Journal of Surgery and Medicine
e-ISSN=2602-2079

Association between SYNTAX II score and Index of electrophysiological balance in patients with stable angina pectoris

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Ethics Committee Approval
All patients gave their informed consent in accordance with a protocol approved by the Ethics Committee of Necmettin Erbakan University, Meram Medical Faculty (date/decision number: 14.04.2021, 2021/3189).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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

Published
2022 March 16

Abstract

Background/Aim: Syntax II scoring system has been established by integrating anatomical features and clinical characteristics of patients in order to achieve better prediction of post-procedural outcomes. On the other hand, its predictive value for the occurrence of life-threatening arrhythmias is inconclusive. Index of cardio electrophysiological balance (iCEB) serve as an ECG based derivative of cardiac wave length and associated with torsades de pointes (TdP) and nontorsadogenic ventricular tachycardia (VT) or ventricular fibrillation (VF). In this study we aimed to investigate the prognostic value of SYNTAX II scoring system for predicting malignant ventricular arrhythmias by using iCEB.
Methods: 297 patients undergoing coronary angiography (CAG) were included in the retrospective cohort study. Patients were divided into two groups based on their calculated SYNTAX Score II. For each group, ECG parameters including heart rate (b.p.m.), QRS interval (ms), QT interval (ms), corrected QT (QT_C) interval (ms), QTc difference (V1-V6), QT/QRS ratio (iCEB) and QT_C/QRS ratio (iCEBc) were analyzed.
Results: According to our study estimated QRS, QT and QTc intervals were signifciantly higher in patients with calculated SYNTAX S II >26 as compared to patients with calculated SYNTAX S II ≤26 (respectively; P=0.001, P=0.014 and P=0.001). In addition, estimated QT/QRS (iECB) and QTc/QRS (iECBc) ratio were significantly lower in patients with calculated SYNTAX S II >26 as compared to those with calculated SYNTAX S II ≤26 (respectively; P=0.002 and P=0.005).
Conclusion: Our data showed that, there was a strong association between $QT_{C,}$ iECB, iECBc and SYNTAX Score II. Therefore, the SYNTAX Score II might be considered as an important tool to predict malignant ventricular arrhythmias.

Keywords: SYNTAX Score II, Index of cardio electrophysiological balance, Electrocardiography

How to cite: Alsancak Y, Sertdemir AL, Duran M, Gürbüz AS, İçli A. Association between SYNTAX II score and Index of electrophysiological balance in patients with stable angina pectoris. J Surg Med. 2022;6(3):386-390.

Introduction

As a result of the Synergy between percutaneous coronary intervention with TAXUS and Cardiac Surgery (SYNTAX) study, researchers aiming to determine whether the percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) was more suitable in patients with coronary artery disease (CAD) requiring revascularization designed a new scoring system [1]. Recent research has shown that patients with left main and multivessel coronary artery diseases who underwent PCI can be evaluated with the SYNTAX scoring system in terms of not only the lesion complexity but also the probability of major cardiovascular events [2]. However, the SYNTAX scoring system is based entirely on the anatomical features of coronary vasculature and lesion properties without putting into consideration clinical variables, making it inefficient [3]. The SYNTAX II scoring system was developed by combining anatomical properties and clinical data of patients to improve the prediction of post-procedural outcomes [4]. Despite the fact that the Syntax II scoring system yields a more accurate and personalized prediction of post-procedural outcomes, its predictive efficacy for life-threatening arrhythmias is unproved.

Recently, a novel noninvasive marker has been introduced that shows the balance between repolarization and cardiac depolarization. The index of cardioelectrophysiological balance (iCEB), which is determined by dividing the QT interval by the QRS duration, is an ECG-based derivative of cardiac wavelength and is linked to torsades de pointes (TdP) and nontorsadogenic ventricular tachycardia (VT) or ventricular fibrillation (VF) [5, 6].

Hence, this retrospective study aimed to research the prognostic importance of the SYNTAX II scoring system in estimating malignant ventricular arrhythmias (VAs) by employing iCEB in stable patients with coronary artery disease.

Materials and methods

Study design

A total of 297 consecutive patients who underwent elective coronary angiography between April and December 2020 at Necmettien Erbakan University Meram Medical Faculty were enrolled in the retrospective study. Chest pain was noted in all patients, and coronary angiography (CAG) was recommended because of objective pieces of evidence of ischemia, such as a positive exercise stress test or radionuclide study positive noninvasive test. We retrospectively analyzed the patients' demographic and clinical data, as well as the indication for the procedure. We excluded the patients with a history of valvular heart disease, hypertrophic, restrictive, and dilated cardiomyopathy, congestive heart failure, left ventricular hypertrophy, vasculitis, history of end-stage renal failure, liver failure, coagulopathy, malignancy, inflammatory disease, pregnancy, use of medications known to have an effect on cardiac conduction (any kind of therapy for chronic obstructive pulmonary disease, antiarrhythmic drugs, non-dihydropyridine calcium channel blockers medication, digitalis, or β-blocker) and the patients with permanent cardiac pacemaker implantation, documented atrial fibrillation (AF), any kind of bundle branch blocks, pre-excitation syndromes, sick sinus syndrome, or atrioventricular block.

Before performing coronary angiography, blood samples were taken from the patients' forearm veins following 12-hour fasting. Full blood count, liver and kidney functions, and lipid profile were all evaluated using routine blood testing. The Cockcroft-Gault formula was employed to calculate the glomerular filtration rate (GFR).

Before the intended procedure, a GE Vingmed Vivid 5 echocardiography device (GE Vingmed Ultrasound, Horten, Norway) was used to perform a comprehensive transthoracic echocardiographic examination in all patients. During the echocardiographic investigation, we took apical 4- and 2-chamber and parasternal long and short-axis images and used continuous-wave, pulsed-wave, and tissue Doppler, M-mode, and 2-D techniques.

An online calculating tool (www.syntaxscore.com) was used to determine the SYNTAX Score II. In a nutshell, this calculation method incorporated anatomical-based Syntax Score I and baseline clinical data (such as age, sex, left ventricle ejection fraction, creatinine clearance, peripheral vascular disease, left main disease, and chronic obstructive pulmonary disease) [4]. Related variables were evaluated and calculated by two blind expert cardiologists who had experience with the website. In this study, patients were split into two groups based on their determined median SYNTAX Score II: Group 1 (patients with a SYNTAX Score II ≤ 26) and Group 2 (patients with a SYNTAX Score II >26). All patients gave their informed consent in accordance with a protocol approved by the Ethics Committee of Necmettin Erbakan University, Meram Medical Faculty (date/decision number: 14.04.2021, 2021/3189).

ECG interpretation

The guidelines of the American Heart Association and the Heart Rhythm Society were used when standardizing and interpreting the ECG parameters [7]. When the patients were lying with the face and torso facing up (supine position), their 12-lead ECGs were recorded at a gain of 10mm/mV and a paper speed of 25mm/s (Nihon Kohden, Tokyo, Japan). In order to diminish the margin of error during the assessment, all ECG recordings were transferred to a digital platform. Subsequently, software (Adobe Photoshop) was used for magnification. For the needed calculations, a suitable ECG was considered at least 10 analyzable leads. Or else, the ECG was seen as inadequate. We analyzed standard ECG parameters such as heart rate (b.p.m.), P wave, QRS interval (ms), QT interval (ms), corrected QT (QTC) interval (ms), QT/QRS ratio (iCEB) and QTC/QRS ratio (iCEBc). A blinded cardiologist performed the ECG measurements. To prevent errors in measurements, the measurements were also confirmed by a second physician. For each lead, a mean value of three measurements was determined. We measured the QT interval from the beginning of the QRS complex to the point at which the tangent of the maximal downslope of the descending limb of the T wave crossed the isoelectric baseline. Later, the Bazett formula: cQT=QT√(R–R interval) was used to correct the QT interval for heart rate. The QTc in lead V6 was subtracted from the QTc in lead V1 to determine the QTc difference (V1-V6). Also, these intervals should be validated as the mean value from at least three to five cardiac cycles [8]. These readings were then used to calculate the iCEB and iCEBc. The intra- and inter-observer coefficients of variation (the SD of differences between two observations divided by the mean value and reported as a percentage) were calculated as 1.0% and 1.6%, respectively.

Statistical analysis

Data analysis was performed using the SPSS software version 24.0 for Windows (SPSS Inc., Chicago, IL, USA). The continuous variables are expressed as mean (SD) while categorical variables as counts and percentages. The distribution of continuous variables was evaluated with the Kolmogorov-Smirnov Test and Shapiro–Wilk tests. The categorical variables were analyzed with the $\chi 2$ test and Fisher's exact test. Normally distributed variables were examined with the student's t-test, whose results were expressed as mean (SD). On the other hand, intergroup comparison of non-normally distributed variables was conducted using the Mann-Whitney U-test. Statistical significance was set at $P<0.05$.

Results

Of a total of 297 patients examined in the first phase, 153 (33% women; mean age: 66.13 (9.76) years) were included in Group 1 (SYNTAX S II ≤ 26) and 144 (44% women; mean age: 68.5 (10.91) years in Group 2 (SYNTAX S II > 26). Table 1 shows the demographic characteristics of the patients. Accordingly, demographic characteristics and baseline laboratory values were similar in both groups. However, Group 2 had more patients with a history of hypertension (HT), peripheral artery disease (PAD), and chronic obstructive pulmonary disease (COPD) (P=0.001). Also, serum creatinine concentrations were significantly higher, and the estimated glomerular filtration rate (eGFR) was lower in Group 2 (P=0.001 for both). As regards the echocardiographic calculations, Group 2 had a significantly lower estimated left ventricular ejection fraction (LVEF) but a significantly higher estimated posterior wall and septum thickness (P=0.001 for both).

Table 1: Demographical characteristic and comparison of parameters between groups

Variables	Study population (n=297)	SYNTAX S II ≤26 group (n=153)	SYNTAX S II >26 group (n=144)	*P*-value
Age, years	65.17 (12)	66.13 (9.76)	68.5 (10.91)	0.459
Men (n, %)	184 (62)	103 (67)	81 (56)	0.063
Hypertension (n, %	200 (67)	86 (52)	114 (79)	0.001
Diabetes mellitus (n, %)	102 (34)	50 (33)	52 (36)	0.535
Smoking (n, %)	174 (59)	102 (67)	72 (50)	0.003
Prior coronary artery disease (n,%)	125 (42)	64 (42)	61 (41)	0.898
COPD, (n, %)	81 (27)	26 (17)	55 (38)	0.019
PAD, (n, %)	31 (10)	11 (7)	20 (13)	0.043
Ejection Fraction, % (n,%)	54.31 (8.5)	57.27 (4.98)	51.17 (10.22)	0.001
Posterior wall thickness (mm)	1.1 (0.11)	1.05 (0.11)	1.14 (0.15)	0.001
Septum wall thickness (mm)	1.13 (0.28)	1.02 (0.12)	1.12 (0.12)	0.001
Hb (g/dL)	13.29 (1.93)	13.65 (1.95)	12.91 (1.85)	0.001
PLT count ($\times 10^3$cells/dL)	252 (70.91)	253 (65.84)	252 (76.39)	0.865
WBC	8.58 (2.81)	8.57 (2.5)	8.59 (3.11)	0.962
Creatinine (mg/dl)	1.18 (1.29)	0.82 (0.19)	1.56 (1.78)	0.001
GFR (mL/min/1.73 m2)	74.58 (17.75)	82.58 (26.58)	52.16 (14.56)	0.001
Potassium	4.42 (0.51)	4.32 (0.36)	4.52 (0.62)	0.059
SGOT	20.61 (14.97)	19.68 (8.91)	21.59 (19.39)	0.277
SGPT	22.42 (18.44)	22.14 (15.21)	22.72 (21.37)	0.787
Albumine	4.11 (0.44)	4.23 (0.35)	4 (0.48)	0.001
CRP	13.57 (0.2-275)	12.66 (0.2-194)	14.43 (0.8-275)	0.605
LDL (mg/dL	95 (41-327)	100 (44-327)	89 (41-195)	0.027
HDL (mg/dL)	40.81 (11.66)	40.77 (11.81)	40.85 (11.54)	0.954
Triglycerides (mg/dL)	167 (44-1429)	181 (59-1429)	151 (44-685)	0.032
Syntax Score I	7.24 (7.27)	5.66 (6.54)	8.46 (8.75)	0.002
Syntax Score II	27.5 (3.9-71)	20.22 (4.26)	35.19 (7.84)	0.001

Table 2 presents the ECG measurement results. Accordingly, Group 2 had significantly higher QRS, QT, and QTc intervals (respectively; P=0.001, P=0.014 and P=0.001). Besides, Group 2 had significantly lower QT/QRS (iCEB) and QTc/QRS (iCEBc) ratios (respectively; P=0.002 and P=0.005). The difference in QT and QTc between leads V1 and V6 was similar in both groups (respectively; P=0.614 and P=0.989. Finally, there was a statistically significant negative relationship between SYNTAX Score II and ECG parameters of iCEB and iCEBc (respectively, r = -0.235, r=-0.222, and P=0.01) (Table 3).

Table 2: Electrocardiographical parameters and comparing of variables between groups

Variables	Study population	SYNTAX Score II ≤26 group	SYNTAX Score II >26 group	*P*-value
Heart rate, bpm	75.07 (13.95)	73.08 (14.12)	76.41 (13.71)	0.111
QT interval	362.82 (40.71)	357.17 (38.79)	368.78 (41.95)	0.014
QTc interval	389.14 (37.97)	381.17 (33.67)	397.49 (40.41)	0.001
QRS interval	79.28 (24.29)	72.96 (21.08)	85.94 (25.71)	0.001
İCEB (QT/QRS ratio)	5.05 (1.88)	5.38 (1.99)	4.71 (1.71)	0.002
İCEBc (QTc/QRS ratio)	5.39 (1.91)	5.71 (1.99)	5.07 (1.77)	0.005
QT in V1, ms	359.73 (40.74)	354.61 (39.33)	365.17 (41.65)	0.026
QTc in V1, ms	385.99 (38.58)	378.56 (34.87)	393.81 (40.83)	0.001
QT in V6, ms	367.20 (41.23)	362.06 (35.94)	372.66 (45.69)	0.027
QTc in V6, ms	393.42 (38.29)	385.96 (31.77)	401.29 (42.85)	0.001
QT difference (V1-V6), ms (median, IQR)	-7 (-20-0)	-7 (-20-0)	-8 (-20-0)	0.614
QTc difference (V1-V6), ms (median, IQR)	-8 (-20-0)	-7 (-20-0)	-7 (-20-0)	0.989
QT ratio in V1/V6	0.98 (0.04)	0.97 (0.04)	0.98 (0.05)	0.614
QTc ratio in V1/V6	0.99 (0.04)	0.98 (0.04)	0.99 (0.04)	0.733

Table 3: Correlation analysis of SYNTAX II score and electrocardiographical variables

Variables	R value	*P*-value
QTc interval	0.192	0.001
iCEB (QT/QRS ratio)	-0.235	0.001
iCEBc (QTc/QRS ratio)	-0.222	0.001
QTc in V1, ms	0.187	0.001
QTc in V6, ms	0.198	0.001
QT difference (V1-V6), ms	-0.018	0.762
QTc difference (V1-V6), ms	-0.021	0.732

Discussion

According to our results, a lower iCEB value correlates with a higher SYNTAX II score. This, therefore, may suggest that in patients with stable coronary artery disease, the high SYNTAX score indicates a risk of non-TDP-related VT or fibrillation.

The SYNTAX score system was used with respect to the SYNTAX study, which compared the best revascularization option and predicted long-term mortality in patients with left main and multivessel CADs [1]. This scoring method, despite its clinical value in interventional cardiology, relies nearly entirely on the anatomical and lesion properties of the diseased coronary arteries and disregards the clinical data of patients [3]. Hence, the previous SYNTAX score was replaced by the SYNTAX Score II that combined patients' clinical data (such as age, sex, creatinine clearance, left main CAD, left ventricular ejection fraction, peripheral vascular disease, and chronic obstructive pulmonary disease) with the anatomical features of the coronary arteries (anatomical SYNTAX score) [4]. This scoring technique was incorporated into the clinical practice by some studies such as Evaluation of the Xience Everolimus-Eluting Stent versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL), which put forward more accurate results than those given by the SYNTAX Score method [9]. A meta-analysis by Chen J et al. [10] showed that SYNTAX Score II, having a significant impact in forecasting negative clinical results in patients who underwent a percutaneous coronary intervention, was more effective than SYNTAX Score.

As regards real-life practice, Song et al. [11] verified the value of SYNTAX Score II in predicting negative outcomes with their observational study, where they divided estimated SYNTAX Score II scores of a total of 4,398 patients into tertiles (with cut-off points at 20 and 26) to analyze their outcomes after three-vessel and/or unprotected LMCA-PCI. The authors found that during the 2-year follow-up period, the upper tertile had a significantly higher mortality rate than the intermediate or lower tertiles (2.7% vs 1.7% vs 0.5%, respectively; $P<0.001$). Also, the results of their multivariate analysis demonstrated that SYNTAX Score II independently predicted 2-year mortality (hazard ratio, 1.66 [95% CI, 1.03-2.68]; $P=0.04$). Furthermore, Rencuzogullari et al. [12] found a strong relationship between the SYNTAX Score II and the development of the first detectable episode of AF in patients with known CAD. The authors noted that in long-term follow-up, the higher the SYNTAX Score II, the worse the prognosis is.

Despite the fact that a lot of research has been put into determining the relationship between adverse cardiac events and SYNTAX Score II, no study has been conducted to examine the relationship between VAs and SYNTAX Score II. Therefore, the present study sought to investigate the clinical importance of SYNTAX Score II in predicting the development of malignant VAs by employing cardiac depolarization and repolarization indices. As far as we know, this study is the first to use iCEB and V1-V6 QT differences to evaluate the relationship between the SYNTAX II scoring system and the development of malignant VAs. We found that SYNTAX Score II statistically significantly correlated with SYNTAX Score II and ECG parameters of QTC, iECB, and iECBc.

iCEB (QT/QRS), which is equivalent to the cardiac wavelength λ (λ=effective refractory period (ERP) x conduction velocity), is a well-known indicator of altered cardiac depolarization and repolarization. It has recently been demonstrated that proarrhythmic risk can better be predicted by this parameter than other ECG parameters including Tp-e, Tp-e/QT, Tp-e/QTc. Studies have associated high iCEB values with Torsades de Pointes (TdP) and low values with non-TdP mediated VT and VF [5,6]. Indeed, Yumurtaci et al. [13] also reported consistent findings, showing that patients with acute myocarditis had higher iCEB and iCEBc values than healthy controls. The authors suggested that higher iCEB and iCEBc values may be the reason why patients with acute myocarditis had an increased frequency of malignant VAs. A strong correlation between iCEB values and increased pericardial fat volume was also reported by Nafakhi et al. [14]. Increased amounts of pericardial fat, because of well-known pro-inflammatory features and anatomical proximity to the cardiac myocytes, results in structural and electrical remodeling of the myocardium and promotes arrhythmogenesis [15-17]. As a consequence, greater iCEB values were correlated with an increase in pericardial fat volume, confirming the findings of prior research that studied the relationship between pericardial fat thickness and arrhythmogenesis.

Limitation

The current research had certain limitations, including being a retrospective, single-center study and having a relatively small size of cases. Therefore, future studies may be recommended to include a larger sample size to verify this study's findings. Although the study sought to explore the association between the SYNTAX Score II and cardiac depolarization and repolarization values, further follow-up of the patients in terms of the development of malignant VAs and sudden cardiac death was not performed. Also, the study excluded the patients who had a QRS duration ≥120 ms, complete bundle branch block, intraventricular conduction delay, and history of permanent pacemaker implantation, making our findings inapplicable to these patient groups.

Conclusion

Our findings point to a strong correlation between QTC, iCEB, iCEBc, and SYNTAX Score II. Hence, malignant VAs can be effectively predicted with the SYNTAX Score II. In terms of exploring the association between SYNTAX Score II and cardiac depolarization and repolarization parameters, this study may offer a clinically helpful method, which can be used in clinical practice because of its ease of use and accessibility.

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