

Prolonged QRS independently predicts long-term all-cause mortality in patients with narrow QRS complex undergoing coronary artery bypass grafting surgery (9-year follow-up results)



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Abstract

Aim: We investigated the association of intermediate QRS prolongation with the long-term all-cause mortality in coronary artery bypass grafting (CABG) surgery patients with a narrow QRS complex in the preoperative electrocardiography (ECG).

Material and methods: A total of 221 consecutive patients with narrow QRS (< 120 ms) sinus rhythm who underwent CABG surgery were included in the study. The patients were followed up for 9.2 years postoperatively in terms of mortality outcomes.

Results: Follow-up data were obtained from 211 (173 men, 38 women) of 221 patients. Death occurred in 57 of them. We examined patients in the two groups according to survival outcomes. In multivariate COX regression analysis EuroSCORE (OR = 1.342, 95% CI: 1.167–1.544, $p < 0.001$), extent of coronary artery disease (OR = 1.768, 95% CI: 1.034–3.020, $p = 0.037$), QRS duration (OR = 1.029, 95% CI: 1.002–1.058, $p = 0.035$) and fasting glucose levels (OR = 0.992, 95% CI: 0.984–0.999, $p = 0.029$) were independent predictors of all-cause mortality. QRS duration > 89.5 ms determined all-cause mortality with a sensitivity of 73.7% and a specificity of 52% (OR = 2.07) due to ROC analysis. All-cause mortality was significantly higher in patients with preop QRS duration > 90 ms from the first year ($\chi^2 = 6.724$, $p = 0.010$).

Conclusions: In CABG patients with a narrow QRS complex, preoperative intermediate prolonged QRS is an independent predictor of all-cause mortality in long-term follow-up.

Keywords: coronary artery bypass grafting, QRS duration, all-cause mortality, long-term follow-up.

Streszczenie

Cel pracy: W pracy analizowano zależność między umiarkowanym wydłużeniem czasu trwania QRS a długoterminową śmiertelnością z jakiegokolwiek przyczyny u pacjentów z wąskim zespołem QRS w przedoperacyjnym badaniu elektrokardiograficznym (EKG) poddanych pomostowaniu tętnic wieńcowych (CABG).

Materiał i metody: Do badania włączono 221 kolejnych pacjentów z rytmem zatokowym i wąskim zespołem QRS (< 120 ms), u których wykonano zabieg CABG. Pacjentów poddano obserwacji pod kątem śmiertelności przez okres 9,2 roku od operacji.

Wyniki: Dane z obserwacji uzyskano dla 211 (173 mężczyzn, 38 kobiet) spośród 221 pacjentów. Zgon nastąpił u 57 osób. Pacjentów analizowano w dwóch grupach w zależności od wyników przeżycia. W wieloczynnikowej analizie regresji Coxa wynik w skali EuroSCORE (OR = 1,342; 95% CI: 1,167–1,544, $p < 0,001$), zasięg choroby wieńcowej (OR = 1,768; 95% CI: 1,034–3,020; $p = 0,037$), czas trwania QRS (OR = 1,029; 95% CI: 1,002–1,058, $p = 0,035$) oraz stężenie glukozy na czczo (OR = 0,992; 95% CI: 0,984–0,999; $p = 0,029$) stanowiły niezależne predyktory długoterminowej śmiertelności z jakiegokolwiek przyczyny. Na podstawie analizy ROC czas trwania QRS > 89,5 ms pozwalał przewidzieć śmiertelność z czułością rzędu 73,7% i swoistością rzędu 52% (OR = 2,07). Śmiertelność z jakiegokolwiek przyczyny była znacznie wyższa u pacjentów z przedoperacyjnym czasem trwania QRS > 90 ms już od pierwszego roku ($\chi^2 = 6,724$; $p = 0,010$).

Wnioski: W długoterminowej obserwacji przedoperacyjne umiarkowane wydłużenie czasu trwania QRS u chorych z wąskim zespołem QRS poddanych CABG stanowi niezależny predyktor śmiertelności z jakiegokolwiek przyczyny.

Słowa kluczowe: pomostowanie tętnic wieńcowych, czas trwania zespołu QRS, śmiertelność z jakiegokolwiek przyczyny, obserwacja długoterminowa.

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Introduction

Surface 12-lead electrocardiography (ECG) is commonly used in cardiology practice. Besides being a guide in diagnosis and treatment, it is low in cost, noninvasive, and easy to apply. QRS duration (QRSd) is an ECG parameter and shows left and right ventricular depolarization time [1]. The QRSd differs in healthy individuals, and > 120 ms is referred to as wide QRS (wQRS), while ≤ 120 ms is considered as narrow QRS (nQRS) [2]. Many factors affect the duration of QRS, such as left ventricular hypertrophy or dilatation, His-Purkinje conduction defect, left or right bundle branch block, intramyocardial conduction defect, and antiarrhythmic drug use. One of the crucial factors associated with QRS prolongation (\uparrow QRS) is left ventricular systolic dysfunction [2, 3].

QRS prolongation causes poor cardiovascular outcomes [2, 4–7]. In the left bundle branch block (LBBB), a mortality increase is prominent, but cardiac resynchronization therapy is effective by shortening the QRSd [8, 9]. QRS prolongation is a poor prognostic marker in patients undergoing coronary artery bypass surgery (CABG), as in other cardiovascular diseases [10–12].

In community-based studies, it has been shown that a QRS duration > 110 ms is associated with increased sudden cardiac death, and in those with a fractional shortening below the average value, each increase of 10 ms is an independent predictor of sudden cardiac death [13]. Even in patients with narrow QRS, intermediate QRS prolongation (QRS 90–110 ms) is associated with poor cardiovascular outcomes [14, 15].

Aim

In the current study, we examined the relationship between QRS duration and long-term survival in patients with narrow QRS, who underwent isolated CABG.

Material and methods

The study is a retrospective cohort study. A total of 211 consecutive patients who were admitted to our cardiology clinic between January 2008 and August 2010 and underwent an isolated CABG operation were included in the research. We followed the patients for an average of 110.6 ± 16.8 months and identified all-cause mortality as an endpoint. Patients' death information was obtained from the official national population registration system, and the clinical data were provided through a medical record system. We performed the study under the principles stated in the Declaration of Helsinki. The local ethics committee approved the protocol.

We recorded the patients' baseline characteristics, laboratory, echocardiographic and ultrasonographic parameters from the routine preoperative assessments. The EuroSCORE calculation was performed using the original score calculation tool available at <http://www.euroscore.org/calc.html>. We defined preoperative myocardial infarction and chronic obstructive pulmonary disease according to guidelines [16,

17]. Carotid stenosis was evaluated with preoperative carotid Doppler ultrasonography. Body mass index (BMI) was calculated by the weight/height² formula. The treatment of the patients was arranged according to the coronary artery disease guidelines before the CABG operation.

Preoperative QRSd > 120 ms was defined as wide QRS, and patients with wide QRS were excluded; preoperative QRSd < 120 ms was defined as narrow QRS, and patients with narrow QRS were included in the study. We planned to examine the effect of QRSd on mortality.

Patients with acute or chronic renal failure, history of CABG, or any other cardiovascular surgery, chronic liver disease, malignancy, QRSd > 120 ms, and other than sinus rhythm were excluded from the study. Hospital deaths and patients with unavailable data were not included in the analysis.

Standard transthoracic and Doppler echocardiographic examinations were performed using a 3.25-MHz transthoracic transducer connected to a Vivid 5 System (GE Vingmed Ultrasound AS, Horten, Norway). Two cardiologists, blinded to patients' data, performed the echocardiography. Left ventricular ejection fraction (LVEF) was calculated with the Simpson method, and other echocardiographic parameters were evaluated according to the American Society of Echocardiography guidelines [18].

Electrocardiography recordings were taken at 50 mm/s and 10 mV/mm amplitude by placing the leads in the standard position. Two expert cardiologists, blinded to patients' data, evaluated the ECG records, and calculated the most extended QRSd in the leads [19–21].

Statistical analysis

Continuous variables were presented as mean values (standard deviation (SD)) or medians with ranges, and the categorical variables were expressed as percentages. The variables were compared using a 2-tailed Student's *t*-test for the continuous variables of a normal distribution or the Mann-Whitney *U* test for non-normal distribution. The χ^2 test was used for the categorical variables. The effects of the various variables on all-cause mortality were calculated by univariate Cox regression analysis. In these analyses, the variables with unadjusted $p < 0.1$ were identified as confounding factors and included in the multivariate regression analyses to determine the independent predictors of all-cause mortality. Factors included in EuroSCORE (age, carotid stenosis, LVEF) were not included in the multivariate analysis. Factors with $p < 0.05$ in the univariate analysis (EuroSCORE, QRSd, number of coronary arteries with $> 50\%$ stenosis, fasting glucose level) were included in the multivariate Cox regression analysis, and the stepwise forward method was used. All the analyses were carried out using SPSS version 16 (SPSS, Inc., Chicago, Illinois).

Results

A total of 211 patients (173 men, 38 women) were followed up to 9.2 ± 1.6 years, and 57 (27%) patients died after discharge from the hospital (Table I). When the survivors and

Table I. Comparison of demographic data

Variable	Survivors (n = 154)	Non-survivors (n = 57)	P-value
Age, mean ± SD [years]	59.4 ± 8.9	66.4 ± 9.2	< 0.001
Gender (female), n (%)	27 (17.5)	10 (17.5)	0.572
Body-mass index [kg/m ²]	28.6 ± 4.3	28.3 ± 4.3	0.777
Diabetes mellitus, n (%)	75 (48.7)	19 (33.3)	0.032
Dyslipidemia, n (%)	85 (55.6)	31 (54.4)	0.501
Hypertension, n (%)	87 (57.5)	42 (73.7)	0.069
Current smoking, n (%)	71 (46.7)	29 (50.9)	0.322
EuroSCORE	2.76 ± 1.6	4.5 ± 2.1	< 0.001
COPD, n (%)	24 (15.7)	14 (24.6)	0.101
Previous MI, n (%)	65 (42.2)	27 (48.2)	0.268
QRS duration, mean ± SD	89.1 ± 9.7	94.7 ± 9.9	< 0.001
Severe carotid stenosis, n (%)	5 (3.3)	8 (14.3)	0.007
LMCA involvement, n (%)	17 (12.6)	4 (8.2)	0.292
LVEF%	53.7 ± 13.1	46.6 ± 12.9	< 0.001
Number of CAD	2.45 ± 0.68	2.63 ± 0.69	0.017
Number of saphenous vein grafts	2.97 ± 1	2.92 ± 0.96	0.579
LIMA usage, n (%)	145 (95.4)	51 (89.5)	0.107
Cross-clamp time [min]	58.3 ± 23.2	64.1 ± 22.5	0.047
Off-pump surgery, n (%)	16 (10.8)	7 (12.3)	0.374
Fasting glucose [mg/dl]	138.6 ± 63.5	115.9 ± 37.5	0.016
Serum creatine [mg/dl]	0.98 ± 0.26	1.04 ± 0.18	0.347
WBC [$\times 10^3/\text{mm}^3$]	8.04 ± 2.03	7.6 ± 2.07	0.782
Neutrophils [$\times 10^3/\text{mm}^3$]	5.01 ± 1.9	4.6 ± 1.51	0.890
Hemoglobin [g/dl]	13.5 ± 1.27	13.1 ± 1.5	0.048
Acetylsalicylic acid, n (%)	152 (98.7)	54 (94.7)	0.896
Clopidogrel, n (%)	39 (25.3)	19 (33.3)	0.163
ACE/ARB, n (%)	78 (50.6)	34 (59.6)	0.247
CCB, n (%)	26 (16.9)	9 (15.8)	0.516
β -Blocker, n (%)	111 (72.1)	38 (66.7)	0.273
Insulin/OAD, n (%)	70 (45.5)	16 (28.1)	0.016
Statin, n (%)	147 (95.4)	53 (92.9)	0.878

ACE – angiotensin converting enzyme inhibitor, ARB – angiotensin renin inhibitor, CAD – coronary artery disease, CCB – calcium channel blocker, COPD – chronic obstructive pulmonary disease, HDL – high-density lipoprotein, LIMA – left internal mammary artery, LMCA – left main coronary artery, LVEF – left ventricular ejection fraction, MI – myocardial infarction, NSTEMI – non-ST elevation myocardial infarction, OAD – oral anti-diabetic, WBC – white blood cells.

non-survivors were compared the mean age (66.4 ± 9.2 vs. 59.4 ± 8.9 years; $p < 0.001$), EuroSCORE (4.5 ± 2.1 vs. 2.76 ± 1.6; $p < 0.001$), severe carotid stenosis (8 (14.3%) vs. 5 (3.3%); $p = 0.007$), and number of coronary arteries with stenosis (2.63 ± 0.69 vs. 2.45 ± 0.68; $p = 0.017$), were lower; furthermore, QRSd (94.7 ± 9.9, 89.1 ± 9.7 ms; $p < 0.001$) and duration of bypass (64.1 ± 22.5 vs. 58.3 ± 23.2 min; $p = 0.047$) were shorter in the survivor group. Left ventricular ejection fraction (46.6 ± 12.9%, 53.7 ± 13.1%; $p < 0.001$) and hemoglobin levels (13.1 ± 1.5, 13.5 ± 1.27 g/dl; $p = 0.048$) were higher in the survival group. Paradoxically, diabetes (19 (33.3%) vs. 75 (48.7%); $p = 0.032$), insulin/oral antidiabetic usage (16 (28.1%) vs. 70 (45.5%); $p = 0.016$), and fasting glucose levels (115.9 ± 37.5 vs. 138.6 ± 63.5 mg/dl; $p = 0.016$) were higher in the survival group.

In univariate Cox regression analysis age (OR = 1.076, 95% CI: 1.042–1.110, $p < 0.001$), EuroSCORE (OR = 1.364,

95% CI: 1.226–1.517, $p < 0.001$), LVEF (OR = 0.957, 95% CI: 0.937–9.978, $p < 0.001$), severe carotid stenosis (OR = 1.805, 95% CI: 1.237–2.632, $p = 0.002$), extent of CAD (OR = 1.694, 95% CI: 1.033–2.776, $p = 0.037$), QRSd (OR = 1.049; 95% CI: 1.023–1.075, $p < 0.001$), and fasting glucose levels (OR = 0.994, 95% CI: 0.998–1.000, $p = 0.039$) were associated with all-cause mortality (Table II). In multivariate Cox regression analysis using the forward stepwise method EuroSCORE (OR = 1.342, 95% CI: 1.167–1.544, $p < 0.001$), extent of CAD (OR = 1.768, 95% CI: 1.034–3.020, $p = 0.037$), QRSd (OR = 1.029, 95% CI: 1.002–1.058, $p = 0.035$) and fasting glucose levels (OR = 0.992, 95% CI: 0.984–0.999, $p = 0.029$) were independent predictors of all-cause mortality. QRS duration > 89.5 ms determined all-cause mortality with a sensitivity of 73.7% and a specificity of 52% (OR = 2.07) due to ROC analysis. Comparing long-term survival of patients, all-cause mortality was significantly higher in pa-

Table II. Factors predicting mortality (Cox regression analysis)

Parameter	Univariate			Multivariate		
	OR	95% CI	P-value	OR	95% CI	P-value
Age* [years]	1.076	1.042–1.110	< 0.001			
Diabetes	0.660	0.379–1.149	0.142			
EuroSCORE	1.364	1.226–1.517	< 0.001	1.342	1.167–1.544	< 0.001
QRS duration	1.049	1.023–1.075	< 0.001	1.029	1.002–1.058	0.035
Severe carotid stenosis*	1.805	1.237–2.632	0.002			
LVEF%*	0.957	0.937–9.978	< 0.001			
Number of CAD	1.694	1.033–2.776	0.037	1.768	1.034–3.020	0.037
Cross-clamp time [min]	1.011	0.997–1.024	0.120			
Fasting glucose [mg/dl]	0.994	0.998–1.000	0.039	0.992	0.984–0.999	0.029
Hemoglobin [g/dl]	0.834	0.675–1.030	0.092			
Insulin/OAD	0.581	0.325–1.039	0.067			

CAD – coronary artery disease, LVEF – left ventricular ejection fraction, OAD – oral anti-diabetic. *Not included in the multivariate analysis because it was scored in EuroSCORE.

tients with preop QRS duration > 90 ms, from the first year ($\chi^2 = 6.724$, $p = 0.010$) (Figure 1).

Discussion

We found that in patients scheduled to have an isolated CABG operation, prolonged QRS, even if it was ≤ 120 ms, was an independent predictor of all-cause mortality over 9 years of follow-up. As QRS was prolonged, survival was significantly reduced at 9.2 years of follow-up.

In the long-term survival study conducted by Ramirez *et al.*, 340 CABG patients were followed for 5 years, and the mortality group had a longer QRSD (100 ms vs. 92 ms; $p = 0.021$) [10]. Nevertheless, QRSD was not an independent predictor of mortality in multivariate analysis. The mentioned study, which had a shorter follow-up time and different design than our study, determined that QRSD was not an independent predictor of mortality, yet it produced data that support our study.

Gomes *et al.* determined that QRSD > 114 ms as an independent predictor of cardiac arrest or arrhythmic death in patients with ischemic cardiomyopathy [22]. This finding supported the results of the GUST study [23]. Pudil

et al. investigated the prognostic significance of QRSD in 1100 acute myocardial infarction patients [14]. The patients were divided into three groups as < 90 ms, 90–110 ms, > 110 ms, according to the QRS duration on the admission ECG. When the mortality data of 7 days, 30 days, and 1 year were compared, the mortality was significantly higher in the 90–110 ms group than the < 90 ms group ($p < 0.001$). In addition, in the group with intermediate QRS prolongation, the peak CK-MB level was higher than in the group with QRS duration < 90 ms, and intermediate QRS prolongation was an independent predictor of all-cause mortality in multivariate analysis (OR = 2.21). This research is essential to reveal the clinical significance of QRSD, even if it is a narrow QRS complex. Remarkably, in our study, the preop QRS duration of > 90 ms was the most sensitive and specific marker in determining the long-term prognosis, and there was a significant difference in the long term between the two groups in the Kaplan-Meier survival graph (Figure 1).

Some researchers have revealed that it is clinically significant to have ≥ 100 ms of QRSD without branch block, and defined it as intermediate QRS prolongation. Brilakis *et al.* reported that intermediate QRS prolongation is an independent predictor of in-hospital mortality in non-ST elevated myocardial infarction (MI) [24]. In a similar study, Tsukahara *et al.* revealed that ST elevated MI patients undergoing reperfusion had more severe CAD in those with intermediate QRS prolongation [25]. Ilkhanoff *et al.* evaluated the relationship between cardiac MR imaging, QRSD, and left ventricular (LV) structure in 4591 patients and found that LV volume and mass were higher, and LVEF was lower in patients with QRSD > 100 ms [26]. Additionally, the incidence of heart failure was higher in patients with prolonged QRS in the 7.1 years of follow-up. Similarly, Kurisu *et al.* reported that intermediate QRS prolongation was positively associated with LV end-diastolic volume and LV end-systolic volume, and was inversely associated with LVEF, in patients with prior anterior MI [27]. Bader *et al.* stated that QRS prolongation is the most critical predictor of ventricu-

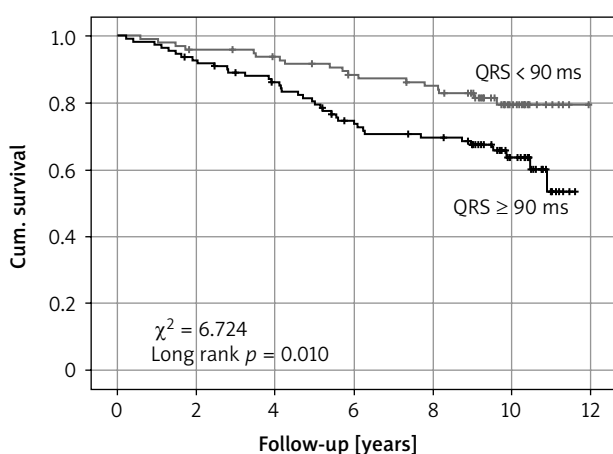


Figure 1. Kaplan-Meier survival curve

lar electromechanical asynchrony, worsening prognosis in heart failure [28]. As a result, for patients with intermediate QRS prolongation, poor LV remodeling is prominent as in wQRS. Thus, intermediate QRS prolongation, clinically and prognostically, seems to mimic the wQRS complex.

Electrocardiography is a cost-effective and practical method that can help to predict sudden cardiac death (SCD) [29]. Increased QRSD is a higher risk for SCD [30]. Implantable cardioverter-defibrillator observational studies and subgroup analyses showed the benefit of narrowing QRS with electrical synchronization [31]. Teodorescu *et al.* evaluated the effect of prolonged ventricular depolarization and repolarization on the ventricular arrhythmia in CAD patients [32]. They found that 642 SCD cases detected from the general population had an increased QRSD of 8 ms compared to 473 control CAD patients.

The QRSD has a poor prognosis also in preserved LV systolic function. Hummel *et al.* demonstrated that QRSD is an essential indicator of long-term mortality in patients with preserved left ventricular systolic function hospitalized for heart failure [33]. Joseph *et al.* reported a similar result [34]. The patients of these studies had the wQRS complex. There are not enough data in the literature related to intermediate QRS prolongation.

In conclusion, for patients undergoing an isolated CABG operation, intermediate prolonged QRS affects prognosis in the long term. The causes are similar to the studies with the wQRS complex. So, in patients undergoing isolated CABG surgery, intermediate prolonged QRS may be a guide in determining long-term increased all-cause mortality risk.

Since the study was retrospective, cardiac death could not be distinguished; therefore, all-cause mortality data could be obtained. The effect of medical treatment on long-term mortality was not evaluated. The number of patients is limited. Only the QRS duration was taken into account in the ECGs of the patients. Fragmented QRS and QRS morphology were not evaluated in the study. Long-term prospective studies may better demonstrate the effectiveness of QRSD measurement, a simple and inexpensive method, in demonstrating long-term risk increases in for patients undergoing CABG surgery.

Conclusions

In patients with narrow QRS sinus rhythm undergoing isolated CABG surgery, intermediate prolonged QRS is an independent predictor of all-cause mortality in a 9.2-year follow-up.

Disclosure

The authors report no conflict of interest.

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