Prolonged QRS duration on surface electrocardiogram is associated with left ventricular restrictive filling pattern

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Abstract: *Background:* Prolonged QRS duration is associated with decreased left ventricular (LV) systolic function. However, the relation between LV restrictive filling pattern (RFP) and QRS duration has not been investigated yet. The purpose of our study was to assess this relationship. *Methods:* We analyzed standard 12-lead surface electrocardiogram (ECG) of 155 consecutive patients. Mitral inflow and septal tissue velocities were obtained using the apical 4-chamber view with pulsed Doppler echocardiography. Patients were divided into 2 groups according to measured deceleration time (DT): restrictive (with DT ≤130 ms) or non-restrictive (with DT >130 ms). *Results:* QRS duration was significantly longer in the restrictive group than in the non-restrictive group (0.101 vs. 0.090 s, $p < 0.0001$). QRS duration of >0.10 s was highly specific (82.6%), but modestly sensitive (64.7%), for the prediction of LV RFP. Multivariate analyses demonstrated that E/A ratio, peak E, peak A, septal e', and a' velocities were significantly associated with RFP. *Conclusions:* Prolonged QRS duration (>0.10 s) obtained from a standard resting 12-lead ECG is associated with LV RFP. However, the relationship of QRS duration with RFP was not independent of echocardiographic parameters.

Keywords: QRS duration, restrictive filling pattern, electrocardiography, deceleration time, tissue Doppler

Introduction

The utility of the ECG for evaluation of cardiac dysfunction has been overshadowed by echocardiography. However, 12-lead electrocardiogram (ECG) is a relatively inexpensive, non-invasive, and rapidly performed test for detection of several cardiac pathologies. Previous studies have demonstrated that a normal 12-lead ECG in patients is a relatively sensitive and specific marker of normal left ventricular (LV) function [1–4]. Murkofsky et al. [5] reported that prolonged QRS duration (>0.10 s) is a specific, but rather insensitive indicator of decreased LV systolic function. Furthermore, several prior studies have shown that QRS prolongation is associated with increased rates of cardiovascular events, sudden death, and all-cause mortality [6–10].

Doppler echocardiography has been widely utilized as a non-invasive method for evaluating diastolic function. Doppler echocardiography may identify three main LV diastolic filling patterns using the mitral inflow: normal, impaired relaxation, or pseudonormal/restrictive filling pattern [11]. Previous studies showed that restrictive filling pattern (RFP) and especially shortened deceleration time (DT) is an independent predictor of adverse outcome in several clinical settings, including acute myocardial infarction, and cardiomyopathy [12–16]. The purpose of this study was to investigate whether prolonged QRS interval duration is associated with LV RFP.

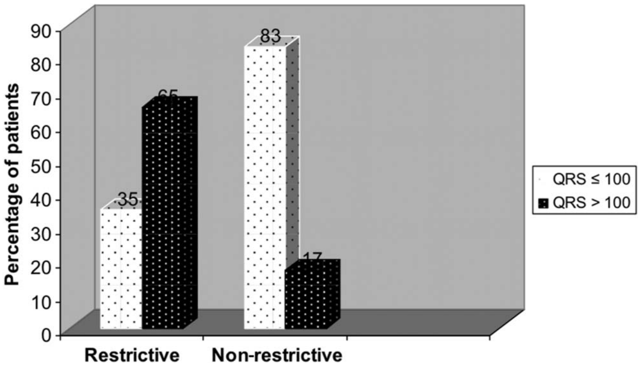

Fig. 1. Distribution of a prolonged QRS duration based on restrictive or non-restrictive filling pattern

Methods

Patients

We prospectively enrolled 155 patients among 343 patients, who were consecutively referred to our echocardiography laboratory for the detection of possible cardiac disease. Exclusion criteria were atrial fibrillation, significant valvular heart disease, typical left or right bundle block, recent myocardial infarction, pacemaker rhythm, and usage of antiarrhythmic drugs. All patients had 12-lead resting ECGs.

Electrocardiographic analysis

Standard resting 12-lead ECGs were obtained at 50 mm/s and 1mV/cm standardization using the Hewlett–Packard Pagewriter Xli Cardiograph (HP, Andover, MA). The ECGs for all patients were reviewed by one of the investigators who were not aware of the echocardiographic data. The widest QRS duration was measured manually in a random sample of 39 ECGs. Manual data were compared to automatized measurements of QRS duration. There was an excellent correlation between the manual and the computer-obtained measurements ($r = 0.94$, $p = 0.0001$). Therefore, the computer-measured QRS duration was used for all analyses.

Echocardiography

Two-dimensional and Doppler echocardiographic examinations were performed by the same examiner with a Hewlett–Packard sonos 5500 echocardiography machine using a 2.5-MHz transducer. LV end-diastolic and end-systolic volumes and ejection fraction (EF) were measured from the apical 2 and 4 chamber views using the Simpson biplane formula according to the recommendations of the American Society of Echocardiography [17]. Tracing of the endocardial borders in end-diastole and end-systole was performed in the technically best cardiac cycle.

LV diastolic filling patterns were determined by the mitral inflow pulsed-wave Doppler examinations. In the apical 4-chamber view, the Doppler sample volume was placed in the middle of the LV inflow tract 1 cm below the plane of mitral annulus between the mitral leaflet tips, where maximal flow velocity in early diastole was recorded [18]. Average values were calculated for the following transmitral parameters using Doppler spectra of 3–5 consecutive cardiac cycles: peak flow velocity of early filling (E), peak flow velocity at atrial contraction (A), their ratio (E/A), and DT of early filling. The isovolumetric relaxation time (IVRT), defined as the time from aortic valve closure to mitral valve opening, was assessed by simultaneously measuring the flow into the LV outflow tract and mitral inflow by Doppler echocardiography [17]. Irrespective of filling profile, patients were assigned to one of two groups: restrictive (with DT ≤130 ms) or non-restrictive (with DT >130 ms) according to DT values. This cutoff point has been shown to be consistent with restrictive hemodynamics and a powerful independent predictor of unfavorable outcome after acute myocardial infarction [19, 20]. Septal tissue Doppler velocities were also acquired using apical 4-chamber view [17]. For each measurement, averaged data were used from three uniform consecutive cardiac cycles. LV mass was calculated according to Devereux formula.

Statistical analysis

Data was analyzed by SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA). The distributions of continuous variables were determined by Kolmogorov–Smirnov test. Data were presented as median (25%/75% interquartile range) or mean ± standard deviation, where applicable. The chi-square test was used for intergroup comparisons. Continuous variables were compared using the Student's *t* or Mann–Whitney *U* tests as appropriate. In addition, the sensitivity and specificity of ECG criteria for predicting LV RFP were determined. The correlation between DT and various electrocardiographic and echocardiographic parameters was analyzed using the Spearman's test. Multiple linear regression analysis was used to determine the predictor(s) with the greatest effect on the presence of restrictive pattern after adjustment for possible confounding factors. Variables with a p value of <0.05 in the univariable test as well as all variables of known clinical importance were accepted as a candidate for the multivariable model. Standardized coefficient of regression and levels of significance for each independent variable were also calculated. All tests of significance were two-tailed. Statistical significance was defined as $p < 0.05$.

Table I Baseline characteristics of the patients

	Restrictive group ($n = 34$)	Non-restrictive group ($n = 121$)	p value
Age (years)	52 ± 12	56 ± 13	0.08
Male (%)	28 (82)	63 (52)	0.002
Diabetes mellitus (%)	8 (24)	11 (9)	0.036
Hypercholesterolemia (%)	23 (67)	69 (57)	0.32
Smoking (%)	15 (44)	30 (25)	0.03
Family history of CAD (%)	19 (56)	43 (36)	0.05
Hypertension (%)	16 (47)	79 (65)	0.07
Obesity (%)	7 (21)	35 (29)	0.38
ACE inhibitors	19 (56)	40 (33)	0.02
β-Blockers	9 (26)	20 (16)	0.21

ACE: angiotensin converting enzyme; CAD: coronary artery disease

Results

Patients were divided into the following two groups according to DT as restrictive (with DT ≤130 ms) or non-restrictive (with DT >130 ms). There were 34 patients (22%) in the restrictive group and 121 patients (78%) in the non-restrictive group. Patients with RFP were more likely to be men with increased prevalence of risk factors for coronary artery disease, except hypercholesterolemia. Demographic and clinical characteristics of the study population are reported in *Table I*.

Electrocardiographic and main echocardiographic parameters of the two groups are presented in *Table II*. The QRS duration in the restrictive group was significantly longer compared to non-restrictive group ($p = 0.0001$). As a group, patients with RFPs had more extensive (LV) dilation and a lower LV EF compared to patients without RFPs. Prolonged QRS duration, defined as QRS > 0.10 s, was detected in 22 patients (64.7%) in the restrictive group; whereas 21 patients (17.3%) had prolonged QRS in the non-restrictive group ($p = 0.0001$; *Fig. 1*). There existed a significant correlation between QRS duration and LV mass ($r = 0.564$, $p < 0.0001$). Tissue Doppler examinations demonstrated lower septal s' and a' velocities, and higher e'/a' ratio, in patients with restrictive filling.

Table II Comparison of electrocardiographic and echocardiographic data

	Restrictive group ($n = 34$)	Non-restrictive group ($n = 121$)	p value
QRS duration (s)	0.101 ± 0.015	0.090 ± 0.011	0.0001
DT (ms)	106 ± 18	209 ± 50	0.0001
IVRT (ms)	56 ± 14	88 ± 18	0.0001
E peak (cm/s)	71 ± 18	105 ± 18	0.0001
A peak (cm/s)	50 ± 14	76 ± 17	0.0001
E/A ratio	2.2 ± 0.58	0.97 ± 0.32	0.0001
EF (%)	34 ± 17	62 ± 10	0.0001
LVEDV (mL)	148 ± 44	92 ± 27	0.0001
LVESV (mL)	97 ± 41	35 ± 22	0.0001
LV mass (g)	267 ± 55	196 ± 58	0.0001
Tissue Doppler velocities			
E'*	9.5 (7/12.2)	10.6 (7.9/14)	0.083
A'	7.4 ± 3.2	11.2 ± 2.2	<0.001
S*	7.1 (4.9/8.4)	10.2 (8.4/12)	<0.001
em/am ratio*	1.38 (0.89/1.9)	0.91 (0.66/1.28)	<0.001

DT = deceleration time; IVRT = isovolumetric relaxation time; E peak = peak velocity of E wave; A peak = peak velocity of A wave; EF = ejection fraction; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LV mass = left ventricular mass
*Data presented as median (25%/75% interquartile range)

Table III Correlation analysis between deceleration time and various electrocardiographic and echocardiographic parameters

Variable	*r*	*p*	Variable	*R*	*p* value
QRS width	−0.042	0.599	LVESV	**−0.406**	**<0.001**
IVRT	**0.749**	**<0.001**	em	**−0.277**	**<0.001**
E	**−0.711**	**<0.001**	am	**0.503**	**<0.001**
A	**0.622**	**<0.001**	sm	**0.232**	**0.003**
E/A ratio	**−0.849**	**<0.001**	em/am ratio	**−0.564**	**<0.001**
EF	**0.340**	**<0.001**	LVM	−0.120	0.128
LVEDV	**−0.371**	**<0.001**	–	–	–

LVM = left ventricular mass; LVEDV = left ventricular end-diastolic volume; *r* = correlation coefficient. Bold values denote statistically significant values

We calculated the sensitivity and specificity of prolonged QRS duration for prediction of RFP. For each successive 0.01 s increase in the definition of prolonged QRS duration (from 0.10 to 0.12 s) specificity increased from 82.6% to 96.8%, with a corresponding decrease in sensitivity from 64.7% to 11.7%.

Correlation analyses revealed that DT was related to IVRT, peak E, peak A, E/A ratio, LV EF, LV end-diastolic volume, LV end-systolic volume, and septal tissue Doppler velocities *(Table III)*. Multivariate analyses demonstrated that E/A ratio, peak E, peak A, septal e', and a' velocities were significantly associated with RFP (*Tables IV* and *V*).

Discussion

The results of our present study demonstrated that prolonged QRS duration (>0.10 s) on a standard 12-lead ECG was associated with LV RFP. To our knowledge, this study is the first to report a relation between QRS duration and LV RFP. However, the relationship between QRS duration and restrictive pattern was not independent, and only E/A ratio, peak E, peak A, septal e', and a' velocities were significantly associated with RFP. Interestingly, EF was not related to restrictive filling.

Table IV Independent clinical and electrocardiographic correlates of restrictive pattern in multivariate linear regression analysis

Variable	Beta (standardized)	*p* value
Age	0.081	0.350
Gender	0.158	0.329
Diabetes mellitus	0.116	0.136
Smoking	0.134	0.113
ACE inhibitor	0.136	0.095
QRS width	0.063	0.407
Adjusted R^2	0.096	

Dependent variable: presence of restrictive pattern

The resting 12-lead ECG is widely available for all patients with suspected cardiac disease. Previous studies indicated that the presence of normal resting ECG is associated with normal LV function in 92%–96% of cases [1–4]. Although previous studies have shown that prolonged QRS interval duration is associated with decreased LV systolic function [5–10], the utility of QRS duration as a marker of LV RFP has been overlooked.

Pulsed wave Doppler assessment of the mitral valve is routinely used in clinical practice to assess LV diastolic filling non-invasively. Three progressive filling categories have been described: normal, impaired relaxation, and pseudonormal/restrictive filling pattern, based on early (E) and late (A) peak filling velocities, IVRT and E-wave DT [11]. RFP is associated with decreased LV compliance and is characterized by short IVRT, reduced mitral E-wave DT, and increased early-to-late peak flow velocity ratio. Doppler indexes are affected by a number of other physiological factors, including heart rate, LV systolic function, and ventricular preload and afterload [16]. However, recent experimental data suggest that early filling DT can quantitatively assess LV chamber stiffness independent of heart rate, contractility, and afterload [21]. For this reason, we used DT as means of assessing LV filling, irrespective of filling pattern, and we classified those with DT ≤130 ms as restrictive. Differentiation of RFP from a non-RFP provides important independent prognostic information. There is growing evidence indicating a strong association between RFP and adverse outcome [12–16]. Murkofsky et al. [5] reported that the presence of a non-specific prolonged QRS duration (>0.10 s) on standard resting 12-lead ECG without typical features of bundle branch block was indicative of decreased resting LV systolic function. As in the present study, several studies have shown that patients with RFPs had more extensive LV dilation and a lower LV EF compared to patients without RFPs [11–15].

Although, QRS duration was longer in patients with RFP, this association was not independent. Moreover, only echocardiographic parameters of mitral inflow and tissue Doppler diastolic velocities were independently associated with DT. Therefore, we think that although

Table V Independent echocardiographic correlates of restrictive pattern in multivariate linear regression analysis

Variable	Beta (standardized)	*p* value	Variable	Beta (standardized)	*p* value
IVRT	–0.162	0.011	LVESV	–0.048	0.788
E	**0.193**	**0.043**	Septal e’	**–0.309**	**<0.001**
A	**–0.209**	**0.023**	Septal a’	**0.176**	**0.013**
E/A ratio	**0.317**	**0.022**	sm	–0.102	0.082
EF	–0.220	0.057	em/am ratio	0.097	0.111
LVEDV	0.106	0.325	–	–	–
Adjusted R^2	0.772				

Dependent variable: presence of restrictive pattern. Bold values denote statistically significant values

longer QRS duration may identify RFP preceding echocardiography, this information loses its predictive value following Doppler echocardiographic evaluation.

Limitations

Invasive procedures were not routinely performed in this study. However, previous studies showed that echocardiographic measurements are related to invasive measures of pressure. In addition, this patient population consisted mostly of stable outpatients and a few stable inpatients without acute decompensation. Thus, these data cannot necessarily be applied to acute presentation of patients other than routine evaluation.

Conclusions

Our data suggests that the determination of QRS duration was highly predictive of LV RFP. Prolonged QRS (>0.10 s) was highly specific, but relatively insensitive, for predicting LV RFP. However, the relationship of QRS duration with RFP was not independent of echocardiographic parameters.

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References

1. O’Keefe JH, Zinsmeister AR, Gibbons RJ: Value of normal electrocardiographic findings in predicting resting left ventricular function in patients with chest pain and suspected coronary artery disease. Am J Med 86, 658–662 (1989)
2. Rihal CS, Davis KB, Kennedy JW, Gersh BJ: The utility of clinical, electrocardiographic, and roentgenographic variables in the prediction of left ventricular function. Am J Cardiol 75, 220–223 (1995)
3. Christian TF, Chareonthaitawee P, Miller TD, Hodge DO, Gibbons RJ: Is it necessary to measure resting left ventricular function in patients with normal resting electrocardiograms? Circulation 94, 11–20 (1996)
4. Christian TF, Miller TD, Chareonthaitawee P, Hodge DO, O’Connor MK, Gibbons RJ: Prevalence of normal resting left ventricular function with normal rest electrocardiograms. Am J Cardiol 79, 1295–1298 (1997)
5. Murkofsky RL, Dangas G, Diamond JA, Mehta D, Schaffer A, Ambrose JA: A prolonged QRS duration on surface electrocardiogram is a specific indicator of left ventricular dysfunction. J Am Coll Cardiol 32, 476–482 (1998)
6. Brilakis ES, Mavrogiorgos NC, Kopecky SL, Rihal CC, Gersh BJ, Williams BA, Clements IP: Usefulness of QRS duration in the absence of bundle branch block as an early predictor of survival in non-ST elevation acute myocardial infarction. Am J Cardiol 89, 1013–1018 (2002)
7. Silvet H, Amin J, Padmanabhan S, Pai RG: Prognostic implications of increased QRS duration in patients with moderate and severe left ventricular systolic dysfunction. Am J Cardiol 88, 182–185 (2001)
8. Rose G, Baxter PJ, Reid DD, McCartney P: Prevalence and prognosis of electrocardiographic findings in middle-aged men. Br Heart J 40, 636–643 (1978)
9. Shamim W, Francis DP, Yousufuddin M, Varney S, Pieopli MF, Anker SD, Coats AJ: Intraventricular conduction delay: A prognostic marker in chronic heart failure. Int J Cardiol 70, 171–178 (1999)
10. Iuliano S, Fisher SG, Karasik PE, Fletcher RD, Singh SN: QRS duration and mortality in patients with congestive heart failure. Am Heart J 143, 1085–1091 (2002)
11. Appleton CP, Hattle LK: The natural history of left ventricular filling abnormalities assessed by 2-dimensional and Doppler echocardiography. Echocardiography 9, 437–457 (1992)
12. Poulsen SH, Jensen SE, Egstrup K: Longitudinal changes and prognostic implications of left ventricular diastolic function in first acute myocardial infarction. Am Heart J 137, 910–918 (1999)
13. Giannuzzi P, Temporelli PL, Bosimini E, Gentile F, Lucci D, Maggioni AP, Tavazzi L, Badano L, Stoian I, Piazza R, Heyman I: Heterogeneity of left ventricular remodeling after acute myocardial infarction: Results of the gruppo italiano per lo studio della sopravvivenza nell’infarto miocardico-3 echo substudy. Am Heart J 141, 131–138 (2001)
14. Werner GS, Schaefer C, Dirks R, Figulla HR, Kreuzer H: Prognostic value of Doppler echocardiographic assessment of left ventricular filling in idiopathic dilated cardiomyopathy. Am J Cardiol 73, 792–798 (1994)
15. Celik S, Baykan M, Erdol C, Gökce M, Durmus I, Örem C, Kaplan S: Doppler-derived mitral deceleration time as an early

predictor of left ventricular thrombus after first anterior acute myocardial infarction. Am Heart J 140, 772–776 (2000)
16. Nishimura RA, Tajik J: Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is clinician's Rosetta stone. J Am Coll Cardiol 30, 8–18 (1997)
17. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ, Chamber Quantification Writing Group, American Society of Echocardiography's Guidelines and Standards Committee, European Association of Echocardiography: Recommendations for chamber quantification: A report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 18, 1440–1463 (2005)
18. Appleton CP, Hatle LK, Popp RL: Relation of transmitral flow velocity patterns to left ventricular diastolic function: New insight from a combined hemodynamic and Doppler echocardiographic study. J Am Coll Cardiol 12, 426–440 (1988)
19. Oh JK, Ding ZP, Gersh BJ, Bailey KR, Tajik AJ: Restrictive left ventricular diastolic filling identifies patients with heart failure after acute myocardial infarction. J Am Soc Echocardiogr 5, 497–503 (1992)
20. Nijland F, Kamp O, Karreman AJP, van Eenige MJ, Visser CA: Prognostic implications of restrictive left ventricular filling in acute myocardial infarction: A serial Doppler echocardiographic study. J Am Coll Cardiol 30, 1618–1624 (1997)
21. Little WC, Ohno M, Kitzman DW, Thomas JD, Cheng CP: Determination of left ventricular chamber stiffness from the time for deceleration of early left ventricular filling. Circulation 92, 1933–1936 (1995)