lifestyle-related cardiovascular risk factors

Tobacco use

Fifty-six (19.0%) of the respondents reported that they had ever smoked. A significantly higher proportion of male respondents reported that they had ever smoked cigarette (28.2% vs. 14.1%, $\chi^2 = 8.529$, odds ratios [OR] [95% CI] = 2.380 [1.317–4.301], $P = 0.003$). Of the respondents who had ever smoked, 10.7% (6/56) were current smokers and smoked an average of 4 sticks of cigarette per day.

Table 1: Sociodemographic profile of respondents

Variables	Categories	Frequency (%)
Age (years)	18-23	96 (32.7)
	24-29	82 (27.9)
	30-35	116 (39.5)
Sex	Male	103 (35.0)
	Female	191 (65.0)
Marital status	Single	152 (51.7)
	Married	98 (33.3)
	Cohabiting	41 (13.9)
	Others (unspecified)	3 (1.0)
Education (years)	<6	24 (8.2)
	6-12	212 (72.1)
	>12	58 (19.7)

Alcohol use

Of the 180 (61.2%) respondents that reported they had drunk alcohol ever, 78 (43.3%) reported they had done so in the past 30 days. A higher proportion of males (67; 65.0%) compared to females (113; 59.0%) reported that they had drunk alcohol ever. The observed gender difference in the prevalence of alcohol consumption was not statistically significant ($P = 0.323$).

Diet

About half (156; 53.1%) of the respondents reported that they ate fruits regularly. A greater proportion of male than female respondents (63; 61.2% vs. 93; 48.7%) admitted to regular fruit intake, and the difference was statistically significant ($\chi^2 = 4.180$, OR [95% CI] = 1.660 [1.019–2.702], $P = 0.041$). None of the respondents who admitted to regular consumption of fruits ate them every day. In a typical week, the number of days fruits were eaten by the respondents was: 1 day (15; 9.6%), 2 days (57; 36.5%), 3 days (48; 30.8%), 4 days (3; 1.9%), 5 days (12; 7.7%), and 6 days (21; 13.5%). On a typical day, about half (81; 51.9%) of the respondents who eat fruits regularly take two portions of fruit per day. The other respondents had either one portion (60; 38.5%) or three portions (15; 9.6%) of fruits on a typical day.

About 60% of the respondents add salt to already cooked food. This practice did not differ by sex ($P = 0.612$). Among the respondents that reported the use of added salt to already cooked food, 42 (24.1%) does so always while it is often and rarely in 15 (8.6%) and 117 (67.2%) of the respondents, respectively.

Exercise

The majority (63.3%) of the respondents walk at least 10 min in a day, and 91.9% (171/186) do so for at least ½ h. However, 225 (76.5%) of the respondents do not walk for travel. In the past month, other than regular jobs, 71.4% of the respondents did not engage in physical activity/exercise that caused an increase in breathing and heart rate for at least 10 min continuously. Male respondents (27, 26.2%) did not differ significantly from females (57, 29.8%) with regard to physical activity ($P = 0.511$). Among the respondents who engaged in physical activity that increase their respiratory or heart rates in the past month, the majority (85.7%) did so either once (39/84) or twice (33/84) per week. Three (3.6%) respondents each exercised 3, 4, 6, and 7 days in a typical week. Respondents who engage in sporting activities spend a mean time of 1.78 h on a typical day.

More than a quarter (87/294) of the respondents regularly view TV/computer screen. The mean time spent watching TV/computer was 2.9 h daily.

Clustering of lifestyle-related risk factors

The self-reported heart-unhealthy behaviors were clustered to determine the number of risk factors per respondent. The factors clustered were current smoking, consumption of alcohol in the past month, lack of regular intake of fruits, adding salt to

already cooked food, and sedentary lifestyle. Six (2.0%) of the respondents had no lifestyle-related cardiovascular risk factor. On the other hand, 100 (34.0%), 61 (20.7%), 124 (42.2%), and 3 (1.0%) of the respondents had 1, 2, 3 and 4 risk factors, respectively.

Knowledge of heart disease and stroke

Of the 20 knowledge questions, only three were correctly answered by more than half of the respondents [Table 2].

The overall mean knowledge score (%) was 39.49 (±19.19) with a 95% CI of 37.29–41.69. One hundred and seventy-four (59.2%) of the respondents had poor knowledge score (<50%).

Knowledge of heart disease and sociodemographic characteristics of respondents

Respondents' knowledge level of heart disease and stroke did not significantly differ with age, sex, marital status, or level of education [Table 3].

Knowledge of heart disease and self-reported lifestyle-related cardiovascular risk factors

The association between knowledge of heart disease and self-reported lifestyle-related cardiovascular risk factors among the respondents is as shown in Table 4.

Perception of heart disease and stroke

Whereas, the three questions on perceived susceptibility showed internal consistency and acceptable reliability ($\alpha = 0.858$), the Cronbach's alpha for the two questions that addressed the perceived seriousness of heart disease and stroke only almost attained acceptable ($\alpha = 0.666$).

Perceived susceptibility to heart disease or stroke

Majority of the respondents had a negative perception of self-risk of heart disease or stroke. About three-quarters of the study population did not feel that they were at risk of heart disease or stroke; neither currently, shortly, nor sometime during their lifetime [Figure 1].

Perceived seriousness of heart disease or stroke

Half of the respondents did not agree that seeking medical checkup for asymptomatic heart disease was any less important than attending to other tangible problems, while about 30% agreed that heart disease and stroke might result in economic disability [Figure 2].

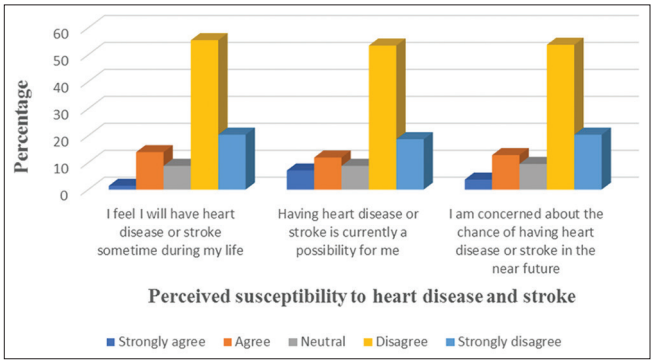


Figure 1: Perceived susceptibility to heart disease and stroke

Table 2: Respondents' knowledge of heart disease and stroke

Questions on knowledge of heart disease	Respondents' answers			Correct response, *n* (%)
	True	False	I don't know	
A person always knows when they have heart disease	106 (36.1)	111 (37.8)	77 (26.2)	False: 111 (37.8)
If you have a family history of heart disease, you are at risk for developing heart disease	108 (36.7)	118 (40.1)	68 (23.1)	True: 108 (36.7)
Most women are likely to die from breast cancer than heart disease	147 (50.0)	46 (15.6)	101 (34.4)	False: 46 (15.6)
Smokers are more likely to die from lung cancer than heart disease or stroke	152 (51.7)	79 (26.9)	63 (21.4)	False: 79 (26.9)
A person who stops smoking will lower their risk of developing heart disease	179 (60.9)	60 (20.4)	55 (18.7)	True: 179 (60.9)
Regular heavy alcohol intake lowers the risk of developing heart disease	115 (39.1)	85 (28.9)	94 (32.0)	False: 85 (28.9)
High blood pressure is a risk factor for heart disease	115 (39.1)	53 (18.0)	126 (42.9)	True: 115 (39.1)
The most important cause of stroke is stress	95 (32.3)	103 (35.0)	96 (32.7)	False: 103 (35.0)
Sudden inability to move one half of the body is a common sign of stroke	144 (49.0)	48 (16.3)	102 (34.7)	True: 144 (49.0)
High cholesterol is a risk factor for developing heart disease	102 (34.7)	49 (16.7)	143 (48.6)	True: 102 (34.7)
Eating fatty foods does not affect blood cholesterol levels	113 (38.4)	82 (27.9)	99 (33.7)	False: 82 (27.9)
Trans fats are healthier for the heart than most other kinds of fats	100 (34.0)	80 (27.2)	114 (38.8)	False: 80 (27.2)
Most of the cholesterol in an egg is in the white part of the egg	94 (32.0)	118 (40.1)	82 (27.9)	False: 118 (40.1)
Eating a lot of red meat increases the risk of heart disease	107 (36.4)	72 (24.5)	115 (39.1)	True: 107 (36.4)
Being overweight increases a person's risk for heart disease	133 (45.2)	51 (17.3)	110 (37.4)	True: 133 (45.2)
Sitting for long hours increases the risk of heart disease	137 (46.6)	90 (30.6)	67 (22.8)	True: 137 (46.6)
Regular physical activity will lower a person's chance of getting heart disease	178 (60.5)	49 (16.7)	67 (22.8)	True: 178 (60.5)
Only exercising at a gym or in an exercise class will lower a person's chance of developing heart disease	46 (15.6)	169 (57.5)	79 (26.9)	False: 169 (57.5)
Diabetes is a risk factor for developing heart disease	100 (34.0)	60 (20.4)	134 (45.6)	True: 100 (34.0)
A person who has diabetes can reduce their risk of developing heart disease if they keep their blood sugar levels under control	146 (49.7)	84 (28.6)	64 (21.8)	True: 146 (49.7)

Discussion

This study has shown that young Nigerian adults commonly engage in lifestyles that put their heart health at risk. Almost all the respondents (98.0%) had at least one lifestyle-related cardiovascular risk factor, and more than 40% had a cluster of three lifestyle-related risk factors. Thus, corroborating earlier reports that the presence of multiple risk factors for heart disease and stroke are not uncommon in individuals.[8,13] Unfortunately, cumulative indulgence in heart-unhealthy lifestyles, especially from a young age, may lead to other physiologic/metabolic cardiovascular risk factors such as obesity, hypertension, dyslipidemia, and type 2 diabetes mellitus.[2]

Compared to other countries in Sub-Saharan Africa, the prevalence of smoking in Nigeria is low.[14] In Nigeria, a report of the 2012 Global Adult Tobacco Survey (GATS) shows that initiation of tobacco smoking was commonly by adolescents and young adults aged <25 years.[15] Although tobacco smoking was the least common heart-unhealthy lifestyle encountered in this survey, it was not surprising that one-in-five of the young adults admitted to ever smoked. The prevalence of regular current smokers in this study (2.0%) was lower than the 4.4% reported by the 2012 GATS in Nigeria among adults aged

Table 3: Sociodemographic characteristics and knowledge of heart disease

Sociodemographic characteristic	Category	Knowledge level	
		Poor (*n*=174; 59.2%)	Good (*n*=120; 40.8%)
Age group (year)	18-23	56 (32.2)	40 (33.3)
	24-29	53 (30.5)	29 (24.2)
	30-35	65 (37.4)	51 (42.5)
		χ^2=1.513, df=2, *P*=0.469	
Sex	Male	66 (37.9)	37 (30.8)
	Female	108 (62.1)	83 (69.2)
		χ^2=1.572, df=1, *P*=0.210	
Marital status	Single	99 (56.9)	53 (44.2)
	Married	55 (31.6)	43 (35.8)
	Co-habiting	18 (10.3)	23 (19.2)
	Others	2 (1.1)	1 (0.8)
		χ^2=6.639, df=3, *P*=0.084	
Highest level of education (years)	<6	15 (8.6)	9 (7.5)
	6-12	125 (71.8)	87 (72.5)
	>12	34 (19.5)	24 (20.0)
		χ^2=0.121, df=2, *P*=0.941	

df: Degree of freedom

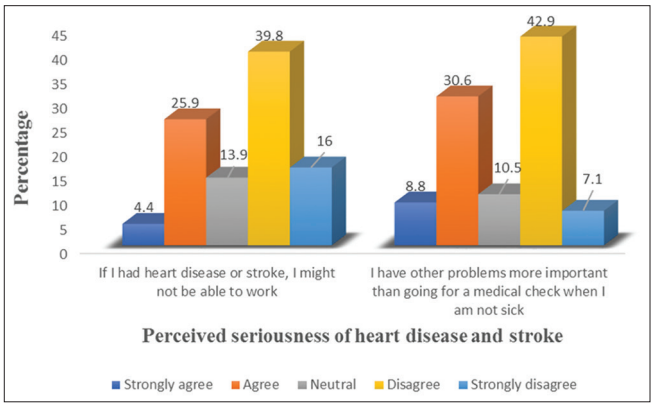


Figure 2: Perceived seriousness of heart disease and stroke

Table 4: Lifestyle-related cardiovascular risk factors and knowledge of heart disease

Variable	Category	Poor knowledge (*n*=174)	Good knowledge (*n*=120)	Total (*n*=294)	χ^2	*P*
Smoking	Ever smoked					
	Yes	45 (80.4)	11 (19.6)	56 (19.0)	12.838	<0.001
	No	129 (54.2)	109 (45.8)	238 (81.0)		
	Current smokers					
	Yes	3 (50.0)	3 (50.0)	6 (2.0)	0.214	0.644
	No	171 (59.4)	117 (40.6)	288 (98.0)		
Alcohol use	Ever drank alcohol					
	Yes	130 (72.2)	50 (27.8)	180 (61.2)	32.669	<0.001
	No	44 (38.6)	70 (61.4)	114 (38.8)		
	Drank alcohol in the past 30 days					
	Yes	72 (92.3)	6 (7.7)	78 (26.5)	48.221	<0.001
	No	102 (47.3)	114 (52.8)	216 (73.5)		
Diet	Eat fruits regularly					
	Yes	106 (67.9)	50 (32.1)	156 (53.1)	10.570	0.001
	No	68 (49.3)	70 (50.7)	138 (46.9)		
	Added salt*					
	Yes	127 (73.0)	47 (27.0)	174 (59.2)	33.631	<0.001
	No	47 (39.2)	73 (60.8)	120 (40.8)		
Exercise	Physical activity in the past month†					
	Yes	52 (61.9)	32 (38.1)	84 (28.6)	0.360	0.548
	No	122 (58.1)	88 (41.9)	210 (71.4)		

*Add salt to already cooked food, †Physical activity that increases heart rate or breathing for at least 10 min

15 years and older.[15] The difference may be accounted for by the inclusion of older adults in the 2012 GATS. The 2012 GATS estimates show that the prevalence of current smoking was highest among older adults aged 35–44 years.[15] In a community-based survey in Delta State, Nigeria, the proportion of current daily smokers was least among the young adults aged between 18 and 27 years.[7]

A significantly higher percentage of male respondents in this survey reported a history of smoking. Previous studies have reported similar gender differences in the prevalence of smoking among young and older adults in Nigeria.[15] The observed gender differences may be attributable to stigmatizing social norms that limit smoking among females, especially in public places in Nigeria.

In this study, many of the respondents reported drinking alcohol, and more than two-fifths of them had done so in the past month. Consumption of alcoholic beverages was without prejudice to sex. It is not uncommon for young and older adults to consume alcoholic beverages in Sub-Saharan Africa.[7,16] For example, in present-day Nigeria, young adults indulge in drinking alcoholic beverages without social, legal, or cultural restrictions as long as they do not become intoxicated or recourse to social vices.[17] Peer pressure and enticing advertisement strongly influence young people to consume alcoholic beverages.[17] Indeed, among young adults globally, alcohol is one of the most frequently consumed psychoactive substances.[16,18] Heavy alcohol consumption is an established cardiovascular risk factor. Previous studies show that young adults frequently drink heavily and in binges.[19] However, the present study did not estimate the quantity of alcohol consumed by respondents. Thus, inferences of alcohol misuse or abuse are limited in this study.

Consumption of unhealthy diet was typical in this study. Low consumption of fruits and vegetables was rife. About half of the respondents indicated they do not eat fruits regularly, while none of the others ate up to the recommended five portions daily by the WHO.[20] Other studies have also reported low intake of fruits among young adults.[21] Increased salt intake is another dietary cardiovascular risk factor. Adding salt to already prepared food is an unhealthy practice that increases the risk of hypertension. In this survey, majority of the respondents admitted to adding salt to already cooked food, howbeit rarely. Although not assessed in the index survey, consumption of salty snacks and processed foods and frequent patronage of fast-food vendors also increase dietary salt intake among young adults.

Physical inactivity was rife in this study and without gender bias. Majority of the young adults reported that they did not walk for travel or engage in recreational physical activities. Adegoke and Oyeyemi also reported a high prevalence of physical inactivity among young Nigerian adults.[22] However, females were more physically inactive in their study.[22] Screen time from watching TV, video games, and other electronic devices contribute to physical inactivity. Although there is no standard or recommended screen time for adults in Nigeria, the mean time spent watching TV daily in this survey was almost 3 h.

Knowledge empowers people to make informed and healthy choices. This study has shown an overall poor knowledge of heart disease among young Nigerian adults living in Delta State. Previous studies among young adults have reported different levels of knowledge of CVD and its risk factors.[23-26] Whereas, a similarly poor level of knowledge was described among the African-Americans in the Coronary Artery Risk Development in Young Adults (CARDIA) study,[24] Ibrahim *et al*.[26] reported high knowledge levels among young adults in Malaysia. Akin to observations by Winham and Jones,[23] the respondents' knowledge of various cardiovascular risk factors differed in this study. Majority of the respondents did not correctly identify diabetes, hypertension, hyperlipidemia, overweight, unhealthy diet, and harmful use of alcohol as risk factors for heart disease. On the other hand, regular physical activity and cessation of smoking were correctly identified by about 60% of the study population as factors that can lower the risk of heart disease.

The index study did not show any association between level of knowledge and sociodemographic factors (age, sex, marital status, and level of education). A similar observation was reported by Awotidebe *et al*. in a previous study of female undergraduates in a Nigerian university.[25] Furthermore, in another study of young Malaysian undergraduates, a lack of association between knowledge of CVD risk factors and sex was observed.[26] In contrast, however, the CARDIA study reported an association between level of education and knowledge of heart disease.[24]

Majority of the respondents in this study with a poor level of knowledge of heart disease and its behavioral risk factors engaged in heart-unhealthy lifestyles. This observation contrasts with the findings of Ibrahim *et al*.,[26] in which the practice of heart-unhealthy lifestyle was prevalent despite a high level of knowledge of heart disease. Indeed, other studies have reported that young adults' adoption of heart-healthy lifestyles to be relatively low in comparison to their knowledge of and even the presence of cardiovascular risk factors.[27,28] Perhaps, the behavior gap may be due to the low self-perceived risk of heart disease.[29]

Knowledge alone is not enough to influence the adoption of a healthy lifestyle. Indeed, risk perception drives risk-reduction strategies. Compared to older adults, young adults generally perceive their health as good.[27] In this study, almost all the respondent felt their health was good. Indeed, more than half of them reported that their general health status was excellent. However, using the HBM to explore the perception of heart disease, underestimation of perceived susceptibility to heart disease was rife in this study. Akin to the present study, Green *et al*.[30] reported the inaccurate perception of heart disease risk among young adults. The perceived seriousness of heart disease was also low in this study.

Conclusion

This study shows that young adults in Delta State, Nigeria, commonly engage in behaviors that can compromise their lifetime heart health. Multiple lifestyle-related cardiovascular risk factors were common among the individuals studied. The knowledge level of heart disease was poor among young adults in this study, irrespective of their sex and educational status. Majority of the respondents had a negative perception of susceptibility to and seriousness of heart disease. This study highlights the need for intensified health education and enlightenment campaigns to address the identified gaps cannot be overemphasized.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Accelerated Dobutamine Stress Echocardiography Protocol versus the Standard One in the Assessment of Coronary Artery Disease

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Abstract

Objectives: The steady-state concentration of dobutamine at any infusion rate is not reached except after 10 min. Nevertheless, dobutamine stress echocardiography (DSE) still employs an incremental 3-min interval infusion protocol. Constant infusion of a higher dobutamine dose appears to overcome this pitfall. We aimed to evaluate the safety and efficacy of an accelerated DSE protocol for the assessment of coronary artery disease. **Methods:** From June 2018 to January 2019, forty consecutive patients underwent accelerated protocol for DSE (constant infusion of 50 μg/kg/min, with discontinuation of infusion at 10 min if no stress endpoint appears). Their hemodynamic responses and adverse effects' profile were compared to a control group (40 patients who underwent the standard protocol within the preceding 6 months). **Results:** Both groups were matched in all baseline characteristics. Peak heart rate (HR) (143 ± 13 vs. 145 ± 13 bpm, $P = 0.54$) and peak systolic blood pressure (160 ± 29 vs. 155 ± 42 mmHg, $P = 0.53$) were similar in both protocols. The accelerated protocol produced a significantly more rapid increase in HR (11.5 ± 2.3 vs. 5.3 ± 1.3 bpm, $P < 0.001$) and resulted in marked reduction in test duration (6 ± 2 vs. 14 ± 3 min, $P < 0.001$). The mean total cumulative dobutamine dose was lower in the accelerated group (275 ± 63 vs. 355 ± 144 μg/kg, $P = 0.029$). Both groups experienced similar rates of both arrhythmic and nonarrhythmic adverse effects. **Conclusion:** Accelerated DSE protocol seems as feasible, safe, effective, and more time-saving compared to the standard one. This might be of value to busy echocardiographic laboratories.

Keywords: Coronary artery disease, dobutamine, stress echocardiography

Introduction

Dobutamine stress echocardiography (DSE) is one of the commonly employed daily tests for the evaluation of the extent and severity of coronary artery disease (CAD) in addition to myocardial viability.[1] Pharmacologically, the steady-state concentration of dobutamine required for a full effect (at any infusion rate) is not reached except after 10 min.[2,3] Nevertheless, DSE is still being performed with an incremental 3-min interval infusion protocol derived as a simulation to the commonly used exercise treadmill protocols. The net result is that the full effect of any infusion rate of dobutamine is not obtained before the next rate of infusion is due, resulting in a rapid nonlinear increase in the dobutamine plasma concentration during the test.[4,5] Moreover, prior studies have consistently showed that patients who cannot stop β-blockers before DSE usually fail to achieve target heart rate (HR) and that the addition to atropine could enhance the sensitivity of the test by improving HR response.[6] Accordingly, infusion of a continuous and high single-dose of dobutamine has been suggested as a potentially more simple, feasible, and effective method for stress induction in DSE, and this has been evaluated in few studies.[7-12] We

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thought that it might be of considerable interest if we could reiterate these findings among our patient population.

Methods

Study design

Forty consecutive patients referred for a clinically indicated DSE were prospectively enrolled in this observational case–control study from June 2018 to January 2019. Another 40 consecutive patients who underwent standard DSE during the past 6 months served as controls. Clinical indications for DSE were the evaluation of angina pectoris in patients with intermediate pretest probability for CAD, evaluation of patients with atypical chest pain, and for those with uninterpretable electrocardiograms (ECGs) at baseline. Exclusion criteria were a recent myocardial infarction (within 3 days), unstable angina, recent ventricular tachycardia, atrial fibrillation with the rapid ventricular response, severe hypertension, and significant aortic stenosis. Concurrent medications were continued at the discretion of the referring physician. The study was approved by our local ethical committee and written informed consents were obtained from all patients.

Dobutamine stress echocardiographic procedure

Baseline two-dimensional (2-D) transthoracic echocardiographic examination (Philips EPIQ 7 Ultrasound System, Andover, MA, USA) was performed in the standard views (parasternal long- and short-axis, apical 2- and 4-chamber views), and a 12-lead ECG at rest was obtained.

Standard dobutamine-atropine infusion protocol

Dobutamine was infused with 3-min dose increments, starting from 5 μg/kg/min and increasing to 10, 20, 30, 40, and 50 μg/kg/min. The ECG was monitored throughout dobutamine infusion and recorded each minute. Cuff blood pressure (BP) was measured at rest, every 3 min during stress, and at maximal stress. When no endpoint was reached, atropine (0.5–1.0 mg) was given to the continuing 40 μg/kg/min dobutamine infusion stage if no contraindications such as glaucoma or prostatic enlargement were present. The infusion was terminated after the maximal dose was reached or at 1 of the following end points:

- More than 85% of the age-predicted maximal HR
- A decrease in BP of >40 mm Hg from the resting value or a systolic BP (SBP) of <90 mm Hg
- The occurrence of severe hypertension (SBP of >240 mm Hg or diastolic BP of >120 mm Hg)
- Significant cardiac arrhythmias
- Severe chest pain
- Horizontal or downsloping ECG ST depression of ≥1 mm measured 80 ms after the J point or ST-segment elevation ≥1 mm in the absence of Q waves
- Marked new echocardiographic regional wall motion abnormalities in multiple locations
- Severe vagal reactions or other intolerable noncardiac symptoms.

Metoprolol was available and was administered intravenously (2.5–5 mg) to reverse the effects of dobutamine if these did not revert spontaneously or rapidly.

Accelerated protocol

Dobutamine was administered at a constant dose of 50 μg/kg/min for up to 10 min. Early echocardiographic images were obtained starting at 20 s (roughly corresponding to the cumulative dose given over 3 min at 5 μg/kg/min). When no endpoint was reached, atropine (0.5 or 1.0 mg) was given to the continuing 50 μg/kg/min dobutamine infusion at 5 min into the study in the absence of contraindications, and repeated to a maximum of 1.0 mg, if necessary. Dobutamine infusion was discontinued after 10 min or for 1 of the endpoints mentioned above.

Images interpretation

Off-line assessment of echocardiographic images was performed by an investigator who was blinded to clinical information, ECG findings, and study protocol. Regional wall motion was assessed according to the recommendations of the American Society of Echocardiography using a 17-segment model,[13] and wall motion was graded as follows: 1 = normal, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic.[13] The test was considered positive when wall motion in any segment deteriorated >1 grade, except for a change from resting akinesia to dyskinesia.[14] Studies were identified as nondiagnostic if the patient reached 85% age-predicted maximal HR in the absence of inducible ischemia. For each individual patient, 2-D echocardiographic images were recorded at baseline, low dose, peak stress, and during recovery. Images of 4 standard imaging planes were digitized and displayed in a standard quad-screen digital format that allowed offline side by side comparison.

Statistical analysis

Data management and statistical analysis were done using SPSS version 25. (IBM, Armonk, New York, United states). Numerical data were summarized as means and standard deviations. Categorical data were summarized as numbers and percentages. Before running comparisons, numerical data were assessed for normality using normality tests and direct visualization methods. Comparisons between two groups were done using independent *t*-test for numerical variables. In comparisons limited only for patients using β-Blockers; Mann–Whitney U-test (nonparametric test) was used due to relatively small numbers in both groups. Categorical data were compared using the Chi-square test or Fisher's exact test if appropriate. All *P* values were two-sided. Values of $P < 0.05$ were considered statistically significant.

Results

Baseline characteristics

The study participants consisted of 80 patients (43 males, mean age 56 ± 10 years). All patients had limited exercise capacity

and intermediate pre-test probability[15] for CAD. They were referred for a clinically indicated DSE to evaluate anginal symptoms. Forty patients underwent accelerated protocol for DSE, and 40 patients underwent the standard protocol. Among the whole study population, 58 patients had angina pectoris, 14 patients had atypical chest pain, and 8 patients had uninterpretable ECG at baseline. There were no statistically significant differences between both groups regarding various baseline criteria [Table 1].

Hemodynamic data

No statistically significant differences were seen between both groups regarding baseline HR (74 ± 9 vs. 74 ± 11 bpm, $P = 0.991$ for accelerated and standard groups, respectively) and baseline SBP (119 ± 10 vs. 121 ± 10 mmHg, $P = 0.355$ for accelerated and standard groups, respectively). Patients in the accelerated protocol achieved a significantly more rapid increase in HR compared to those in the standard protocol (11.5 ± 2.3 vs. 5.3 ± 1.3 bpm, respectively, $P < 0.001$). Peak HR, peak SBP, and percent of patients achieving target HR were similar between both groups [Table 2].

Echocardiographic data

There were no statistically significant differences between both groups regarding wall motion score index, left ventricular end-diastolic volume, left ventricular end-systolic volume , and left ventricular ejection fraction (LVEF) both at rest and at peak stress [Table 3].

Test parameters

Patients who underwent the accelerated protocol had a significantly shorter stress times compared to those who underwent the standard protocol (6 ± 2 vs. 14 ± 3 min respectively, $P < 0.001$) [Figure 1a]. Moreover, the total cumulative dobutamine dose was significantly lesser in the group of the accelerated protocol (275 ± 63 vs. 355 ± 144 µg/kg, $P = 0.029$) [Figure 1b]. There was no statistically significant difference between accelerated and standard protocol groups in the frequency of atropine use (12.5 vs. 10%, respectively, $P = 1$) nor in the final test results (positive in 35 vs. 37.5%, respectively, $P = 0.816$) with others being negative. No tests were reported to be nonconclusive.

Effect of β-blockers

Among patients who did not stop β-blockers before the test (31 patients), differences observed between accelerated and standard protocols for the entire population were also maintained. This included a significantly shorter stress time, lesser total cumulative dobutamine dose, and a more rapid HR increase. Again, with similar peak SBP, peak HR, percent achieving target HR, and percent use of atropine [Table 4].

Test tolerability

No major complications occurred in either group. There were no statistically significant differences between accelerated and standard protocol groups regarding occurrence of both arrhythmic side effects (30% vs. 32.5%, $P = 0.809$) and nonarrhythmic side effects (27.5 vs. 30%, $P = 0.805$). Table 5 shows the frequency of adverse effects and arrhythmias induced in both DSE protocols. The most frequent nonarrhythmic side effect was hypotension, which occurred in six patients and warranted termination of the test in only 1 patient. All arrhythmic episodes were asymptomatic and did not warrant test termination in any patient.

Discussion

In the present study, a single, high, and continuous infusion of dobutamine for stress induction in DSE appears as safe

Table 1: Baseline characteristics of the study population*

	Accelerated regimen ($n=40$)	Standard regimen ($n=40$)	*P*
Age (years), mean±SD	57±10	56±11	0.635
Gender			
Males	21 (52.2)	22 (55.0)	0.823
Females	19 (47.5)	18 (45.0)	
DM (yes)	21 (52.5)	20 (50.0)	0.823
HTN (yes)	25 (62.5)	24 (60.0)	0.818
smoker (yes)	17 (42.5)	19 (47.5)	0.653
Dyslipidemia (yes)	15 (37.5)	16 (40.0)	0.818
Obesity (yes)	24 (60.0)	23 (57.5)	0.82
FH of premature CAD (yes)	11 (27.5)	13 (32.5)	0.626
Clinical indication for DSE			
Angina pectoris	30 (75)	28 (70)	0.837
Atypical chest pain	6 (15)	8 (20)	
Uninterpretable ECG	4 (10)	4 (10)	
Weight (kg)	87±6	87±7	0.806
Height (cm)	175±10	175±10	0.886
BB use (yes)	15 (37.5)	16 (40.0)	0.818
CCB use (yes)	16 (40.0)	15 (37.5)	0.818
Dihydropyridine	12 (75)	13 (86.6)	0.653
Nondihydropyridine	4 (25)	2 (13.3)	
Both BB and CCB use (yes)	10 (25.0)	8 (20.0)	0.592

*Independent *t*-test was used for age. Chi-square test was used for categorical data. BB: Beta blockers, CAD: Coronary artery disease, CCB: Calcium channel blocker, DSE: Dobutamine stress echocardiography, DM: Diabetes mellitus, FH: Family history, HTN: Hypertension, ECG: Electrocardiogram, SD: Standard deviation

Table 2: Hemodynamic data in study groups*

	Accelerated regimen ($n=40$)	Standard regimen ($n=40$)	*P*
HR at rest (bpm), mean±SD	74±9	74±11	0.991
Peak HR (bpm), mean±SD	143±13	145±13	0.54
Increase in HR per min (bpm), mean±SD	11.5±2.3	5.3±1.3	<0.001
Target HR achieved?, yes	37 (92.5)	36 (90.0)	1
SBP at rest (mmHg), mean±SD	119±10	121±10	0.355
Peak SBP (mmHg), mean±SD	160±29	155±42	0.529

*Independent *t*-test was used for numerical data. Fisher's exact test was used for target HR achieved. HR: Heart rate, SBP: Systolic blood pressure, SD: Standard deviation

and effective as the standard protocol. This finding reaffirms other few previous studies examining the issue[7-12] and adds to the accumulating body of evidence supporting the use of the accelerated DSE protocol.

Similar to Burger *et al*.[8] and Minardi *et al*.,[11] we showed that the accelerated protocol resulted in a more rapid increase in HR, which enabled patients to achieve their target HR rapidly resulting in significantly shorter stress time and lower total cumulative dobutamine dose compared to the standard protocol.

Table 3: Echocardiographic data in study groups*

	Mean±SD		*P*
	Accelerated regimen (*n*=40)	Standard regimen (*n*=40)	
WMSI			
Rest	1.03±0.14	1.03±0.11	0.921
Stress	1.12±0.2	1.13±0.28	0.888
LVEDV			
Rest (ml)	133±19	135±29	0.75
Stress (ml)	116±20	128±33	0.071
LVESV			
Rest (ml)	55±11	56±17	0.731
Stress (ml)	42±16	50±26	0.129
EF			
At rest (%)	59±5	59±4	0.902
At peak stress (%)	64±8	62±12	0.231

*Independent *t*-test was used. EF: Ejection fraction, LVEDV: Left ventricular end diastolic volume, LVESV: Left ventricular end systolic volume, WMSI: Wall motion score index

The fact that the accelerated DSE protocol resulted in a shorter stress time without sacrificing safety makes sense. It implies that this protocol could be of value for some very busy laboratories with a high volume of patients referred for the assessment of CAD. However, we do not recommend the universal use of such a protocol for all patients. Cardiologists should still employ an individualized approach in test selection.

Interestingly, we demonstrated that differences between both protocols in terms of shorter stress times and lower cumulative dobutamine dose were maintained among the subgroup of patients whose physicians preferred not to stop β-blockers before the test. This gives more validity to the accelerated DSE protocol and indicates that it could be applied to a wide spectrum of patients, considering that withholding β-blockers before DSE is not always possible for all patients.

Because dobutamine in the accelerated protocol is administered in a single, high, and continuous fashion (without increments), a major concern is a potential rise in arrhythmic and ischemic adverse effects. Nevertheless, we did not find any significant increase in either arrhythmic or nonarrhythmic complications between both protocols. The explanation why the accelerated protocol did not result in a significantly higher incidence of arrhythmic complications is difficult, but we speculate that the lower total cumulative dobutamine dose could be the key player here (in light of the normal mean LVEF of the included patients). Actually, there are data from the literature supporting this theory; with some investigators suggesting that dobutamine triggers arrhythmia only in the presence of an ischemic substrate,[15] and others demonstrating the occurrence of serious ventricular arrhythmias in doses of dobutamine as low as 20

Table 4: Test parameters in patients receiving β-blockers*

	Accelerated regimen (*n*=15)	Standard regimen (*n*=16)	*P*
Stress time (min), mean±SD	6±2	15±3	<0.001
Total cumulative dobutamine dose (µg/kg), mean±SD	310±76	400±134	0.017
Atropine use, yes	1 (6.7)	3 (18.8)	0.6
Peak HR (bpm), mean±SD	138±14	140±11	1
Increase in HR per min (bpm), mean±SD	11.6±1.8	5.2±1.2	<0.001
Target HR achieved, yes	13 (86.7)	14 (87.5)	1
Peak SBP (mmHg), mean±SD	157±36	157±36	0.984

*Mann-Whitney U-test was used for numerical data. Fisher's exact test was used for categorical data, HR: Heart rate, SBP: Systolic blood pressure, SD: Standard deviation

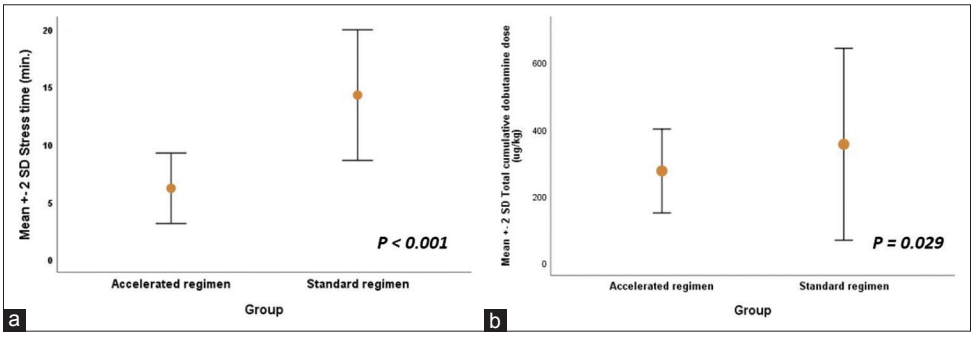


Figure 1: Total stress time (a) and total cumulative dobutamine dose (b) in both study groups

Table 5: Adverse effects during dobutamine stress testing

	Accelerated protocol ($n=40$)	Standard protocol ($n=40$)
Nonarrhythmic side effect		
Nausea	2	2
Hypotension	3	3
Anxiety	1	2
Headache	2	0
Anginal pain	0	3
Tremors	2	1
Severe HTN	1	0
Dyspnea	0	1
Type of arrhythmic side effect		
PVCs (≥6/min)	8	8
PACs (≥6/min)	3	5
NSVT	1	0

HTN: Hypertension, NSVT: Nonsustained ventricular tachycardia, PVCs: Premature ventricular contractions, PACs: Premature atrial contractions

μg/kg/min or even after cessation of infusion![16] Of note, no patients in the accelerated group developed anginal pain (as a complication of the test), in contrast to three patients only in the standard group. This was unexpected given the limited exercise capacity as described in the baseline criteria of the included patients. Nevertheless, we think that this may be a play of chance due to the small sample size in the current study.

The current study is not without limitations. First, small sample size and the single-center experience lack the power to detect differences in uncommon side effects. Second, the diagnostic accuracy of DSE for detection of the presence of CAD was not evaluated in the present study, as this would require a much larger sample size and a large-scale multicenter design to determine both sensitivity and specificity. Third, although echocardiographic images in the current study were obtained starting at 20 s (which roughly corresponds to a low dose dobutamine of 5 μg/kg/min) and thus might be advocated for "viability" assessment, we should state that this work was not designed primarily to test this hypothesis. A separate standard low dose of dobutamine (5 μg/kg/min) should be employed if the evaluation of viability is clinically needed.

Conclusion

The accelerated protocol of DSE consisting of infusion of a single, high, and continuous dose of dobutamine is as safe and effective as the standard one. It resulted in significantly shorter stress times and lower total cumulative dobutamine dose, which might translate into a more rapid patient turnover in busy laboratories. Further large-scale studies are needed to test the diagnostic accuracy of such a protocol.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Coronary Artery Dominance and Atrial Fibrillation Recurrence after Cryoballoon Pulmonary Vein Isolation

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Abstract

Background and Aim: Catheter-based atrial fibrillation (AF) ablation primarily for pulmonary vein isolation (PVI) has become a significant therapeutic alternative for symptomatic and drug-refractory AF patients. It is evident that AF time and left atrium diameter (LAD) have the most critical impact on AF recurrence. In this study, we aimed to evaluate the role of coronary artery dominance for predicting AF recurrence after cryoballoon PVI. **Methods:** We retrospectively analyzed clinical, laboratory, and angiographic data from consecutive patients who underwent coronary angiography and successful cryoballoon PVI. Images of the coronary angiography were retrospectively reviewed for the coronary artery dominance by two experienced observers. The coronary artery system was classified as right dominant (RD) and left dominant. **Results:** A total of 140 patients without coronary artery disease and structural heart disease who underwent successful cryoballoon PVI were included in the study. There were 101 RD (72%) and 39 left-dominant (28%) patterns. A total of 26 patients (22%) had developed AF recurrence during follow-up. AF recurrence rates were 41% in the left coronary-dominant group and 15% in the right coronary-dominant group ($P = 0.001$). According to AF recurrence after cryoballoon PVI, only follow-up time (15.7 ± 2.4 vs. 14 ± 1.8 months, $P = 0.001$), LAD (41.8 ± 2 vs. 40.6 ± 1.8 mm, $P = 0.003$) and coronary artery disease (CAD) (left CAD, 51.6% vs. 21.1%, $P = 0.001$) were significantly associated with AF recurrence. AF recurrence rates in multivariable logistic regression analysis according to AF recurrence after cryoballoon PVI, follow-up time, LAD, and CAD were independent predictors of AF recurrence. **Conclusions:** Our findings suggested that left CAD may be related to AF recurrence after cryoballoon PVI. Coronary artery dominance may be an additional predictor of AF recurrence if supported by larger prospective studies.

Keywords: Atrial fibrillation, coronary artery, cryoballoon, dominance, pulmonary vein

Introduction

Atrial fibrillation (AF) is the most common type of sustained cardiac arrhythmia in clinical practice.[1] Catheter-based AF ablation, primarily by pulmonary vein isolation (PVI), has

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emerged as a promising therapeutic alternative with improved efficacy and safety in symptomatic and drug-refractory AF patients.[2] Although there has been a significant improvement in procedural success through the use of recently developed ablation techniques, postprocedural AF recurrences continue to be a major clinical problem following catheter ablation, occurring in approximately 25%–50% of patients.[3]

Anatomical coronary dominance is defined based on the origin of the posterior descending artery (PDA) that supplies the posterior portion of the interventricular septum.[4,5] In a right-dominant (RD) circulation, the right coronary artery (RCA) gives off the PDA, while in a left-dominant (LD) circulation, the left circumflex (LCX) artery supplies this territory.[4,5] In the present study, we evaluate the relationship between coronary arterial dominance and AF recurrence after cryoballoon ablation (CA).

Methods

We analyzed retrospectively clinical, laboratory, and angiographic data of consecutive patients who underwent a coronary angiography and a successful CA for 12-lead confirmed, symptomatic, and drug-refractory paroxysmal AF. Patients whose episodes of AF terminated spontaneously within 7 days of onset were defined as having paroxysmal AF.

Patients with valvular disease, a thrombus in the left atrium (LA), thyroid dysfunction, preprocedural significant coronary artery stenosis, myocardial infarction, previous cardiac surgery, contraindication to anticoagulation, pregnancy, and an LA diameter (LAD) >50 mm were excluded from the study, along with subjects with recent infections, malignancies, blood dyscrasias, autoimmune or inflammatory diseases, renal failure, or hepatic failure.

The recorded patient data, accessed from the records from the time of CA, included both clinical and demographic characteristics, including age, gender, history of arterial hypertension (HT), diabetes mellitus (DM) and tobacco use, and echocardiographic parameters.

Periprocedural interventions related to the catheter CA were performed as outlined in the current guidelines and studies.[3,6,7] The study participants continued to receive the anticoagulation and antiarrhythmic drug regimen prescribed prior to the ablation procedure for the following 3 months. When the patients developed symptoms compatible with recurrent AF, follow-up visits were made in the 3rd, 6th, and 12th months and then at most every 6 months afterward. In the postprocedural 3rd month, a 24–48-h Holter electrocardiograph (ECG) was made, and antiarrhythmic treatment was ceased if no arrhythmia was detected. At the 3rd month and every 6 months thereafter, another 24–48-h Holter ECG was performed and recorded. The requirement for oral anticoagulation was also assessed after the 3rd month, based on the CHA2DS2-VASc score.[8] The time from the date of ablation to the date of recurrence or the last follow-up was used to calculate the AF-free period. The blanking period was defined as the first 3 months following AF ablation. No atrial arrhythmias that arose during the blanking period were defined as a recurrence. The detection of AF (at least 30 s when evaluated with ECG or Holter ECG monitoring) occurring more than 3 months after the AF ablation procedure was used to define AF recurrence.

Images of the coronary angiography were obtained using standardized angiographic projections, based on the guidelines of the American College of Cardiology/American Heart Association, and stored digitally.[9] All images were reviewed retrospectively for coronary dominance by two experienced observers. The coronary artery system was classified as RD if the RCA gave off the PDA and as LD if the LCX supplied this territory. Significant coronary artery disease (CAD) was defined as a ≥50% narrowing of luminal diameter in at least one projection of at least one major epicardial artery, and these subjects were excluded.

The study was in compliance with the principles outlined in the Declaration of Helsinki and approved by the institutional ethics committee.

Statistical analysis

The normality of distribution of all study parameters was evaluated. For the comparison of continuous data with normal distribution, a Student's *t*-test was used. A Mann–Whitney U-test was used to compare data with skewed distribution. A Chi-square test was used to compare categorical variables. Continuous variables are presented as mean ± SD, whereas categorical data are presented as percentages. To clarify the clinical predictors of outcomes, a univariate Cox proportional analysis was performed initially. Sequentially, all variables with $P < 0.10$ in the univariate analyses were included in a multivariate analysis, and hazard ratios and 95% confidence intervals were calculated. For all tests, a two-tailed $P < 0.05$ was considered statistically significant. The statistical analysis made using SPSS version 20.0 software (IBM Corp., Armonk, NY, USA).

Results

A total of 140 patients without significant CAD who underwent CA for AF were included. The mean age of the cohort was 41.8 ± 7.8 years; 59% were men; 13% had diabetes; 38% had HT; and 27% were smokers. Of the 140 patients enrolled in the study, 31 (22%) had AF recurrence, 101 (72%) had RD circulation, and 39 (28%) had LD circulation. The baseline characteristic features of the study population are presented in Table 1.

The patients were divided into two groups, based on the recurrence of AF. There were no significant differences between the two groups in the mean age; gender ratio; mean body mass index (BMI); smoking rate; or frequency of DM, HT, or hyperlipidemia. No significant difference was detected in any other baseline laboratory parameters. LAD was larger in the AF recurrence group than that in the AF nonrecurrence group (41.8 ± 2.0 mm vs. 40.6 ± 1.8 mm, $P = 0.003$). Similarly, when compared to the AF nonrecurrence

Table 1: Baseline characteristics and demographical features of the study population

	Minimum-Maximum	Median	Mean±SD/*n* (%)
Age	19.0-63.0	43.0	41.8±7.8
Sex			
Female			57 (41)
Male			83 (59)
BMI	21.3-34.6	28.9	29.4±4.3
Coronary dominance			
Right			101 (72)
Left			39 (28)
Smoking			38 (27)
DM			18 (13)
HT			53 (38)
Recurrence			
Yes			31 (22)
No			109 (78)
LAD, mm	37.0-47.0	40.0	40.8±1.9
Follow-up time	12.0-20.0	14.0	14.4±2.1
WBC, $\times 10^9$/L	4.1-14.2	7.1	7.4±2.0
Neutrophil, $\times 10^9$/L	1.9-11.2	4.4	4.5±1.5
Lymphocytes, $\times 10^9$/L	1.0-6.6	2.2	2.4±0.9
Hgb, g/dL	9.6-18	13.9	14.1±1.5
PLT, $\times 10^9$/L	122-472	262	267±65
Glucose, mg/dL	81-373	96	98±28
Creatinine, mg/dL	0.5-1.2	0.8	0.8±0.1
Total protein, g/dL	5.8-8.5	7.4	7.4±0.5
Albumin, g/dL	3.7-5.1	4.5	4.5±0.3
TG, mg/dL	70-760	144	180±144
Total cholesterol, mg/dL	101-360	200	202±48
HDL, mg/dL	28-77	47	47±11
LDL, mg/dL	58-255	118.0	120±38
NLR	0.8-6.2	20	2.0±0.8
PLR	43-286	20	120±41

BMI: Body mass index; DM: Diabetes mellitus, HT: Hypertension, Hgb: Hemoglobin, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, LAD: Left atrium diameter, NLR: Neutrophil-to-lymphocyte ratio, PLT: Platelet, PLR: Platelet-to-lymphocyte ratio, TG: Triglyceride, WBC: White blood count, SD: Standard deviation

group, the follow-up period was longer in the AF recurrence group (14.0 ± 1.8 months vs. 15.7 ± 2.4 months, $P = 0.001$). A comparison of the baseline characteristics and laboratory parameters of the AF recurrence and AF nonrecurrence groups is presented in Table 2.

In the AF recurrence group, LD circulation was observed in 16 cases (51.6%) and RD circulation was observed in 15 cases (48.4%). RD circulation was significantly more common than LD circulation in the AF nonrecurrence group (86 cases [78.9%] vs. 23 cases [21.1%], respectively, $P = 0.001$). The rate of LD circulation correlated significantly with AF recurrence [Table 3 and Figure 1]. In the multivariate logistic regression analysis, LD circulation, LAD, and duration of follow-up were independent predictors of AF recurrence ($P < 0.05$) [Table 4].

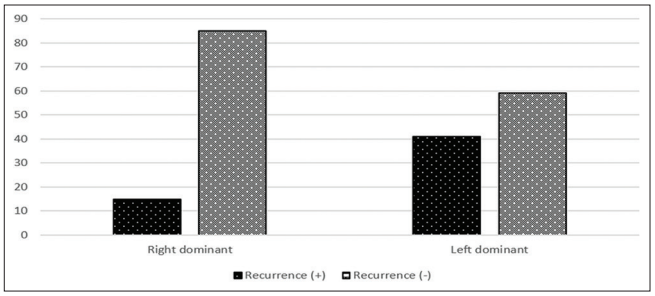


Figure 1: The relationship between coronary artery dominance and recurrence of paroxysmal atrial fibrillation after cryoballoon pulmonary vein isolation

Discussion

The findings of the present study suggest an association between LD circulation and AF recurrence after PVI CA. Moreover, a larger LAD and a longer follow-up time were identified as other independent predictors of AF recurrence. In the present study, the rate of recurrence after CA was 22%, which is similar to the results of other studies.[10-12]

Previous studies indicate that several factors, including age, HT, duration of AF, early recurrence of AF, obesity, LAD,

Table 2: Baseline characteristics and laboratory parameters of the study population according to atrial fibrillation recurrence after cryoballoon pulmonary vein isolation

	Recurrence (+) (*n*=31)		Recurrence (−) (*n*=109)		*P*
	Mean±SD/*n* (%)	Median	Mean±SD/*n* (%)	Median	
Age	42.6±5.9	42	41.6±8.3	43	0.850 (M)
Sex					
Female	15 (48.4)		42 (38.5)		0.324χ^2
Male	16 (51.6)		67 (61.5)		
BMI	30.3±3.7	29.7	29.2±4.4	27.8	0.070 (M)
Coronary dominance					
Right	15 (48.4)		86 (78.9)		0.001 (χ^2)
Left	16 (51.6)		23 (21.1)		
Smoking	7 (22.6)		31 (28.4)		0.517 (χ^2)
DM	2 (6.5)		16 (14.7)		0.217 (χ^2)
HT	10 (32.3)		43 (39.4)		0.466 (χ^2)
LAD, mm	41.8±2.0	42.0	40.6±1.8	40.0	0.003 (M)
Follow-up time, months	15.7±2.4	15.0	14.0±1.8	14.0	0.001 (M)
WBC, $\times10^9$/L	7.6±1.9	7.1	7.4±2.1	7.2	0.547 (M)
Neutrophil, $\times10^9$/L	4.7±1.4	4.6	4.5±1.5	4.2	0.221 (M)
Lymphocytes, $\times10^9$/L	2.6±0.8	2.5	2.4±0.9	2.1	0.073 (M)
Hgb, g/dL	14.1±1.3	14.4	14.0±1.6	13.7	0.511 (M)
PLT, $\times10^9$/L	263±61	258	268±67	263	0.648 (M)
Glucose, mg/dL	93±19	96	99±29	95.0	0.530 (M)
Creatinine, mg/dL	0.8±0.1	0.9	0.8±0.1	0.8	0.239 (M)
Total protein, g/dL	7.3±0.4	7.4	7.4±0.5	7.4	0.337 (*t*)
Serum albumin, g/dL	4.4±0.3	4.3	4.5±0.3	4.5	0.076 (M)
TG, mg/dL	163±69	151	185±59	139	0.962 (M)
Total cholesterol, mg/dL	208±54	193	200±46	200	0.646 (M)
HDL, mg/dL	48.8±12.6	46	46.9±10.8	47	0.614 (M)
LDL, mg/dL	126.5±43.7	121	117.9±36.1	118	0.462 (M)
NLR	2.0±0.7	2.0	2.0±7	1.8	0.681 (M)
PLR	110.4±42	107	122.2±0.9	118	0.054 (M)

t=*T*-test, M=Mann-Whitney U-test, χ^2=Chi-squared test. BMI: Body mass index, DM: Diabetes mellitus, HT: Hypertension, Hgb: Hemoglobin, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, LAD: Left atrium diameter, NLR: Neutrophil-to-lymphocyte ratio, PLT: Platelet, PLR: Platelet-to-lymphocyte ratio, TG: Triglyceride, WBC: White blood count

Table 3: The relationship between coronary artery dominance and recurrence of paroxysmal AF after cryoballoon PVI

	Recurrence(+) *n* = 31 (22%)	Recurrence(-) *n* = 109 (78%)	*P* value
Right coronary dominance *n* = 101, (72%)	15 (15%)	86 (85%)	0.001
Left coronary dominance *n* = 39, (28%)	16 (41%)	23 (59%)	

inflammation, and LA fibrosis (determined by magnetic resonance imaging), are predictors of AF recurrence.[10,12-14] In the present study, LD circulation was found to be associated with AF recurrence in patients who underwent PVI CA for paroxysmal AF. In addition, in line with the findings of previous studies, LAD and a longer follow-up time were identified as independent predictors of AF recurrence also in the present study. However, we found no association between AF recurrence and demographic data such as age, HT, DM or BMI, or inflammatory markers such as neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and albumin. In our study, similar to some previous studies,[7,10,11] gender and smoking were not associated with AF recurrence. However, there are studies in the literature that smoking and female gender are independent predictors of AF recurrence.[15-17] This inconsistency may be due to the age of the patients in our study being younger than other studies. In addition, this inconsistency could be explained by the fact that our study consisted of only paroxysmal AF patients and its small and retrospective design. Further studies are warranted to confirm and assess the possible mechanisms of these links.

Previous studies indicate that RCA is dominant in 85% of patients, while about half of the remaining 15% appear to have left coronary artery (LCA)-dominant circulation.[18] Previous studies also suggest a prognostic association between coronary artery dominance and CAD, acute ST-elevation myocardial infarction (STEMI), and chronic total coronary artery occlusion.[19-21] Although the available data are inconclusive,

Table 4: Multivariate logistic regression analysis showing independent predictors of atrial fibrillation recurrence after cryoballoon pulmonary vein isolation

Variables	Odds ratio	95% CI	*P*
PLR	0.840	0.650-1.250	0.358
Albumin	0.753	0.135-4.215	0.747
LAD	1.670	1.266-2.203	<0.001
Follow-up time	1.518	1.182-1.950	0.001
Coronary dominance	5.701	1.994-16.301	0.001

LAD: Left atrium diameter, PLR: Platelet-to-lymphocyte ratio, CI: Confidence interval

previous studies involving patients who underwent PCI demonstrated that LD was associated with increased risk of death or re-infarction during long-term follow-up.[22-24] Similarly, patients with an LD or codominant coronary artery system had lower left ventricular ejection fraction early after STEMI.[25,26] An LD coronary artery tree may have a less well-balanced circulation than other systems, resulting in a larger area of myocardium at risk in the face of various cardiovascular diseases. In patients with LD, blood supply to the sinoatrial node may be disturbed and may predispose patients to arrhythmias such as AF.

A P-wave duration (PWD) in sinus rhythm preablation has been hypothesized to be a noninvasive ECG marker associated with increased AF recurrence after PVI.[27,28] There is a newer study showed that prolonged PWD with a cutoff of >120 ms to >150 ms in sinus rhythm before ablation may be associated with AF recurrence after PVI regardless of age, gender, left atrial size, and the presence of structural heart disease.[29] Nabi Aslan *et al*. investigated the relationship between coronary dominance and AF from PWD and P-wave dispersion in a previous study.[30] At the end of their study, they suggested that atrial blood flow may depend mainly on the RCA, as the RCA territory is relatively weak in LD patients, and left dominancy may increase the risk of AF.[30] Likewise, in the present study, AF recurrence was more common in patients with LD circulation than in patients with RD circulation, leading us to hypothesize that blood supply to the sinoatrial node is disturbed in patients with LD circulation.

Blood flow within a coronary branch located close to an radiofrequency (RF) electrode renders a protective effect via convective cooling, hindering RF energy from overheating the vascular endothelium,[31] and this "heat sink" protects the coronary arteries. On the other hand, it may also limit the success of ablation procedures as a result of the "shadow effect" phenomenon. It is thought that blood flow through the small intramyocardial vessels may disrupt the formation of transmural lesions, may preserve conduction through an RF lesion, and in this way, may prevent complete conduction block.[32,33] In the present study, AF ablation was achieved through CA rather than RF, although similar mechanisms may have taken place in both procedures. The arteries supplying the LA are among the earliest branches of the LCA, usually from the LCX.[34] We suggest that better circulation of the LA may be seen in patients with LD circulation, thus preventing the success of CA. This may be the reason why AF recurrence is more common in patients with LD circulation.

Study limitations

Our study had several limitations. First, the study was performed in a single center and included only paroxysmal AF patients. The second limitation is the fact that although follow-up visits and questioning of symptoms were performed and all participants underwent 24–48-h Holter monitoring, some patients with recurrent AF may have been overlooked. Finally, the sample size was relatively small and the retrospective design of the study does not make it possible to draw conclusions about cause-effect relationship.

Conclusions

The findings of the present study suggest an increased risk of AF recurrence after PVI CA in patients with left-dominant coronary artery circulation. Coronary artery dominance may be considered an additional predictor of AF recurrence, provided that the findings of the present study can be confirmed in future prospective controlled studies.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Diagnostic Modality for Evaluation of Right Ventricle in Chronic Thromboembolic Pulmonary Hypertension Patients

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Abstract

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is a progressive disease of pulmonary hypertension (PH) as a consequence obstructive of pulmonary arteries with thromboembolism. Augmented pulmonary vascular resistance and pulmonary artery pressure (PAP) can ultimately lead to the right ventricular dysfunction, which leads to adaptive and maladaptive changes. Right ventricle (RV) remodeling can cause clinical deterioration and RV failure. **Aims and Objectives:** We aimed to evaluate the RV functions with a new diagnostic modality 2-deoxy-2-(18F)-fluoro-D-glucose (FDG)-positron emission tomography (PET) in patients with CTEPH. **Materials and Methods:** We included 53 patients diagnosed with CTEPH who were planned to have pulmonary thromboendarterectomy (PEA) and did not have any contraindication for cardiac PET/computed tomography (CT). We performed transthoracic echo, cardiac PET/CT, 6-minute walk distance (6-MWT), and right heart catheterization 1 week before PEA surgery. **Results:** The patients divided into two groups according to RV/left ventricle (LV) FDG-PET uptake ratio, RV/LV ≤1, and RV/LV >1. Six-MWD was significantly higher in the RV/LV ≤1 group ($P = 0.005$). Pro-BNP was considerably higher in the RV/LV >1 group ($P = 0.041$). **Conclusion:** The present study aims to demonstrate the RV/LV FDG-PET uptake ratio could be used in the noninvasive diagnostic method in diagnosing, treatment strategy, and clinical follow-up in patients with CTEPH.

Keywords: Cardiac fluoro-D-glucose positron emission tomography, chronic thromboembolic pulmonary hypertension, pulmonary vascular resistance, right ventricular remodeling

Introduction

Chronic thromboembolic pulmonary hypertension is the development of progressive pulmonary hypertension (PH) due to occlusion of pulmonary vascular bed and formation of structural changes by recurrent and organized pulmonary thromboembolism or *in situ* (in place) thrombosis.[1] This causes increased pulmonary vascular resistance (PVR) and pulmonary arterial pressure in pulmonary vascular bed over time. Adaptive remodeling such as compensatory right ventricle hypertrophy and increased contractility occur against increased afterload in RV. In time, these compensatory mechanisms become inadequate, and functional deterioration progresses by maladaptive changes in RV.

As a consequence of increased RV afterload, a clinical syndrome called RV failure develops due to insufficient blood flow in pulmonary vascular bed during resting or exercise and increased systemic venous pressure.[2] This anatomical, physiological, and

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metabolic remodeling in RV is responsible for essential subclinical and clinical features of CTEPH, and RV functions determine mortality and morbidity. For these reasons, the development of novel diagnostic and therapeutic approaches to RV functions is gaining importance. In the analyses about PH in recent years, pulmonary vascular structure and right heart were analyzed as a combined group as a cardiopulmonary unit.[3] Three primary mechanisms may be cause adaptive and maladaptive changes resulting in RV failure. These are ischemia due to pulmonary arterial hypertension (PAH), mitochondrial remodeling, and metabolic shift.[4] The myocardial metabolism that changes from oxidative glycolysis to nonoxidative glycolysis in RV due to PAH can be used as a novel diagnostic modality for 2-deoxy-2-(^{18}F) fluoro-D-glucose-positron emission tomography/computed tomography (FDG-PET/CT) to evaluate RV functions. In our study, we aimed to assess the relationship between RV functions in CTEPH patients with a diagnostic modality, FDG-PET/CT, and functional capacity.

Methods

This study included patients with CTEPH between June 2013 and January 2015 and planned to have pulmonary thromboendarterectomy procedure at our center. The Ethical Committee of Marmara University Medical School evaluated our study, and no objections were found for conduction. Informed consent forms were obtained from patients who found to be eligible for the survey regarding their approval for participation. It was a prospective study. A total of 53 patients with an exact diagnosis of CTEPH according to a multidisciplinary assessment at our center, who had no contraindication for a cardiac PET examination (overweight patients, pregnant, etc.). Patients with moderate-to-severe valve diseases, left heart failure with any reason, chronic obstructive lung disease with FEV1 below 50%, chronic renal failure, diabetes mellitus, uncontrolled hypertension, coronary artery disease, and hypertrophic cardiomyopathy, and those that not approved to participate were excluded from the study.

Each patient had diagnostic workups 1 week before the operation. The same operator conducted all echocardiographic evaluations according to the recommendations of the American Society of Echocardiography guidelines[5] using a Vivid 7 Ultrasound System (General Electric, Horten, Norway). Right heart catheterization (RHC) was performed by the femoral approach using a Swan–Ganz catheter to confirm the diagnosis of PH. Cardiac output was calculated by the Fick method. Each patient presented the (6-MWD) according to the 6-MWD Protocol of American Thorax Surgery Society.[6] The Qanadli Score is calculated in acute pulmonary thromboembolism by pulmonary CT angiography and pulmonary angiography and based on thrombus load in the pulmonary arterial bed.[7] For the first time in this study, we use Qanadli score to calculated based on thrombus burden in pulmonary arterial bed in CTEPH patients. An integrated PET/CT system (Discovery-16 LS, GE Healthcare, USA) was used for imaging. It included include the entire free walls of the right and the (LV). Our center is used to 0.8 ratios as usual in right ventricle/LV ratio.[8,9] Data computing and assessment were performed on a workstation (Advantage Windows Workstation 4.5, GE Healthcare, USA) following the imaging. The volume of interest was drawn over the right and LV free walls, and myocardial glucose involvement levels on these walls were obtained by measuring semiquantitative maximum standardized uptake values (SUV). Right/LV glucose metabolism proportions were calculated by calculating right and LV maximum SUV levels [Figure 1a-c].

Statistical analysis

SPSS 20 software (SPSS 20.0 for Windows, SPSS Inc., Chicago, IL, USA) was used for the statistical analyses of the study. The one-sample Kolmogorov–Smirnov test evaluated the distribution of data. If numerical data were normally distributed, then presented as mean ± standard deviation; and if not normally distributed, then given as median (minimum–maximum). Chi-square test evaluated categorical variables. Customarily distributed numerical data were compared with Student's *t*-test, and nonnormally distributed statistical data was compared with the Mann–Whitney U-test. Pearson or Spearman's correlation tests were used for correlation analysis. The Pearson correlation was used in the linear relationship between two continuous variables. The Spearman correlation was used the monotonic relationship between two continuous or ordinal variables. P <0.05 values were considered as statistically significant.

Results

A total of 53 patients diagnosed with CTEPH by a multidisciplinary evaluation, and those planned to have PEA

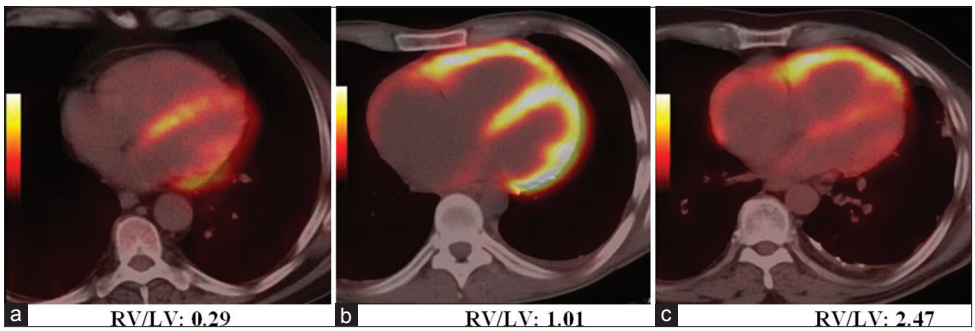


Figure 1: Sample of FDG PET uptake (a, b and c)

were included in the study. Mean age of the patients was 55 ± 13.8 years. Thirty-four patients were female (64.2%) and 19 were male (35.8%). General clinical characteristics and basal laboratory values of the patients are shown in Table 1. We have no data on their clinical symptoms and disease's duration.

Table 1: Demographic, and clinical datas of study population

Demographic and clinical datas	Means (*n*:53)
Blood pressure (mmHg)	
Systolic	120.0 (175-98)
Mean	92.8±17.4
Diastolic	75.4±11.1
BMI	27.8 (19.5-43.7)
6-MWT (meters)	266.5±161.7
Pace (beat/min)	86.6±14.1
Qanadli score	23.2±8.1
Symptom	
Present	43 (%81.1)
None	10 (%18.9)
WBC, ($\times10^3/\mu L$)	7.6 (2.8-18.9)
Hemoglobin, (g/dL)	13.0±2.7
Hematocrit, (%)	38.8±6.1
Thrombocyte, ($\times10^3/\mu L$)	233.5 (83-690)
Creatinine (mg/dL)	0.86±0.29
BUN (mg/dL)	19.0±9.2
D-dimer (mg/L)	0.4 ± (0.09-2.87)
Uric acid (mg/dL)	7.6±2.6
ProBNP (pg/ml)	986 (12-17020)
CRP (mg/L)	8.4 (0.9-75.0)

BMI: Body mass index, 6-MWT: 6 Minute Walk Test, CRP: C reactive protein, WBC: White blood cell

Table 2: Echocardiography and right heart catheterization parameters of study population

ECHO and RHC Parameters	Means (*n*:53)
TAPSE (mm)	14.4±4.3
MPI (mm)	0.63±0.17
RVS (mm)	10.7±3.1
RA area (cm^2)/LA area (cm^2)	23.9±7.7/16.1±4.3
RVEDD (mm)	40.1±6.7
LVEDD (mm)/LVESD (mm)	43.5±6.0/27.7±4.9
sPAP (mmHg)	71.5±28.4
Systolic Pulmonary Artery Pressure (mmHg)	76.5±27.3
Mean Pulmonary Artery Pressure (mmHg)	48.1±15.6
Diastolic Pulmonary Artery Pressure (mmHg)	29.2±11.9
Wedge (mmHg)	10.9±4.2
Cardiac Output (lt/dk)	4.2±1.7
Cardiac Index (lt/dk/m^2)	2.3±1.0
Transpulmonary gradient (mmHg)	38.0±15.6
Diastolic pulmonary gradient (mmHg)	18.5±10.9
PVR (woods)/SVR (woods)	10.4±6.3/21.8±9.0

RVEDD: Right ventricle end-diastolic diameter LVEDD: Left ventricle end-diastolic diameter; LVESD: left ventricle end systolic diameter; EF: Ejection fraction; RA: Right atrium area; LA: Left atrium area; sPAP: Systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion; RVS: tricuspid annulus tissue Doppler systolic velocity; LV: Left ventricle

Decreases in RV systolic function parameters and increases incorrect heart diameters were observed before the operation in patients. PAP, PVR, and the transpulmonary gradient were found to be high, and cardiac output and cardiac index were found to be low in RHC [Table 2].

The patient population was separated into two groups according to right ventricle/LV FDG-PET uptake ratio. Groups formed according to the right ventricle uptake less than LV Group 1 (RV/LV ≤1) and proper ventricle uptake equals to and more than LV Group 2 (RV/LV >1). Twenty-seven patients were Group 1 and 25 patients were Group 2. Six-MWD, Qanadli score, Pro-BNP, Echo parameters, and RHC findings were compared between groups [Table 3]. Six-MWD was high in Group 1. The Qanadli score was calculated to be lower in Group 1, but it was not statistically significant. Pro-BNP was high in Group 1 when compared with Group 2. There were no significant differences between groups regarding echocardiography and RHC parameters [Table 3].

Correlation analyses were performed to determine the associations between clinical findings and RV/LV FDG-PET uptake levels in patients. A negative correlation was established between 6-MWD and RV/LV FDG-PET uptake ratio [Figure 2]. Furthermore, a positive relationship was found between increased Qanadli score, which determines the thrombus burden in the pulmonary arterial bed and RV/LV FDG-PET uptake ratio. There was a positive correlation between laboratory parameters of D-dimer and Pro-BNP and RV/LV FDG-PET uptake. There were no correlations between echocardiographic parameters of tricuspid annular plane systolic excursion (TAPSE), Myocardial Performance Index, and RV tissue systolic Doppler wave, which are frequently used to evaluate RV functions, and RV/LV FDG-PET uptake. There was a significant correlation between echocardiographic parameters of right ventricle area, LV diameter, and systolic pulmonary arterial pressure and RV/LV FDG-PET uptake [Figure 3]. There

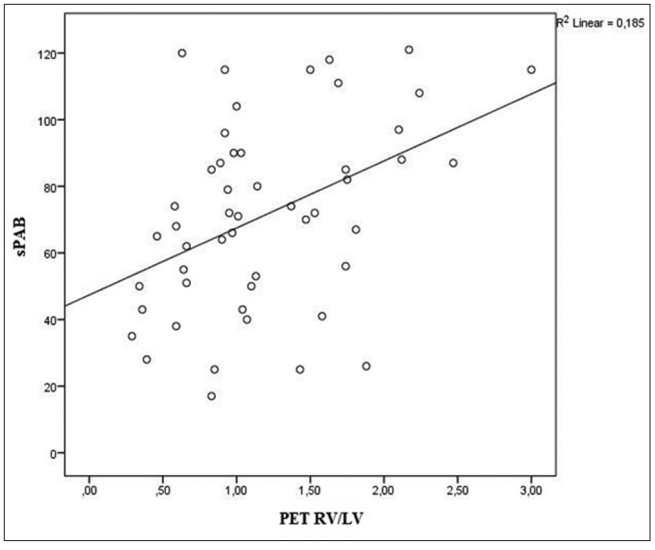


Figure 2: Relationship between 6-MWT and RV and LV FDG PET uptake

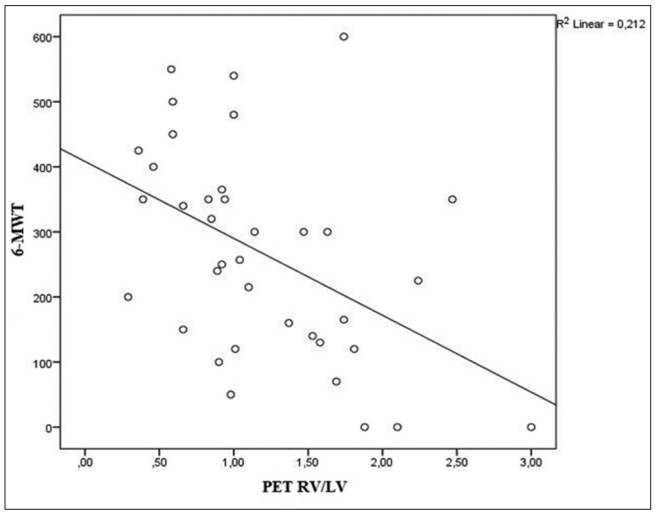


Figure 3: Correlation between echocardiographic parameters and FDG-PET uptake

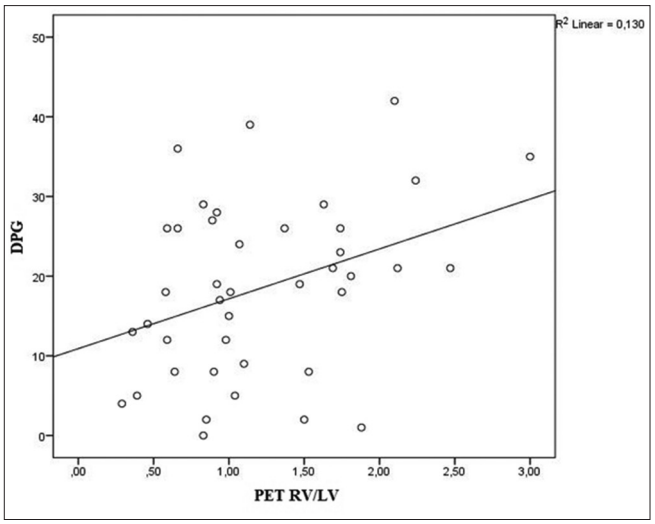


Figure 4: Relationship between diastolic transpulmonary gradient and FDG-PET uptake

was a significant correlation between RHC parameters diastolic PAP, diastolic pressure gradient and PVR, and FDG-PET uptake [Figure 4]. However, there were no significant correlations between other RHC parameters as cardiac output, cardiac index, and pulmonary capillary wedge pressure (PCWP) [Table 4].

Discussion

Noninvasive evaluation of RV functions, which have a crucial role in morbidity and mortality in PH, is essential for diagnosis, risk classification, and determining the therapeutic strategy prognosis of PH patients. PH causes remodeling in RV due to chronic pressure burden. The critical role of RV remodeling in prediction makes RV functions important in studies of PAH. However, the reviews on this topic remained inadequate to be reflected in the clinical approach to the disease. In our research, RV functions were evaluated in patients with CTEPH that planned to have PEA, by a diagnostic modality of FDG-PET/CT; and its associations with 6-MWD distance, Qanadli score, pro-BNP, other blood parameters, RHC parameters,

Table 3: Right ventricle FDG-PET uptake of study population

	RV/LV ≤1 (*n*=27)	RV/LV >1 (*n*=26)	*P*
6-MWT (meters)	337±143.1	191±148.8	0.005
Qanadli score	21.1±6.8	24.9±8.9	0.138
ProBNP (pg/ml)	448 (15-6791)	1799.5 (12-17020)	0.041
Mean Pulmonary Artery Pressure (mmHg)	45.7±17.0	50.4±14.2	0.298
PCWP (mmHg)	11.1±4.5	10.6±4.0	0.699
Cardiac Output (lt/dk)	4.4±1.5	3.9±1.8	0.296
Cardiac Index (lt/dk/m^2)	2.4±0.7	2.1±1.1	0.357
Transpulmonary gradient (mmHg)	35.0±17.6	40.7±13.2	0.250
Diastolic pulmonary gradient (mmHg)	16.0±10.1	20.9±11.3	0.147
PVR (woods)	9.2±6.0	11.6±9.9	0.170
SVR (woods)	21.6±8.2	22.1±9.9	0.858
TAPSE (mm)	14.8±4.6	14.0±4.1	0.552
MPI (mm)	0.65±0.09	0.62±0.22	0.684
RVS (mm)	11.3±3.1	10.1±3.0	0.203
RA area (cm^2)	21.8±7.4	26.0±7.6	0.06
LA area (cm^2)	16.6±3.9	15.7±4.4	0.487
RVEDD (mm)	38.6±5.2	41.6±7.6	0.142
LVEDD (mm)	45.3±6.0	41.8±5.6	0.039
LVESD (mm)	28.4±4.3	27.1±5.5	0.364
sPAP (mmHg)	66.2±27.8	76.4±28.7	0.211

RVEDD: Right ventricle end-diastolic diameter LVEDD: Left ventricle end-diastolic diameter; LVESD: left ventricle end systolic diameter; EF: Ejection fraction; RA: Right atrium area; LA: Left atrium area; sPAP: Systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion; RVS: tricuspid annulus tissue Doppler systolic velocity; LV: Left ventricle, PCWP: Pulmoner capillary wedge pressure

Table 4: RV/LV FDG-PET uptake correlation findings

	r	*P*
Age (range) - year	0.200	0.156
6-MWT (meters)	-0.460	0.004
Qanadli score	0.358	0.023
D-dimer (mg/L)	0.585	0.002
ProBNP (pg/ml)	0.397	0.018
TAPSE (mm)	-0.215	0.138
MPI (mm)	-0.241	0.123
RVS (mm)	-0.270	0.072
RA area (cm^2)	0.393	0.005
LA area (cm^2)	-0.218	0.142
RVEDD (mm)	0.222	0.148
LVEDD (mm)	-0.467	0.001
LVESD (mm)	-0.337	0.018
sPAP (mmHg)	0.431	0.002
Systolic Pulmonary Artery Pressure (mmHg)	0.309	0.050
Mean Pulmonary Artery Pressure (mmHg)	0.244	0.092
Diastolic Pulmonary Artery Pressure (mmHg)	0.334	0.033
PCWP (mmHg)	-0.101	0.523
Cardiac Output (lt/dk)	-0.166	0.249
Cardiac Index (lt/dk/m^2)	-0.129	0.376
Transpulmonary gradient (mmHg)	0.319	0.042
Diastolic pulmonary gradient (mmHg)	0.360	0.021
PVR (woods)	0.297	0.038
SVR (woods)	0.107	0.469

RVEDD: Right ventricle end-diastolic diameter LVEDD: Left ventricle end-diastolic diameter; LVESD: left ventricle end systolic diameter; EF: Ejection fraction; RA: Right atrium area; LA: Left atrium area; sPAP: Systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion; RVS: tricuspid annulus tissue Doppler systolic velocity; LV: Left ventricle; PVR: Pulmonary vascular resistance; SVR: Systemic vascular resistance

and echocardiography parameters were evaluated. Lundgrin *et al*.[10] determined in their study on PAH patients that there was an increase in the synthesis of hypoxia-inducible factor-1α in pulmonary vascular bed, and this factor caused a shift to nonoxidative glycolysis by affecting mitochondrial metabolism in RV myocytes, which partly explained the ischemic biochemical mechanism that developed in RV. Fang *et al*.[11] conducted a study on 25 patients with PH and 43 patients with PAH associated with congenital heart disease, and at the end of 2 years of follow-up, they compared the RV/LV FDG-SPECT uptake rates and patients' prognosis and reported that patients with higher RV FDG uptake had a worse prognosis. Our study is conducted on patients in a subcategory of PH, the CTEPH patients, and RV/LV FDG-PET uptake ratios were compared with 6-MWD – which is an important parameter that related with functional capacity and prognosis of patients, echo parameters – which are frequently used, noninvasive, and easy-to-perform determinants of RV functions, RHC parameters – which are considered as the gold standard for hemodynamic measurements in PH, and Qanadli score – which determines the pulmonary artery thrombus burden. Based on significant associations with frequently used parameters that assess RV functions, FDG-PET uptake ratio was shown to be a valuable method that can be used for diagnosis and follow-up of patients with CTEPH. However, our theory must be supported with an extensive trial and proved by RHC.

Kepez *et al*.[12] reported in their study on CTEPH patients that decreased RV functions determined by echocardiography were correlated with 6-MWT, which is an indicator of functional capacity. In our research, 6-MWD distances were found to be lower in Group 2 patients that have increased RV FDG-PET uptake, when compared with Group 1 patients (P = 0.005). Farber *et al*.[13] reported in their study that 6-MWD had prognostic importance in PH patients, and temporally decreased 6-MWD was related to poor prognosis. In this study, 1-year survival was reduced to 68.4% in patients with 6-MWD <165 m.[11] The higher RV/LV FDG-PET uptake in patients with 6-MWD <165 m in our study showed the prognostic value of RV/LV FDG-PET uptake ratio (P = 0.008). Despite the primary pathology was on the pulmonary vascular bed as expected, the main reason for symptoms and decreased effort capacity in the disease is increased ischemia due to pressure load, and reduced RV functions. RV FDG-PET uptake can be an essential alternative diagnostic method and prognostic modality in cases that 6-MWD cannot be performed due to reduced effort capacity, advanced age, orthopedic barriers, or comorbid diseases. Functions of RV decrease progressively in patients with high thrombus burden due to theoretically higher PAP and consequently higher pressure load on RV. Qanadli score, which determines acute thrombus burden in pulmonary artery bed, was used for the first time in this study to assess chronic thrombus burden.[7] Qanadli score was found to be associated with RV FDG-PET uptake (P = 0.023). Higher PVR develops when thrombus amount increases in the pulmonary vascular bed. Increased PVR causes increased pressure load on RV, adverse remodeling in RV, and decreased RV functions. RV FDG-PET uptake is a valuable diagnostic modality candidate for indirectly showing thrombus burden in the pulmonary vascular bed, and predicting thrombus amount that can be removed by PEA from vascular bed during the planning of CTEPH treatment and subsequently postoperative clinical improvement. Pro-BNP, which is synthesized in myocardial cells that exposed to volume and pressure load, and which is a frequently used blood parameter in left heart failure, was found to be correlated with RV FDG-PET uptake as expected due to the high-pressure gradient. This shows that Pro-BNP is an essential parameter in clinical follow-up and treatment of CTEPH, which provides vital information about disease severity and can be used in the clinical monitoring of PH patients with these properties.

D-dimer is used in the diagnostic algorithm of acute pulmonary thromboembolism as a fibrin degradation product and more preferred in diagnostic exclusion of acute pulmonary thromboembolism. However, previous studies showed that it has no prognostic value in CTEPH patients, despite being related to disease prognosis in PH patients.[14,15] In our study, we found that serum D-dimer levels were associated with RV/LV FDG-PET uptake ratio (P = 0.002). The high levels of

D-dimer in patients with increased RV/LV FDG-PET uptake suggest that thromboembolism cycle and *in situ* thrombus cycle continues in particular in distal arterial bed. These high-risk patients with ongoing *in situ* thrombus cycle may have a higher risk regarding residual PH after PEA, particularly following distal arteriopathy.

In our study, we have evaluated the associations between echo parameters that assessed RV functions and RV FDG-PET uptake. Accordingly, FDP uptake was significant in patients with elevated systolic PAP and right atrium area. Recent studies about RV functions also reported similar findings, and most frequently used and most important parameter among those, the TAPSE, was accepted to show RV functions. Li *et al*.[16] evaluated RV functions by three-dimensional-real-time echocardiography and reported that RV ejection fraction and RV fractional area change are correlated with RV tissue Doppler systolic wave and myocardial performance index, but not with TAPSE. The authors suggested that oscillation of RV apex significantly decreases in a minimal volume or pressure load due to its elastic structure, and this yields TAPSE to be measured less that it is. The limited abilities of echo parameters that are frequently used in the evaluation of RV functions, and their changeability according to operator increases the importance of a more objective evaluation method, the RV FDG-PET.

Diagnosis and treatment of PH are primarily based on hemodynamic parameters of RHC. According to the European Society of Cardiology (ESC) 2015 PH diagnosis and treatment guidelines, mPAP ≥25 mmHg and PCWP ≤15 mmHg for precapillary PH and mPAP ≥25 mmHg and PCWP >15 mmHg values remained, the transpulmonary gradient was removed, and diastolic pressure gradient and PVR were added to criteria for revised PH diagnosis. This revision was made due to systolic and mPAP were affected by PCWP during the cardiac cycle.[15] A significant correlation between RV FDG-PET uptake and the diastolic PAP, PVR, transpulmonary gradient, and diastolic pressure gradient, which are all hemodynamic parameters of RHC that is the gold standard in diagnosis, treatment, and follow-up of PAH patients. However, there were no significant correlations between systolic and mean PAP, cardiac output and cardiac index, and RV FDG-PET uptake. As Vachiéry *et al*.[17] reported in their study that referenced in ESC 2015 guideline, systolic and mean PAP is affected by PCWP during the cardiac cycle. Transpulmonary gradient loses its significance in discrimination of PH as precapillary or postcapillary. However, diastolic PAP and diastolic pulmonary gradient show precapillary PH, since diastolic PAP is affected by PCWP minimally during the cardiac cycle. But, since mPAP, which is the primary diagnostic criteria of PH, is also indirectly affected from PCWP, a similar revision can be done for patients who are in the grey zone with mPAP 21–24 mmHg and can be subject to misdiagnosis due to doubts about the diagnosis. At this point, utilization of diastolic PAP for PH diagnosis by determining a reference range can be discussed, because diastolic PAP is affected very less than mPAP from PCWP. Furthermore, since we found that RV FDG-PET uptake is correlated with RHC parameters, which are the gold standard in PH diagnosis, and which were revised in new ESC PH guidelines; right ventricle FDG-PET/CT can be a diagnostic method that can be used along with RHC for PH diagnosis in the future.

Specific treatment in PH is applied by targeting pulmonary arterial bed. However, symptoms and prognosis of the disease are determined by right heart failure. Right ventricle-targeted therapies have not been evaluated in detail in patients with PAH and right heart failure. The most promising data are about metabolic modulation among right ventricle-targeted medications. Phase 1 and 2 trials of mitochondrial modulators like dichloroacetate have been completed in patients with metabolic changes in the right heart and pulmonary vascular bed in PH.[18] Today, research is needed about stem cell and gene therapies targeting RV, specifically in PH.

Limitations of the study

Significant limitations of this study are mainly about the low number of patients, which caused many parameters to have a marginal statistical significance that could not reach to relevance. The follow-up of patients after the operation could not be done, and associations of right ventricle FDG-PET with long-term prognosis could not be evaluated. Furthermore, right ventricle FDG-PET evaluations after surgery could not be performed, and more detailed data about RV functions could not be obtained.

Conclusion

Our study is particularly important for evaluating associations between right ventricle FDG-PET uptake and clinical characteristics, 6-MWD, Qanadli score, echocardiographic, and RHC parameters of CTEPH patients. Under the light of these data, right ventricle FDG-PET uptake was shown to be an innovative noninvasive method that can be used in diagnosis, treatment strategy, and follow-up of CTEPH patients undergoing PEA.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Is Vitamin D Level Elevated in Patients on Statin Treatment?

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Abstract

Context: Statins are effective agents on both primary and secondary prevention in patients who are at high risk of cardiovascular disease, and the number of patients taking statins has significantly raised recently. **Aims:** The aim of this study was to evaluate the association between Vitamin D levels and statin usage, statin type, dose, and duration. **Settings and Design:** We enrolled 210 control and 174 patients who were taking statins, and whose Vitamin D levels were checked in the past 3 months. 25-hydroxy Vitamin D levels were analyzed by immunoassay. Subgroup analysis was done firstly according to statin types and other lipid-lowering agents, namely fenofibrate. **Subjects and Methods:** Statin dosage's effect on Vitamin D levels were analyzed in patients taking low-dose (10–20 mg/day) and high-dose (40–80 mg/day) atorvastatin. Patients were divided into three groups according to statin usage duration (short term: >1 month, less than a year, medium-term: 1–5 years, long term: >5 years). **Statistical Analysis Used:** Kolmogorov–Smirnov, Kruskal–Wallis, Bonferroni Dunn's multiple comparisons, Spearman rank tests were used. **Results:** About 71.26% of the patient group was using atorvastatin, 13.21% rosuvastatin, 4.59% pitavastatin, and 10.91% were on fenofibrate treatment. Vitamin D levels were statistically different among statin subtypes ($P < 0.001$); the highest level was observed in patients taking atorvastatin (23.03 ± 9.94). Vitamin D levels were statistically significantly higher in short-term and medium-term statin usage than control group ($P < 0.001$). **Conclusions:** Our study demonstrated that even low-dose statin has a positive effect on Vitamin D. Thereby, it encourages patients to continue with statin therapy more willingly.

Keywords: Cardiovascular disease, statin, Vitamin D

Introduction

Statins are effective agents on both primary and secondary prevention in patients who are at high risk of cardiovascular disease (CVD).[1-4] Recently, published articles reveal that statins prevent major cardiovascular events including all-cause mortality, cardiovascular mortality, morbidity, repeating cardiovascular events, and ischemic stroke in patients who have CVD.[5-8] Hence, the number of patients taking statins has significantly raised recently, and this upward trend will continue upon the rising number of high-risk patients and the aging population.[9-11]

7-dehydrocholesterol (7-DHC) is the precursor of both Vitamin D and cholesterol in mammal tissues; therefore, statins are expected to affect their metabolism.[12] Statins diminish production of cholesterol and Vitamin D by reducing 7-DHC; however, there are some studies demonstrating higher serum Vitamin D levels in statin users.[13,14] Moreover, there are few researches aligning no correlation between statins and Vitamin D levels in the literature.[15-17]

Our aim in this retrospective cross-sectional study was to evaluate the association between Vitamin D levels and statin usage, group, dose, and duration.

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Subjects and Methods

This study was conducted in cardiology and internal medicine outpatient clinics of the hospital between March 2018 and March 2019. Ethical approval was obtained from Local Ethical Committees of the hospital (2018/427).

We enrolled patients who were taking statins, and whose Vitamin D levels were checked in the past 3 months. The control group was consisted of age- and sex-matched patients who were not using statins.

Patients who had Vitamin D replacement in the past 6 months, under treatment which might effect Vitamin D levels, chronic renal failure, malabsorption syndrome, pregnancy, malignancy, under the age of 18 years, and not capable of giving an informed consent were excluded from the study. Seasonal effects on Vitamin D levels were also taken into account; therefore, the patient and control group was balanced on seasons.

Subgroup analysis was done first according to statin subtypes and other lipid-lowering agents, namely fenofibrate. Statin dosage's effect on Vitamin D levels was analyzed in patients taking low-dose (10–20 mg/day) and high-dose (40–80 mg/day) atorvastatin. Besides, patients were divided into three groups according to statin usage duration (short term: >1 month, less than a year, medium term: 1–5 years, long term: >5 years).

Venous blood samples were collected from patients after 12 h of starvation. Each serum sample was aliquoted into two tubes after centrifuge at 1400 rcf for 10 min, and stored at −80°C until it could be analyzed for 25-hydroxy Vitamin D (25[OH] D). Serum 25(OH) D concentrations were analyzed using Beckman Coulter, UniCel DxI800 Immunoassay analyzer (Beckman Coulter Inc, U.S.A.) device by immunoassay method.

Number Cruncher Statistical System (NCSS) 11 (NCSS, 2017 Statistical Software) program was used for statistical analysis. Categorical variables were defined by frequency and percentage values. Continues variables were defined by mean, standard deviation, median, minimum, and maximum values. Normal distribution of continuous variables was analyzed by Kolmogorov–Smirnov test. Nonnormally distributed variables were analyzed using Kruskal–Wallis test. Bonferroni Dunn multiple comparison tests was used to determine the source of significance difference among groups with more than two variables. Spearman rank test was employed to analyze correlations among numeric variables. Statistical significance was accepted as $P < 0.05$.

Results

A total of 384 patients (210 control group) were included in the study. Totally, the mean age was 61.01 ± 12.21, and 57.92% ($n = 223$) were female.

About 71.26% of the patients group was using atorvastatin, 13.21% rosuvastatin, 4.59% pitavastatin, and 10.91% was on fenofibrate treatment [Table 1]. Patients Vitamin D level was statistically higher than control group ($P < 0.001$). Vitamin D levels were statistically different among statin subtypes ($P < 0.001$), when the pitavastatin data excluded due to the number of patients, the highest level was observed in patients taking atorvastatin (23.03 ± 9.94) [Table 1]. In order to find the source of this difference Bonferroni Dunn's multiple comparison tests was applied for statin subtype dosage, duration, and Vitamin D levels. Overall, Vitamin D levels were statistically significantly higher in short-term and medium-term statin usage than control group ($P = 0.002$, $P < 0.001$) [Table 2]. On the other hand, Vitamin D levels were similar among different atorvastatin and rosuvastatin doses and duration [Table 3]. Vitamin D levels were not different among low-dose (10 mg/d) and high-dose (20 mg/d) rosuvastatin short, medium, and long-term usage ($P > 0.05$) [Table 4]. Pitavastatin dosage and duration was not evaluated due to few numbers of patients on pitavastatin treatment.

Discussion

Our study demonstrated that Vitamin D levels are significantly elevated in patients taking atorvastatin ($P < 0.001$). This finding

Table 1: Vitamin D levels according to cholesterol drugs and control group

	Vitamin D (*n*) Mean.±SD Med. (Min.-Max.)	*P*
Cholesterol drugs		
Atorvastatin	(*n*=124)%71.26, 23.03±9.94, 22- (6-59)	*P*<0.001
Rosuvastatin	(*n*=23)%13,21, 21.52±7.83, 21- (6-42)	
Pitavastatin	(*n*=8)%04,59, 24.5±12.82, 23- (5-50)	
Fenofibrate	(*n*=19)%10,91, 18.74±8.68, 17- (5-38)	
Control group	(*n*=210), 18.14±10.21, 16- (3-65)	

Table 2: Vitamin D levels due to statin usage duration

	Vitamin D (*n*) Mean±SD Med. (Min.-Max.)	*P*
Statin Duration		
Short term (≤1 year)	(*n*=92), 22.34±10,3, 21- (5-59)	*P*<0.001
Medium term (2-5 year)	(*n*=47), 23.58±8.03, 23- (8-46)	
Long term (≥6 years)	(*n*=31), 21.19±11.03, 19- (6-52)	
Control group	(*n*=210), 18.22±10.13, 16- (3-65)	

Kruskall Wallis H testi

Table 3: Vitamin D levels in atorvastatin users, due to dosage and duration

Atorvastatin	Vitamin D, (*n*); mean±SD; median (minimum-maximum)	*P*
Low-dose atorvastatin (years)		
Short term (≤1)	(41); 22.46±8.62; 22 (9-44)	>0.05
Medium term (2-5)	(31); 24.43±8; 24 (12-46)	>0.05
Long term (≥6)	(15); 23.93±10.84; 21 (8-46)	>0.05
High-dose atorvastatin (years)		
Short term (≤1)	(19); 24±12.95; 22 (8-59)	>0.05
Medium term (2-5)	(5); 24.2±9.78; 23 (13-40)	>0.05
Long term (≥6)	(10); 17.8±13.5; 14.5 (6-52)	>0.05

Kruskal–Wallis H test. SD: Standard deviation

Table 4: Vitamin D levels in rosuvastatin users, due to dosage and duration

Rosuvastatin	Vitamin D, (*n*); mean±SD; median (minimum-maximum)	*P*
Low-dose rosuvastatin (years)		
Medium term (2-5)	(4); 23±5.42; 25 (15-27)	>0.05
Long term (≥6)	(2); 19.5±9.19; 19.5 (13-26)	
High-dose rosuvastatin (years)		
Short term (≤1)	(5); 20.4±13.39; 19 (6-42)	>0.05
Medium term (2-5)	(4); 23.75±9; 22 (16-35)	>0.05
Long term (≥6)	(4); 23.75±9; 22 (16-35)	>0.05

Kruskal–Wallis H test. SD: Standart deviation

is correlated with the findings of Yavuz *et al*.[13] They also revealed higher 25(OH) D and 1, 25-dihydroxy Vitamin D3 (1, 25[OH] 2D3) in patients under rosuvastatin and atorvastatin treatment.[13] Meanwhile, Ertugrul *et al*. showed raised 25(OH) D levels with rosuvastatin, whilst fluvastatin was not associated with 25(OH) D.[18] On the other hand, although there were few patients in pitavastatin group, Vitamin D was high in all kinds of statin subgroups. Similarly, there are plenty of studies demonstrating an elevation in Vitamin D levels in different statin subtypes.[19,20] Wilczek *et al*. indicated that serum 25(OH) D levels are rising after 3 months of lovastatin 20–80 mg/day usage.[21] Likewise, simvastatin escalates levels of plasma Vitamin D metabolites and 1,25(OH)2D3 significantly.[22]

On the other hand, there are some studies displaying no association between statins and Vitamin D in the literature. Pravastatin was found not to be not affecting Vitamin D production in a research conducted on patients who took daily 10–80 mg pravastatin and was exposed to ultraviolet B light for 3 months.[16] Furthermore, two other studies could not demonstrate a difference in Vitamin D levels between patients who were taking pravastatin 20 mg/day and 40–80 mg/day for 24 and 8 weeks, respectively.[17,23]

Meanwhile, analysis about the effect of statin usage duration on Vitamin D levels revealed that Vitamin D levels were significantly lower in the control group than short- and medium-term statin users in our study. Pérez-Castrillón *et al*. also demonstrated similar findings in their study conducted in 2007.[14] Patients who had coronary artery disease and Vitamin D deficiency were given 10–80 mg/day atorvastatin for 12 months, and at the end, mean Vitamin D levels were raised to 18.8 ± 7.6 ng/mL from 16.4 ± 7.6 (P = 0.003).[24] The ratio of patients with Vitamin D deficiency was diminished to 57% after 12 months of statin treatment.[14] The mechanism of the ability of statins to raise Vitamin D levels is not completely understood yet. While statins decrease both 7-DHC and cholesterol production, Vitamin D levels are expected to deescalate; however, no study has shown a drop in Vitamin D levels in statin users.[24] According to the hypothesis of Grimes, there is a striking similarity between benefit of Vitamin D and statins which may be related with the activation of Vitamin D receptors by statins.[24] Other researchers have also suggested plenty of potential mechanisms about this unexpected rise in Vitamin D with statins.[12,25,26] First, Vitamin D is metabolized in liver and intestines by CYP3A4, and statins are also metabolized by CYP3A4.[25] The competition in this common pathway might be associated with increased Vitamin D levels in patients on statin treatment.[25] Second, 3-hydroxy-3-methylglutaryl-CoA (HmG-CoA) reductase inhibition by statins may be increasing 7-DHC levels in skin which is essential for 25(OH) D synthesis.[12] This increment can explain bone mineral density increase and bone fracture decrease in statin users.[12] A research related with this view was done by Aloia *et al*.[26] They demonstrated higher Vitamin D levels in patients taking statins than who were not on statin treatment (20.51 ± 8.05 vs. 17.31 ± 7.21 ng/mL, respectively) (P < 0.008) in a study aimed to show the benefits of Vitamin D3 on bone calcium levels conducted on postmenopausal African American women.[26]

The main limitations of our study are its single-centered basis and relatively low number of patients. Besides, as this was a cross-sectional study, we did not know initial Vitamin D levels before statin usage; hence, we could not evaluate the rise in Vitamin D levels with statins.

Conclusion

Advances in therapeutic methods led to longer life span, so increased number of patients with CVD and on statins is inevitable. Hence, the effects of statins besides cardiovascular ones will continue to interest researchers. Although our study aligned higher Vitamin D levels in statin users, large scale comprehensive studies are needed to validate these results.

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Conflicts of interest

There are no conflicts of interest.

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