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Original Article

Evaluation of CHA_2DS_2-VASc Score and R_2CHADS_2 Score in Patients with Acute Pulmonary Thromboembolism and Right Ventricular Dysfunction

Çağrı Zorlu, Sefa Erdi Ömür[1], Cemal Köseoğlu[2]

Department of Cardiology, Tokat Gaziosmanpaşa University, [1]Department of Cardiology, Tokat State Hospital, Tokat, [2]Department of Cardiology, Alanya Alaaddin Keykubat Training and Research Hospital, Alanya, Turkey

ORCID:

Çağrı Zorlu: http://orcid org/0000-0003-4085-8151

Sefa Erdi Ömür: http://orcid org/0000-0002-6209-1732

Cemal Köseoğlu: http://orcid org/0000-0001-8911-3340

Abstract

Background and Aim: Acute pulmonary embolism (APE) is one of the fatal emergencies. Imaging methods are not available to all physicians as an emergency and depend on the individual. For this reason, besides imaging methods, more easily applicable and individual-independent parameters are investigated to help the diagnosis. Some scoring systems are also used according to the patient's current disease status. R_2CHADS_2 score is used more in patients with chronic renal failure (CRF). The aim of the study was to compare CHA_2DS_2-VASc and R_2CHADS_2 scores in patients with APE and right ventricular dysfunction (RVD). **Methods:** The study was conducted retrospectively. The patient group of the study consisted of 392 patients diagnosed with APE. Patients with nonmassive pulmonary embolism and submassive pulmonary embolism (SPE) without RVD were defined as Group 1 ($n = 213$) and massive pulmonary embolism and SPE with RVD were defined as Group 2 ($n = 179$). CHA_2DS_2-VASc and R_2CHADS_2 scores were compared as a scoring system in patients. **Results:** CHA_2DS_2-VASc scores and R_2CHADS_2 scores were evaluated in the two groups. The R_2CHADS_2 score was statistically significant in Group 2 ($P < 0.001$). There was a statistically significant difference between the groups in terms of CRF and estimated glomerular filtration rate (15 [7.2%] vs. 29 [16.4%], $P < 0.001$, and 57.6 vs. 46.4 mL/min/1.73 m^2, $P < 0.001$). **Conclusions:** Our findings show that the CHA_2DS_2-VASc score and R_2CHADS_2 are independent predictors of RVD in patients with APE. However, the R_2CHADS_2 scoring system is observed better than the CHA_2DS_2-VASc scoring system in patients with APE and RVD.

Keywords: Acute pulmonary embolism, CHA_2DS_2-VASc, chronic kidney disease, echocardiography, R_2CHADS_2

Introduction

Acute pulmonary embolism (APE) is an emerging form of pulmonary thromboembolism (PTE), a medical emergency that can result in death.[1] Inhospital mortality rate varies according to the clinical course. Clinical course of APE can be examined in three groups as massive, submassive, and nonmassive. This classification of cases with APE is very important as it is decisive for the management of treatment to be applied to patients. APE – as a result of pulmonary arterial occlusion – can lead to life-threatening acute but potentially reversible right ventricular dysfunction (RVD). Inhospital mortality of patients with massive pulmonary embolism (MPE) varies from 25% to 50%.[2] RVD is the most important predictor of mortality in submassive APE and its detection is vital,[3] and these patients should be given thrombolytic treatments. The fastest and simplest method to detect RVD is

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Address for correspondence: Dr. Sefa Erdi Ömür, Department of Cardiology, Tokat State Hospital, Tokat, Turkey.
E-mail: sefaerdi61@gmail.com

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echocardiography (ECHO) in APE, however, it is cardiologist dependent, and also in some patients, it is not possible to evaluate right ventricular function due to imaging difficulties. Therefore, in cases where there is no cardiologist or the right ventricle is not evaluated clearly due to imaging difficulties, a different marker predicting RVD is required. We thought that CHA_2DS_2-VASc and R_2CHADS_2 scores, which are especially used in the risk stratification of atrial fibrillation (AF), may help the risk stratification in AF patients with APE.

The CHA_2DS_2-VASc (C: congestive heart failure [HF] or left ventricular systolic dysfunction, H: hypertension, A: age of ≥75 years, D: diabetes mellitus, S: previous stroke, V: vascular disease, A: age between 65 and 74 years, and Sc: female gender) score is a scoring system that is used to determine the risk of thromboembolism in nonvalvular AF and also enables the management of anticoagulant therapy in diagnosed patients.[4] Moreover, it has also been shown in the literature that it can be used in thrombotic cases that develop after percutaneous coronary interventions.[5,6]

R_2CHADS_2 score was described as $CHADS_2$ score plus one point for renal dysfunction (estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2). Impaired renal function was shown to be a predictor of stroke and systemic embolism in AF patients without valvular disease.[7] In Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in AF, the study demonstrated that R_2CHADS_2 score was superior to predict stroke risk than $CHADS_2$ score.[7] All components of R_2CHADS_2 had predictive value for both prognosis and complications of ischemic heart disease and AF.

This study aimed to evaluate the comparison of CHA_2DS_2-VASc score and R_2CHADS_2 score to predict RVD in patients with APE, and we aimed to assist clinicians in the decision of APE risk classification in cases where ECHO cannot be performed.

Methods

Study population and design

We retrospectively collected the data of patients with acute pulmonary embolism who applied to the emergency department between January 2016 and June 2019, we retrospectively attended the study. A total of 392 patients were included in the study. The patients over 18 years of age, who presented to the emergency department with symptoms of shortness of breath, hemoptysis, and chest pain and who were diagnosed with APE after undergoing pulmonary computed tomography angiography with a prediagnosis of APE, were included in the study.

All patients had transthoracic ECHO within 48 h of hospitalization that it is routinely (using the General Electric Vivid 3 ultrasound system, Chicago, IL, USA). A review of patient files revealed that ECHO images had been obtained from all cases in semi-supine position, apical four chambers, parasternal short-long axis, and subcostal positions. ECHO was carried out by using a 3.4 MHz transducer probe with two dimensional, classical, and tissue Doppler. Systolic pulmonary artery pressure (sPAP) was calculated by using Bernoulli equation devaluating tricuspid regurgitation pressure gradient (TIPG = 4 × tricuspid regurgitation velocity^2) in addition to right atrial pressure. Pulmonary hypertension was defined as sPAP >36 mmHg.[8] The tricuspid annular plane systolic excursion (TAPSE) method was used to evaluate the RVD. A value of TAPSE ≤15 was accepted to confirm the presence of the RVD. Laboratory parameters were recruited from our hospital electronic database. The blood parameters of the patients consisted of the values when they first applied with APE. The demographic characteristics of the patients, comorbidities, patient histories, vital signs, treatment regimens at the hospital, monitoring findings daily, and the duration of hospital stays were obtained from the medical files of the patients.

Patients with chronic obstructive pulmonary disease, sleep breathing disorders, intracardiac lesions, sepsis or septic shock, serious pericardial and pleural effusions, acute renal failure, malignancies, collagen tissue disease, congenital heart disease, and valvular heart disease were excluded from the study.

The APE cases were assigned to three subgroups, according to their hemodynamic and radiological characteristics. The patients developing hypotension were assigned to the massive PTE subgroup (MPE), the patients with stable hemodynamics but with RVD detected by ECHO were assigned to the submassive PTE group (SPE), and the patients with stable hemodynamics with no RVD confirmed by ECHO were assigned to the nonmassive PTE group (nonmassive pulmonary embolism [NPE]).[9] We organized these three subgroups into two groups according to RVD in accordance with the purpose of our study. Patients with NPE and SPE without RVD were defined as Group 1 and MPE and SPE with RVD were defined as Group 2.

The CHA_2DS_2-VASc score was calculated by summing the points assigned to each of the risk factors, which include congestive HF (1 point), hypertension (1 point), age ≥75 (2 points), diabetes mellitus (1 point), previous stroke, transient ischemic attack or thromboembolism (2 points), vascular disease (history of myocardial infarction, peripheral arterial disease, or complex aortic plaques) (1 point), age between 65 and 74 years (1 point), and female gender (1 point).

The R_2CHADS_2 score was calculated by summing the points assigned to each of the risk factors, which include renal dysfunction (2 points), congestive HF (1 point), hypertension (1 point), age ≥75 (2 points), diabetes mellitus (1 point), previous stroke, transient ischemic attack, or thromboembolism (2 points).

The simplified Pulmonary Embolism Severity Index (sPESI) scores of the patients were calculated using data obtained from FONET software program (version 3.1.1.6 b5) FONET, Ankara, Turkey. The sPESI score was calculated

by summing the points assigned to each risk factor, which include history of cancer (1 point), age >80 (1 point), history of HF or chronic lung disease (1 point), pulse rate >110 beats/min (1 point), systolic blood pressure <100 mmHg (1 point), and SaO_2 <90% (1 point). The patients with sPESI risk scores of 0 were accepted to have low sPESI scores. The patients with sPESI scores of 1 were accepted to have high sPESI scores.

Definition of congestive HF was based on a previous diagnosis of HF. HF was defined according to the criteria recommended by the working group on HF of the European Society of Cardiology.[10] Hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg in at least two separate measurements or if a patient was already receiving antihypertensive medications. Diabetes mellitus was defined as a patient already receiving antidiabetic drugs and/or insulin or if fasting blood glucose level was ≥126 mg/dL. Stroke and transient ischemic attack were assessed with patient history, and only the events owing to thromboembolism were included as a component of CHA_2DS_2-VASc score. Stenosis of ≥50% in noncoronary arteries was defined as peripheral arterial disease.

Definition of chronic renal failure (CRF) was based on a creatinine clearance of <60 mL/minute, which was calculated by the Modification of Diet in Renal Disease formula and utilizing the baseline creatinine level.[11]

The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

All analyses were performed using SPSS for Windows version 18.0 (SPSS, Chicago, Illinois, USA). Quantitative data are presented as means ± standard deviations (SD) for parametric variables or medians with interquartile ranges (lower and upper quartiles) for nonparametric variables. Kolmogorov–Smirnov test was used to assess the compatibility of our data with normal distribution. Comparisons of parametric values among groups were performed by one-way analysis of variance. Comparisons of nonparametric values among groups were performed by the Kruskal–Wallis test. Tukey's HSD (for parametric variables) and Bonferroni adjustment Mann–Whitney *U*-test (for nonparametric variables) were used as *post hoc* test for multiple comparisons among the groups. Multiple linear regression analysis was performed for parameters affecting the presence of RVD. Normally distributed data are expressed as mean ± SDs and nonnormally distributed data are expressed as percentage. $P < 0.05$ was considered statistically significant. Receiver-operating characteristic (ROC) curves were estimated for CHA_2DS_2-VASc and R_2CHADS_2. ROC analysis was used to determine the cutoff values of CHA_2DS_2-VASc and R_2CHADS_2 in predicting RVD in patients with APE.

Ethical statement

Approval was obtained from the Ethics Committee of the Tokat Gaziosmanpasa University – date: April 30, 2020, number: 20-KAEK-081 – where our institution was conducted.

Results

The study population consisted of 392 patients (mean age, 60.2 ± 10.4 years and 55.3% of females). In this study, according to RVD, we divided the patients into two groups: the NPE and SPE without RVD group (n = 120, 56.33%) determined as Group 1 (n = 213) and the MPE and SPE with RVD (n = 3, 1.67%) determined as Group 2 (n = 179). The main characteristics of PTE subgroups are shown in Table 1. Systolic PAB was 42.23 ± 19.24 mmHg in Group 2 and 35.62 ± 18.21 mmHg in Group 1 ($P < 0.001$). Group 2 was older than those in Group 1 (68.2 ± 9.4 vs. 52.2 ± 11.4, $P < 0.001$). There were a total of 217 female patients in the study, and there was no significant difference between the groups in terms of gender ($P = 0.134$). Cardiac diseases were detected at a higher rate in Group 2, and this finding was statistically significant (63 [29.6] vs. 91 [50.7%], $P = 001$).

Newly detected deep vein thrombosis (DVT) was statistically significantly higher in Group 2 (87 [40.7%] vs. 107 [60%], $P = 0.001$). Again, compared to other groups, inhospital mortality rate was detected to be higher in Group 2 (2 [1.1%] vs. 16 [8.9%], $P < 0.001$).

The CHA_2DS_2-VASc scores and R_2CHADS_2 scores were classified into two groups as follows: the scores between 0 and 1 were classified as the low-risk group and the scores of >1 were classified as the high-risk group [Table 1]. When CHA_2DS_2-VASc score was compared in high-risk groups, it was found 108 in Group 1 and 123 in Group 2 ($P < 0.001$). When the R_2CHADS_2 score was compared in high-risk groups, it was found 119 in Group 1 and 141 in Group 2 ($P < 0.001$). The associations of the variables with these groups are summarized in Table 2. The R_2CHADS_2 score was statistically significant in Group 2 ($P < 0.001$). There was a statistically significant difference between the groups in terms of CRF and eGFR (15 [7.2%] vs. 29 [16.4%], $P < 0.001$, and 57.6 versus 46.4 mL/min/1.73 m^2, $P < 0.001$). In addition, the sPESI scores are used to estimate the early mortality rate. sPESI score of all patients included in the study has been calculated. while it was 1.2 ± 0.61 in Group 1, it was found 3.8 ± 0.8 in Group 2 ($P < 0.001$). Our results indicated that a CHA_2DS_2-VASc score of ≥2 could be used as a predictor of RVD in patients presenting with APE with a sensitivity of 76% and a specificity of 68%, an area under the curve of 0.808, and a 95% confidence interval (CI) of 0.756–0.859. $RCHA_2DS_2$ score of ≥2 could be used as a predictor of RVD in patients presenting with APE a sensitivity of 82% and a specificity of 64%, an area under the curve of 0.882, and a 95% CI of 0.844–0.921 [Figure 1].

In multivariate logistic regression analysis, CHA_2DS_2-VASc score (odds ratio [OR]: 1.486, 95% CI: 1.024–2.162, $P = 0.030$), R_2CHADS_2 score (OR: 2.225, 95% CI: 1.1892–

Table 1: The association of variables with acute pulmonary embolism subgroups

Variable	Group 1 (*n*=213), *n* (%)	Group 2 (*n*=179), *n* (%)	*P*
Scores			
CHA_2DS_2-VASc score			
0-1	104 (49.1)	55 (30.9)	0.011
≥2	108 (50.8)	123 (69)	0.009
$R_2CHA_2DS_2$-VASc score			
0-1	112 (52.5)	62 (34.7)	0.154
≥2	119 (55.8)	141 (78.8)	<0.001
sPESI	1.2±0.61	3.8±0.8	<0.001
Demographıc data and dıseases			
Age (years)	52.2±11.2	68.2±9.4	<0.001
Female gender	121 (56.9)	96 (53.9)	0.134
Smoking	63 (29.6)	70 (38.9)	0.216
CRF	15 (7.2)	29 (16.4)	<0.001
DVT	87 (40.7)	107 (60)	0.001
Prior pulmonary thromboembolism	12 (5.5)	7 (3.7)	0.564
Cardiac disease	63 (29.6)	91 (50.7)	0.01
Liver disease	6 (2.7)	18 (9.8)	0.028
Neurological disease	27 (12.8)	29 (16.4)	0.525
Prior DVT	12 (5.5)	8 (4.2)	0.534
Diabetes mellitus	31 (14.5)	21 (11.7)	0.155
Symptoms and hemodynamıc status			
AF	42 (19.9)	34 (18.9)	0.536
Systolic blood pressure (mmHg)	126±27	113±32	0.029
Diastolic blood pressure (mmHg)	75±15	73±20	0.405
Dyspnea	167 (78.2)	168 (93.8)	<0.001
Chest pain	98 (45.8)	87 (48.8)	0.133
Hemoptysis	21 (9.8)	19 (10.6)	0.542
O_2 saturation (%)	94±5	92±5	0.089
PaO_2 (mmHg)	76±25	74±24	0.109
Echocardıographıc fındıngs			
LVEF (%)	55±10	50±11	<0.001
TAPSE (mm)	17±4	12±2	<0.001
RV systolic dysfunction	88 (41.3)	108 (60.5)	<0.001
RV dilatation	121 (56.9)	148 (82.6)	<0.001
Laboratory fındıngs			
eGFR (mL/min/1.73 m^2)	57.6±5	46.4±4	<0.001
Creatinine (g/dL)	1.02±0.4	1.32±0.4	<0.001
White blood cell ($\times10^9$/L)	8.68±2.48	8.88±4.49	0.494
Hemoglobin (g/dL)	13.93±16	12.96±1.7	<0.001
Inhospital mortality	2 (1.1)	16 (8.9)	<0.001

Definition: Group 1: Nonmassive PTE and submassive PTE without RVD. Group 2: Massive PTE and submassive PTE with RVD. CHA_2DS_2-VASc=Congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), and vascular disease, age 65-74 years, and sex category (female); sPESI=Simplified Pulmonary Embolism Severity Index; CRF=Chronic renal failure; DVT=Deep venous thrombosis; AF=Atrial fibrillation; PaO_2=Partial pressure of oxygen; LVEF=Left ventricular ejection fraction; TAPSE=Tricuspid annular plane systolic excursion; RV=Right ventricle; eGFR=Estimated glomerular filtration rate; PTE=Pulmonary thromboembolism; RVD=Right ventricular dysfunction

3018, $P = 0.02$), sPAP (OR: 1.216, 95% CI: 1.154–1.262, $P < 0.001$), eGFR (OR: 2.281, 95% CI: 2.124–3.221, $P < 0.001$), and DVT (OR: 3.554, 95% CI: 1.249–9.624, $P = 0.006$) were independent predictors of RVD in patients with APE [Table 2]. TAPSE was found to be 17 mm in Group 1 patients, while it was 12 mm in Group 2 patients, and this was statistically significant [Table 1, $P < 0.001$]. This statistical significance was maintained when multivariate analysis was performed for TAPSE in patients with APE who developed RVD [Table 2].

Thrombolytic therapy was given to three patients in Group 2 who had SPE and developed RVD. In total, 143 patients in Group 2 received thrombolytic therapy [Table 1].

R_2CHADS_2 score and CHA_2DS_2-VASc score were compared with ROC statistical analysis to show the development of RVD

Table 2: Predictors of right ventricular dysfunction in patients with acute pulmonary embolism

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Smoking	1.024 (0.692-1.374)	0.874		
Systolic blood pressure	0.960 (0.952-1.024)	0.316		
Cardiac disease	2.390 (1.628-3.498)	<0.001	2.302 (0.786-6.721)	0.106
Prior DVT	1.386 (0.650-2.824)	0.321		
DVT	2.473 (1.702-3.610)	<0.001	3.554 (1.249-9.626)	0.006
Prior PTE	1.348 (0.588-3.152)	0.443		
eGFR	1.828 (1.204-5.571)	0.004	2.281 (2.124-3.221)	<0.001
Systolic PAP	1.224 (1.183-1.216)	<0.001	1.206 (1.154-1.262)	<0.001
TAPSE	1.416 (1.274-1.55)	<0.001	1.401 (1.253-1.569)	<0.001
sPESI	1.401 (1.063-1.846)	0.017	1.359 (1.019-1.814)	0.037
PaO_2	0.896 (0.895-0.932)	<0.001	0.988 (0.941-1.030)	0.697
O_2 saturation	0.897 (0.860-0.943)	<0.001	0.944 (0.885-1.028)	0.724
CHA_2DS_2-VASc score	1.266 (1.139-1.432)	<0.001	1.486 (1.024-2.162)	0.030
R_2CHADS_2 score	2.102 (1.986-2.224)	<0.001	2.225 (1.892-3.018)	0.002

CHA_2DS_2-VASc=Congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), and vascular disease, age 65-74 years, and sex category (female); DVT=Deep venous thrombosis; CI=Confidence interval; PAP=Pulmonary artery pressure; PaO_2=Partial pressure of oxygen; PTE=Pulmonary thromboembolism; $RCHA_2DS_2$: Renal failure addition to CHA_2DS_2; TAPSE=Tricuspid annular plane systolic excursion; OR=Odds ratio; sPESI=Simplified Pulmonary Embolism Severity Index; eGFR=Estimated glomerular filtration rate

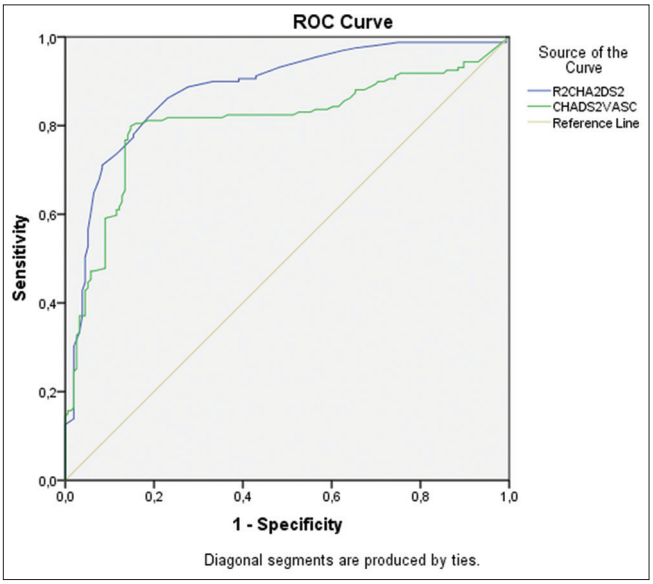


Figure 1: Receiver-operating characteristic curve of CHA_2DS_2-VASc and R_2CHADS_2

in patients with APE (AUC: 0.88, 95% CI: 0.844–0.921 AUC: 0.80, 95% CI: 0.756–0.859, respectively) [Figure 1].

Discussion

This study compares the association between CH_2ADS_2-VASc score and R_2CHADS_2 score about development of RVD in patients with APE. In the present study, we have determined that both scores are independent indicators of RVD.

Despite new diagnosis and treatment methods, APE still has significant morbidity and mortality rates. RVD is one of the most important causes of death in patients who die of PTE.[12] Hypoxia develops after thrombus-induced bronchoconstriction in APE, and this increases right ventricular pressure after a sudden rise in pulmonary artery pressure (PAP), causing right ventricular enlargement. The importance of RVD in determining the prognosis in patients with APE has led researchers to investigate this issue. Ates *et al*. showed that PLR (by dividing the number of platelets by the number of lymphocytes) was found to be associated with the clinical severity of the patients with PTE.[13] The role of platelet activity on embolic events is well known. Increased platelet activity in patients with APE is associated with increased severity of the clinical condition in pulmonary embolism.[14] Since detecting RVD in these patients or predicting its development during follow-up will trigger thrombolytic therapy option, the importance of RVD is more important in patients presenting with clinical signs and symptoms of submassive PTE rather than those presenting with massive PTE. RVD development in APE settings has been associated with certain specific clinical and laboratory variables, such as diabetes, advanced age, and female gender.[15,16] Risk scores containing these variables may be more accurate than those that are included alone. Both CHA_2DS_2-VASc and R_2CHADS_2 scores separately cover risk factors for RVD in patients with PTE.

Abnormal vascular function is recommended as a mediator of stroke.[17] Microvascular dysfunction plays a role in the pathogenesis of RVD. Although thrombus load and embolism constitute an important part of APE etiology, microvascular dysfunction and obstruction are seen in APE patients. The CH_2ADS_2-VASc score is recommended by current guidelines as a proven predictor of thromboembolic events in patients with nonvalvular AF.[4,18] The CHA_2DS_2-VASc score was matched with the results of various diseases such as PTE, AF, chronic obstructive pulmonary disease with or without

AF, decreased left ventricular ejection fraction, and coronary artery disease.[19-21] Recent studies have shown that the CHA_2DS_2-VASc score is independently associated with RVD development in patients with APE.[22] In our study, we also found that CHA_2DS_2-VASc score was an independent risk factor for predicting RVD in patients with APE.

Kidney failure has been shown to increase the risk of thromboembolism two-fold.[23] In International Cooperative Pulmonary Embolism Registration, high creatinine concentration (>177 mol/L) has been found to be a determinant for mortality at 3 months.[24] Similarly, in the large NIS database,[25] inhospital mortality in chronic kidney disease patients or patients with end-stage renal failure was doubled compared to patients with normal kidney function. On the other hand, some records have emphasized that the prevalence of PE or venous thromboembolism is higher in patients with chronic kidney disease.[25-27] In our study, we found an inverse relationship between eGFR and RVD, and we found that the R_2CHADS_2 score was significantly higher in the RVD group.

Once and for all, many risk factors in APE etiology overlap with risk factors for thromboembolism and endothelial and microvascular dysfunction. CHA_2DS_2-VASc score and R_2CHADS_2 also involve the risk factors related to atherosclerosis, vascular spasm, and microvascular dysfunction as the common risk factors. Both have a high predictive power of thromboembolic events and simultaneously contain common risk factors of APE and thromboembolism. They can be used as an exclusive risk estimation tool in APE. And also, according to our data, we found that both the R_2CHADS_2 score and CHA_2DS_2-VASc score are independent indicators of RVD and both scores can be used to predict RVD risk. Although the CHA_2DS_2-VASc score is an important helpful parameter in predicting APE, however, the R_2CHADS_2 score may also be considered as another auxiliary parameter in patients with renal dysfunction.

Study limitations

Our study has several limitations. It was an observational, retrospective, single-center study with a relatively small number of patients.

Conclusions

Our findings suggest CHA_2DS_2-VASc score and R_2CHADS_2 to be an independent predictor of RVD in patients with APE. Both scores can be very useful in this regard as an easily applicable instrument in prediction of high-risk patients. We recommend that clinicians may consider using more priority R_2CHADS_2 scores to predict RVD in patients with decreased renal function.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Role of Serum Adiponectin Levels and IL-10 as a Marker for Angiographic Stenosis in Coronary Artery Disease

Nitin Tyagi, Charanjeet Kaur

Department of Biochemistry, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India

ORCID:

Nitin Tyagi: http://orcid org/0000-0001-9465-9743

Charanjeet Kaur: http://orcid org/0000-0002-5225-6898

Abstract

Objectives: This study aimed to determine the association of interleukin (IL)-10 and adiponectin (Ad) levels with the angiographic severity of coronary artery disease (CAD). **Methods:** In this case–control study, the study population included 50 patients with angiographically proven CAD as the case group and 50 apparently healthy age and sex-matched adults as a control group. The severity of CAD was assessed by SYNTAX scores. Serum Ad levels and IL-10 were measured using ELISA-based kits. The levels of Ad and IL-10 were associated with angiographic severity of CAD. $P < 0.05$ was considered statistically significant. **Results:** Cases had significantly lower Ad level (1.89 ± 1.18 vs. 2.59 ± 1.48, $P = 0.0003$) and significantly higher IL-10 level (8.96 ± 6.84 vs. 3.5 ± 3.57, $P < 0.0001$) as compared to controls. There was a significant correlation between the levels of Ad and IL-10 ($r = 0.315$, $P = 0.026$). There was a significant negative correlation between the Ad and angiographic stenosis of CAD ($r = –0.939$, $P < 0.001$). Both Ad and IL-10 showed a significant association with the severity of CAD in terms of SYNTAX score. **Conclusion:** Patients with CAD had lower Ad levels and higher IL-10 levels. Ad levels showed a significant decrease with increasing coronary artery stenosis. Both the markers (Ad and IL-10) showed significant association with the severity of CAD, thereby signifying their role as a marker for CAD.

Keywords: Adiponectin, coronary artery disease, stenosis

Introduction

The term "coronary artery disease" (CAD) includes diseases caused due to the atheromatous changes in coronary vessels. CAD is "a condition in which there is an inadequate supply of blood and oxygen to the myocardium," which is due to the coronary arteries occlusion and leads to mismatch of demand-supply of oxygen. CADs have been gaining importance in India recently because of the increased incidence of the disease. It is a leading cause of morbidity and mortality in India.[1] The current prevalence is estimated to be 3%–4% in rural areas and 8%–10% in urban areas, according to population-based cross-sectional surveys.[2]

CAD mediated by atherosclerosis is initiated very early in human life and manifests itself clinically after a long latent phase of integrative and cumulative insults to the vessel wall by genetic, environmental, behavioral, and dietary risk factors. Identification of CAD in the early stages may help in reducing the complications arising out of it. Biochemical markers may play an important role, as depicted by their rise with increasing severity of CAD.[2]

Adiponectin (Ad) is one such marker which is a 30-kDa peptide hormone exclusively secreted by adipose tissue. It plays an important role in the regulation of lipid metabolism and glucose metabolism. Ad is an adipocyte-derived peptide which is also known as GBP 28, Acrp30, AdipoQ, and apM1.[3] It has been proven to have a role in the prevention of development

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Address for correspondence: Dr. Nitin Tyagi, Department of Biochemistry, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi - 110 029, India.
E-mail: drnitintyagi1903@gmail.com

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of atherosclerosis by inhibiting vascular adhesion factors in endothelial cells,[4] inhibiting foam cell formation, and suppressing growth and function of macrophages.[5]

Ad also influences interleukin-10 (IL-10) levels, which is an anti-inflammatory cytokine. IL-10 protects against atherosclerosis by exerting an anti-apoptotic and anti-inflammatory action through downregulation of Th1 response, inhibiting matrix-degrading matrix metalloproteinases and tissue factor, thereby preventing plaque instability.[6]

Both these markers fluctuate with the increasing levels of coronary artery stenosis and thus their monitoring may be helpful in monitoring the increasing severity of the CAD.[7]

Hence, the study was conducted to evaluate the Ad levels and its correlation with the angiographic stenosis of CAD. We also aimed to study the association of serum Ad and IL-10 levels in patients with CAD.

Methods

This case-control study was conducted in the Department of Biochemistry and Department of Cardiothoracic and Vascular Surgery, New Delhi, over a period of 18 months from October 2016 to March 2018.

Ethical clearance was obtained from the Institutional Ethics Committee* before proceeding for the study (IEC/VMMC/SJH/Thesis/October/2016, dated 22.10.16).

Study population

Fifty patients with angiographically proven (>60% stenosis in one or more vessels) were included as cases. Fifty apparently healthy age- and sex-matched people were taken as controls. Individuals with obesity, diabetes mellitus (DM), hypertension, liver, kidney diseases, and chronic inflammatory disease and with history of intake of drugs such as peroxisome proliferator-activated receptor agonists, angiotensin-converting enzyme inhibitors, angiotensin receptor type 1 blockers, anticonvulsant, and glucocorticoids were excluded from the study. The case history was recorded duly on the pro forma, and a complete clinical examination was performed. The control group consisted of healthy people who underwent a routine checkup that consisted of an electrocardiography, chest X-ray, and serum analysis. They were classed as healthy because their physical examination was uneventful without any previous symptoms of chest pain or shortness of breath, and they had no personal or family history of, or reasons for suspecting CAD.

Informed written consent was obtained from each subject before enrolling them in the study. Height, weight, and body mass index (BMI) for all patients and controls were recorded.

Definition and extent of coronary artery disease

For investigating CAD, coronary angiography was done by an experienced independent observer. The significant CAD was defined as "≥50% stenosis in lumen diameter in any major epicardial coronary arteries including the left main coronary artery, left anterior descending artery, left circumflex artery, right coronary artery, or one of their major branches." Distribution of the CAD was categorized as one-vessel disease (one-VD; disease in one vessel), two-vessel disease (two-VD; disease in two vessels or left main trunk disease without right coronary artery stenosis), or three-vessel disease (three-VD; disease in three vessels or left main trunk disease with right coronary artery stenosis)."[8]

The severity of CAD was assessed by SYNTAX and Gensini scores. The SYNTAX score was assessed using the guidelines.[9] The calculation was performed with the Internet-based SYNTAX calculator version 2.10 from the web address: www.syntaxscore.com. SYNTAX scores were estimated by scoring all coronary lesions producing a ≥50% diameter stenosis in vessels ≥1.5 mm, by the use of the algorithm present at the website. The angiographic visual analysis was done by an interventional cardiologist for evaluating the SYNTAX score. SYNTAX scores were categorized into:

SYNTAX $score_{HIGH}$ ≥22

$SXscore_{LOW\text{-}INTERMEDIATE}$ <22

No significant CAD (reference category)[10]

Blood investigations: Interleukin-10 and adiponectin

Three milliliter venous blood was collected in (ethylene diamine tetraacetic acid) vial and 3 mL was collected in the plain vial for serum separation in a single prick. The blood samples were used for biochemical (lipid profile, liver functions tests, and renal function tests) and molecular analysis. Ad estimation was done using a commercially available ELISA kit by QAYEE-BIO. The serum was used to analyze biochemical parameters, including kidney function test (urea and creatinine), liver function tests (total bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase (AST), and alkaline phosphatase [ALP]) and lipid profile. The remaining serum was stored at −70°C, which was later used to measure the levels of IL-10 and Ad.

IL-10 estimation was done using a commercially available kit by *Diaclone* following manufacturer's instructions. Serum Ad estimation was done using a commercially available kit by *QAYEE-BIO* following the manufacturer's instructions. The outcomes measures were the severity of CAD and its relation with IL-10 and Ad.

Statistical analysis

Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean ± standard deviation and median. Normality of data was tested by the Kolmogorov–Smirnov test. If the normality was rejected, then nonparametric test was used. Quantitative variables were compared using the Independent *t*-test/Mann–Whitney Test between the two groups and ANOVA/Kruskal–Wallis test was used for comparison between three groups. Qualitative variables were correlated using Chi-square test/

Fisher exact test. Odds ratio with a 95% confidence interval was calculated. Spearman rank correlation coefficient was used to assess the association of IL-10 and Ad. $P < 0.05$ was considered statistically significant.

Results

The mean age of cases was 52.74 ± 12.42 years and of controls was 48.42 ± 15.05 years ($P = 0.434$) [Table 1]. There were 86% males in cases and 74% males in the control group ($P = 0.134$) [Figure 1].

Table 2 shows the baseline parameters of cases and controls. It was observed that serum levels of AST, ALT, and urea were significantly higher in cases as compared to controls. On the other hand, levels of low-density lipoprotein, total cholesterol, and triglycerides were lesser in the cases as compared to controls. All other baseline parameters, such as height, weight, BMI, serum triglyceride, total bilirubin, ALP, and creatinine were comparable in the two groups.

As compared to control group, cases had significantly lower Ad level (1.89 ± 1.18 vs. 2.59 ± 1.48, $P = 0.0003$) and significantly higher IL-10 level (8.96 ± 6.84 vs. 3.5 ± 3.57, $P < .0001$) [Table 3]. There was a significant correlation between the levels of Ad and IL-10 ($r = 0.315$, $P = 0.026$) [Figure 2].

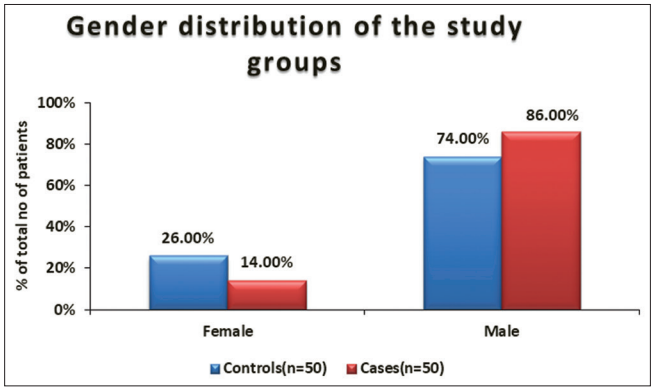


Figure 1: Gender distribution of study subjects

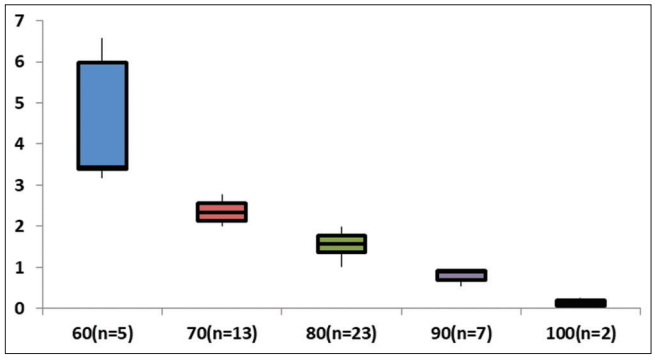


Figure 3: Comparison of adiponectin (μg/mL) between % of stenosis in one of the three highest stenotic vessels. (nonparametric variable, Box-whisker plot)

There were decreasing levels of Ad from 4.51 to 0.13 μg/mL, with increasing stenosis of coronary arteries from 60% to 100% [Table 4 and Figure 3]. A significantly negative correlation was seen between Ad levels and stenosis % in one of the highest stenotic coronaries ($r = –0.939$, $P < 0.001$) [Figure 4].

Compared to patients with SYNTAX score <22 ($n = 15$), patients with SYNTAX score ≥22 ($n = 35$) had significantly higher IL-10 (10.85 ± 4.56 vs. 7.76 ± 5.84, $P = 0.049$) and significantly lower Ad levels (1.16 ± 1.02 vs. 1.93 ± 1.29, $P = 0.0286$) [Table 5].

Discussion

One of the major risk factors for CAD is obesity, and adipose tissue forms a storehouse of fat. Among the various adipocytokines released by the adipose tissue, Ad is a specific marker that modulates the relationship of risk factors and stenosis of CAD. It plays an anti-atherogenic role along with IL-10 (anti-inflammatory) and can be considered as one of the prognostic markers for CAD.

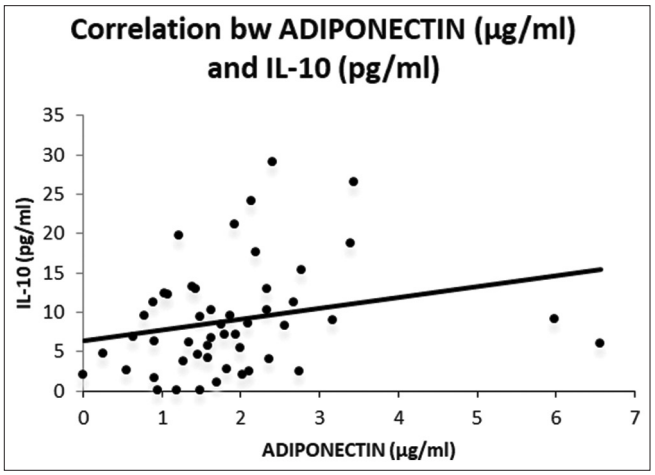


Figure 2: Correlation between interleukin-10 and adiponectin levels in coronary artery disease patients. (Correlation coefficient = 0.315, $P = 0.026$, statistically significant)

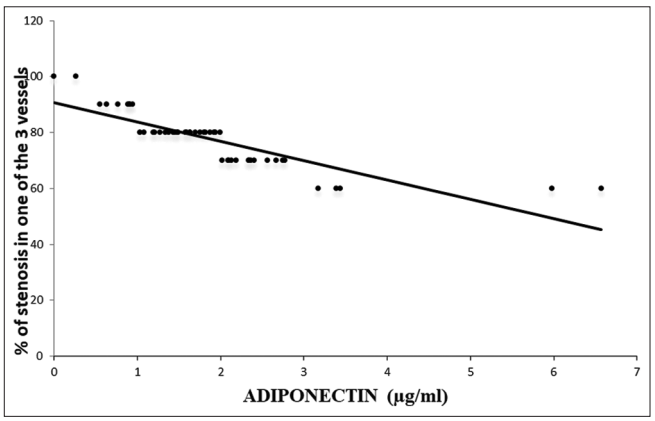


Figure 4: Correlation between ADIPONECTIN (μg/mL) and % of stenosis in one of the three highest stenotic vessels

Table 1: Age distribution of study subjects

Age distribution (years)	CAD		Total, *n* (%)	*P*
	Controls (*n*=50), *n* (%)	Cases (*n*=50), *n* (%)		
≤30	8 (16.00)	5 (10.00)	13 (13.00)	0.434
31-40	6 (12.00)	2 (4.00)	8 (8.00)	
41-50	11 (22.00)	11 (22.00)	22 (22.00)	
51-60	15 (30.00)	22 (44.00)	37 (37.00)	
61-70	5 (10.00)	7 (14.00)	12 (12.00)	
>70	5 (10.00)	3 (6.00)	8 (8.00)	
Mean ± SD	48.42 ± 15.05	52.74 ± 12.42	50.58 ± 13.80	

CAD: Coronary artery disease, SD: Standard deviation

Table 2: Baseline parameters of the study groups

Baseline characteristics	Control (*n*=50)		Case (*n*=50)		*P*
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
Height (cm)	162.12 ± 5.61	160 (158-165)	162.66 ± 6.09	162 (158-166)	0.637
Weight (kg)	59.94 ± 6.09	60 (55-65)	60.92 ± 7.07	62 (55-65)	0.534
BMI (kg/m^2)	22.77 ± 1.64	22.7 (21.800-24.200)	23.01 ± 2.35	23 (21.300-24.500)	0.552
Serum triglyceride (mg/dL)	133.3 ± 97.11	101.5 (71-154)	130.26 ± 44.38	127 (94-152)	0.081
Serum cholesterol (mg/dL)	154.48 ± 39.11	149.5 (126-186)	127.94 ± 26.58	123.5 (109-148)	0.0001
LDL (mg/dL)	104.94 ± 36.8	97.5 (75-134)	84.94 ± 27.29	85.5 (62-101)	0.008
Total bilirubin (mg/dL)	0.57 ± 0.31	0.5 (0.400-0.600)	0.72 ± 0.42	0.6 (0.500-1)	0.065
SGOT/AST (U/L)	27.54 ± 15.12	25 (18-31)	56.66 ± 45.16	38.5 (26-68)	<0.0001
SGPT/ALT (U/L)	24.68 ± 22.53	16.5 (11-32)	42.94 ± 32.5	29.5 (19-57)	0.0001
ALP (U/L)	90.64 ± 28.9	81 (69-111)	87.3 ± 30.28	79.5 (65-106)	0.364
Blood urea (mg/dL)	24.96 ± 9.25	24.5 (19-28)	29.3 ± 12.48	27 (23-31)	0.036
Creatinine (mg/dL)	0.72 ± 0.21	0.7 (0.600-0.800)	0.75 ± 0.16	0.7 (0.600-0.900)	0.283

IQR: Interquartile range, SD: Standard deviation, BMI: Body mass index, LDL: Low-density lipoprotein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, SGPT: Serum glutamic pyruvic transaminase, SGOT: Serum glutamic-oxaloacetic transaminase

Table 3: Comparison of adiponectin and interleukin-10

	Cases (*n*=50)		Control (*n*=50)		*P*
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
Adiponectin (µg/mL)	1.89 ± 1.18	1.72 (1.210-2.340)	2.59 ± 1.48	2.6 (1.700-3.400)	0.0003
IL-10 (pg/mL)	8.96 ± 6.84	7.75 (4-12.300)	3.5 ± 3.57	2.15 (0.100-6.100)	<0.0001

IQR: Interquartile range, SD: Standard deviation, IL-10: Interleukin-10

Table 4: Comparison of adiponectin (µg/mL) between percentage of stenosis (60-100%) in one of the three highest stenotic vessels

Adiponectin (µg/mL)	60 (*n*=5)	70 (*n*=13)	80 (*n*=23)	90 (*n*=7)	100 (*n*=2)	Total	*P*	Test performed
Mean ± SD	4.51 ± 1.63	2.36 ± 0.26	1.55 ± 0.28	0.8 ± 0.15	0.13 ± 0.18	1.89 ± 1.18	<0.0001	Kruskal-Wallis test; χ^2=43.204
Median (IQR)	3.44 (3.39-5.98)	2.34 (2.13-2.56)	1.58 (1.36-1.775)	0.89 (0.7-0.905)	0.13 (0.065-0.195)	1.72 (1.225-2.302)		
Range	3.17-6.57	2.02-2.77	1.03-1.99	0.55-0.94	0-0.26	0-6.57		

IQR: Interquartile range, SD: Standard deviation

We found a significant negative correlation of Ad levels with increasing angiographic stenosis of CAD. Even, there was a significant association of Ad with IL-10 in CAD patients. Our findings were in line with various other studies showing a similar negative correlation of Ad with CAD.[7,11-14]

In a case-control study like ours, the comparability of the baseline characteristics such as age and gender ensures that the final outcome measures of Ad and IL-10 levels may be purely ascribed to the differences in the severity of CAD. We found cases to have significantly higher liver enzyme levels and lower cholesterol levels as compared to controls (though the levels were within the range). This may be due to higher ongoing vigilance and control of the diet and other factors among cases as compared to controls. The cases already knew

Table 5: Comparison of adiponectin and interleukin-10 between SYNTAX score <22 and ≥22

Parameters	SYNTAX				*P*
	<22 (*n*=15)		≥22 (*n*=35)		
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	
Adiponectin (µg/mL)	1.93±1.29	1.89 (1.27-2.58)	1.16±1.02	1.22 (1.110-2.108)	0.0286
IL-10 (pg/mL)	7.76±5.84	6.55 (3-9.5)	10.85±4.56	9.8 (6-13.4)	0.049

IQR: Interquartile range, SD: Standard deviation, IL-10: Interleukin-10

that they had an underlying CAD and they need to monitor and change their lifestyle habits.

We found that the median value of Ad in cases was significantly less than controls (1.72 vs. 2.6, $P = 0.0003$). Ad is an adipocytokine, which is secreted from the white adipose tissue. It is also synthesized by cardiomyocytes, osteoblasts as well as skeletal muscle. At increased levels, it has favorable antidiabetic and anti-atherogenic properties. Its levels vary according to gender, body fat distribution, as well as metabolic status.[15] The effect of Ad on CAD can be described by the effects of Ad on vascular structure and function, such as endothelial thickening inhibition, arterial vasodilatation induction, foam cell formation inhibition, and adhesion molecules suppression.[12]

Comparable to our study, Laughlin *et al*.[13] also reported that the level of Ad was lower in patients with prevalent CHD than individuals without CHD, but the difference was borderline statistically significant (11.0 vs. 11.9, $P = 0.056$). Kumada *et al*.[7] also reported similar results as the median Ad level in the CAD patients was 4.7 µg/mL and in control subjects was 5.9 µg/mL; thus, in the CAD patients, plasma Ad levels were significantly lower as compared to control subjects ($P < 0.0001$).

Moreover, we found a significant association of IL-10 and Ad with the severity of CAD in terms of SYNTAX score and coronary stenosis, with Ad levels being decreased and IL-10 levels being increased with increasing severity of the disease.

In a study by Otsuka *et al*.,[12] also, plasma Ad levels were found to be significantly lower in stable CAD patients with complex coronary lesions as compared to those with simple lesions (4.14 vs. 5.27 µg/mL, $P = 0.006$). Ji *et al*.[15] reported that Ad levels in patients with CAD, stable angina pain, unstable angina pain, and acute myocardial infarction were significantly lesser than controls (5.95 ± 3.13 vs. 6.74 ± 3.01 vs. 6.19 ± 3.14 vs. 4.92 ± 3.02 vs. 8.34 ± 3.06, $P < 0.05$). Similarly, Hascoet *et al*.[16] reported that Ad levels were significantly lower in CAD patients than controls (5.6 vs. 7.1).

On the other hand, the median value of IL-10 in cases was significantly higher than controls (7.75 vs. 2.15, $P < 0.0001$). In contrast to our study, Waehre *et al*.[17] reported that in the patients with unstable angina, in those with stable angina, and in the controls, there was no significant difference in IL-10 levels. While Smith *et al*.[18] in their study observed that there were reduced levels of IL-10 in unstable angina patients than stable angina patients.

In the pathophysiology of atherosclerotic events (like CAD), the role of inflammatory responses is confirmed by the growing evidences. CAD develops by the formation of plaque and its deposition in the arteries walls, which leads to disruption of blood flow; it is known as atherosclerosis. Cytokines are potent inflammatory factors, which regulate each stage of atherosclerosis and thus result in the development of CAD. IL-10 is an important anti-inflammatory cytokines; it serves as an anti-inflammatory agent by downregulation of the Th1 as well as suppression of pro-inflammatory cytokines, like IL-1, IL-6, IFN-γ, and TNF-α. It leads to atherosclerosis by inhibition of the metalloproteinase synthesis. In addition, stability of plaque is promoted by IL-10 by preserving the extracellular matrix and fibrous cap. Furthermore, the IL-10 gene consists of variable sites (polymorphisms and microsatellites) that influence the IL-10 expression level. Thus, it may be associated directly and indirectly with CAD development.[19]

We found a significant association between Ad and IL-10. An anti-inflammatory action of the v is the IL-10 induction. The Ad is sufficient to induce the expression of anti-inflammatory cytokines such as IL-10 and IL-1RA in many myeloid cell types, such as monocytes, a myeloid cell line (THP-1), primary human dendritic cells, and monocyte-derived macrophages. Ad is a significant adipose tissue-derived regulator of immunological processes, which is mainly mediated by the modulation of macrophage function.[20] Thus, it always seems appropriate to measure and assess both Ad and IL-10 levels to monitor the patients of CAD.

Limitations of the study

The study was a cross-sectional study, and thus, the patients were not followed up for risk assessment and outcomes of CAD. Furthermore, simultaneous assessment of other risk factors such as diabetes, hypertension and obesity was not done. Finally, the sample size was small, and thus, we recommend future multicentric studies to have a better sample size and long-term follow-up evaluation to determine the mortality and morbidity outcomes.

Conclusion

Patients with CAD had lower Ad level and higher IL-10 level as compared to controls. Ad levels showed a significant decrease with increasing severity of coronary artery stenosis.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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Original Article

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

Mahmoud Shawky Abdelmoneum, Mohammed I. Eitta, Khaled A. Elrabat, Ahmed Mahmoud Bendary

Faculty of Medicine, Benha University, Banha, Egypt

ORCID:

Mahmoud Shawky Abdelmoneum: http://orcid org/0000-0002-5639-6521

Mohammed I Eitta: http://orcid org/0000-0001-6054-5166

Khaled A Elrabat: http://orcid org/0000-0003-1527-3506

Ahmed Mahmoud Bendary: http://orcid org/0000-0002-0161-3779

Abstract

Background: The use of intravenous nitroglycerin by intermittent bolus doses in hypertensive acute heart failure patients (AHF) is still unclear. **Aim and Objectives:** This study aimed to determine intermittent bolus nitroglycerin's effect on the use of resources, admissions to intensive care unit (ICU), hospital length of stay (LOS), and safety. **Patients and Methods:** This prospective, randomized, parallel, single-blind clinical study, which included patients diagnosed with hypertensive AHF, was conducted from May 2019 to October 2020 at Benha University Hospital. Two hundred patients were recruited and randomly allocated into two groups, each composed of 100 patients. **Results:** The prevalence of hypertension and chronic obstructive pulmonary disease patients was significantly higher in patients given intermittent boluses of nitroglycerin than in standard therapy (88.0 vs. 77.0%, $P = 0.041$) and (27.0 vs. 15.0%, $P = 0.037$), respectively. Dyslipidemia was significantly lower in patients on intermittent doses of nitroglycerin than those on standard infusion therapy (30 vs. 66%, $P < 0.001$). The median initial troponin was significantly higher in group I compared to group II (0.145 vs. 0.065 ng/ml, $P < 0.001$). **Conclusion:** Nitroglycerin intravenous boluses were associated with fewer ICU admissions and a shorter LOS in the hospital as opposed to ordinarily infusion therapy. In addition, the mean mechanical ventilation duration was slightly shorter. Finally, continuous nitroglycerin infusion use in AHF management is being questioned.

Keywords: Bolus, continuous infusion, heart failure, hypertensive, nitroglycerin

Introduction

Vasodilators are known to be one of the primary stays of acute heart failure (AHF) treatment. Current guidelines promote the use of vasodilators to minimize preload and afterload in hypertensive AHF.[1]

Although vasodilating agents boost hemodynamics in hypertensive AHF patients, they appear to have a little effect on mortality or readmissions.[2]

Nitroglycerin is the vasodilator of choice for hypertensive AHF patients when intravenously (IV) administered. It is usually given as a continuous infusion. Continuous nitroglycerin infusion, on the other hand, is correlated with higher costs and (LOS), and raising concerns regarding its effectiveness in the treatment of AHF.[3]

When high doses of nitroglycerin were given through an intermittent bolus approach, nitrates produced excess arterial dilation and a significant decrease in afterload, resulting in beneficial central pressure dynamics changes.[4]

Current evidence on bolus high-dose nitrates use indicates that these hemodynamic effects may be correlated with a reduction in myocardial infarction, endotracheal (ET) intubation, and admission to the intensive care unit (ICU),[5] while the actual

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Address for correspondence: Dr. Mohammed I. Eitta, Faculty of Medicine, Benha University, Banha, Egypt. E-mail: mohammed.eita.me@gmail.com

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influences of this strategy on the use of resources have not been assessed.

Previous studies demonstrated that bolus nitroglycerin therapy became the usual clinical practice in several institutions as a part of the treatment of hypertensive AHF.[5]

Accordingly, the present study hypothesized that intermittent bolus nitroglycerin was as effective and safe as continuous infusion when compared in a prospective randomized study.

To the best of our knowledge, this was the first prospective, randomized trial evaluating both strategies for nitroglycerin use in hypertensive AHF patients.

This study compared the efficacy and safety of intermittent bolus nitroglycerin against continuous infusion for the treatment of AHF.

Patients and Methods

This prospective, randomized, parallel, single-blind clinical study, which included patients diagnosed with hypertensive AHF, was conducted in the period from May 2019 to October 2020. This study was done at Benha University Hospital.

Two hundred patients were recruited and randomly allocated into two groups, each composed of 100 patients. Group I received nitroglycerin (NTG) in an intermittent bolus fashion (In a 10 mL syringe, nitroglycerin 10 mg was prepared and administered every three to five minutes in increments by IV push up to 2 mg) with close monitoring of blood pressure and adjustment of nitroglycerin bolus doses according to it. Group II was ordinarily given continuous intravenous NTG infusion at an initial rate of 0.3–0.5 mcg/kg per minute as a starting dose. Nitroglycerin infusion titration was allowed everyone to 3 min in increments of 20 mcg/min guided by blood pressure monitoring and tolerability. At 400 ug/minute, the maximum intravenous nitroglycerin infusion rate was fixed.

Both groups were observed for the need of ET intubation, development of cardiovascular complications, total length of stay (LOS), and worsening of renal functions throughout the duration of the hospital stay.

Upon admission, all patients enrolled in the study underwent many investigations. Full labs were drawn such as complete blood count, electrolytes, kidney function tests, and liver function tests and on regular basis throughout the hospital stay as a follow-up for both groups. In addition, brain natriuretic peptide (BNP) was ordered for some patients when needed. Complete patient history was taken, including history of present illness, medical history hypertension, diabetes, ischemic heart disease, medication history, included prescribed medications, supplements, and over-the-counter medications. Patients of both groups were subjected to physical examination on admission, including vital signs, fluid balance, lower limb edema, heart sounds, and lung base auscultation and then repeated daily for follow-up. All patients had a 12-lead electrocardiogram (ECG) on admission and then was repeated daily postadmission to detect any abnormal changes like arrhythmias or ischemic changes. Echocardiography was performed for patients of both groups at admission for overall estimation of EF, regional wall motion abnormalities, and valvular heart diseases and then again for follow-up. Patients in the study were additionally required to provide written informed consent.

Using a computer software program, simple randomization was done. Sealed opaque envelopes were used for allocation concealment. The trial has been registered in the Pan-African Clinical Trial Registry (PACTR), www.pactr.org, with the registration number ID PACTR20190568443778. Key.

Inclusion criteria

All adult patients who presented to the emergency department (ED) with hypertensive AHF were included in the study. The hypertensive AHF diagnosis was made clinically on the basis of the existence of pulmonary rales, an X-ray consistent with pulmonary edema as determined by the treating physician, and one or more of the following: tachypnea (>30 c/min), significant dyspnea (accessory respiration muscles use or obvious air hunger), marked hypoxia (Oxygen saturation (SpO_2) <90% or <95% on room air and supplemental oxygen, respectively), or hypoxemia (room air partial pressure of oxygen (PaO_2) <50 mm Hg), and a history of heart failure.

Eligibility criteria for patients are as follows: age above 18 years, at least systolic blood pressure (SBP) of 160 mmHg, or mean arterial pressure of 120 mm Hg.

Before enrollment in the study, all patients or close relatives provided written informed consent.

Exclusion criteria

It included any of the following: sublingual, transdermal, or intravenous nitroglycerin sensitivity or intolerance, failure to obtain informed consent, a need for urgent intubation or cardiopulmonary support, noncardiogenic pulmonary edema, pregnancy, suspected right-sided ventricular ischemia, or acute ST-segment elevation myocardial infarction.

Endpoints

Primary efficacy endpoints: Need for ICU admission, total hospital LOS, and posttherapy SBP and diastolic blood pressure (DBP). Primary safety endpoints: Neurologic complications as any new sensory, speech, or movement deficits, diagnosed on a clinical basis or by subsequent computed tomography (CT) brain as stroke or transient ischemic attacks, or cardiovascular complications such as hypotensive attacks that need intervention or acute myocardial injury diagnosed by the troponin rising within the 1st 24 h of presentation by at least 0.25 ng/ml). Secondary endpoints: Need and duration of bilevel positive airway pressure (BiPAP), need and length of mechanical ventilation during hospital stay period, ET intubation requirement within 6 h after treatment initiation, renal dysfunction worsening (>0.5 mg/dL increase in serum creatinine level at 24 or 48 h), and in-hospital mortality.

Supplementary issues in the care of patients in the ED and thereafter

Diagnosis of heart failure was done through physical examination and rapid assessment of systolic and diastolic functions of LV and RV using ECHO in addition to the role of biomarkers such as BNP. Ventilatory aid was allowed during the patient's treatment period with either BiPAP or ET intubation. The treating emergency physician made the decision whether to conduct ET intubation or BiPAP. Blood pressure decline, characterized by a decrease in SBP or mean arterial pressure of >30%, was a reason to stop bolus treatment temporarily and decrease the nitroglycerin infusion rate. If there is no spontaneous recovery within 5 min or after administration of a fluid bolus (500 mL of 0.9% saline), the procedure was terminated. Other reasons for termination were new onset chest pain associated with ECG changes suggesting myocardial ischemia or infarction, bradycardia (<60 beats/minute), more than 1-mm ST-segment elevation or more than 2-mm depression in two contiguous leads, new onset of neurologic deficits, or new left bundle branch block. For these conditions, the recommended treatment protocols were performed in accordance with standard advanced cardiac life support guidelines. However, the treating physician selected the treatment. Patients who needed intensive care were admitted to a monitored unit bed and then transferred to a general medical ward when they became hemodynamically and clinically stable. During their in-hospital stay, all enrolled patients underwent repeated serum laboratory tests 24–48 h after admission.

Ethical approval

The Ethics Committee of Benha Faculty of Medicine approved the study's protocol.

Statistical methods

SPSS (version 25.0; SPSS, Chicago, IL, USA) was used for data management and data analysis. Means and standard deviations or medians and ranges were used to summarize numerical variables. Numbers and percentages were used to summarize categorical variables. The two group comparisons were conducted using an independent test for normally distributed numerical variables or the Mann–Whitney *U*-test for nonnormally distributed variables. For categorical variables, Chi-square or Fisher's exact test was used for comparisons. All the tests were two-sided. The level of significance was 0.05.

Results

Age, gender, diabetes mellitus, smoking, coronary artery disease (CAD) history, coronary intervention history, intervention type, known chronic kidney disease (CKD), rate of *de novo* HF, and body mass index showed no significant differences between both groups [Table 1].

In the current study, the prevalence of hypertensive patients was significantly higher in Group I (88.0%) compared to Group II (77.0%), $P = 0.041$.

Dyslipidemia was found in 30% and 66% of patients in Groups I and II, respectively, $P < 0.001$.

The prevalence of known chronic obstructive pulmonary disease (COPD) patients was significantly higher in Group I (27.0%) compared to Group II (15.0%), $P = 0.037$.

The mean EF of all patients was 48.45 ± 10.5%; however, there was no significant difference between the two groups.

The median interquartile range (IQR) duration of nitroglycerin infusion therapy group was 16.7 (5.2–37.2) hours. In the bolus group, the median (IQR) total dose of nitroglycerin was 2 (1–2) mg; 78% of patients received 1 dose, 16% received 2 doses, 4% received 3 doses, and 2 patients received at least 4 doses [Table 2].

The mean total length of hospital stay in Group II was significantly longer (5.4 days) than in Group I (4.3 days), with $P < 0.001$.

In Group II, in comparison to Group I, the need for ICU admission was significantly higher; 69.0% compared to 51%, $P = 0.009$, there was no between-groups significant difference regarding primary safety outcomes (relative risk [RR] = 0.706 with 95% confidence interval [CI] ranging from 0.356 to 1.4. $P = 0.315$), hypotension required intervention ($P = 1.0$) and myocardial injury ($P = 0.315$) [Table 3].

Regarding blood pressure posttherapy, SBP and DBP were significantly lower in Group I compared to Group II ($P = 0.001$, 0.012, respectively) as illustrated in [Table 3].

The need for ET intubation showed no significant differences between both the study groups (RR = 0.8 with 95% CI ranging from 0.395 to 1.622. $P = 0.535$). In Group II, compared to Group I, the secondary outcomes were significantly higher; 72% compared to 56%. RR for the secondary outcome between both groups = 0.495 with a 95%**,** CI ranging from 0.275 to 0.892, *P* value of 0.018. In Group II, the mean length of mechanical ventilation was significantly higher (2 days) than in Group I (1.4 days), $P = 0.006$ [Table 4].

In comparing Group 1 with Group 11, Group I showed a significant reduction in the ICU admission rate 27% ($P = 0.001$).

In this study, in group I, the median initial troponin was significantly higher (0.145) than Group II (0.065), $P < 0.001$.

Regarding adverse effects, hypotension requiring intervention was reported in two patients in both groups ($P = 1.0$) and myocardial injury (Group I 12%, Group II 17%, $P = 0.315$). No neurological complications were reported. No in-hospital mortality was reported.

Discussion

This research evaluated the effectiveness and safety of intermittent bolus versus continuous nitroglycerin infusion for managing acute hypertensive heart failure.

In the current study, the prevalence of hypertensive patients was significantly higher in Group I (88.0%) compared to Group II (77.0%), $P = 0.041$.

Dyslipidemia was found in 30% and 66% of patients in Groups I and II, respectively, $P < 0.001$. The prevalence of known COPD patients was significantly higher in Group I (27.0%) compared to Group II (15.0%), $P = 0.037$. No statistical differences were found between the study groups regarding diabetes mellitus, smoking, CAD history, coronary intervention history, and known CKD.

Table 1: General characteristics in both group

	Group I (*n*=100)	Group II (*n*=100)	*P*
Age (years), mean±SD	57±12	58±8	0.502
Gender, *n* (%)			
Males	47 (47.0)	46 (46.0)	0.887
Females	53 (53.0)	54 (54.0)	
Diabetes mellitus (yes), *n* (%)	34 (34.0)	36 (36.0)	0.767
Hypertension (yes), *n* (%)	88 (88.0)	77 (77.0)	0.041
Smoking (yes), *n* (%)	33 (33.0)	35 (35.0)	0.765
Known dyslipidemia (yes), *n* (%)	30 (30.0)	66 (66.0)	<0.001
PH of CAD (yes), *n* (%)	17 (17.0)	18 (18.0)	0.852
PH of coronary interventions (yes), *n* (%)	11 (11.0)	14 (14.0)	0.521
De-novo HF (yes), *n* (%)	3 (3.0)	5 (5.0)	0.471
Type of intervention, *n* (%)			
PCI	6 (54.5)	12 (85.7)	0.177
CABG	5 (45.5)	2 (14.3)	
Known COPD (yes), *n* (%)	27 (27.0)	15 (17.0)	0.037
Known CKD (yes), *n* (%)	13 (13.0)	10 (10.0)	0.506
BMI (kg/m^2), mean±SD	27±3.12	26.29±3.21	0.113

Independent *t*-test or Chi-square test was used for numerical and categorical data, respectively. SD: Standard deviation, CAD: Coronary artery disease, PH: Past history, PCI: Percutaneous coronary intervention, CABG: Coronary artery bypass graft, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, BMI: Body mass index, HF: Heart failure

Our results were also comparable with Özlek *et al*.,[6] (gender disparities in heart failure with mid-range and preserved ejection fraction). In addition, they were comparable with the Swedish Heart Failure Registry, which included over 18,000 patients with heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF). 78% of patients had hypertension, 33% of patients were smokers, 27.7% were diabetics, 29.5% had hyperlipidemia, 14.8% of patients had COPD, 15% had CKD, and 29.5% had coronary disease.

According to Wilson *et al*.,[7] who studied the bolus nitroglycerin use in acute hypertensive heart failure patients for prevention of ICU admission, patients with a history of hypertension who received combined therapy were significantly higher than patients who received bolus or continuous nitroglycerin therapy (87.6 vs. 81.5, and 81.5%, $P = 0.04$). Known COPD patients who received bolus therapy were significantly higher in number than patients who received bolus or continuous nitroglycerine therapy (29.8 vs. 15.4, and 13.5%, $P = 0.002$). No significant differences were reported between patients who received bolus nitroglycerin therapy, continuous nitroglycerin infusion, and combined therapy as regards age, gender, diabetes mellitus, history of CAD, and known CKD.

In this study, compared to group II, significantly higher mean SBP and mean respiratory rate were observed in Group I. No statistical differences between groups in terms of DBP and pulse oxygenation were observed.

This was disconcordant to Wilson *et al*.,[7] who found that initial SBP and DBP were significantly higher in the combined group, and there was no statistical difference between the IV nitroglycerine bolus and continuous infusion

Table 2: Clinical data and medication history in both groups

	Group I (*n*=100)	Group II (*n*=100)	*P*
SBP (mmHg), mean±SD	193±19	185±15	0.001
DBP (mmHg), mean±SD	103±8	103±8	0.854
HR (bpm), mean±SD	106±11	101±9	0.170
Pulse oxygenation (%), mean±SD	86±3	86±3	0.459
Respiratory rate (cycle/min), mean±SD	36±3	35±4	0.049
Initial serum creatinine (mg/dl), median (range)	1.1 (0.5-3.6)	1.1 (0.6-3.9)	0.221
Initial troponin (ng/ml), median (range)	0.145 (0.01-0.32)	0.065 (0.013-0.5)	<0.001
Baseline EF (%), mean±SD	47±12	49±12	0.149
ACEIs/ARBs (yes), *n* (%)	45 (45.0)	41 (41.0)	0.568
Digoxin (yes), *n* (%)	8 (8.0)	5 (5.0)	0.39
Beta-blockers (yes), *n* (%)	59 (59.0)	42 (42.0)	0.016
Nitrates (yes), *n* (%)	11 (11.0)	12 (12.0)	0.825
Aspirin (yes), *n* (%)	29 (29.0)	29 (29.0)	1
Loop diuretics (yes), *n* (%)	44 (44.0)	32 (32.0)	0.08
Nonloop diuretics (yes), *n* (%)	8 (8.0)	6 (6.0)	0.579
MRA (yes), *n* (%)	9 (9.0)	5 (5.0)	0.268

Independent *t*-test or Mann-Whitney U-test was used for numerical data. Chi-square test was used for categorical data. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, EF: Ejection fraction, ACEIs: Angiotensin-converting enzyme inhibitors, ARBs: Angiotensin receptor blockers, MRA: Mineralocorticoid receptor antagonists, bpm: Beat per minute, SD: Standard deviation

Table 3: Primary efficacy and safety outcome in both groups

	Group I (*n*=100)	Group II (*n*=100)	*P*
Primary safety outcomes (yes), *n* (%)	12 (12.0)	17 (17.0)	0.315
Need for ICU admission (yes), *n* (%)	51 (51.0)	69 (69.0)	0.009
Total length of hospital stay (days), mean±SD	4.3±1.1	5.4±1.2	<0.001
Posttherapy SBP (mmHg), mean±SD	132.7±11.38	138.1±12.42	0.001
Posttherapy DBP (mmHg), mean±SD	81.29±8.12	84.13±7.65	0.012
Neurological complications (yes), *n* (%)	0	0	-
Hypotension requiring intervention (yes), *n* (%)	2 (2.0)	2 (2.0)	1
Myocardial injury (yes), *n* (%)	12 (12.0)	17 (17.0)	0.315

Chi-square or Fisher's exact test was used. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SD: Standard deviation, ICU: Intensive care unit

Table 4: Secondary outcomes in both groups

	Group I (*n*=100)	Group II (*n*=100)	*P*
Secondary outcomes (yes), *n* (%)	56 (56.0)	72 (72.0)	0.018
Need for BiPAP (yes), *n* (%)	26 (26.0)	25 (25.0)	0.871
Duration of BiPAP (h), median (range)	0 (0-13.2)	0 (0-23)	0.666
Need for mechanical ventilation (yes), *n* (%)	9 (9.0)	10 (10.0)	0.809
Length of mechanical ventilation (days), mean±SD	1.4±0.5	2±0.4	0.006
Need for ET intubation (within 6 h) (yes), *n* (%)	12 (12.0)	15 (15.0)	0.535
Worsening of renal functions (yes), *n* (%)	10 (10.0)	13 (13.0)	0.506
In-hospital mortality (yes), *n* (%)	0	0	-

Independent *t*-test or Mann-Whitney U-test was used for numerical data. Categorical data were compared using Chi-square test. BiPAP: Bi-level positive airway pressure, ET: Endotracheal tube, SD: Standard deviation

groups (206 [186–231] vs. 186 [169–212] and 184 [159–210] respectively, $P < 0.001$).

Similarly, the Group I median initial troponin was significantly higher (0.145) than Group II (0.065), $P < 0.001$. This was concordant with Wilson *et al*.,[7] who found that initial troponin was significantly higher in Group I (0.11) in comparison to Group II (0.06) and Group III (0.09), $P < 0.001$. This may be because the study was randomized, so there were some imbalances between groups in baseline criteria, which could explain the finding that at baseline, troponin was higher in Group I than Group II.

There was no significant difference as regard to mean baseline EF between the two groups, according to this study, 47% and 49%, respectively, $P = 0.149$. This was in agreement with Özlek *et al*.[6] as the median EF was 45% in the studied cases. While in Wilson *et al*.,[7] EF was 30% and 35% in Groups I and II, respectively, and no significant difference was noted between the three groups regarding mean baseline EF ($P = 0.23$).

In this study, beta-blockers use in Group I was significantly higher (59.0%) in comparison to group II (42.0%), $P = 0.016$. No significant differences were noted between the rest of the clinical data and medications (angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ARBs), digoxin, nitrates, aspirin, or loop diuretics).

This was concordant with Wilson *et al*.,[7] who found that previous usage of B-blockers was higher in Group I in comparison to Group II and Group III ($P = 0.07$).

Importantly, ET intubation showed no significant difference between both groups (RR = 0.8 with 95% CI ranging from 0.395 to 1.622, $P = 0.535$), primary safety outcomes (RR = 0.706 with 95% CI ranging from 0.356 to 1.4, $P = 0.315$), hypotension requiring intervention ($P = 1.0$), and myocardial injury (Group I 12%, Group II 17%, $P = 0.315$).

These results were concordant to Wilson *et al*.,[7] who stated no significant difference between the IV nitroglycerin bolus and continuous infusion as regard to hypotension requiring intervention (1.9% vs. 1.3%, $P > 0.05$) and myocardial injury (12.4% vs. 17.2%, $P > 0.05$).

On the other hand, Levy *et al*. studied severe decompensated heart failure treatment with intravenous high-dose nitroglycerin.[5] Twenty-nine patients received a titratable nitroglycerin infusion and were given a high-dose nitroglycerin bolus (2 mg). Every 3 min, repeated high-dose nitroglycerin was allowed, up to total of 10 doses (Group I), and 45 patients were treated without high-dose nitroglycerin (Group II). Levy *et al*. found that ET intubation need in group II was higher than in Group I (26.7% and 13.8%, respectively).[5]

In our study, secondary outcomes in Group II were significantly higher (72.0%) than in Group I (56.0%) (RR = 0.495 with a 95% CI ranging from 0.275 to 0.892 and $P = 0.018$). The need for ICU admission in Group II (69.0%) was significantly higher than Group I (51.0%), $P = 0.009$. In Group II, the mean length of mechanical ventilation was significantly higher (2 days) than Group I (1.4 days), $P = 0.006$. The mean total length of hospital stay in Group II was significantly higher (5.4 days) than Group I (4.3 days), $P < 0.001$.

Similarly, Wilson *et al*.[7] found that patients receiving only a nitroglycerin bolus were unlikely to need ICU admission (48.4% for a bolus compared to 68.7% and 83% for infusion and combination, respectively, $P = 0.0001$). Furthermore, the median hospital stay was significantly shorter (3.7 days for bolus compared to 4.7 days and 5 days for infusion and combination, respectively, $P = 0.2$). The duration of ICU LOS showed no significant differences among the study groups. This was also concordant with Levy *et al*.,[5] who found that the need for ICU admission in Group II was higher than Group I (80% and 37.9%, respectively).

In our study, in Group II, the mean length of mechanical ventilation was significantly higher (2 days) than Group I (1.4 days), $P = 0.006$. This contrasted with Wilson *et al*.,[7] who found that mechanical ventilation rates were comparable, but in the combination category, a tendency toward higher rates was noticeable (16.9% in the combination group compared to 8.9% and 8.8% in the bolus and infusion groups, respectively).

No significant difference was noted between groups regarding renal function worsening, the need for BiPAP, the duration of BiPAP (hours), and the need for mechanical ventilation. Wilson *et al*. had a similar observation as no significant difference was noted between groups as regards renal function worsening, need for BiPAP, duration of BiPAP (hours), and need for mechanical ventilation.[7] This was dis-concordant with Levy *et al*.,[5] who found that the need for BiPAP ventilation in group II was higher than Group I (20% and 6.9%, respectively). Furthermore, Cotter *et al*.,[8] who compared the effectiveness of high-dose isosorbide dinitrate with low-dose furosemide versus high-dose furosemide with low-dose isosorbide dinitrate in patients with a confirmed diagnosis of pulmonary edema. Patients who were admitted to the ED with signs of congestive heart failure received oxygen therapy at a rate of 10 liters/min, in addition to furosemide 40 mg and morphine 3 mg IV. Mechanical ventilation was a decision in 7 (13%) out of 52 patients who received high-dose nitrates and 21 (40%) out of 52 patients who received high-dose diuretics, with a $P = 0.004$.

Limitations

The following were some of the study's limitations: The results were from a single medical center and did not include follow-up for patients. Patients in our sample indicated less use of medical treatment for hypertension that has been recommended by guidelines, such as ARBs, angiotensin-converting enzyme inhibitors, loop diuretics, and β-blockers.

Conclusion

Nitroglycerin intravenous boluses were associated with fewer ICU admissions and a shorter LOS in the hospital as opposed to ordinarily infusion therapy. In addition, the mean mechanical ventilation duration was slightly shorter in bolus group in comparison to continuous infusion group. Furthermore, the safety and efficacy of the bolus method were comparable with the conventional infusion therapy. Finally, continuous nitroglycerin infusion use in AHF management is being questioned.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

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

Adem Aktan, Tuncay Güzel[1], Bayram Arslan[2], Mehmet Özbek[3], Muhammed Demir[3], Burhan Aslan[1]

Department of Cardiology, Mardin Training and Research Hospital, Mardin, [1]Department of Cardiology, Health Science University, Gazi Yaşargil Training and Research Hospital, [2]Department of Cardiology, Ergani State Hospital, [3]Department of Cardiology, Dicle University Faculty of Medicine, Diyarbakır, Turkey

ORCID:

Adem Aktan ORCID: http://orcid org/0000-0003-0505-9784
Tuncay Güzel ORCID: http://orcid org/0000-0001-8470-1928
Bayram Arslan ORCID: http://orcid org/0000-0003-2984-9094
Mehmet Özbek ORCID: http://orcid org/0000-0003-2243-6190
Muhammed Demir ORCID: http://orcid org/0000-0002-9049-7123
Burhan Aslan ORCID: http://orcid org/0000-0002-8994-7414

Abstract

Introduction: Patients receiving anticoagulant therapy experience a serious problem at a time when the rates of outpatient visits for the international normalized ratio (INR) monitoring are gradually decreasing owing to the risk of virus transmission during the pandemic. The aim of this multicenter study was to investigate how the coronavirus disease 2019 pandemic affected the time in therapeutic range (TTR) value, which shows the use of effective doses of warfarin, and its monitoring in patients using warfarin. **Materials and Methods:** A total of 158 patients with 3 consecutive prepandemic INR levels and at least 3 postpandemic INR levels without time limitation were retrospectively evaluated. TTR values were calculated and the preepidemic and postepidemic values were compared. TTR was obtained using the conventional method. **Results:** The mean preepidemic and postepidemic TTR values were found to be 64.4 (61.8%–67.0%) and 34.9 (30.8%–39.0%), respectively. TTR rate was statistically significantly lower in the postpandemic period than in the prepandemic period ($P < 0.001$). While the prepandemic TTR of 68 (43%) patients was <60, the postpandemic TTR of 125 (79%) patients was <60. **Discussion and Conclusion:** Patients using warfarin were found to have lower TTR values during the pandemic. One of the most important reasons for this result is patients' delayed admission to the hospital due to fear of infection. The importance of regular follow-ups and alternative solutions should be emphasized for the effective treatment of these patients.

Keywords: COVID-19, ınternational normalized ratio, prothrombin time, time in therapeutic range, warfarin

Introduction

In late 2019, a type of virus that was found to cause pneumonia was identified in Wuhan City, Hubei Province of China. This virus was defined as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and in February 2020, the disease was named coronavirus disease 2019 (COVID-19) by the World Health Organization. It became a serious public health issue and was considered a pandemic in a short period. Due to the significant differences in surveillance, diagnostic tests, and practices worldwide, it is thought that there are more cases of COVID-19 than the number of detectable COVID-19 cases.[1] While the medical community was directing their studies and health-care services to this problem in this period, the care and follow-up of patients with chronic diseases could have been endangered.[2] The importance and awareness of social distancing to prevent the spread of COVID-19 are increasing. Especially in his past medical history; patients with prosthetic heart valves, atrial fibrillation, and thromboembolism use warfarin. The international normalized ratio (INR) is of great

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Address for correspondence: Dr. Adem Aktan, Department of Cardiology, Mardin Training and Research Hospital, Mardin 47000, Turkey.
E-mail: dradem21@hotmail.com

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importance for the follow-up of these patients, and routine follow-up requires regular contact. Data obtained from clinical studies show that even in a controlled study environment with adequate monitoring and follow-up and special study nurses, the time in therapeutic range (TTR) values achieved by patients are between 55% and 64%.[3,4] Moreover, a large retrospective cohort study of more than 50,000 patients with atrial fibrillation who were on warfarin showed that only 40,570 patients had adequate INR results to assess TTR, and less than half (41%) of these patients had a TTR value ≥65%.[5] Some studies have also demonstrated the importance of providing service options such as telehealth to maintain social distance while continuing the management of chronic diseases, including the management of anticoagulant therapy.[2,6,7] In a period when the importance of social distance is increasing and the rate of outpatient visits for INR monitoring is decreasing due to the risk of virus transmission, patients receiving anticoagulant therapy experience a serious problem.

The aim of this multicenter study was to investigate how the COVID-19 pandemic affected the TTR value, which shows the use of effective doses of warfarin, and its monitoring in patients using warfarin.

Materials and Methods

While patients were included in the study; they were selected from outpatient clinic applications from four different centers in Turkey and in a single geographical region between May 1 and July 30, 2020. One hundred and eighty-five patients using warfarin for any reason were reviewed retrospectively. Patients were selected sequentially. INR levels and other laboratory parameters of patients were recorded. Prepandemic INR levels and other laboratory parameters of the same patients between May 1 and July 30, 2019, were recorded. Demographic and clinical characteristics of the selected patients, and the reason for using warfarin were obtained from the hospital registry system. Exclusion criteria were as follows: younger than 18 years old, using warfarin less than 2 years, patients with no follow-up data, pregnancy, patients on routine hemodialysis, and active malignancies. In the prepandemic period, 3 consecutive INR levels were recorded at the time of admission to the hospital at periodic intervals of 2 or 3 weeks. In the pandemic period, admissions to hospitals were somewhat less frequent. Furthermore, according to the course of the pandemic, admissions to hospitals were irregular. Therefore, INR levels could not be reported at frequent and regular periodic intervals. During the pandemic period, the 3 INR levels obtained during the time the study was determined were recorded. One hundred and fifty-eight patients who met the criteria were included in the study. Twenty-seven patients were excluded from the study. TTR values were calculated and the prepandemic and postpandemic values were compared. Percentage of time in the therapeutic INR range was calculated according to the Rosendaal method, assuming changes between consecutive INR measurements were linear with time.[8] The study was conducted in accordance with the principles of the Helsinki Declaration (2013) and the study protocol was approved by the local ethics committee.

Statistical analysis

IBM SPSS version 24.0 software package was used for analyses. The histogram and Shapiro–Wilk test were used to confirm the normal distribution of the data. Baseline continuous variables were presented as mean ± standard deviations or median and first and third quartiles (Q1-Q3) depending on the distribution of data. Wilcoxon test was used for two measurements of dependent variables. Categorical variables were expressed as frequency and percentage. A $P < 0.05$ was considered statistically significant for all tests.

Results

The mean age of 158 patients included in the study was 52.6 ± 14.3 years, and 87 (55.1%) of them were females. Forty-three patients (27.2%) were receiving warfarin therapy for AVR, 52 patients (32.9%) for MVR, 15 patients (9.5%) for aortic valve replacement + mitral valve replacement (AVR + MVR), 3 patients for deep vein thrombosis, 3 patients for pulmonary embolism, 36 patients for atrial fibrillation, and 6 patients for other reasons [Table 1]. The mean prepandemic and postpandemic TTR were found to be 64.4 (61.8%–67.0%) and 34.9 (30.8%–39.0%), respectively. TTR rate was statistically significantly lower in the postpandemic period than in the prepandemic period ($P < 0.001$). While the prepandemic TTR of 68 (43%) patients was <60, postpandemic TTR of 125 (79%) patients was <60. There was no statistically significant difference between the patients' prepandemic and postpandemic glucose, creatinine, aspartate transaminase, alanine transaminase, leukocyte, hematocrit, platelet, albumin, and lactate dehydrogenase values [Table 2].

Discussion

In this study, we examined the effect of the COVID-19 pandemic on TTR rates of patients with chronic warfarin use who presented to the outpatient clinics of 5 different health institutions. We found that patients had significantly lower TTR rates during the pandemic period compared to the prepandemic period. We are of the opinion that the most important reason for this result is the fear of viral transmission, national restrictions, and changing health-care priorities during the pandemic period, which affected outpatient visits. In a recent study by Emren *et al*., they found the mean TTR value during the COVID-19 pandemic to be significantly lower than during the pre-COVID-19 pandemic period. Furthermore, in this study, the vast majority of patients did not seek medical help even in case of bleeding.[9] In this respect, the results of the study also support our study. Restriction of access to care for patients in need of care with warfarin use also constituted a serious problem in this period. In addition, the change in eating habits during the pandemic, sleep, and stress disorders during the quarantine period may have also affected this situation. Furthermore, it can be thought that the lack of access

Table 1: Warfarin therapy indications and demographic data of patients

Parameters	All Patients
Age, years	52.6±14.3
Gender, *n* (%) (female-male)	87 (55.1)-71 (44.9)
MVR, *n* (%)	52 (32.9)
AVR, *n* (%)	43 (27.2)
MVR + AVR, *n* (%)	15 (9.5)
DVT + pulmonary embolism, *n* (%)	6 (3.8)
AF, *n* (%)	36 (22.8)
Other, *n* (%)	6 (3.7)

MVR: Mitral valve replacement, AVR: Aortic valve replacement, DVT: Deep vein thrombosis, AF: Atrial fibrillation

Table 2: Time in therapeutic range and other laboratory parameters of patients

	Pre-COVID-19	Post-COVID-19	*P*
TTR, %	64.4 (61.8-67.0)	34.9 (30.8-39.0)	<0.001
Glucose, mg/dl	106.7±29.8	104.3±27.5	0.677
Creatinine, mg/dL	0.83±0.5	0.81±0.5	0.321
AST, U/L	24 (19-30)	25 (21-28)	0,224
ALT, U/L	20 (15-29)	22 (19-27)	0,251
Leukocyte, 10^3/uL	8.02±2.25	7.90±2	0.152
Hematocrit	41.2±5.4	38.3±4.7	0.013
Platelet, 10^3/uL	253±71.7	249±69.5	0.183
Albumin, g/L	40±5.5	42±4.8	0.304
LDH, U/L	300±120.3	295±118.4	0.181

TTR: Time in therapeutic range, AST: Aspartate transaminase, ALT: Alanine transaminase, LDH: Lactate dehydrogenase

to health-care services due to the spread of the COVID-19 pandemic among laboratory technicians may have led to this situation. However, we did not encounter such a problem in the centers included in the study. There was no difference in the test kit and tubes, with which INR levels were measured, between the prepandemic and postpandemic periods.

We do not have data on whether these patients were exposed to the COVID-19 virus during their follow-ups. The patients included in the study during the pandemic period might have had COVID-19 infection during the period of INR follow-up, inducing coagulopathy.[10,11] We know that warfarin is eliminated through hepatic metabolism and that acute and chronic liver diseases affect INR levels. We could not definitively exclude whether patients developed any additional liver disease during the postpandemic INR follow-up intervals. We believe that the use of prophylactic drugs that have not yet been scientifically proven, and the use of food supplements to strengthen the immune system during the pandemic and quarantine period may also interact with warfarin.

If there are no obstacles such as health policies and persuasion of the patient in such pandemic and emergency situations, switching to new generation oral anticoagulants can be considered for eligible patients. For patients who have to use warfarin, safe health-care service conditions of health centers can be supported by increasing measures such as the use of masks, social distancing, and personal hygiene. A separate unit can be established in hospitals for patients to be provided with INR monitoring service so that INR can be monitored more frequently and the time spent in health institutions can be minimized. Another solution suggestion is to take blood samples from the patients at home and carry out the INR monitoring without visiting health institutions.[12] However, we are of the opinion that it will not be effective in terms of both establishing suitable conditions for delivery and transfer of the samples to health institutions. It is important to provide telemedicine health-care services to patients in such periods. It is also important to increase the patient adherence to warfarin therapy, to inform the patients correctly and safely, and to make appointments for face-to-face meetings in health institutions in safe conditions when necessary. In our study, we attempted to determine the results of INR follow-ups and TTR rates and the reasons for the lack of follow-up in this specific patient population during the pandemic and emergency situations; however, there is a need for further studies in terms of clarification of these reasons and solution suggestions.

Study limitations

The study has several limitations. First, the study may have led to subjective and not generalizable results since it had a retrospective design and the centers where the study was conducted included a relatively small-scale geographical region and race. The fact that the data obtained in this study were based on hospital records and patient information may have led to biased and inaccurate results. Another important limitation was that TTR calculations in a short period such as 3 months may be less informative than 6-or 12-month TTRs.[13]

Conclusion

Patients using warfarin were found to have lower TTR values during the pandemic. One of the most important reasons for this result is patients' delayed admission to the hospital due to fear of infection. The importance of regular follow-ups and alternative solutions should be emphasized for the effective treatment of these patients as TTR rates are associated with increased bleeding or thrombosis.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

An Unusual Co-occurrence of Lown-Ganong-Levine Syndrome with Neonatal Focal Lipomatous Hypertrophy of Interatrial Septum with Patent Foramen Ovale

Debasish Das, Satya Mishra, Tutan Das, Subhas Pramanik

Department of Cardiology, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India

ORCID:

Debasish Das: http://orcid org/0000-0002-6228-9554

Tutan Das: http://orcid org/0000-0003-0634-5299

Abstract

We report an extremely rare co-occurrence of focal lipomatous hypertrophy of the interatrial septum (LHIS) with patent foramen ovale (PFO) in a neonate and electrocardiogram evidence of Lown-Ganong-Levine syndrome (LGL). Although atrial arrythmias in the form of supraventricular tachycardia like atrial premature contractions, atrial fibrillation, and atrioventricular block have been described in lipomatous hypertrophy interatrial septum, co-occurrence of LGL syndrome with LHIS has not been described in literature so far. Baby presented in the cardiology outpatient department for presurgical cardiological evaluation of congenital hydrocephalus. Typically, LHIS spares fossa ovalis and affects both side of the interatrial septum making interatrial septum dumbbell shaped. There is even no literature description of focal hypertrophy of interatrial septum in early infancy and child hood including neonatal period. Our case is a unique illustration of a rare co-occurrence of LGL syndrome in focal lipomatous hypertrophy of interatrial septum in a neonate with PFO.

Keywords: Focal, interatrial septum, lipomatous hypertrophy, patent foramen ovale

Introduction

Lipomatous hypertrophy of interatrial septum (LHIS) is characterized by benign fatty infiltration of the interatrial septum. It is commonly found in the elderly and obese patients as an incidental finding during echocardiography. The prevalence of LHIS is approximately between 1% and 8% in general population with higher incidence in women.[1] The incidence of LHIS increases with age, body mass, and chronic corticosteroid therapy. Focal LHIS in a neonate with LGL syndrome has not been described in literature so far. Both conditions are usually incidentally detected and are asymptomatic in nature.[2] Although focal hypertrophy of interatrial septum can present with atrial arrhythmias or superior vena cava syndrome if superior vena cava is encased, co-occurrence of LGL with LHIS has not been described. Histologically, LHIS is characterized by fatty infiltration between the myofibers of the interatrial septum.[3] Lipomatous hypertrophy of the interatrial septum typically occurs anterior to the fossa ovalis and it characteristically spares it.[3] It involves both sides of the interatrial septum with a characteristic dumbbell-shaped appearance of interatrial septum. Rarely, it also presents like a cardiac mass. The present case is unique to illustrate a focal LHIS involving the lower half of the septum only.

Address for correspondence: Dr. Debasish Das, Department of Cardiology, All India Institute of Medical Sciences, Bhubaneswar - 751 019, Odisha, India.
E-mail: dasdebasish54@gmail.com

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Case Report

A 2-day-old new born baby boy presented to the cardiology outpatient department for presurgical routine cardiological evaluation of congenital hydrocephalus secondary to aqueductal stenosis. The child was term baby with normal birthweight of 2.8 kg without any history of perinatal asphyxia. The child was born out of nonconsanguineous marriage with no maternal history of exanthematous fever suggestive of congenital TORCH infection. Cardiovascular system examination was within normal limit. Electrocardiogram (EKG) revealed the presence of sinus rhythm with heart rate of 128 beats/min with the presence of short PR interval of 82 msec without the presence of delta wave suggestive of Lown-Ganong-Levine (LGL) syndrome [Figure 1]. ECG of Wolf Parkinson White (WPW) syndrome reveals short PR interval with delta wave and Mahaim fiber presents with only delta wave without the presence of short PR interval. Paroxysmal junctional re-entrant tachycardia remains a specific entity in the neonatal period with presence of short PR and delta wave and EKG evidence of right posteroseptal pathway, presenting as incessant tachycardia more than 12 h and characteristic initiation with a sinus beat. Echocardiography revealed the presence of focal echoluscent bulge below fossa ovalis suggestive of LHIS [Figure 2] without the presence of any capsule. Baby had an associated patent foramen ovale of 2 mm size with left to right shunt [Figure 3]. Interestingly, it spared the fossa ovalis along with upper half of the septum [Figures 4 and 5] and septum did not appear dumbell shaped. Baby had intact interventricular septum, had no associated patent ductus arteriosus or coarctation of aorta with normal biventricular function. Serum electrolytes, blood glucose, calcium, magnesium, and serum thyroid-stimulating hormone levels were within normal limit. Baby boy had LGL syndrome which is eventually rare to encounter in routine clinical practice and presence of LGL syndrome in LHIS is not yet described. We encountered a case of focal LHIS which is extremely rare to observe in a neonate; paradoxic to the rule that incidence of incidental detection of LHIS increases with age.

Discussion

LHIS is defined as fatty infiltration of the interatrial septum which is rare to encounter in routine clinical practice and seen in adults. It was first described by American pathologist John T Prior (1917-2007) at Syracuse College of Medicine, New York in 1964.[4] The incidence of LHIS increases with age. Characteristically, LHIS spares fossa ovalis and the septum looks dumbell shaped. Diagnosis of LHIS is made in computed tomography (CT) when a smooth well-marginated expansion of the interatrial septum is identified exceeding 2 cm in transverse diameter in adults. Cardiac MRI delineates LHIS with characteristics bilobar interatrial septal thickening with homogeneous high signal intensity similar to subcutaneous fat tissue. T_1 weighted MRI reveals high signal, T_2 weighted non-fat suppressed MRI reveals high signal, and T_2 fat suppressed MRI reveals low signal. Fatty nature of LHIS is well appreciated in fat-suppressed imaging. Fluro deoxyglucose (FDG) positron emission tomography reveals a moderate degree of FDG uptake in lipomatous hypertrophy. Previously, it was thought due to metabolic activity of brown adipose tissue,[5,6] recently, it is attributed to the presence of subclinical inflammation in the adipose tissue.[7]

Only differential diagnosis that exists in a neonate is a cardiac lipoma which has a characteristic encapsulated appearance in echocardiography. Although LHIS most often behaves as a benign anomaly, it may present with severe superior vena cava obstruction or intractable arrhythmia in which cases surgical excision with reconstruction of the interatrial septum is sometimes considered. As lipomatous hypertrophy occurs in the area of anterior and middle internodal pathways, their interruption could be the major reason for occurrence of supra ventricular arrhythmias in the form of atrial premature contractions, atrial fibrillation, atrioventricular block, syncope, and sudden cardiac death.[8,9] Lipomatous septal hypertrophy if very large gives rise to obstructive flow symptoms including dyspnea.[1,10]

Pathologists coin lipomatous hypertrophy as "lipomatous hyperplasia" because of unencapsulated deposition of mature adipose tissue with cells resembling brown fat with vacuolated cytoplasm with more centrally placed nuclei.[11,12] Typically, the fatty mass extends from above the aortic root to the level

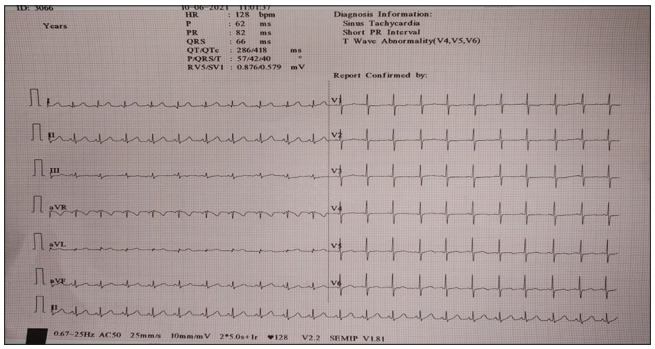


Figure 1: Lown-Ganong-Levine syndrome (PR interval 82 ms without the presence of delta wave)

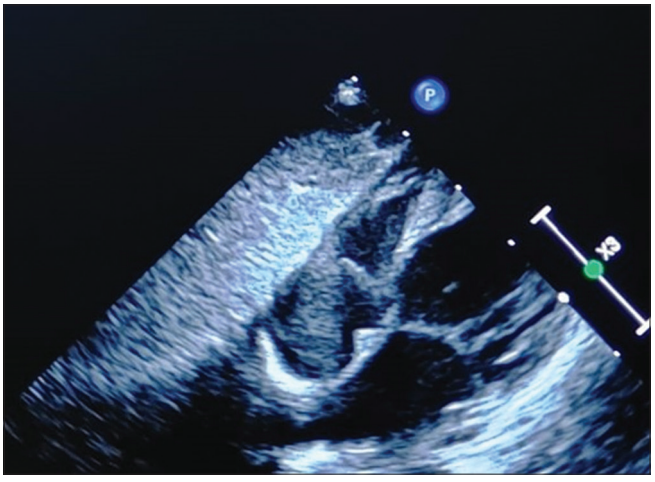


Figure 2: Focal lipomatous hypertrophy of lower IAS

of coronary sinus[13] but interestingly, in our case, it was a focal fatty infiltration limited to the lower interatrial septum only. Co-occurrence of LGL syndrome with focal LHIS has not been described in the literature so far.

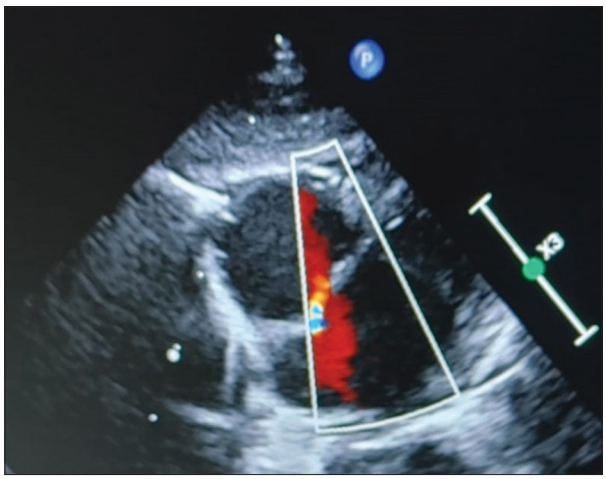


Figure 3: Presence of patent foramen ovale with L-R shunt

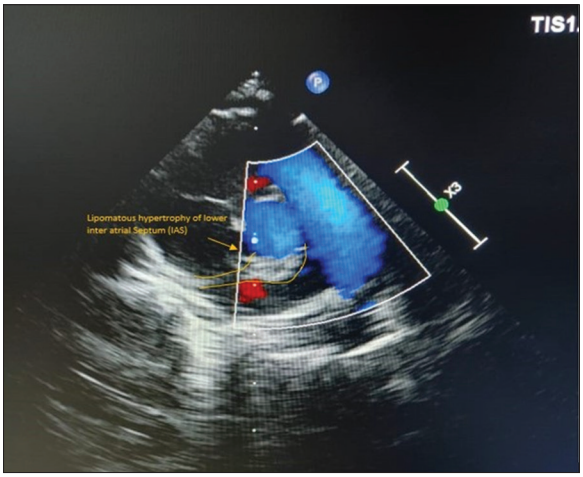


Figure 4: Lipomatous hypertrophy of lower inter atrial septum (IAS) in parasternal short axis (PSAX) view

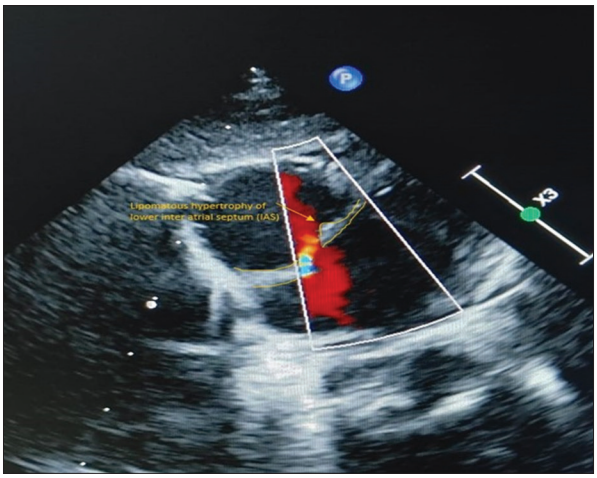


Figure 5: Lipomatous hypertrophy of IAS in subcostal modified apical 4 chamber view

LGL syndrome is a clinical syndrome consisting of paroxysms of tachycardia with ECG evidence of short PR interval (<120 ms) with normal QRS duration through atriohisian accessory pathway or James fibers. Even there is not any consensus about it, clinical tachycardia should be present for LGL diagnosis and otherwise short PR interval without delta wave is named as enhanced av nodal conduction. Clerc, Levy and Critesco in 1938 first described the occurrence of frequent paroxysms of tachycardia in patients with short PR interval and normal QRS duration.[14] This syndrome was again described by LGL in 1952 forming todays eponym.[15] James described atriohisian fibers originating in the low atrium and terminating in the His bundle.[16] Criteria for LGL include a PR interval <120 ms with normal QRS complex duration of <120 ms.[17] The most common tachycardia that occurs in LGL syndrome is atrioventricular nodal re-entrant tachycardia followed by accessory pathway-mediated tachycardia, atrial fibrillation, atrial flutter, and ventricular tachycardia.[18,19]

Lown and associates described tachyarrhythmia in 17% of patients with LGL syndrome.[15] The frequency of LGL is approximately 0.5% of the adult population. The incidence of paroxysmal supraventricular tachycardia in LGL syndrome appears to be 11%.[20] The average age of onset of tachycardia in LGL syndrome is 33.5 years.[20] The newborn had no documented supraventricular tachycardia in the past 24 h. No studies have shown an increased rate of sudden death or decreased survival in patients with LGL syndrome. They have a higher risk of developing tachyarrhythmia with sympathomimetics which is commonly used in children in cough remedies.[20] LGL described six patients with paroxysmal atrial fibrillation two of whom developed sudden cardiac death due to faster conduction through James fiber to the ventricle causing ventricular fibrillation.[15]

Adult patients are advised not to drive or operate public transport for 6 months after the most recent episode of syncope. The absence of a rapid heart rate does not exclude LGL as a possible diagnosis as the tachycardia in LGL is paroxysmal.[20] No specific therapy is indicated although there should be a focus on preventing tachyarrhythmia thhrough the accessory pathway. In acute setting of tachycardia, identifying the cause of tachycardia and controlling the ventricular rate is of utmost importance.[21] Baby was quite asymptomatic, no documented tachycardia in the last 24 h, both LHIS and LGL syndrome are relatively benign and incidentally detected, we manged the baby conservatively and advised the baby to undergo requisite surgery as advised by neurosurgeons.

Conclusion

Our case is unique illustration of co-occurrence of LGL syndrome in a case of LHIS in a neonate. Although both conditions are benign and incidentally detected, it further warrants a close scrutiny in adulthood if at all symptoms in the form of rhythm abnormality occurs. Baby should not be administered sympathomimetics, especially the

cough suppressants as both conditions may precipitate supraventricular tachycardia which can be catastrophic in the presence of accessory James fiber in LGL syndrome with rapid conduction to the ventricles.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that name and initials will not be published and due efforts will be made to conceal patient identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Radial Loop: Can Straightening of the Loop Push the Guiding Catheter? Do We Need to Be More Watchful? A Case Report and Literature Review

Bhupesh Shah, Harshal Shah, Darshil Shah

Department of Cardiology, NHL Municipal Medical College, Ahmedabad, Gujarat, India

ORCID:

Bhupesh Shah: http://orcid org/0000-0001-5059-9291

Harshal Shah: http://orcid org/0000-0002-7655-2632

Darshil Shah: http://orcid org/0000-0003-0328-4689

Abstract

Radial loops are the most common radial anatomical entity for deferring or failure of transradial approach. Complex loops may not straighten immediately after traversing the loop and may take a few minutes to straighten out. Here, we describe a case of a complex radial artery loop encountered during transradial percutaneous coronary intervention. We furthermore present a literature review and outline tips and techniques to successfully traverse the radial loop.

Keywords: Access site, dissection, guide catheter, percutaneous coronary intervention, radial loop

Introduction

Transradial access for coronary angiography and percutaneous coronary intervention (PCI) has rapidly emerged as the predominant access route favored by several operators worldwide. The paradigm shift witnessed this past decade has emanated from lower access site complications, increased patient comfort, and earlier ambulation as compared to traditional transfemoral intervention.[1] However, in some cases, tracking and navigating hardware through radial artery vasculature prove challenging due to smaller radial artery diameter, or complex, variable, or anomalous anatomy.[2] Radial loop is one of the more challenging coronary anomalies encountered and is synonymous with procedural failure. Its prevalence ranges from 0.8% to 2.3%.[3] We describe one such challenging case of a radial loop encountered through transradial PCI.

Case Report

A male patient presented with unstable angina. Coronary angiography revealed 95% occlusion in left anterior descending (LAD) coronary artery, 70% occlusion in the obtuse marginal branch, and a mild diffuse lesion in right coronary artery [Figure 1a and b]. However, while pushing the guiding catheter through the radial artery, a radial loop was encountered [Figure 2a and b] and attempts were made to straighten the catheter [Figure 1c]. A 1.5-mm GLIDEWIRE Baby-J Hydrophilic Coated Guidewire (Terumo Interventional Systems) successfully crossed the radial loop. A drug-eluting stent (DES) was implanted in LAD. However, we noticed left main coronary artery (LMCA) dissection. Attempts to straighten the loop might have pushed the catheter into the LMCA causing dissection of the artery. A second DES was deployed from the LMCA to LAD by overlapping with the first DES to treat the dissection. The DES was postdilated. However, the dissection was still visible, so postdilation

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Address for correspondence: Dr. Bhupesh Shah, Department of Cardiology, NHL Municipal Medical College, Ahmedabad - 380 006, Gujarat, India.
E-mail: shahbhupesh@hotmail.com

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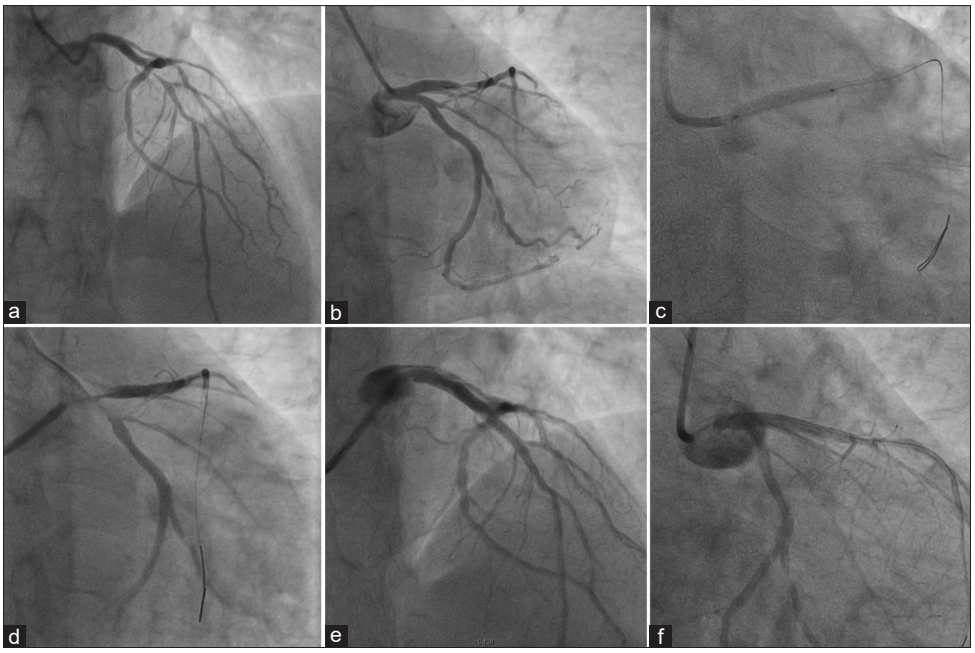


Figure 1: Coronary angiography revealed: (a) 95% occlusion in the left anterior descending coronary artery, (b) 70% occlusion in the obtuse marginal branch, (c) looping of the catheter whilst attempting to straighten the loop, another stent was deployed from left main coronary artery to left anterior descending by overlapping the first stent (d and e) dissection still visible after postdilation, hence another postdilation was performed (f) final thrombolysis in myocardial infarction III flow

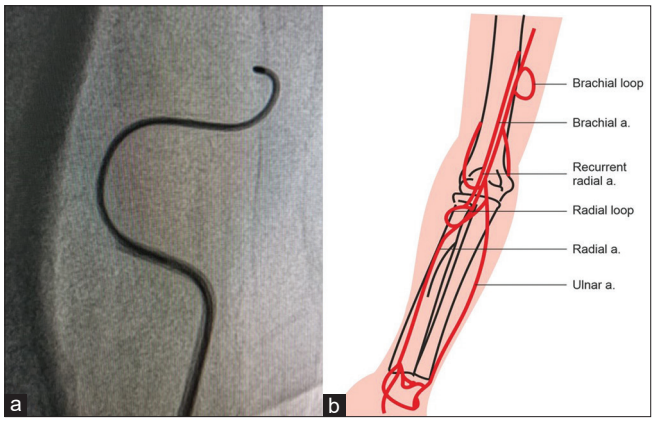


Figure 2: Coronary angiography revealed: (a) A radial loop and (b) schematic vascular anatomy of a radial artery with a radial loop

was performed again [Figure 1d and 1e]. Thrombolysis in myocardial infarction III was achieved, and the patient was discharged 2 days later [Figure 1f].

Discussion

Radial loop is the most encountered anatomical variation responsible for procedural failure even for experienced radial interventionalists. However, with the growing numbers of transradial interventions, interventional cardiologists are bound to face obstacles at various anatomical levels beginning from the radial artery to the coronary artery level, as demonstrated in the present case and Figure 2. We present a case from our institution along with a literature review [Table 1].[1-9] We also outline tips and techniques to successfully traverse the loop.

After obtaining an arteriogram, the first strategy is to traverse the radial loop with specialized wires. If a 0.035"J-wire is unsuccessful, an atraumatic 0.035" wire such as a Wholey guidewire (Medtronic) or Magic Torque guidewire (Boston Scientific Corporation) followed by a 0.014" angioplasty wire or a 0.025–0.035" hydrophilic wire may be attempted. The 0.035" 1.5-mm GLIDEWIRE Baby-J Hydrophilic Coated Guidewire (Terumo Interventional Systems) is a more advanced specialized wire that can also be employed in such cases. This wire provides lubricity of a hydrophilic wire while maintaining safety of a small trackable J-tip. If greater support is necessitated to straighten out the loop, a 4-F multipurpose diagnostic catheter or a hydrophilic catheter, such as a Glidecath Hydrophilic Coated Catheter (Terumo Interventional Systems), can be employed to track over the wire. Furthermore, rotating a low-profile catheter while pullback may straighten the loop.[10]

Mother–daughter technique can be employed if the loop has been crossed with a wire but difficulty straightening out the loop for safe delivery of the diagnostic catheter persists. An earlier method details a pigtail-assisted tracking method. In this method, a 5-F pigtail catheter is loaded in a 6-F guide catheter. The distal pigtail is extended outside the guide and tracked over the wire through the loop. This method circumvents the razor-blade effect of the guide catheter as it passes through the tortuous segment of the radial loop. This avoids dissection in cases where the catheter is aggressively passed through the loop. The protruding pigtail lessens contact between the sharp edge of the guide catheter tip and the vessel wall.[11]

Table 1: Clinical and technical details of other cases of radial loop in recent literature

Year	Author	Gender	Patient age	Anomaly	Challenge	Technique
2002	Esent *et al*.[4]	Male	80	Radial loop	Guidewire blockage	0.035" glidewire used
2003	Barbeau[5]	Male	76	Radial loop	GLIDEWIRE blockage/ perforation	Hydrophilic-coated coronary guidewire
2003	Barbeau[5]	Female	74	Radial loop	GLIDEWIRE blockage/ perforation	Hydrophilic-coated coronary guidewire
2010	Farman *et al*.[6]	Male	60	Radial loop	Guidewire blockage	0.035" guidewire was used to cross the loop
2011	Sarji and Sricharoen[7]	Female	60	Radial loop	Guidewire blockage	Loop successfully negotiated with a 0.035″×150 cm GLIDEWIRE
2012	Chitsaz *et al*.[3]	Male	90	Radial loop and perforation at vortex of radial loop	Guidewire blockage	0.035" GLIDEWIRE used
2014	Deora *et al*.[1]	Female	69	Small caliber radial artery with radial loop	Guidewire blockage	Balloon-assisted tracking
2014	Deora *et al*.[1]	Male	63	Radial loop	Guidewire blockage	The loop was crossed with 0.014" BMW PTCA guidewire, followed by balloon-assisted tracking
2014	Patel *et al*.[2]	Male	60	Radial loop	Guide catheter blockage	The loop was crossed with 0.014" BMW PTCA guidewire, followed by balloon-assisted tracking
2015	D'Amario *et al*.[8]	Male	76	Radial loop	Resistance to sheath insertion and catheter blockage	Balloon-assisted tracking
2020	Dossani *et al*.[9]	Male	75	Radial loop	Inability to negotiate with the conventional technique	Microcatheter system with stiff microwire used to navigate and straighten radial loop under road map guidance

BMW: Balance middleweight, PTCA: Percutaneous transluminal coronary angioplasty

The balloon-assisted tracking (BAT) is a technique that may be adopted. This is a technique wherein an inflated percutaneous transluminal coronary angioplasty balloon is partially protruded through the distal end of a guide catheter and deployed at 3 or 6 atm. Low-pressure inflation aids the catheter to negotiate extreme curves and loops. A 1.5-mm balloon is recommended for a 5-F diagnostic or guide catheter, whereas a 2.0-mm balloon is recommended for 6-F guide catheter. Balloons of 15 or 20 mm are sufficient. Once the balloon is partially protruded from the distal end of the catheter and deployed, the entire assembly is advanced over a soft-tipped 0.014" guidewire facilitating smooth and nontraumatic progression through difficult vasculature. The key benefit of BAT is prevention of the "razor effect" of the catheter tip to the radial artery endothelium.[1,2]

Conclusion

Radial loop is a rare, yet challenging anomaly associated with transradial intervention. However, technical difficulties can be overcome with adequate training, specialized wires, and techniques such as pigtail-assisted tracking and BAT. After crossing the loop with a wire, slight pull on the catheter or wire can straighten the loop. However, caution should be taken as straightening the loop may push the guide catheter a little deep into the artery.

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Conflicts of interest

There are no conflicts of interest.

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