The Relationship between P Wave Dispersion and Diastolic Dysfunction in Patients with Significant and Insignificant Coronary Artery Disease

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Abstract: We investigated the relationship between P wave dispersion, which is easily measured on the surface electrocardiogram and left ventricular end diastolic pressure and echocardiographic markers of diastolic dysfunction in patients with coronary artery disease (CAD). Methods: We studied 50 patients with CAD: 8 patients with non significant CAD (16%) and 42 patients with significant CAD (84%). P wave dispersions were calculated by measuring minimum and maximum P wave duration values on the surface electrocardiogram. The relationships between P wave dispersion and the left ventricle end diastolic pressure (LVEDP), Left atrial volume (LAV), left atrial diameter (LAD) and echocardiographic measurements of diastolic dysfunction were investigated. Results: P wave dispersion was 65.7 ± 18.8 ms. The magnitude of P wave dispersion was higher in group of LVEDP > 15 than those who had their LVEDP < 15 mmHg, (70.6 ± 15.2 vs. 60 ± 20.4 respectively and p value 0.04). There was a significant positive correlation between the values of p wave dispersion and LVEDP, LAD and LAV as the correlation factor was (0.3, 0.5, 0.6, respectively and the p values were significant) . Also P wave dispersion was found to be higher in the group of significant CAD than insignificant CAD (68.7 ± 18.5 vs. 50 ± 10.35 respectively and p value 0.008). When patients with LVDD were staged, PD was 49 ± 9 ms in stage 1(9 pts.), 55 ± 10 ms in stage 2 (26 pts), and 58 ± 7 ms in stage 3 (15 pts.). As the severity of diastolic dysfunction increased, P wave dispersion increased but the difference did not reach statistical significance (P 0.07). Conclusion: We conclude that P wave dispersion is a non invasive marker for LVEDP and highly correlated to LA volume. P wave dispersion is another alternative for assessment of LV diastolic Dysfunction in CAD. P wave dispersion did not show a significant change in the 3 stages of diastolic dysfunction in our small studied groups so larger studies might be of help to elucidate that difference. [Journal of American Science. 2011;7(1):108-115]. (ISSN: 1545-1003).

Keywords: Wave Dispersion, Diastolic Dysfunction, Coronary Artery Disease

1. Introduction

There is growing recognition that congestive heart failure caused by a predominant abnormality in left ventricular (LV) diastolic function as in hypertensive and ischemic heart disease (that is, diastolic heart failure) is common and causes significant morbidity and mortality[(1)]. In left ventricular diastolic dysfunction (LVDD), maintenance of sinus rhythm and atrial contractions is vital for stability of cardiac output. If atrial fibrillation occurs, atrial output decreases considerably and results in an increase of LVEDP and progression of diastolic heart failure, which worsens the patient's clinical condition [(2)].

Today, several noninvasive electrocardiographic (ECG) indicators have been investigated to predict the occurrence of arrhythmia in patients with LVDD. It has been shown, for example, that P wave dispersion (PD) because of its relation to the nonhomogenous and interrupted conduction of sinusal impulses both intra and interatrially is a noninvasive indicator that enables the calculation of atrial fibrillation risk on the 12-lead surface ECG and correlates to LVEDP (left ventricle end diastolic pressure) [(3,4)].

We investigated the relationship between PD and the presence of LVDD as detected by Doppler echocardiography and LVEDP as measured invasively during coronary angiography in patients with significant and insignificant ischemic heart disease.

2. Patients and Methods

Population:

After local ethics committee approval and guardian oral and written consent the study was conducted. The study was designed as a prospective study and the population consisted of 50 patients who were scheduled for elective left heart catheterization (between the year 2008 and 2010) in critical care department at Cairo University. We excluded patients

with thyroid dysfunction, uncontrolled diabetes mellitus, chronic liver or renal disease, valvular heart disease, electrolyte imbalance, or alcohol use

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Echocardiography:

All patients were examined by trans-thoracic Doppler echocardiography within 2 hours of catherization by an operator who was blinded to the patient's history and hemodynamic data. An ATL 5000 with S3 probe was used to perform echocardiography using the following protocol.

1. Left atrial volume (LAV) was calculated, using an ellipse formula, as:

$$LAV = \frac{\pi}{6} \times D1 \times D2 \times LAD$$

Where D1 is the LA dimension in a long-axis measurement from the mitral coaptation point to the LA posterior wall, and D2 is the transverse LA dimension.LAD is measured using American Society of Echocardiography (ASE) guidelines. All are measured as end-systole.

2. Mitral valve inflow assessment by Pulsed wave Doppler, sampling volume (1-2 mm) placed between the mitral leaflet tips, parallel with the mitral inflow, as determined by color flow Doppler echocardiography in apical four chamber view. Doppler variables were recorded from the velocity tracing as early mitral inflow peak velocity (E), deceleration time of E wave (DT), peak velocity of late mitral inflow (A) and isovolumic relaxation time (IVRT).
3. Tissue Doppler imaging (TDI) measurements of the mitral annulus were obtained from the apical four chambers view. Tissue Doppler mode was selected, at a rate of 100-133 color Doppler frames/sec using a velocity range of 0.1-16 cm/sec. A 1.5 mm sampling volume was placed sequentially at the medial and lateral mitral annulus.

Analysis was performed for the early (Ea) and late (Aa) diastolic peak velocity of medial and lateral mitral annulus. These variables were analyzed individually, and as the average of the medial and lateral annulus. All measurements must be averaged from at least three beats. To determine intra-observer variability of Doppler echocardiographic measurements, variables in randomly selected patients were analyzed on two different occasions.

In patients without LVDD, we looked for false normalization patterns by applying the Valsalva maneuver, checking pulmonary venous flow. In addition, we measured left ventricular ejection fraction (LVEF) by the Simpson method, LV diastolic and systolic diameters with M mode echocardiography, and segmental wall motion defects with 2-dimensional (2-D) echocardiography.

Patients who had LVDD were classified accordingly: stage 1, prolonged relaxation pattern; stage 2, pseudonormalization pattern; and stage 3, restrictive pattern.

Electrocardiogram:

Twelve-lead ECGs of all patients at rest, with 1 mV/cm amplitude and 50 mm/sec rate, were obtained. Measurements were performed on high resolution tracings. The beginning of the P wave was defined as the point where the initial deflection of the P wave crossed the isoelectric line, and the end of the P wave was defined as the point where the final deflection of the P wave crossed the isoelectric line. Patients whose measurements could be performed in at least 8 derivations were included in the study. In all patients, derivations were excluded if the beginning or the ending of the P wave could not be clearly identified. P wave dispersion was calculated by subtracting the minimum P wave duration from the maximum P wave duration.

Cardiac Catheterization:

After complete echocardiographic examination, left ventricular catheterization was performed via the femoral approach, using 6-8 French sheaths. Left ventricular diastolic pressure was directly measured by fluid filled pigtail catheter attached to a pressure transducer (model P23XL or P10EZ, Becton Dickinson, Critical Care Systems, Singapore).

The Fourth intercostal spaces between the A-P diameters of the chest wall measured as Zero level. All hemodynamic data were recorded before the left ventriculogram was performed. The left ventricular end diastolic pressure (LVEDP) was obtained by computer recording.

Results from at least 5 beats were averaged. After that, standard technique coronary angiography was performed. Demographic data including age, sex, underlying disease, risk factors for coronary artery disease, drug administration and indications for catheterization were recorded.

Statistical analysis:

Data were summarized using mean Data. They were collected, verified, revised and edited on PC. They were then analyzed statistically using SPSS statistical package version 11.5. The data were presented as mean and standard deviation for continuous variables, independent samples *t*-test for normal distributed quantitative variables while quantitative variables that were not normally distributed were compared using non-parametrical Mann-Whitney test & Wilcoxon signed

rank test. Percentages were compared using Chi-square test or Fisher's exact test. Logistic regression was used for assessment of single independent factor relation to binary factors. Pearson's correlation coefficient was used for correlation of continuous variables and LVEDP. The predictive accuracy for LVEDP>15 mmHg was assessed from receiver operating characteristic curves (ROC). Intra-observer variation was presented by means of absolute percent differences between two sampling. A P value of <0.05 was accepted as statistically significant.

3. Results:

The mean age was 53.6±9.7 years and 66% were men. There were 8 patients with non significant CAD (16%) and 42 patients with significant CAD (84%). The mean ejection fraction (EF) by modified Simpson's rule was 57.7±11.9%. The patients with significant coronary artery disease (CAD) had higher prevalence of hypertension (23/42 versus 3/8 but the p value was not significant 0.4). Mean LVEDP was 17.6±6 mmHg in patients with significant coronary artery disease versus 15.7±5.1 mmHg in non significant CAD and p value was 0.4 (Table 1).

The Doppler echocardiographic parameters are shown in Table 2. There were minor intraobserver variations; 1.00±2.39% for E/Ea derived from medial mitral annulus and 2.64±0.35% for E/Ea derived from lateral mitral annulus.

Table 1: Demographic and clinical data in both CAD groups

Characteristics	Overall N(50)	Non significant CAD N(8)	Significant CAD N(42)	P value
Age	53.6±9.7	54.625±10.716	53.357+9.679	0.76
Sex (male)	33 (66%)	4/8	29/42	0.4
Underlying disease				
Diabetes mellitus	20(40%)	2/8	18/42	0.45
Hypertension	26(52%)	3/8	23/42	0.5
Dyslipidemia	20(40%)	1/8	19/42	0.12
Smoking	27 (54%)	3/8	24/42	0.44
Indication for catheterization				
IHD	27 (54%)	5/8	22/42	0.7
Post MI	18 (36%)	2/8	16/42	
CHF	5 (10%)	1/8	4/42	
Medications used within 2 months				
ACEI	17 (34%)	4/8	13/42	0.4
ARBS	5 (10%)	0/8	5/42	0.6
Statins	37 (74%)	5/8	32/42	0.4
Nitrates	40 (80%)	7/8	33/42	0.5
Diuretics	11 (22%)	1/8	10/42	0.66
ASA	47 (96%)	8/8	39/42	0.58
Clopidogrel	40 (80%)	3/8	37/42	0.008*
Hemodynamic values:				
SBP mmHg	123.9±19.15	127.500±29.640	123.214±16.886	0.70
DBP mmHg	76.2±10.8	74.375±15.909	76.547±9.783	0.71
HR b/min	74.5±13.9	73.875±16.012	74.619±13.737	0.90
LVEDP mmHg	17.3±6.6	15.750±5.120	17.595±6.843	0.4

Table 2: The Doppler echocardiographic parameters

	Overall (50)	No significant CAD	Significant CAD	P value
E	69.626±21.620	55.687±10.908	72.281±22.208	0.004
A	64.682± 23.597	68.412+20.375	63.971±24.317	0.59
E/A	1.290± 0.877	0.850±0.200	1.373±.931	0.002

DT	176.420± 53.805	168.000+51.790	178.023±54.639	0.63
IVRT	88.96± 25.852	94.125±28.940	87.976±25.486	0.59
Ea medial	8.270± 3.948	10.351±3.598	7.874±3.926	0.10
Ea lateral	9.812± 3.392	9.625±2.603	9.847±3.547	0.83
Ea mean	9.042± 3.090	9.993±2.798	8.861±3.140	0.32
Aa medial	9.494± 2.514	11.175±1.566	9.173±2.545	0.01
Aa lateral	10.564± 3.525	12.512+1.644	10.193+3.675	0.009
Aa mean	10.029±2.756	11.843±1.427	9.683±2.822	0.004
E/Ea medial	10.923±6.356	8.271±3.466	11.428±6.679	0.004
E/Ea lateral	8.459±6.793	6.270±2.357	8.876±7.286	0.07
E/Ea mean	9.632±6.406	7.270±2.767	10.082±6.815	0.06
EF%	57.7± 11.9	64.7±8.4	56.36±12.16	0.03
LAD	3.7±0.5	3.5±0.4	3.8±0.6	0.08
LAV	39±16.8	29.6±11.5	40.9±17.1	0.037
P wave dispersion	65.7±18.8	50±10.35	68.69±18.58	0.008

The magnitude of P wave dispersion was higher in group of LVEDP > 15 than those who had their LVEDP < 15 mmHg, (70.6±15.2 vs 60±20.4 respectively and P value 0.04). Also P wave dispersion was found to be higher in the group of significant CAD than insignificant CAD (68.7±18.5 vs 50±10.35 respectively and P value 0.008). There was no significant difference regarding p wave dispersion between the two groups of high and low LVEF (64.4±15.9 vs. 69±25.6, respectively and P value 0.4) as sown in Table (3).

Table 3: P wave dispersion in different population subgroups

	P wave dispersion	P value
LVEDP>15 (27pts)	70.6±15.2	0.04
LVEDP<15 (23pts)	60±20.4	
Significant CAD	68.7±18.5	0.008
Insignificant CAD	50±10.35	
LVEF>50%	64.4±15.9	0.4
LVEF<50%	69±25.6	

There was a significantly positive correlation between P wave dispersion and LAD, LAV, LVEDP, E/A, E/Ea medial, RWMA score and QRS score, but not to age, DT, IVRT, LVEF. The correlation factor and p wave are shown in Table (4):

Table 4: P wave dispersion and other echocardiographic data

	P wave dispersion	
	R	P wave

LAD	**0.5**	**0.0001**
LAV	**0.6**	**0.0001**
LVEDP	**0.3**	**0.03**
E/A ratio	**0.47**	**0.0001**
DT	**-0.18**	**0.19**
IVRT	**-0.12**	**0.39**
E/Ea medial	**-0.41**	**0.003**
E/Ea lateral	**-0.1**	**0.4**
A/Aa medial	**-0.2**	**0.15**
A/Aa lateral	**-0.3**	**0.02**
LVEF	**-0.23**	**0.09**
RWMA	**0.3**	**0.03**
QRS score	**0.3**	**0.01**
Age	**-0.5**	**0.8**

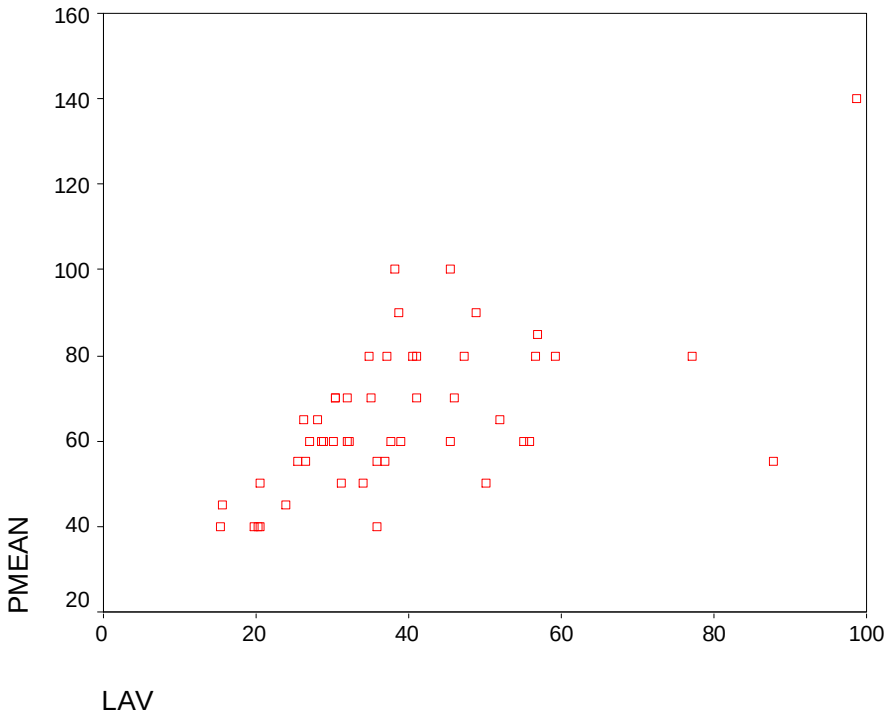

Figure 1: PD and LAV scatter plot

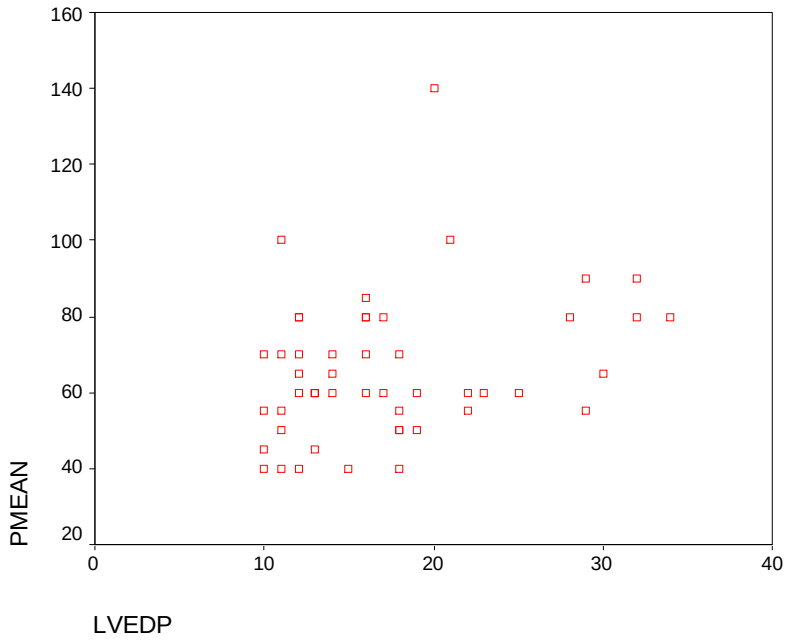

Figure 2: PD and LVEDP scatter plot

When patients with LVDD were staged, PD was 49± 9 ms in stage 1(9 pts.), 55 ± 10 ms in stage 2 (26 pts), and 58 ± 7 ms in stage 3 (15 pts.). Although PD increased as the severity of LVDD increased, these differences did not reach statistical significance (P value 0.07).

4. Discussion:

In a study investigating the clinical variables that affect PD, Aytemir and colleagues17 found that among age, sex, and heart rate, only age was related. In our study, none of those variables had an effect on PD and that was in concordance of Huseyin Gunduz et al [(22)].

Thirty to forty percent of patients who show clinical signs of heart failure have normal systolic function but LVDD. Diastolic function usually declines before systolic function, and this precedes clinical signs. Therefore, diagnosis of diastolic dysfunction is very important, specially in patients with coronary artery disease (CAD), for early diagnosis, follow-up, treatment, and prognosis evaluation in cardiac patients [(5-8)].

Because of increased end-diastolic pressure in LVDD, the maintenance of sinus rhythm and atrial contractions is vital for the stability of cardiac output. If atrial fibrillation occurs, the loss of atrial kick, which accounts for 40% of atrial output, results in an increase of LVDD and in progression of diastolic heart failure [(2)].

Hypertension and ischemic heart disease are among the most important causes of atrial fibrillation. Left ventricular diastolic dysfunction in a hypertrophic or ischemic ventricle results in an increase in left ventricular end-diastolic (LVED) pressure and in left atrial dimensions. The increase in left atrial dimensions as a result of rising intra-atrial pressure changes the geometry of atrial fibrils; this, in combination with nonhomogenous fibrosis of the left atrial wall, interrupts the conduction of sinus impulses. As a result, reentry focuses appear, which can start atrial fibrillation [(9-12)].

P wave dispersion is related to the nonhomogenous and interrupted conduction of sinus impulses intraand interatrially. Currently, PD is described as a noninvasive indicator of atrial fibrillation risk, which can be calculated easily on a 12-lead surface ECG [(3,4)].

Although it has been stated that left atrial diameter is not an important predictor for atrial fibrillation and that P wave duration is unrelated to left atrial diameter [(3,18)], other studies have reached contrary conclusions [(19, 20)]. Our finding that an increase in PD is related to left atrial diameter and volume but not to stage of LVDD although highly correlated to LVEDP in CAD. As a result, PD a variable easily measured on the surface ECG

increases significantly in patients with LVDD. This increase is apparent from the 1st stage of diastolic function.

In the literature, no study investigates the relationship between PD and each stage of LVDD or between the PD values of patients with significant and non significant CAD. Dogan and colleagues [13] compared hypertensive patients who had stage 1 LVDD with hypertensive patients who did not have LVDD and found PD to be higher in LVDD patients.

In 2005, Huseyin Gunduz [22] used transthoracic echocardiography to measure diastolic function variables and then compared the PD values of LVDD patients with the values of patients who did not have LVDD. In addition, he divided LVDD patients into 3 groups according to stage and into 2 groups according to cause (ischemic versus hypertensives). Our results showed that P wave dispersion is significantly correlated to LAV, LAD, E/A ratio and E/Ea medial and also to LVEDP in all studied population whether having significant or non significant CAD in concordance to Huseyin Gunduz's subgroup of ischemic patients despite the limitation of Huseyin Gunduz's study who did not perform angiography to all studied population.

As LVDD progresses from an "impaired relaxation" pattern to a restrictive pattern, increases in left atrial pressure and dimensions are expected. In our study, as the LVDD stage of patients progressed, left atrial dimensions increased significantly, but the increase in PD was unrelated to the stage of LVDD. It is known that PD increases in ischemic heart disease and hypertension [12,14-16]. Therefore, an increase in PD is expected in patients whose LVDD is associated with ischemic heart disease and hypertensive but there was no significant difference in the frequency of hypertension between our 2 subgroups of significant and non significant CAD.

Limitations of the Study:

Most of our hypertensive patients were on antihypertensive medications that may affect. Although we excluded patients who were using drugs that might affect atrial conduction or replaced the medications with other suitable antihypertensive drugs but still there are no good data on the effect of antihypertensive agents on PD. Isovolumetric relaxation time and deceleration time were measured by means of Doppler echocardiography. Interobserver and intraobserver variability in these measurements can be relatively high, so our Doppler by 2 investigators. There were minor intraobserver variations; 1.00 ± 2.39% for E/Ea derived from medial mitral annulus and 2.64±0.35% for E/Ea derived from lateral mitral annulus and 1.1+ 0.9 % for PD that is to avoid hidden mistakes if that done by a single investigator as other studies. Both investigators had no knowledge of the status of the patients. In our patients with LVDD, PD increased; but this increase was not related to the severity of LVDD. However, our number of patients was relatively low, and our data need support by larger studies. In addition, we did not investigate the relationship between P wave duration and the number and location of coronary lesions in patients with ischemic heart disease.

Conclusion:

P wave dispersion is a non invasive marker for LVEDP and highly correlated to LA volume. P wave dispersion is another alternative for assessment of LV diastolic Dysfunction in CAD. P wave dispersion did not show a significant change in the 3 stages of diastolic dysfunction in our small studied groups so larger studies might be of help to elucidate that difference.

References

1. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part II: causal mechanisms and treatment. Circulation; 105:1503-8, 2002.
2. Vasan RS, Levy D. The role of hypertension in the pathogenesis of heart failure. A clinical mechanistic overview. Arch Intern Med; 156:1789-96, 1996.
3. Dilaveris PE, Gialafos EJ, Andrikopoulos GK, Richter DJ, Papanikolaou V, Poralis K, Gialafos JE. Clinical and electrocardiographic predictors of recurrent atrial fibrillation. Pacing Clin Electrophysiol; 23:352-8, 2000.
4. Dilaveris PE, Gialafos EJ, Sideris SK, Theopistou AM, Andrikopoulos GK, Kyriakidis M, et al. Simple electrocardiographic markers for the prediction of paroxysmal idiopathic atrial fibrillation. Am Heart J; 135(5 Pt 1):733-8, 1998.
5. Mandinov L, Eberli FR, Seiler C, Hess OM. Diastolic heart failure. Cardiovasc Res; 45:813-25, 2000.
6. Vitarelli A, Gheorghiade M. Diastolic heart failure: standard Doppler approach and beyond. Am J Cardiol; 81(12A):115G-121G, 1998.
7. Dougherty AH, Naccarelli GV, Gray EL, Hicks CH, Goldstein RA. Congestive heart failure with normal systolic function. Am J Cardiol; 54:778-82, 1984.
8. Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. J Am Coll Cardiol; 26:1565-74, 1995.

9. Murgatroyd FD, Camm AJ. Atrial arrhythmias. Lancet; 341:1317-22,1993
10. Myeburg RJ, Kessler KM, Castellanos A. Recognition, clinical assesment and management of arrhytmias and conduction disturbances. In: Alexander RW, Schlant RC, Fuster V, editors. Hurst's the heart, arteries and veins. 9th ed. New York: McGraw-Hill; p. 873-941,1998.
11. Ciaroni S, Cuenoud L, Bloch A. Clinical study to investigate the predictive parameters for the onset of atrial fibrillation in patients with essential hypertension. Am Heart J; 139:814-9, 2000.
12. Dilaveris PE, Gialafos JE. P-wave dispersion: a novel predictor of paroxysmal atrial fibrillation. Ann Noninvasive Electrocardiol; 6:159-65, 2001.
13. Dogan A, Ozaydin M, Nazli C, Altinbas A, Gedikli O, Kinay O, Ergene O. Does impaired left ventricular relaxation affect P wave dispersion in patients with hypertension? Ann Noninvasive Electrocardiol; 8:189-93, 2003.
14. Dilaveris PE, Gialafos EJ, Chrissos D, Andrikopoulos GK, Richter DJ, Lazaki E, Gialafos JE. Detection of hypertensive patients at risk for paroxysmal atrial fibrillation during sinus rhythm by computer-assisted P wave analysis. J Hypertens; 17:1463-70, 1999.
15. Ozer N, Aytemir K, Atalar E, Sade E, Aksoyek S, Ovunc K, et al. P wave dispersion in hypertensive patients with paroxysmal atrial fibrillation. Pacing Clin Electrophysiol; 23 (11 Pt 2):1859-62, 2000.
16. Dilaveris PE, Andrikopoulos GK, Metaxas G, Richter DJ, Avgeropoulou CK, Androulakis AM, et al. Effects of ischemia on P wave dispersion and maximum P wave duration during spontaneous anginal episodes. Pacing Clin Electrophysiol; 22:1640-7, 1999.
17. Aytemir K, Hnatkova K, Malik M. Duration of the P wave dispersion in normal healthy population. Turk J Intervent Cardiol; 3:142-7, 1999.
18. Ishimoto N, Ito M, Kinoshita M. Signal-averaged P-wave abnormalities and atrial size in patients with and without idiopathic paroxysmal atrial fibrillation. Am Heart J; 139:684-9, 2000.
19. Flaker GC, Fletcher KA, Rothbart RM, Halperin JL, Hart RG. Clinical and echocardiographic features of intermittent atrial fibrillation that predict recurrent atrial fibrillation. Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. Am J Cardiol; 76:355-8, 1995.
20. Kerr CR, Boone J, Connolly SJ, Dorian P, Green M, Klein G, et al. The Canadian Registry of Atrial Fibrillation: a noninterventional follow-up of patients after the first diagnosis of atrial fibrillation. Am J Cardiol; 82(8A):82N- 85N, 1998.
21. Ashino K, Gotoh E, Sumita S, Moriva A, Ishii M. Percutaneous transluminal mitral valvuloplasty normalizes baroref lex sensitivity and sympathetic activity in patients with mitral stenosis. Circulation; 96:3443-9, 1997.
22. Huseyin Gunduz, MD Emrah Binak, MD Huseyin Arinc, MD: The relationship between P Wave Dispersion and Diastolic Dysfunction *(Tex* Heart Inst J; 32:163-7, 2005.

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