Diagnostic Value of Poor R-Wave Progression in Electrocardiograms for Diabetic Cardiomyopathy in Type 2 Diabetic Patients

Address for correspondence:
Ulas Bildirici, MD
Department of Cardiology
Kocaeli University Medical Faculty
41380 Kocaeli, Turkey
ihubildir@gmail.com

Ulas Bildirici, MD; Dilek Ural, MD; Eser Acar, MD; Aysen Agacdiken, MD; Ertan Ural, MD

Cardiology Department, Kocaeli University Medical Faculty, Kocaeli, Turkey

ABSTRACT

Background: Diabetic cardiomyopathy (DCMP) is a common complication of diabetes and is associated with increased mortality. It has been suggested that a poor R-wave progression in a resting electrocardiogram (ECG) could be a sign of cardiomyopathy.

Hypothesis: The aim of this study was primarily to analyze the relationship between poor R-wave progression and DCMP, and the effect of poor R-wave progression on cardiac functions in long-term follow-up.

Methods: Seventy type 2 normotensive diabetics (33 female, 37 male; mean age, 52.9 ± 10.4 years) were included in the study. Poor R-wave progression in an ECG was defined as an R wave <3 mm in V1-3 derivations. The patients were randomized in 2 groups, which were those without (group I, $n = 34$) and those with poor R-wave progression (group II, $n = 36$). All patients underwent conventional and tissue Doppler echocardiography and were followed in an outpatient clinic setting for 4 years.

Results: Demographic variables were similar between the 2 groups. In group II, left ventricular (LV) relaxation abnormality was more prevalent, the Tei index was higher, and in tissue Doppler mitral annulus Em velocities were significantly lower and Am velocities were higher than those with normal R-wave progression. At the end of the 4-year follow-up period, LV ejection fraction was decreased in group II, whereas LV mass index and Tei index were significantly increased.

Conclusions: LV diastolic dysfunction is more frequently observed in diabetic patients with poor R-wave progression in ECG, which may be an early sign of LV dysfunction and DCMP in diabetics.

Introduction

The prevalence of diabetes is steadily increasing, and the number of diabetic people is expected to reach 300 million globally by 2025.¹ Cardiovascular disease is a serious of complication of diabetes and is responsible for 80% of the deaths among diabetics.² Although coronary artery disease is very common, heart failure is also a major cause of mortality and morbidity in patients with diabetes mellitus.³ Up to 75% of patients with unexplained idiopathic dilated cardiomyopathy were found to be diabetic.⁴ The Framingham Heart Study showed that the frequency of heart failure in diabetic men is twice that of nondiabetics, and it is 5 times higher in diabetic women compared to nondiabetic women.^{1,5}

Diabetic cardiomyopathy (DCMP) was first reported in 1972 by Rubler.⁶ It is characterized by the development of diastolic dysfunction at the early stage followed by systolic dysfunction in the absence of coronary artery disease, hypertension, or significant valvular heart disease.⁷⁻⁹ In the Strong Heart Study, diabetes was significantly related to higher left ventricular (LV) mass and wall

thickness, increased arterial stiffness, and systolic dysfunction when compared with a matched control group.¹⁰ In the early phase of DCMP, the pathologic changes can be reversible with strict metabolic control, but in the continuous process the myocardial changes become irreversible and the risk of developing heart failure increases.^{8,11,12}

Although it is common, diagnosis of DCMP is very difficult. Of the many methods under evaluation, the most frequently used methods are magnetic resonance imaging and echocardiography. In electrocardiograms (ECGs), the poor R-wave progression can be seen in patients with LV hypertrophy, clockwise rotation, and previously transmitted anteroseptal myocardial infarction. Poor R-wave progression has been correlated with myocardial cell loss and can occur in several cardiac diseases, such as alcoholic and amyloid cardiomyopathies.^{13,14} Diabetes mellitus is also known to cause myocardial hypertrophy, necrosis, and apoptosis, and to increase interstitial tissue. The aim of the present study was to investigate the value of poor R-wave progression in the resting electrocardiogram as a diagnostic measure of DCMP in diabetic patients, and to evaluate its relation to the risk of developing heart failure and DCMP in these patients.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Methods

Patients

The study group consisted of 76 normotensive (blood pressure <130/80 mm Hg) patients who had type 2 diabetes mellitus for ≥ 5 years. The presence of ischemic heart disease was eliminated by myocardial perfusion scintigraphy. Patients older than 65 years, using insulin treatment, using antihypertensive treatment, with suspicious previous myocardial infarction, and with chronic renal failure were excluded.

Poor R-wave progression was defined as an R-wave amplitude <3 mm in V1-3 derivations in the resting electrocardiogram.¹⁵ The patients were divided into 2 groups according to their electrocardiographic findings: patients without (group I) and patients with poor R-wave progression (group II).

Echocardiography

Two-dimensional and Doppler echocardiographic examinations were performed with a standard ultrasonography machine (GE Vivid 7; GE Vingmed, Horten, Norway). LV wall thickness, left atrial, right ventricular, and LV dimensions were measured from parasternal long-axis M-mode tracings, according to standard criteria.¹⁶ The LV ejection fraction (LVEF) was estimated from an apical 4-chamber view using Simpson's method.¹⁷ Mitral and tricuspid flow velocities were obtained from the apical 4-chamber view, with the pulsed-wave Doppler sample volume placed at the tips of the mitral leaflets as previously described.¹⁸ Abnormal relaxation was defined as a proportion of mitral early filling velocity to atrial filling flow velocity <1.0, deceleration time >240 msec, and isovolumetric relaxation time <90 msec. The Tei index was calculated for the general evaluation of LV functions.

For tissue Doppler echocardiographic examination, recordings from 4 parts of the mitral annulus (septal, lateral, anterior, and inferior) in the apical 4-chamber view were taken. Systolic, early diastolic, and atrial filling velocities were recorded.

Blood Samples

Peripheral blood samples were drawn and placed in tubes using 21-gauge multiple-draw blood collection needles in the fasting state and without venous occlusion. Hemogram, blood glucose, lipid profile, urea, and creatinine measurements of the study group were carried out by the analytical unit of the biochemistry department of our institution using standard methods. Insulin level was measured with electrochemiluminescence assay, and HbA1c was measured with high-performance liquid chromatography method. Microalbuminuria was detected by urine dipstick method.

The patients were invited for an annual checkup for the next 4 years and their clinical and echocardiographic

findings were re-evaluated at the end of the follow-up period. An exercise stress test was done yearly to identify the development of coronary artery disease. The 2 groups were compared in terms of development of DCMP and heart failure.

The study was approved by the local ethical committee and written informed consent was obtained from all patients.

Statistical Evaluation

The SPSS 13.0 (SPSS Inc., Chicago, IL) statistical software package was used for statistical analysis. Data are given as mean and standard deviation. Normality tests were used for all variables. For comparison of echocardiographic and biochemistry test results of the 2 groups, the Student *t* test was used for continuous changes fitting normal distribution, and the Mann-Whitney *U* test was used for constant changes that did not fit the normal distribution. The χ^2 or Fischer exact test were applied for the categorical data. *AP* value <0.05 was accepted as statistically significant.

Results

Five patients who developed coronary artery disease during the follow-up were excluded from the study, and 1 patient was excluded because of lack of communication. Statistical analysis was performed for the remaining 70 patients. Baseline characteristics of the patients with and without poor R-wave progression are presented in Table 1. No differences were found in age, sex, body mass index, and duration of diabetes mellitus. Only resting heart rate and insulin levels were significantly higher in group II compared to group I patients (Table 1).

The standard echocardiographic findings of both groups are given in Table 2. In group II, LV wall thickness, LV mass index, and left atrial diameter were significantly greater than in group I. Patients in group II more frequently had an abnormal LV relaxation pattern and higher Tei index. In tissue Doppler echocardiographic examination of group II, mean Em velocities were markedly lower, and Am velocities were higher than in patients without poor R-wave progression.

Clinical characteristics were compared at the end of the 4-year follow-up. Signs of dyspnea or moderate effort intolerance were detected in 7 patients (19%) with and in 4 patients (12%) without poor R-wave progression (*P* = not significant). Body mass index, blood pressure, and lipid profile were not different between the 2 groups and also when compared to baseline values (data not shown). Blood glucose control was significantly worse in patients with poor R-wave progression. At the end of the 4-year follow-up, their fasting blood glucose and HbA1c levels were significantly higher (group II: 151 ± 64 mg/dL vs group I: 111 ± 23 mg/dL; *P* = 0.05 and group II: $7.2\% \pm 1.5$ vs

Table 1. Demographic Properties of the Patients

	Group I (n = 34)	Group II (n = 36)	P
Age, y	52.7 ± 11	53.2 ± 10	NS
Sex, male/female	18/16	19/17	NS
Duration of diabetes, y	7 ± 1.7	8 ± 2.5	NS
Body mass index, kg/m ²	28.5 ± 2.6	27.9 ± 3.3	NS
Heart rate/min	87 ± 12	94 ± 23	0.02
Fasting glucose, mg/dL	167 ± 38.4	172.5 ± 51.3	NS
HgA1c, %	7.5 ± 0.6	9.1 ± 1.3	NS
Insulin level, µU/mL	17.3 ± 5.1	31 ± 9.5	0.03
LDL-cholesterol, mg/dL	112 ± 52	104 ± 28	NS
Triglycerides, mg/dL	164 ± 65	183 ± 95	NS
HDL-cholesterol, mg/dL	45 ± 16	43 ± 12	NS
Medications ^a			
ACEI/ARB, no. (%)	21 (62)	17 (47)	NS
Statins, no. (%)	12 (35)	11 (31)	NS
Metformin, no. (%)	22 (65)	36 (100)	<0.001
Sulfonylurea, no. (%)	12 (35)	10 (28)	NS
Insulin, no. (%)	3 (9)	11 (31)	0.023
Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocking agent; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NS, not statistically significant (<i>P</i> > 0.05). Group I patients were those without poor R-wave progression in electrocardiogram (ECG), and group II patients were those with poor R-wave progression in ECG.			
^a Medications at the end of the follow-up period.			

group I: 6.2% ± 1.2; *P* = 0.01, respectively), and more patients needed insulin treatment to control their blood glucose (Table 1). Microalbuminuria was more frequently detected in group II (14 patients, 39%) compared to group I patients (10 patients, 29%), but the difference was not statistically significant. During the study period, due to microalbuminuria and other diabetic complications, renin-angiotensin system blockers were started, but there was no statistically significant difference between the 2 groups (Table 1).

The changes in echocardiographic parameters during the study period are compared in Table 3. At the end of the follow-up period, Tei index and LV mass index increased, and LVEF decreased significantly in group II when compared to baseline. Among patients with baseline diastolic dysfunction, 1 patient in group I and 7 patients in group II developed systolic dysfunction (ejection fraction

Table 2. Echocardiographic Parameters of the Patients

	Group I (n = 34)	Group II (n = 36)	P
LA, mm	35 ± 3	37 ± 2	0.04
LVDD, mm	47 ± 3	46 ± 4	NS
IVS, mm	8.8 ± 0.6	9.5 ± 1.2	0.04
PW, mm	8.9 ± 0.6	9.3 ± 1.3	NS
LV mass index, g/m ²	113.9 ± 12.2	124.6 ± 21.9	0.03
EF, %	70 ± 15	68 ± 12	NS
RV, mm	21.6 ± 3	22.9 ± 2	0.003
E, cm/s	75 ± 13	64 ± 13	0.001
A, cm/s	69 ± 13	81 ± 11	<0.001
DT, ms	215 ± 27	239 ± 32	0.001
IVRT, ms	108 ± 9	109 ± 11	NS
Tei index	0.60 ± 0.06	0.64 ± 0.05	0.02
Patients with LV relaxation abnormality, no. (%)	7 (21)	34 (94)	<0.001
Tissue Doppler echocardiography findings ^a			
Sm, cm/s	7.85 ± 0.65	7.88 ± 0.69	NS
Em, cm/s	8.82 ± 0.80	7.00 ± 0.94	<0.001
Am, cm/s	7.49 ± 1.04	8.24 ± 1.03	0.003
Abbreviations: A, mitral A-wave velocity; DT, deceleration time; E, mitral E-wave velocity; EF, ejection fraction; IVRT, isovolumetric relaxation time; IVS, interventricular septum; LA, left atrium; LV, left ventricle; LVDD, left ventricular diastolic diameter; NS, not statistically significant (<i>P</i> > 0.05); PW, posterior wall; RV, right ventricle. Group I patients were those without poor R-wave progression in electrocardiogram (ECG), and group II patients were those with poor R-wave progression in ECG.			
^a Mean of the 4 sites of mitral annulus.			

<0.45) and dilatation in LV dimension (LV end-diastolic diameter >55 mm) (3% vs 19%, *P* = 0.04).

Discussion

Although clinically manifested DCMP takes years to develop, cardiac abnormalities can be identified with echocardiography at the early stages before any heart failure symptoms exist.² Among the early pathological changes, diastolic dysfunction and LV hypertrophy can be

Table 3. Echocardiographic Parameters of the Patients at the End of the 4-Year Follow-Up

	Group I (n = 34)			Group II (n = 36)		
	Baseline	End of follow-up	P	Baseline	End of follow-up	P
LA, mm	35 ± 3	36 ± 4	NS	37 ± 2	38 ± 3	NS
LVDD, mm	47.4 ± 3.8	49.7 ± 5.3	NS	46.5 ± 4.9	50.7 ± 8.8	NS
IVS, mm	8.8 ± 0.6	8.8 ± 1	NS	9.5 ± 1.2	10.1 ± 1.2	NS
PW, mm	8.9 ± 0.6	9.0 ± 0.8	NS	9.3 ± 1.3	9.7 ± 1.1	NS
LV, mass index, g/m ²	114 ± 12	113 ± 16	NS	125 ± 22	134 ± 30	0.05
EF, %	70 ± 15	68 ± 15	NS	68 ± 12	58 ± 14	0.038
RV, mm	21.6 ± 3	21.7 ± 2.9	NS	22.9 ± 2	23.1 ± 2.7	NS
E, cm/s	75 ± 13	74 ± 15	NS	64 ± 13	61 ± 21	NS
A, cm/s	69 ± 13	70 ± 13	NS	81 ± 11	79 ± 12	NS
DT, ms	215 ± 27	215 ± 31	NS	239 ± 32	240 ± 41	NS
IVRT, ms	108 ± 9	109 ± 9	NS	109 ± 11	110 ± 12	NS
Tei index	0.60 ± 0.06	0.59 ± 0.08	NS	0.64 ± 0.05	0.69 ± 0.1	0.04
Patients with LV relaxation abnormality, no. (%)	7 (21)	9 (26)	NS	34 (94)	35 (97)	NS
Patients with LV systolic dysfunction, no. (%) ^a	0	1 (3)	NS	0	7 (19)	0.03

Abbreviations: A, mitral A wave velocity; DT, deceleration time; E, mitral E wave velocity; EF, ejection fraction; IVRT, isovolumetric relaxation time; IVS, interventricular septum; LA, left atrium; LV, left ventricle; LVDD, left ventricular diastolic diameter; NS, not statistically significant ($P > 0.05$); PW, posterior wall; RV, right ventricle.

Group I patients were those without poor R-wave progression in electrocardiogram (ECG), and group II patients were those with poor R-wave progression in ECG.

^a LV ejection fraction <0.45.

seen to accompany preserved LV systolic function.^{2,4–6,8,19} Heart failure can occur after these pathological changes in subsequent years.^{2,4–8}

This study aimed to investigate whether a simple electrocardiographic finding, poor R-wave progression, which is a marker for LV hypertrophy in the absence of anteroseptal myocardial infarction, can be a useful sign for early cardiac involvement of DCMP.

The study group was selected from apparently uncomplicated diabetics without clinically manifested hypertension and ischemic heart disease. Presence of poor R-wave progression was significantly associated with LV hypertrophy, and consistent with diastolic dysfunction, to an enlarged left atrium. Both conventional and tissue Doppler echocardiographic examinations revealed that these patients had a markedly increased frequency of abnormal relaxation compared to patients without this finding (94% vs 21%). LV hypertrophy and abnormal relaxation seemed to be independent of the blood pressure due to the inclusion criteria of the patients, but as other blood pressure measurements such as ambulatory monitoring was not

performed, the presence of masked hypertension or a nondipper pattern could not be excluded. The use of renin-angiotensin system blockers may have masked the real blood pressure levels.

During follow-up, more patients in group II developed systolic dysfunction compared to patients without poor R-wave progression (19% vs 3%). Poor blood glucose control seemed to be the most important metabolic factor for triggering DCMP. At the beginning of the study, higher insulin level was the only significantly different metabolic parameter between patients with and without poor R-wave progression. During follow-up, fasting blood glucose and HbA1c levels remained higher, and more patients needed insulin treatment to control their blood glucose among patients with poor R-wave progression. The main pathophysiologic event resulting from hyperglycemia is an increase in glycolysis end-products, and as a result nitric oxide becomes deactivated.² Hyperglycemia activates the local myocardial renin-angiotensin and endothelial systems, and consequently myocyte necrosis and fibrosis increase.^{8,20} In previous studies, the degree of diastolic dysfunction

was correlated with HbA1c and insulin levels.^{2,10,21} Diastolic dysfunction could be detected in 52%–60% of the patients in echocardiography even under close glycemic control.²⁰ It is also known that hyperinsulinemia can cause LV hypertrophy.²² The findings of this study are consistent with the previous data about the relation of hyperinsulinemia to LV diastolic dysfunction and support the role of poor blood glucose control in the development of DCMP.

Even though poor R-wave progression indicates anterior wall myocardial infarction in many cases, it is often seen in patients with a variety of cardiac disorders, such as incomplete or complete left bundle branch block, right bundle branch block, LV hypertrophy, left anterior hemiblock, Wolf-Parkinson-White syndrome, pseudo-Q wave caused by perpendicular orientation of the initial QRS deflection to the lead axis, mitral valve prolapse, and abnormally low diaphragm position in pulmonary emphysema.²³ Several cardiomyopathies may also present with poor R-wave progression (eg, amyloidosis, alcoholic cardiomyopathy).¹³ Recently, Anttila and coworkers²⁴ evaluated the prognostic impact of poor R-wave progression in a general population and showed that it predicts risk for cardiovascular mortality especially in women. In their study, poor R-wave progression was associated with higher age, hypertension, and diabetes. The clinical implication of this finding in diabetic patients was evaluated by only 1 study. Krahulec et al²⁵ assessed the manifestations of cardiovascular autonomic neuropathy on ECG at rest and identified lower R-wave voltage as a possible sign of cardiomyopathy. In our study, the presence of anterior myocardial infarction was excluded by myocardial perfusion scintigraphy and echocardiographic evaluation wall motion. To our knowledge, this is the first study that showed an association between poor R-wave progression in ECG and LV diastolic followed by systolic dysfunction in diabetic patients.

The main limitations of the study can be stated as follows. DCMP is a common complication of diabetes, but its diagnosis is not very easy, and factors such as coronary or valvular heart disease should be eliminated. In this study, coronary artery disease was excluded with myocardial perfusion scintigraphy and valvular heart disease with echocardiography at the beginning of the study. Coronary angiography was not performed due to ethical concerns. Still, 5 patients developed significant coronary artery disease and were excluded from the analysis. Magnetic resonance imaging might have been another imaging modality to assess myocardial involvement. The study group consisted of a relatively small number of patients, and the findings need to be confirmed by larger studies.

Conclusion

Identification of poor R-wave progression in resting ECG of diabetic patients appears to be a promising marker for

DCMP after eliminating all the other diseases that might cause poor R-wave progression. Close monitoring of blood glucose control and the cardiac functions of these patients seems to be important for long-term prognosis.

References

1. Khavandi K, Khavandi A, Asghar O, et al. Diabetic cardiomyopathy—a distinct disease? *Best Pract Res Clin Endocrinol Metab.* 2009;23:347–360.
2. Hayat SA, Patel B, Khattar RS, et al. Diabetic cardiomyopathy: mechanisms, diagnosis and treatment. *Clin Sci (Lond).* 2004;107:539–557.
3. Cohen-Solar A, Beauvais F, Loqart D. Heart failure and diabetes mellitus: epidemiology and management of an alarming association. *J Card Fail.* 2008;14:615–625.
4. Bertoni AG, Tsai A, Kasper EK, et al. Diabetes and idiopathic cardiomyopathy: a nationwide case-control study. *Diabetes Care.* 2003;26:2791–2795.
5. Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham study. *JAMA.* 1979;241:2035–2038.
6. Rubler S, Dlugash J, Yuceoglu YZ, et al. New type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am J Cardiol.* 1972;30:595–602.
7. Boudina S, Abel ED. Diabetic cardiomyopathy revisited. *Circulation.* 2007;115:3213–3223.
8. Aneja A, Tang WH, Bansilal S, et al. Diabetic cardiomyopathy: insights into pathogenesis, diagnostic challenges, and therapeutic options. *Am J Med.* 2008;121:748–757.
9. Regan TJ, Lyons MM, Ahmed SS, et al. Evidence for cardiomyopathy in familial diabetes mellitus. *J Clin Invest.* 1977;60:884–899.
10. Asghar O, Al-Sunni A, Khavandi K, et al. Diabetic cardiomyopathy. *Clin Sci (Lond).* 2009;116:741–760.
11. Maya L, Villarreal FJ. Diagnostic approaches for diabetic cardiomyopathy and myocardial fibrosis. *J Mol Cell Cardiol.* 2010;48:524–529.
12. Wold LE, Relling DP, Colligan PB, et al. Characterization of contractile function in diabetic hypertensive cardiomyopathy in adult rat ventricular myocytes. *J Mol Cell Cardiol.* 2001;33:1719–1726.
13. Zema MJ, Collins M, Alonso DR, et al. Electrocardiographic poor R-wave progression. Correlation with postmortem findings the normal variant. *Chest.* 1981;79:195–200.
14. Libby P, Bonow R, Mann D, et al. The cardiomyopathies. In: *Braunwald's Heart Disease.* 7th ed. Philadelphia, PA: Saunders Elsevier; 2008:1659–1696.
15. Savage RM, Wagner GS, Ideker RE, et al. Correlation of postmortem anatomic findings with electrocardiographic changes in patients with myocardial infarction. *Circulation.* 1977;55:279–285.
16. Sahn DJ, De Maria A, Kisslo J, et al. Recommendations regarding quantification in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation.* 1978;58:1072–1083.
17. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr.* 1989;2:358–367.
18. Oh JK, Appleton CP, Hatle LK, et al. The noninvasive assessment of left ventricular diastolic function with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr.* 1997;10:246–270.

19. Hoit BD, Castro C, Bultron G, et al. Noninvasive evaluation of cardiac dysfunction by echocardiography in streptozotocin-induced diabetic rats. *J Card Fail.* 1999;5:324–333.
20. Seferovic PM, Lalic NM, Seferovic JP, et al. Diabetic cardiomyopathy: old disease or new entity [in Serbian]? *Srp Arh Celok Lek.* 2007;135:576–582.
21. Okoshi K, Guimaraes JFC, Di Muzio BP, et al. Miocardiopatia diabetica. *Arq Bras Endocrinol Metab.* 2007;51:160–167.
22. Karason K, Sjostrom L, Wallentin I, et al. Impact of blood pressure and insulin on the relationship between body fat and left ventricular structure. *Eur Heart J.* 2003;24:1500–1505.
23. Surawicz B, Knilans TK *Chou's Electrocardiography in Clinical Practice.* 6th ed. Philadelphia, PA: Saunders Elsevier; 2008; 193–194.
24. Anttila I, Nikus K, Nieminen T, et al. Prevalence and prognostic value of poor R-wave progression in standard resting electrocardiogram in a general adult population. The Health 2000 Survey. *Ann Med.* 2010;42:123–130.
25. Krahulec B, Mikes Z, Balazovjech I. The effect of cardiovascular autonomic neuropathy on resting ECG in type 1 diabetic patients. *Bratisl Lek Listy.* 2002;103:54–58.