# The Evaluation of Left Ventricular Systolic and Diastolic Functions in Patients With Friedreich Ataxia

## A Pulse Tissue Doppler Study

Filiz KOC,[1] MD, Onur AKPINAR,[2] MD, Deniz YERDELEN,[1] MD, Mesut DEMIR,[2] MD, Yakup SARICA,[1] MD, *and* Mehmet KANADASI,[2] MD

**SUMMARY**

Friedreich's ataxia (FRDA), the most common subtype of early onset hereditary ataxia, is an autosomal recessive neurodegenerative disorder caused by unstable GAA expansions. Two-dimensional, pulse, and pulse tissue Doppler echocardiographic examinations were performed on 21 patients with GAA expansion.

There was no association between left ventricle ejection fraction, tissue Doppler systolic s wave, and left ventricle diastolic functions examined by pulse and tissue Doppler. The septum thickness of patients with Friedreich's ataxia was significantly increased when compared with that of the control group and wall thickness was found to be associated with GAA repeats.

In patients with FRDA, despite a correlation between genetic abnormality with left ventricular early and late diastolic parameters, global diastolic functions were preserved when examined by tissue Doppler. (Int Heart J 2005; 46: 443-452)

**Key words:** Friedreich ataxia, GAA repeats, Pulse wave tissue doppler

FRIEDREICH'S ataxia (FRDA) is an autosomal recessive neurodegenerative disorder and one of the most common forms of hereditary ataxia, caused by unstable GAA expansions in the first intron of the FRDA gene located at 9q13-q21.1, which is the site of the gene encoding for the 210-amino-acid protein frataxin.[1)] The gene was mapped in 1988 and, in 1996, it was cloned by Campuzano, *et al*.[2)] FRDA was estimated to affect about 1:50,000 people with an estimated carrier prevalence of about 1:110.[3)]

Clinical findings are characterized by neurologic signals and symptoms of the dorsal root ganglia, the posterior columns, and pyramidal and spinocerebellar tracts.[4)] Cardiac abnormalities in Friedreich's ataxia are accepted to be part of this disease. Concentric or asymmetric left ventricular hypertrophy has been recognized as a cardiac manifestation in Friedreich's ataxia.[4,5)] The severity of left ven-

From the [1]Departments of Neurology and [2] Cardiology, School of Medicine, Cukurova University, Adana, Turkey.
Address for correspondence: Filiz Koc, MD, Department of Neurology, Cukurova University, Turgut Ozal Bulvarı Güzelyalı Mah. 64 sok. Güler apt. Kat: 3 Daire:301170 Adana-Turkey.
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tricular hypertrophy is related to the number of GAA repeats.[5] The left ventricular cavity and systolic function are usually normal but patients with dilated cardiomyopathy are also present and generally they are seen at the end of the hypertrophic cardiomyopathy.[5]

Recently, a few studies calculated myocardial velocity gradient (MVG) by using tissue Doppler in patients with FRDA and the systolic and diastolic parameters in these patients were shown to be abnormal when compared with controls.[5-7] However, it is difficult to calculate MVG and it is not used in clinical practice. The aim of the present study was to evaluate left ventricular systolic and diastolic functions using pulse tissue Doppler in patients with FRDA.

## METHODS

**Patients:** Twenty-one patients with Friedreich's ataxia (14 men and 6 women, mean age: 23.3 ± 6.8 years) and 20 healthy participants as controls (11 men and 9 women, mean age: 23.9 ± 5.6 years) who visited the Department of Neurology at the Medical College of Cukurova University were studied. A complete medical history was obtained and neurological and cardiac examinations were performed in all patients. Patients with rheumatic heart disease, hypertension, diabetes mellitus, renal failure, or documented coronary artery disease were excluded. All patients with Friedreich's ataxia were homozygous for the GAA expansion. The median number of triplet repeats in the smaller expanded allele was 730, with a range of 530 to 1300.

**Analysis of the GAA expansion:** Venous blood samples were drawn and DNA was isolated from leukocytes using a standard extraction method.[8] GAA triplet repeats in the A gene were analyzed by long template polymerase chain reaction (PCR). Each genomic DNA sample (~ 250 ng) was amplified in 25 $\mu$L of reaction mixture consisting of 200 $\mu$M of each dNTP, 2.25mM of $MgCl_2$, 25 pmol of each primer, and 2.5 units of Pwo DNA polymerase (Roche). The relevant portion of intron 1 was amplified with forward (5'-GGG ATT GGT TGC CAG TGC TTA AAA GTT AG-3') and reverse (5'-GAT CTA AGG ACC ATC ATG GCC ACA CTT GCC-3') primer pairs in 35 cycles. Initial denaturation of DNA was performed at 95°C for 5 minutes. The amplification reaction was performed at 94°C for 40 seconds and at 68°C for 5 minutes during 20 cycles and then at 94°C for 40 seconds and at 68°C for 6 minutes with incremental increases of 15 seconds per cycle during 15 cycles and final elongation at 68°C for 10 minutes. PCR products were loaded on 1.5% agarose gel containing ethidium bromide (0.5 $\mu$g/mL) and electrophoresis was carried out at 90 V for 1.5 hours and then visualized under UV fluorescence (Table I).

**Table I.** Clinical Findings and GAA Repeats of Study Patients

| Number | Name | Age | Sex | Onset | M. Retard. | Cerebellar Sign | Dysarthria | Nystagmus | DTRLU | | Babinsk's sign | Power | Fundus | Skeletal Def. | EMG (PNP) | Deep sensation | Cranial MRI | Spinal MRI | GAA repeats |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | İ.T | 20 | M | 15 | - | + | + | + | ϕ | + | + | PP | N | + | + | + | CA | + | 680 |
| 2 | D.O | 25 | M | 11 | - | + | + | + | ϕ | ϕ | + | PP | N | + | + | + | CA | N | 845 |
| 3 | Z.K | 15 | F | 3 | - | + | + | - | ϕ | ϕ | + | N | N | + | + | + | - | - | 745/745 |
| 4 | S.K | 22 | M | 7 | + | + | + | + | ϕ | ϕ | + | N | N | + | + | + | - | - | 100 |
| 5 | E.E | 22 | F | 14 | - | + | + | + | ϕ | + | + | PP | P | + | + | + | N | - | 625 |
| 6 | F.K | 34 | M | 9 | - | + | + | + | ϕ | ϕ | + | PP | N | + | + | + | - | - | 708 |
| 7 | D.G | 18 | F | 16 | - | + | + | + | ϕ | + | + | N | N | + | + | + | CA | - | 530 |
| 8 | M.G | 14 | M | 11 | - | + | + | + | ϕ | + | + | N | N | + | + | + | CA | - | 530 |
| 9 | C.E | 20 | M | 18 | + | + | + | + | ϕ | + | + | PP | P | + | + | + | CA | N | 680 |
| 10 | N.A | 17 | F | 13 | - | + | + | + | ϕ | ϕ | + | PP | N | + | + | + | CA | N | 425 |
| 11 | Z.B | 25 | F | 15 | - | + | + | + | ϕ | ϕ | + | PP | N | + | + | + | N | N | 800 |
| 12 | K.S | 34 | F | 14 | + | + | + | + | ϕ | ϕ | + | TP | N | + | + | + | CA | N | 845 |
| 13 | HŞ | 18 | M | 12 | + | + | + | + | ϕ | ϕ | + | PP | P | + | + | + | CA | N | 850 |
| 14 | MY | 22 | F | 14 | - | + | + | + | ϕ | ϕ | + | N | N | + | + | + | N | - | 645 |
| 15 | F.B | 13 | F | 7 | - | + | + | + | ϕ | ϕ | + | TP | P | + | + | + | CA | N | 925 |
| | Fat. | 42 | M | | | | | | | | | | | | | | | | 6-14 |
| | Moth. | 36 | F | | | | | | | | | | | | | | | | 6-14/100 |
| F1 | Sist. 1 | 6 | F | - | | | | | | | | | | | | | | | 925 |
| | Sist. 2 | 4 | F | - | | | | | | | | | | | | | | | 600 |
| 16 | V.E | 34 | M | 16 | - | + | + | + | ϕ | ϕ | + | PP | P | + | + | + | CA | + | 125 |
| | Moth | 56 | F | | | | | | | | | | | | | | | | 6-14 |
| | Fath. | 55 | M | | | | | | | | | | | | | | | | 6-14/39 |
| F2 | Brot.1 | 32 | M | | | | | | | | | | | | | | | | 6-14/39 |
| | Sist.2 | 24 | F | | | | | | | | | | | | | | | | 6-14 |
| | Brot 3 | 22 | F | | | | | | | | | | | | | | | | 6-14 |
| 17 | M.Ö | 30 | M | 10 | + | + | + | + | ϕ | ϕ | + | PP | P | + | + | + | CA | - | 1300 |
| | Fath. | 58 | M | | | | | | | | | | | | | | | | 6-14/900 |
| | Moth. | 51 | F | | | | | | | | | | | | | | | | 6-14 |
| F3 | Brot 1 | 27 | M | 12 | | | | | | | | | | | | | | | 1300 |
| | Brot 2 | 26 | M | | | | | | | | | | | | | | | | 6-14 |
| | Sist 3 | 17 | F | | | | | | | | | | | | | | | | 6-14 |
| 18 | Z.T | 33 | M | 15 | - | + | + | + | ϕ | ϕ | + | TP | P | + | + | + | CA | - | 850 |
| | Moth | 60 | F | | | | | | | | | | | | | | | | 6-14 |
| F4 | Sist 1 | 28 | F | 13 | | | | | | | | | | | | | | | 6-14/850 |
| | Brot 2 | 26 | M | | | | | | | | | | | | | | | | 6-14 |
| | Brot 3 | 23 | M | | | | | | | | | | | | | | | | 6-14 |
| 19 | Y.U | 22 | M | 13 | + | + | + | + | ϕ | + | + | TP | P | + | + | + | CA | - | 680 |
| | Moth | 72 | F | | | | | | | | | | | | | | | | 6-14 |
| F5 | Brot 1 | 42 | M | | | | | | | | | | | | | | | | 6-14 |
| | Sist 4 | 27 | F | | | | | | | | | | | | | | | | 6-14 |
| | Sist 5 | 26 | F | 14 | | | | | | | | | | | | | | | 675 |

F = family; M. Retard = mental retardation; DTR = deep tendon reflexes; U = upper; L = lower; TP = tetraparesis; PP = paraparesis; P = palor; N = normal; CA = cerebellar atrophy; Def = deformities; + = Affected; - = Nonaffected; ϕ = Absent; PNP = polyneuropathy; MRI = magnetic resonance imaging; Moth = mother; Fath = father; Sist = sister; Brot = brother.

**Standard echocardiography:** Two-dimensional and Doppler echocardiographic examinations were performed with an Acuson Sequoia C 256 echocardiograph (Acuson Corporation, Mountain View, CA, USA). A 3.5-MHz transducer was positioned at the left sternal border between the third and fifth left intercostal spaces with the patient in a supine position. We recorded 3 to 7 cardiac cycle echocardiograms from all subjects. All echocardiographic measurements represented the average values of these cardiac cycle recordings.

Echocardiographic images were obtained from parasternal long axis, apical four-chamber views and all echocardiograms were recorded. M-mode measurements were performed according to the criteria of the Society of American Echocardiography.[9] Left ventricular end-diastolic and end-systolic diameters, volumes, ejection fraction, and thicknesses of the interventricular septum and posterior wall were measured using M-mode. Left ventricular diastolic functions; early (E) and late (A) peak velocity (cm/s) and their ratios, E wave deceleration time (DT) (ms), and isovolumic relaxation time (IVRT) (ms) were evaluated using pulse wave Doppler.

**Tissue Doppler imaging and time intervals:** The spectral pulsed Doppler signal was adjusted to obtain a Nyquist limit of 15 or 20 cm/s, with the lowest wall filter settings and the minimum optimal gain to eliminate the signals produced by transmitral flow. Peak velocities during systole ($S_m$), early diastole ($E_m$), and late diastole ($A_m$) (cm/s) were taken from the apical four-chamber using the lateral side of the mitral annulus. The $E_m/A_m$ ratio was calculated to examine diastolic functions.

**Statistical Analysis:** SPSS for Windows (version 9.0, SPSS Inc, Chicago, Illinois) was used for statistical analysis. Data are expressed as the mean ± SD. Statistical comparison between normal subjects and patients with FRDA was performed by the unpaired *t* test. The chi-square test was used for categorical data. Correlation analysis was performed to investigate the statistical relationships between the GAA expansion and echocardiographic parameters. A *P* value of 0.05 or less was considered statistically significant.

## RESULTS

The septum thickness of patients with Friedreich's ataxia was significantly increased compared to that of the control group ($P < 0.05$), but posterior wall thickness was similar. There were no differences in left ventricular mass index, left atrial diameter, left ventricular diameter, or end-systole and end-diastole volumes and ejection fractions between the patients with FRDA and the control group (Table II). Left ventricular diastolic parameters examined by pulse and tissue Doppler and systolic Sm wave examined by tissue Doppler were similar in the two groups (Table III).

**Table II.** M-mode Echocardiographic Findings in Patients With Friedreich's Ataxia and Controls

| | Friedreich's ataxia | Control groups | *P* |
|---|---|---|---|
| LA (mm) | 30.0 ± 3.4 | 30.1 ± 3.6 | NS |
| IVS (mm) | 9.4 ± 1.8 | 8.1 ± 0.9 | < 0.01 |
| Posterior wall (mm) | 8.1 ± 1.0 | 7.6 ± 1.1 | NS |
| LVS (mm) | 28.6 ± 3.8 | 29.4 ± 2.5 | NS |
| LVD (mm) | 44.8 ± 5.4 | 45.6 ± 3.4 | NS |
| LVS volume (mL) | 32.1 ± 9.9 | 33.5 ± 6.5 | NS |
| LVD volume (mL) | 92.7 ± 25.6 | 96.5 ± 16.2 | NS |
| LV mass index | 136.3 ± 30.5 | 162.9 ± 42.7 | NS |
| EF (%) | 66.0 ± 4.2 | 65.4 ± 3.0 | NS |

NS = not significant; LA = left artrium diameter; IVS = intraventricular septum; VS = ventricular septum diameter; LVS = left ventricular septum diameter; LVS = left ventricular systolic diameter; LVD = left ventricular diastolic diameter; LV = left ventricular; EF = ejection fraction.

**Table III.** Conventional Pulse Wave Diastolic Parameters and Pulse Wave Tissue Doppler Echocardiographic Findings in Patients With Friedreich's Ataxia and Controls

| | Friedreich's ataxia | Control groups | *P* |
|---|---|---|---|
| E (cm/s) | 81.5 ± 18.1 | 87.4 ± 13.3 | NS |
| A (cm/s) | 53.7 ± 10.7 | 57.0 ± 8.9 | NS |
| E/A ratio | 1.56 ± 0.40 | 1.55 ± 0.24 | NS |
| DT (ms) | 167.7 ± 52.3 | 182.6 ± 34.3 | NS |
| IVRT (ms) | 80.6 ± 8.8 | 81.7 ± 7.0 | NS |
| Tissue $S_m$ (cm/s) | 14.4 ± 2.9 | 13.8 ± 2.3 | NS |
| Tissue $E_m$ (cm/s) | 21.0 ± 5.7 | 23.2 ± 4.7 | NS |
| Tissue $A_m$ (cm/s) | 12.5 ± 4.4 | 12.1 ± 4.2 | NS |
| Tissue $E_m/A_m$ ratio | 1.80 ± 0.57 | 2.06 ± 0.65 | NS |

NS = not significant; DT = deceleration time; IVRT = isovolumetric relaxation time; E = early peak velocity; A = late peak velocity; Sm = peak velocity during systole; Em = peak velocity during early diastole; Am = peak velocity during late diastole.

FRDA was diagnosed earlier in patients with left ventricular hypertrophy (9.6 ± 2.9 versus 12.3 ± 4.4 years), however, the difference was not statistically significant. Also, as the age of the patient increased, the diameter and volume of the left ventricle increased as well. Thus, survival after the diagnosis was more important than the age of onset of the disease.

Septum and posterior wall thickness, end-diastolic left ventricular diameter and volume, left ventricular ejection fraction, and GAA repeats were compared among the patients (Table IV) and wall thickness was found to be associated with

**Table IV.** Correlation of M-mode Echocardiographic Parameters and GAA Repeats in Patients With Friedreich's Ataxia

| | GAA Repeats | |
|---|---|---|
| | R | *P* |
| IVS | 0.502 | 0.024* |
| Posterior wall | 0.528 | 0.017* |
| LV diameter | -0.149 | 0.531 |
| LV volume | -0.174 | 0.462 |
| LV mass index | 0.283 | 0.226 |

* = Significant; VS = ventricular septum; IVS = intraventricular septum; LV = left ventricular.

GAA repeats. Tissue Doppler systolic $S_m$ wave, left ventricular diastolic E, $E_m$ and A, $A_m$ waves were examined by pulse and tissue Doppler. Septum wall thickness and GAA repeats were compared. Septum thickness and tissue Doppler $E_m$ and $A_m$ waves were found to be significantly related with GAA (Table V).

## DISCUSSION

FRDA is caused primarily by unstable expansion of GAA repeats in the first intron of the gene that accounts for 96% of mutant alleles.[1,10,11] The hypothesis that FRDA is due to accumulation of mitochondrial iron leading to increased production of free radicals impairing the mitochondria and cell functions was more directly evidenced by Delatycki, *et al*.[10,12-15] Studies have reported a relationship between the number of GAA repeats in the smaller frataxin allele and cardiomyopathy in about two-thirds of patients homozygous for the GAA expansion.[16-18] Isnard, *et al* showed that the severity of left ventricular hypertrophy was related to the number of GAA repeats.[17] Similarly, there was a positive relation between septal and posterior wall thickness and GAA expansion in our study (Figure 1). When GAA repeats were more than 745, there was septum hypertrophy with 80% sensitivity and 74% specificity.

In a study in FRDA patients performed recently, it was reported that left ventricular hypertrophy is more frequently seen in patients diagnosed at a younger age.[6,18,19] In our study, patients with left ventricular hypertrophy were younger, although the difference was not statistically significant. Also, in the present study left ventricular hypertrophy was not present in any of the patients with FRDA (< 56 mm), although increases in left ventricular end-diastolic diameter and volume were observed as the age increased. In this positive relation,

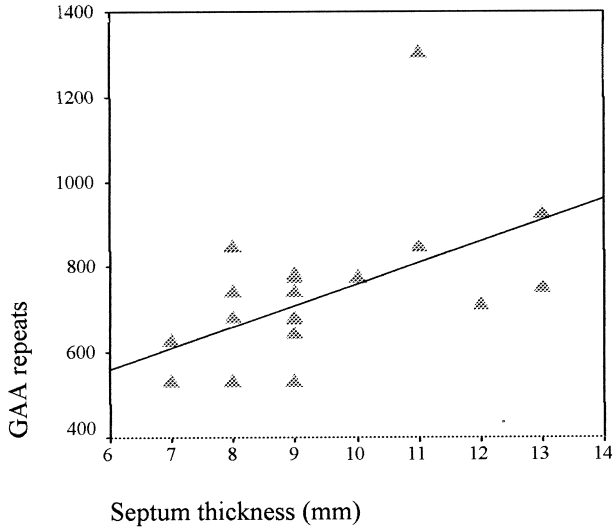



**Figure 1.** Correlation of septum thickness and GAA repeats.

survival rate after the diagnosis was most important, not the age when the diagnosis was made. The thought that hypertrophic cardiomyopathy (CMP) deteriorates to dilated CMP during the course of the disease becomes more stronger because septal hypertrophy is found in patients diagnosed at a younger age and dilatation in the left ventricle occurs several years after the diagnose.

There is disagreement in the literature concerning abnormal diastolic function in patients with FRDA.[6,8,20-22] One study reported that left ventricular hypertrophy is not present with abnormal diastolic function.[22] However, in our study as left ventricle wall thickness increased diastolic function became slightly abnormal, although the abnormality in diastolic function was not statistically significant. In addition, IVRT, which is a sensitive parameter for diastolic functions, and the pulse tissue Doppler $E_m/A_m$ ratio were similar to that of the control groups. The results obtained by tissue Doppler indicate that patients with FRDA do not have disordered diastolic functions.

Myocardial velocity gradient (MVG) is a new indicator of regional left ventricular function and global left ventricular systolic and diastolic function.[23] Mori, *et al* showed that MVG parameters in the short-axis direction were more sensitive than mitral annulus velocity in patients with Duchenne's progressive muscular dystrophy.[24] However, MVG is affected by regional left ventricular wall motion and is especially useful in assessing myocardial tissue characteris-

tics. Dutka, *et al* calculated MVG in a study using tissue Doppler in these patients and left ventricular systolic and diastolic functions were found to be abnormal,[7] and this abnormal function was related to GAA gene repeats. In this study, MVG was measured in posterior wall and hypertrophy was prominent in septum and posterior wall. However, these measurements may reflect regional wall motion more than global functions. Nagueh, *et al* reported that pulse TDI from the lateral mitral annulus was useful for the evaluation of global diastolic functions in patients with severe coronary artery disease.[25] The base of the lateral wall is sel-

**Table V.** Correlation of Tissue Doppler Parameters, GAA Repeats and Septum Thickness in Patients With Friedreich's Ataxia

| | GAA Repeats | | Septum Thickness | |
|---|---|---|---|---|
| | R | *P* | R | *P* |
| Tissue $S_m$ (cm/s) | -0.155 | 0.515 | -0.129 | 0.587 |
| Tissue $E_m$ (cm/s) | -0.446 | 0.049 | -0.764 | 0.000 |
| Tissue $A_m$ (cm/s) | -0.501 | 0.024 | -0.300 | 0.199 |
| Tissue $E_m/A_m$ ratio | 0.393 | 0.087 | -0.303 | 0.194 |

Sm = peak velocity during systole; Em = peak velocity during early diastole; Am = peak velocity during late diastole.

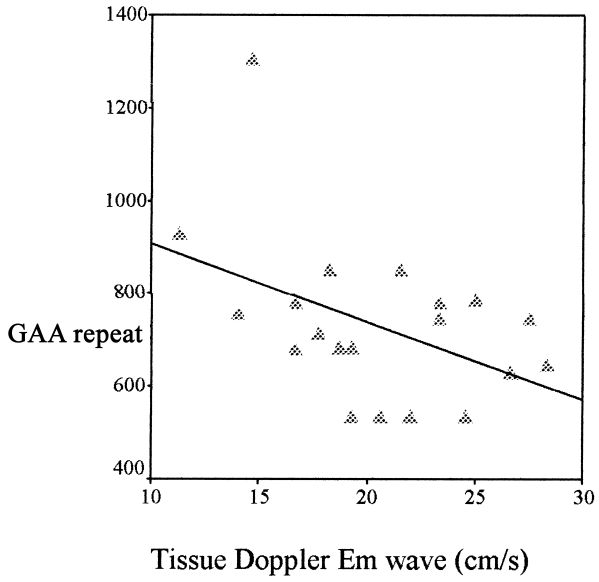



**Figure 2.** Correlation of tissue doppler Em wave and GAA repeats.

dom involved in ischemic heart disease. For this reason, we studied lateral mitral annular velocity using pulse TDI to evaluate global left ventricular systolic and diastolic functions. In addition, there has never been a study that measured mitral annular velocity using pulse TDI in patients with FRDA. The present results have demonstrated that GAA gene repeats are associated with tissue Doppler $E_m$ and $A_m$ waves in mitral lateral annulus, although there was no relation between GAA repeats with systolic $S_m$ wave and $E_m/A_m$ ratios, representing global systolic and diastolic functions (Table V, Figure 2). And it was also seen that the same parameters were changing with left ventricle wall thickness and regression analyses that showed that this relation was not due to GAA.

**Conclusion:** In patients with FRDA, despite a correlation between genetic abnormality and left ventricular early and late diastolic parameters, global diastolic functions were preserved examined by tissue Doppler.

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