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Relation of interatrial duration and *p* wave terminal force as a novel indicator of severe mitral regurgitation

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Abstract. – OBJECTIVES: Interatrial duration is defined as prolonged *p* wave on electrocardiogram. *p* waves with a negative terminal phase recorded in V1 enclosing an area of one small square on the electrocardiogram is significantly and strongly correlated with interatrial duration. The aim of study was to investigate whether interatrial duration with *p* terminal force can be used as reflection of echocardiographic severity of mitral regurgitation.

MATERIALS AND METHODS: Sixty two consecutive patients with mitral regurgitation. were prospectively studied. Age/gender matched 57 subjects who had normal mitral structure and did not have mitral regurgitation. Patients with mitral regurgitation referred to a single cardiac center for echocardiography and who met the entry criteria documented moderate or severe mitral regurgitation with sinus were included. The interatrial duration was defined on the routine 12-lead electrocardiogram (50 mm/s, 10 mm/mV) using the greatest duration of *p* waves from D2, D3, AVF and V1.

RESULTS: There was a positive correlation between interatrial duration (≥ 110 ms) and effective regurgitant orifice (r = 0.3, *p* < 0.001). However, left atrial diameter and brain natriuretic peptide were significantly higher in cases with mitral regurgitation. There was also strong correlation between interatrial duration (≥ 110 ms) and *p* terminal force and left atrial diameter. ROC analysis revealed that interatrial duration of > 110 msec. could predict of severe mitral regurgitation with 88% sensitivity and 100% specificity.

CONCLUSIONS: Severe mitral regurgitation, left atrial diameter was correlated with *p* terminal force and interatrial duration. Significant interatrial duration (≥ 110 ms) and *p* terminal force might be considered as novel indicators of severe mitral regurgitation.

Key Words:
Mitral regurgitation, Interatrial duration, *p* wave terminal force, Echocardiography, Brain natriuretic peptide.

Introduction

Interatrial block or duration denotes excessive time for sinus impulses to conduct from the right to the left atrium[1]. Interatrial duration is defined as a prolonged *p* wave (≥ 110 ms) on electrocardiogram[2]. It is depicted as prolonged, often notched, *p* waves with distinguishable right atrium and left atrium components on the electrocardiogram[3]. Currently, interatrial duration has been demonstrated to be a predictor of atrial fibrillation, an indicator of dilated and impaired left atrial function and a predictor of embolic stroke[4-6]. *p* waves with a negative terminal phase (*p* terminal force) recorded in V1 enclosing an area of one small square on the electrocardiogram (≥ 40 ms × 1 mm) is significantly and strongly correlated with interatrial duration[7]. The importance of interatrial duration and *p* terminal force as reflection of echocardiographic severity in mitral regurgitation has not been studied extensively. The aim of this study was to investigate whether interatrial duration with *p* terminal force can be used as a reflection of severe mitral regurgitation.

Patients and Methods

All patients were asymptomatic, minimally symptomatic or mild symptomatic and the echocardiographic examination was requested on the basis of the presence of a systolic murmur. Patients with mitral regurgitation referred to a single cardiac center for echocardiography and between June 2010 and September 2011, and who met the entry criteria [documented moderate (grade 2 or 3) or severe (grade 3 or 4) mitral regurgitation with sinus rhythm] were included. A

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total of 62 consecutive patients (mean age 45 ± 13 years) with mitral regurgitation were prospectively studied. Age/gender matched 57 subjects (mean age 44.,3 ± 12 years) who had normal mitral valvular structure and did not have mitral regurgitation served as controls. All patients were asymptomatic, minimally symptomatic or mild symptomatic.

Echocardiographic Data

Complete transthoracic echocardiography was performed in all subjects (Vivid S6, GE Vingmed Ultrasound AS, Horten, Norway) and underwent a comprehensive examination, including M-mode, two-dimensional and Doppler echocardiography. Conventional left venricular M-mode measurements included the estimation of left ventricular end-diastolic dimension, left ventricular end-systolic dimension, thickness of interventricular septum, posterior wall and left atrial dimension. Left ventricular end-systolic and end-diastolic dimensions, the left ventricular ejection fraction and left atrial dimensions were measured according to the guidelines of the American Society of Echocardiography[8]. Left atrial dimension was estimated from the parasternal long-axis view. Ejection fraction was measured from the apical four-chamber view using the modified Simpson's single plane method. The degree of mitral regurgitation was identified by using mitral effective regurgitant orifice and regurgitant volume. The largest proximal isovelocity surface area radius (at the negative aliasing velocity of 38-42 cm/s) was selected for analysis and effective regurgitant orifice was calculated by the simplified formula ($r^2/2$). Mitral regurgitation was graded as moderate if the valve effective regurgitant orifice was 0,20-0,39 cm^2 and regurgitant volume was 30-59 mL, severe mitral regurgitation if it was > 0,4 cm^2 and mitral regurgitant volume > 60 mL[9]. Mitral regurgitation grade was assessed by one independent cardiologist blinded to the patient's echocardiographic results.

Measurement of Brain Natriuretic Peptide

Blood sampling was obtained for all patients immediately after enrollment in the echocardiographic laboratory. 10 ml of blood sample was drawn from a peripheral vein, immediately placed on ice and transferred to the laboratory facilities. The AxSYM (Abbott Laboratories, Abbott Park, IL, USA) analyzer was used for brain natriuretic peptide measurement, a microparticle enzyme immunoassay that is a 2-site assay which uses a monoclonal anti- brain natriuretic peptide antibody and measures a fluorescence product.

Measurement of interatrial Duration and p Terminal Force

The interatrial duration was defined on the routine 12-lead electrocardiogram (filter range, 0.15 to 100 Hz; 50 mm/s, 10 mm/mV) using the greatest duration of *p* waves from D2, D3, AVF and V1. Because 1 mm represents 20 ms on electrocardiogram with such standardization to increase diagnostic specificity we used ≥ 110 ms as our criterion for interatrial duration diagnosis. For increased specificity, a *p* wave of ≥ 110 ms was used to diagnose significant interatrial duration (Figure 1). P-terminal force was defined as a biphasic *p* in lead V1 with an area of ≥ 1 small square on the electrocardiogram (Figure 2). Etiologies of mitral regurgitation were chronic rheumatic disease and mitral valve prolapse. Patients with any of the following were excluded: atrial fibrillation, the presence of moderate to severe mitral stenosis, the presence of moderate to severe aortic regurgitation, the presence of aortic stenosis, concomitant organic tricuspid stenosis, blood pressure > 140/90 mmHg, heart failure and ischemic cause of mitral regurgitation. All patients were in normal sinus rhythm. The electrocardiogram was analyzed by an independent

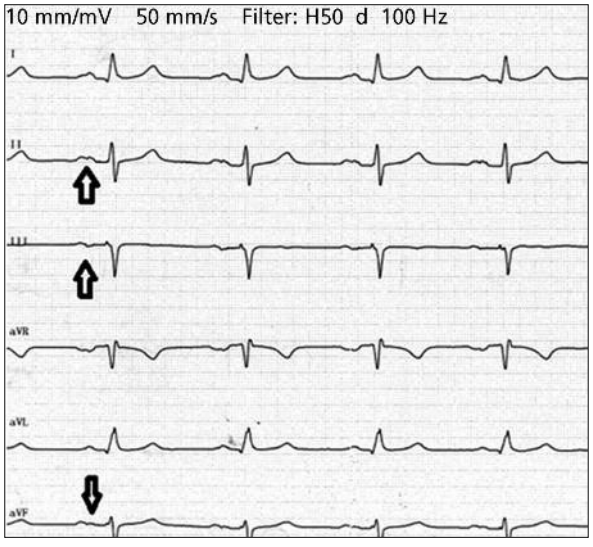

Figure 1. Surface electrocardiogram revealing interatrial duration in inferior leads *(arrows)*.

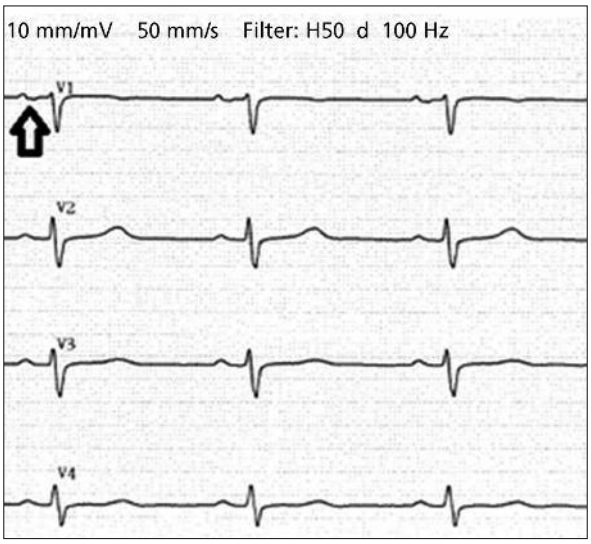

Figure 2. Surface electrocardiogram revealing P terminal force in V1 *(arrows)*.

readers blinded to the echocardiographic findings. Correlations for interobserver variability were good.

Statistical Analysis

Statistical Package for Social Sciences software (SPSS 12, SPSS Inc., Chicago, IL, USA) was used for analysis. Descriptive parameters were shown as mean±standard deviation or in percentages. Student *t*-test and Pearson's chi-square tests were used to analyze the differences in means and proportions between groups. Correlation analysis was done by Pearson test. A *p* value of < 0.05 was considered significant.

Results

We analyzed 62 consecutive patients with mitral regurgitation and 57 normal subjects. Twenty seven patients with mitral regurgitation had severe and 35 had moderate regurgitation, 34 of them had fibrotic mitral valve and the rest had mixomatous type valvular degeneration. In three patients there were cordal rupture in severe mitral regurgitation group and they were mild symptomatic. In these three patients' interatrial duration was < 110 ms.

Comparison of demographic characteristics, electrocardiographic/echocardiographic features and brain natriuretic peptide levels between groups were shown in Table I. Age, gender and heart rate were statistically similar between patients with mitral regurgitation and controls. However, mean ejection fraction, effective regurgitant orifice; regurgitant volume, left ventricular end-diastolic diameter, left atrial diameter and brain natriuretic peptide were significantly higher in cases with mitral regurgitation. Furthermore, interatrial duration and *p* terminal force were significantly more frequent among patients with mitral regurgitation (Table I).

Echocardiographic variables of patients with mitral regurgitation according to the presence of *p* terminal and interatrial duration were further analyzed. Mean effective regurgitant orifice, regurgitant volume, left atrial diameter and brain natriuretic peptide were significantly higher in patients with *p* terminal and interatrial duration whereas mean ejection fraction was significantly lower (Table II). Comparison of patients in mitral

Table I. Comparison of demographic, electrocardiogram, echocardiographic characteristics and brain natriuretic peptide levels of patients with controls.

	Patient (n = 62) mean ± SD	Control (n = 57) mean ± SD	*p*
Age	45 ± 13	44 ± 12	NS
Male/Female	30/32	29/28	NS
Heart rate	73 ± 9	74 ± 8	NS
Left ventricular ejection fraction (%)	59 ± 4	63 ± 2	0.001
Left ventricular end-diastolic diameter (mm)	54 ± 4	45 ± 3	< 0.001
Left ventricular end-systolic diameter (mm)	38 ± 4	31 ± 3	< 0.001
Interventricular septum (mm)	10.5 ± 1.2	9.7 ± 1	= 0.001
Posterior wall (mm)	9.4 ± 1.2	9.4 ± 1.1	NS
Left atrial dimension (mm)	49 ± 6	35 ± 2	< 0.001
Effective regurgitant orifice (mL)	0.35 ± 0.12	-	
Regurgitant volume (mL)	53 ± 15	-	
Interatrial duration (≥110 ms) (n, %)	27 (43)	0	< 0.001
P terminal force (n, %)	47 (75)	11 (19)	< 0.001
Brain natriuretic peptide (pg/mL)	61 ± 40	16 ± 7	< 0.001

Table II. Echocardiographic variables of patients with mitral regurgitation according to the presence of *p* terminal and interatrial duration (≥ 110 ms).

	***p* terminal force present (n = 47) mean ± SD**	***p* terminal force absent (n = 15) mean ± SD**	***p* value**
Effective regurgitant orifice (mL)	0.4 ± 0.1	0.2 ± 0.1	< 0.001
Regurgitant volume (mL)	58 ± 14	38 ± 10	< 0.001
Left atrial dimension (mm)	48 ± 7	36 ± 5	< 0.001
Ejection fraction (%)	59 ± 4	63 ± 2	= 0.001
Brain natriuretic peptide (pg/mL)	59 ± 40	20 ± 10	< 0.001
	Interatrial duration (≥ 110 ms) present (n = 27)	**Interatrial duration (≥ 110 ms) absent (n = 35)**	***p* value**
Effective regurgitant orifice (mL)	0.5 ± 0.1	0.3 ± 0.1	< 0.001
Regurgitant volume (mL)	67 ± 10	43 ± 11	< 0.001
Left atrial dimension (mm)	55 ± 4	39 ± 5	< 0.001
Ejection fraction (%)	57 ± 5	62 ± 3	< 0.001
Brain natriuretic peptide (pg/mL)	76 ± 35	38 ± 17	< 0.001

regurgitation groups according to the presence of interatrial duration and *p* terminal force showed that most of the patients with interatrial duration and *p* terminal had severe mitral regurgitation (Table III).

Correlation analysis revealed that there was a statistically positive correlation between interatrial duration (≥ 110 ms) and effective regurgitant orifice, regurgitant volume, left ventricular end-diastolic dimension, left ventricular end-systolic dimension (r = 0.3, $p < 0.001$; r = 0.4, $p < 0.001$; r = 0.3, $p < 0.001$; and r = 0.4, $p < 0.001$, respectively) and a strong negative correlation between left ventricular ejection fraction and presence of interatrial duration (≥ 110 ms) (r = –0.4, $p < 0.001$). The presence of left atrial enlargement was associated with high prevalence of significant interatrial duration (r = 0.4, $p < 0.001$). There was also a strong correlation between interatrial duration (≥ 110 ms), left atrial diameter and *p* terminal force (r = 0.5, $p < 0.001$) (Figure 3).

ROC analysis revealed that a cut-off value of interatrial duration of > 110 msec. could predict of severe mitral regurgitation with 88% (95% Confidence interval; 67-96%) sensitivity and 100% specificity (95%; 90-100%); [Area under the curve = 0.98 (95% Confidence interval; 0.9-0.99; positive predictive value = 0.100, negative predictive value = 0.90] (Figure 4).

Discussion

The present study questioned the utility of interatrial duration with *p* terminal force on electrocardiogram as an indicator of severity in chronic mitral regurgitation. This is the first study reporting that severe mitral regurgitation was associated with presence of significant *p* terminal force and interatrial duration.

The most common causes of mitral regurgitation are mitral valve prolapse, chronic rheumatic disease or degeneration[10]. Mitral valve prolapse

Table III. Number of patients in mitral regurgitation groups according to the presence of interatrial duration and *p* terminal force.

	Control (n = 57)	**Moderate mitral regurgitation (n = 35)**	**Severe mitral regurgitation (n = 27)**	**Total**	***p***
interatrial duration (≥ 110 ms) (n)	0	3	24	27	< 0.001
p terminal force (n)	11	20	27	58	< 0.001

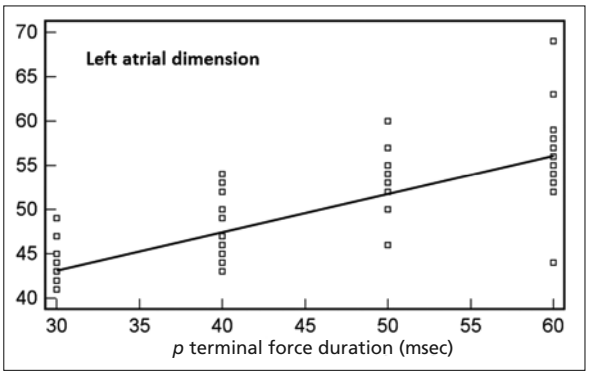

Figure 3. Correlation between left atrial dimension (mm) and *p* terminal force duration in patients with mitral regurgitation.

has been described as one of the most common cardiac valvular abnormalities in industrialized countries and the clinical manifestations of mitral valve prolapse are multiple[11]. In the developing countries of the world, rheumatic fever and rheumatic valve disease remain significant medical and public health problems[12]. Normal P-wave duration, as classified by the World Health Organization/International Society and Federation of Cardiology Task Force[2], is <110 ms. Significant interatrial duration for increased specificity, *p* wave ≥ 110 ms is used to diagnose and predict atrial fibrillation, stroke and left atrial enlargement[5,6] interatrial duration is also correlated with severe mitral regurgitation, effective regurgitant orifice, regurgitant volume, left ventricular end-diastolic dimension, left ventricular end-systolic dimension and increased brain natriuretic peptide levels. It has been shown that P-wave duration increases along with the progression of disease severity in mitral stenosis[13]. Recently published in a study Yuce et al[14] have demonstrated associate interatrial duration and *p* terminal force in patients with mitral stenosis.

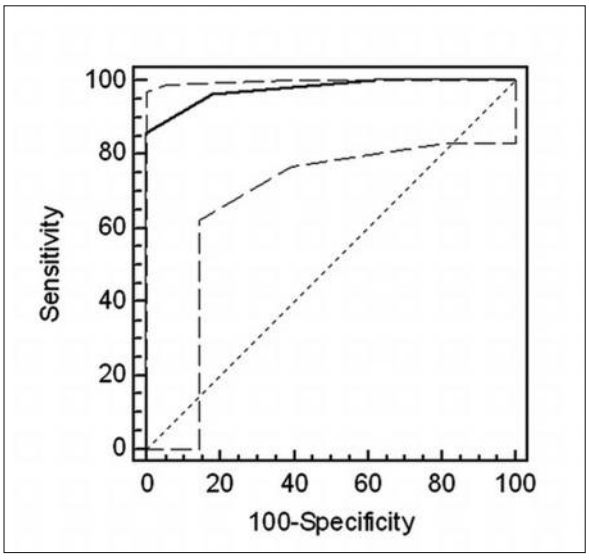

Figure 4. ROC curve of interatrial duration in prediction of severe mitral regurgitation.

Excessive time reflection should be termed significant interatrial duration if *p* wave duration is ≥ 110 ms to improve specificity. However, interatrial duration is a frequently overlooked and ignored electrocardiogram finding and a precise interpretation of the electrocardiogram is, therefore, mandatory. We recommend that attention and consideration should be given to these easily measurable waves in the determination of severity of mitral regurgitation. The presence of significant *p* wave terminal force and interatrial duration on surface electrocardiogram would most likely be helpful to guide the timing of echocardiography in asymptomatic patients under the age of 50 with mitral regurgitation. This would provide a potentially alternative screening tool for patients with mixomatous and chronic rheumatic diseases with cardiac murmur in young and middle age patients. But this may not meet in patients with acute cordal rupture in severe mitral regurgitation group.

Conclusions

This study demonstrated that significant interatrial duration (≥ 110 ms) and *p* terminal force might be considered as a novel indicator of echocardiographic severity of mitral regurgitation during follow-up.

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