

# Analysis of Echocardiograms in a Large Heterogeneous Cohort of Patients With Friedreich Ataxia

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Although Friedreich ataxia (FA) is associated with cardiomyopathy, the severity and evolution of cardiac disease is poorly understood. To identify factors predicting cardiomyopathy in FA, we assessed echocardiograms from a large heterogeneous cohort and their relation to disease traits. The most recent echocardiograms from 173 subjects with FA were analyzed in a core laboratory to determine their relation to disease duration, subject age, age of onset, functional disability score, and GAA repeat length. Mean age of the cohort was 19.7 years, mean age of disease onset was 10.6 years, and mean shorter GAA length was 681 repeats. Echocardiograms collectively illustrated systolic dysfunction, diastolic dysfunction, and hypertrophy. Measurements of hypertrophy correlated moderately with each other ( $r = 0.39$  to  $0.79$ ) but not with measurements of diastolic dysfunction ( $r < 0.35$ ). Diastolic measurements correlated poorly with each other, although 26% of the cohort had multiple diastolic abnormalities. The most common diastolic dysfunction classification was pseudonormalization. Classification of diastolic dysfunction was predicted by GAA repeat length but not by age or gender. Ejection fraction was below normal in 20% of the cohort. In linear regression analysis, increasing age predicted decreasing ejection fraction. Functional disability score, a measurement of neurologic ability, did not predict any echocardiographic measurements. In conclusion, hypertrophy and diastolic and systolic dysfunctions occur in FA and are substantially independent; diastolic dysfunction is the most common abnormality with most patients having an assigned diastolic dysfunction class of pseudonormalization. © 2011 Elsevier Inc. All rights reserved. (Am J Cardiol 2011;xx:xxx)

Friedreich ataxia (FA) is an autosomal recessive neurodegenerative disorder associated with cardiomyopathy and other system features.<sup>1</sup> Most hypotheses on cardiac progression in FA have been based on a model in which hypertrophy occurs early in the disorder with subsequent conversion to fibrosis.<sup>2-5</sup> The small size of most patient cohorts, variability of assessment, and inconsistent follow-up have limited the understanding of the direct relation between wall hypertrophy and development of systolic dysfunction. Studies have simplified interpretation of data by stratifying cohorts based on subject age or age of onset, thus removing analysis of the temporal course.<sup>5,6</sup> Such approaches may also remove the understanding of the degree to which cardiomyopathy in FA is a continuum rather than a categorical process. We analyzed echocardiograms from a large diverse cohort at a central core laboratory to identify the diversity of

cardiac features of FA and to integrate these findings into a model portraying cardiac severity related to genetic severity and age.

## Methods

The study protocol was approved by institutional review boards of all participating institutions. The most recent clinically indicated echocardiogram was acquired on VHS or compact disk for 173 patients with clinically confirmed FA. Patients were recruited through a natural history study in FA, clinic populations of the investigators, and the Friedreich Ataxia Parents Group. A subgroup of studies represented the baseline evaluation ( $n = 70$ ) from a therapeutic trial of idebenone.<sup>6</sup> Functional disability scores<sup>1</sup> (an index of neurologic dysfunction) were assigned from a pre-existing natural history database (72%) or using a review of medical records when no natural history visit was available. Ninety-six percent had genetic confirmation with GAA repeat length available.

Echocardiograms were quantified without knowledge of patients' demographics at the echocardiographic core laboratory at the University of Pennsylvania. Digital echocardiographic images and Doppler velocity signals were analyzed using commercially available software (Tomtec Imaging Systems, Munich, Germany). Standard echocardiographic parameters were measured: left ventricular (LV)

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Table 1  
Correlations of examined parameters

	Gender	Age	AOO	FDS	GAA
Shortening fraction	-0.02	-0.29	-0.13	-0.30	0.06
Ejection fraction	0.05	-0.33	-0.17	-0.23	0.05
Wall motion score	0.04	0.30	0.12	0.21	-0.05
Isovolumic relaxation time	-0.23	0.00	-0.10	0.08	0.17
Transmitral E/A ratio	-0.10	-0.24	-0.29	-0.01	0.15
E'/A'	0.01	-0.22	-0.22	-0.13	0.17
E/E'	-0.04	-0.08	-0.14	0.13	0.11
Intraventricular septal thickness index	-0.13	-0.29	-0.22	-0.11	0.25
Posterior wall thickness index	-0.13	-0.48	-0.34	-0.25	0.18
Left ventricular internal diameter index in diastole	0.03	-0.36	-0.36	-0.42	-0.02
Left ventricular internal diameter index in systole	0.03	-0.10	-0.06	-0.16	-0.06
Relative wall thickness in diastole	-0.13	-0.19	-0.21	0.08	0.18
Left ventricular mass index	-0.27	-0.07	-0.14	0.05	0.16

Pearson correlation values of echocardiographic parameters with demographics and disease features. Left ventricular mass was indexed by height<sup>2.7</sup> and wall thicknesses were indexed by body surface area.

AOO = age of disease onset; FDS = functional disability score.

end-systolic dimension, LV end-diastolic dimension, shortening fraction, ejection fraction, interventricular septal thickness in diastole, posterior wall thickness in diastole, relative wall thickness in diastole (RWTd), peak blood flow velocities during rapid filling (E wave) and atrial systolic contraction (A wave), transmitral E/A ratio (E/A), tissue Doppler index E', tissue Doppler index A', deceleration time, and isovolumic relaxation time, LV mass measured in M-mode, and wall motion score. For most analyses LV mass was indexed by meters<sup>2.7</sup> to decrease the effects of age and size<sup>7,8</sup>; wall thicknesses and LV cavity diameters (interventricular septal thickness in diastole, posterior wall thickness in diastole, LV end-diastolic dimension, LV end-systolic dimension) were indexed by body surface area.<sup>9-11</sup> Normalized diastolic function values for age were available from the American Society of Echocardiography for >15 years of age.<sup>12</sup> For children ≤15 years old, normal ranges for diastolic parameters were defined from previous studies.<sup>13,14</sup>

Results were also classified by LV geometry as normal (RWTd <0.42, normal indexed LV mass), concentric remodeling (RWTd >0.42, normal indexed LV mass), concentric hypertrophy (RWTd >0.42, increased indexed LV mass), or eccentric hypertrophy (RWTd <0.42, increased indexed LV mass).<sup>15</sup> To assess progression of diastolic function, subjects were assigned to 1 of 4 classes: normal, impaired relaxation (prolonged isovolumic relaxation time; low E/A), pseudonormal (E/A above lower limit of normal; prolonged isovolumic relaxation time), or restrictive filling (shortened isovolumic relaxation time; E/A above lower limit of normal).<sup>16,17</sup>

Statistical analysis was performed using STATA SE 11 (STATA Corp., College Station, Texas) including creation of linear regression models between echocardiographic parameters and GAA repeat length, gender, and age. Functional disability score was also included in some models. Analysis of variance was used to compare GAA repeat length, gender, and age between abnormal and normal populations for selected echocardiographic parameters and to examine differences in classifications of hypertrophy and diastolic dysfunction. Pairwise correlations were used to assess relations among individual measurements. The Cen-

Table 2  
Summary values of echocardiographic parameters

	Mean ± SD	High (%)	Low (%)
<b>Systolic function</b>			
Left ventricular internal diameter in diastole (cm)	4.01 ± 0.58	—	—
Left ventricular internal diameter in systole (cm)	2.71 ± 0.65	—	—
Stroke volume (cm <sup>3</sup> )	42.9 ± 20.2	—	—
Shortening fraction (%)	32.9 ± 8.66	9.30	9.30
Ejection fraction (%)	54.5 ± 8.63	1.4	20.4
<b>Hypertrophy</b>			
Posterior wall thickness index in diastole (cm/m <sup>2</sup> )	0.70 ± 0.18	62.9	
Intraventricular septal thickness index in diastole (cm/m <sup>2</sup> )	0.76 ± 0.24	52.7	
Relative wall thickness in diastole	0.52 ± 0.13	77.9	
Left ventricular outflow tract diameter in diastole (cm)	1.96 ± 0.23	—	
Left ventricular mass index (g/m <sup>2.7</sup> )	48.0 ± 17.8	40.2	
<b>Diastolic function</b>			
Transmitral E/A ratio	1.79 ± 0.59	8	4
E'/A'	2.02 ± 0.71	5	1
E/E'	6.97 ± 2.42	24	—
Isovolumic relaxation time	91.4 ± 21.1	85	1

Systolic function measurements were decreased in a significant number of subjects (normal ranges, shortening fraction 20% to 44%, ejection fraction 50% to 70%). Hypertrophy measurements were increased with a large percentage of the cohort above the normal range (normal ranges, posterior wall indexed by body surface area <0.62 cm/m<sup>2</sup>, interventricular septal thickness indexed by body surface area <0.69 cm/m<sup>2</sup>, relative wall thickness in diastole 0.42, indexed left ventricular mass <51 g/m<sup>2.7</sup> in men and 48 g/m<sup>2.7</sup> in women). Diastolic function was also abnormal in a large percentage of the cohort by the isovolumic relaxation time criterion, but E/A ranges remained in the normal range (normal range, E/E' <8; see Supplemental Table 1 for others).

ters for Disease Control body mass index calculator and growth charts were used to convert height and body mass index measurements to percentile ranks based on gender and age.

Table 3  
Multivariate analysis of echocardiographic parameters

	Systolic			Hypertrophy				Diastolic			
	EF	SF	WMS	IVSTi	PWTi	RWTd	LVMi	E/A	E'/A'	E/E'	IVRT
GAA	0.12	0.41	0.03	0.07	0.96	0.12	0.08	0.54	0.67	0.48	0.08
Gender	0.17	0.25	0.39	0.38	0.59	0.28	<0.01	0.38	0.96	0.66	0.02
Age	<0.01	<0.01	<0.01	0.04	<0.01	0.30	0.55	<0.01	0.03	0.62	0.40
Overall	<0.01	0.02	0.02	<0.01	<0.01	0.06	<0.01	0.01	0.06	0.65	0.03
R <sup>2</sup>	0.14	0.09	0.07	0.13	0.08	0.05	0.10	0.08	0.08	0.02	0.09

Linear regression analysis of systolic, hypertrophic, and diastolic parameters, with hypertrophic measurements indexed by body surface area or height; p values for individual variables are shown in addition to R<sup>2</sup> and p values for the models. When accounting for multiple comparisons by setting the standard of significance at a p value <0.01, age predicted measurements of systolic function and scattered measurements of hypertrophy and diastolic function. Surprisingly, GAA repeat length did not clearly predict any parameters. R<sup>2</sup> values were relatively low, showing the unexplained variability in echocardiographic parameters.

EF = ejection fraction; IVRT = isovolumic relaxation time; IVSTi = interventricular septal thickness indexed by body surface area; LVMi = left ventricular mass indexed by height<sup>2,7</sup>; PWTi = posterior wall indexed by body surface area; RWTd = relative wall thickness in diastole; SF = shortening fraction; WMS = wall motion score.

## Results

Mean age of the cohort was  $19.7 \pm 11.6$  years, disease duration was  $8.8 \pm 7.7$  years, and average age of onset was  $10.6 \pm 7.9$  years. Length of the shorter GAA allele, available in 96% of subjects, was  $681 \pm 189$  GAA repeats. Mean functional disability score was  $3.3 \pm 1.5$ , equivalent to a patient walking with moderate assistance. The cohort was predominantly women (62%) with 66% of subjects <18 years of age. Seven percent of subjects had diabetes and 76% had scoliosis.

Specific findings were grouped into measurements of systolic function (shortening fraction, ejection fraction, wall motion score), hypertrophy/mass (indexed LV mass, RWTd, interventricular septal thickness in diastole indexed by body surface area, posterior wall thickness in diastole indexed by body surface area), and diastolic function (E/A, E'/A', E/E', isovolumic relaxation time). Overall, data for most measurements were normally distributed (skewness <1) such that parametric statistics and linear regression approaches could be used.

Systolic function varied widely in the cohort and measurements of systolic function correlated modestly to moderately with each other (Table 1; Supplemental Table 2). Ejection fraction was <50% in 30 patients but <40% in only 6 patients. Shortening fraction showed less variation with only 9.3% decreasing below normal (Table 2). Overall relations to disease-related features were of modest significance but R<sup>2</sup> values were generally low. Age was the strongest predictor of decreased systolic function in linear regression models accounting for gender and GAA repeat length (Table 3). Measurements of systolic function (ejection fraction and shortening fraction) were not predicted by GAA length in linear regression analysis modeled with the entire cohort. Wall motion score was significantly predicted only by age (p <0.01) and correlated poorly with measurements of hypertrophy and diastolic function (Table 2; Supplemental Table 2). Hypertrophy measurements correlated moderately with each other and were generally increased (Table 2). Classifications of LV geometry (based on RWTd and indexed LV mass) were abnormal in 82%, with 42% having concentric remodeling, 35% having concentric hypertrophy, and only 5%

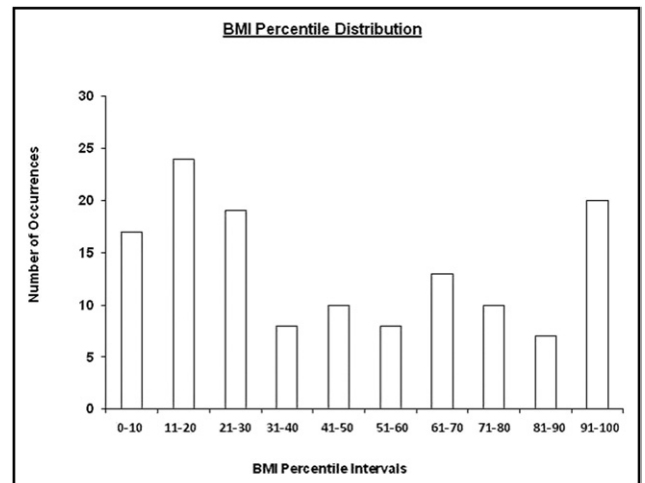


Figure 1. Histogram of body mass index (BMI) values in Friedreich ataxia show that these values were abnormal with patients on average having a lower body mass index.

Table 4  
Multivariate regression and analysis of variance of diastolic class

	Regression (p values)	ANOVA (p values)
GAA	0.02	0.02
Gender	0.13	0.32
Age	0.59	0.15
Overall	0.02	
R <sup>2</sup>	0.10	

Multivariate regression and analysis of variance were used to test the hypothesis that GAA, gender, and age significantly differed among diastolic classifications. GAA repeat length was significantly different between classifications by analysis of variance and a significant predictor of increasing classification with increasing GAA repeat length.

ANOVA = analysis of variance.

having eccentric hypertrophy. However, these classifications showed no significant relation to GAA repeat, gender, or age in linear regression analysis or by analysis of variance (data not shown). Similarly, when assessed by linear regression, few

relations of measurements of hypertrophy associated with disease features and  $R^2$  values were low. RWTd was increased in 77% of the population but showed no relation to disease features (Tables 1 and 2). Gender predicted higher indexed LV mass in linear regression models.

Because hypertrophy measurements were indexed by body surface area or height, we also considered the possibility that indexing might obscure relations with disease features because subjects with FA have an atypical body habitus. We first investigated the features of height and body mass index in FA. In an essentially identical cohort ( $n = 179$ ), subjects with FA had a lower mean body mass index percentile rank ( $43.6 \pm 31.2$ ,  $p < 0.01$ ) and height percentile rank ( $43.7 \pm 2.3$ ,  $p < 0.003$ ) compared to the United States population. The difference in means reflected a large number of subjects (19%) whose body mass index values were below the tenth percentile and some whose body mass index was pathologically low (below fifth percentile; Figure 1). This suggested that regression models with height and weight as independent variables might better test associations of hypertrophy measurements with features of FA. In such models, weight predicted increasing values in measurements of hypertrophy and  $R^2$  values were generally higher (Supplemental Table 3). However, few new associations were identified; only GAA repeat length significantly predicted interventricular septal thickness in diastole.

There was substantial evidence of diastolic dysfunction, with 84% of subjects having  $\geq 1$  abnormal diastolic parameter and 26% having  $\geq 2$  abnormal parameters (Table 2). However, diastolic function measurements correlated poorly with each other, and none correlated with disease duration. E/E' ratios moderately correlated with hypertrophy measurements (Supplemental Table 2) but were not predicted by GAA repeat, gender, or age (Table 3). In linear regression analyses, the only significant predictor of increasing isovolumic relaxation time was female gender (Table 3). In general, individual diastolic measurements were not predicted by disease features in linear regression models and thus not readily explained by association with gender, age, or GAA repeat length. Diastolic dysfunction was further characterized by classification of diastolic dysfunction class: normal (25%), impaired relaxation (25%), pseudonormalization (70%), or restrictive filling (3%). GAA repeat length differed among classifications by analysis of variance (Table 4) and predicted more severe diastolic dysfunction class in linear regression, although the  $R^2$  value was relatively low and marginally significant. No other factors predicted diastolic dysfunction class.

Functional disability score correlated modestly to poorly with echocardiographic parameters ( $r < 0.42$  for all comparisons; Table 1). No associations between functional disability score and diastolic or systolic parameters were found.

## Discussion

The major finding of the present study is the diversity of echocardiographic findings in subjects with FA. Most striking is the lack of correlation among individual parameters between and within subjects. In cross-sectional analysis,

dissecting the relation of different parameters can be difficult in FA because the heart may hypertrophy initially with later development of fibrosis.<sup>2-4</sup> This biphasic temporal course confounds analysis, but the present cohort size and use of a centralized echocardiographic laboratory conceivably could allow for the identification of novel relations.

Although previous studies of the heart in FA have focused on the presence of systolic dysfunction and hypertrophy,<sup>4,18</sup> the present cohort had quantifiable abnormalities in all aspects of cardiomyopathy. Diastolic dysfunction was the most common echocardiographic finding. Previous studies have addressed diastolic function to a modest degree<sup>4,19,20</sup> but have not concentrated on factors that predict diastolic dysfunction.<sup>21</sup> When examined in isolation, only E/A showed any relation to age, with higher values being associated with younger age. This matches the normal age dependence of E/A, but there was no significant lessening of E/A with age in linear regression models, suggesting a loss of the normal pattern and thus consistent with the presence of early diastolic dysfunction. Similarly, isovolumic relaxation times were abnormal even in younger subjects. Using a graded model of diastolic dysfunction, GAA repeat length but not age marginally predicted degree of diastolic dysfunction. Because a large majority of the cohort had evidence of diastolic dysfunction and age did not predict presence or severity, diastolic dysfunction may be an early or intrinsic component of the heart in FA that reflects genetic severity to a greater degree than neurologic disability.

The present data confirm cardiac hypertrophy and systolic dysfunction as components of FA. Increasing age predicted lower systolic function in linear regression models, matching increasing interstitial fibrosis identified by cardiac magnetic resonance imaging with older age.<sup>3</sup> The incidence of hypertrophy in this cohort was similar to that of previous studies when interpreted in the scope of eccentric and concentric hypertrophy.<sup>2,6</sup> Concentric remodeling, recently reported in a cardiac magnetic resonance imaging study,<sup>3</sup> had the highest prevalence in this cohort (43%). Gender consistently predicted measurements of hypertrophy, but age and GAA repeat length only predicted interventricular septal thickness in diastole.

In attempting to integrate the multiple components of cardiomyopathy in FA, it is necessary to include findings from a wide variety of ages, thus necessitating normalization for changes in body size over such time. Traditionally, such normalizations are based on height (i.e., meters<sup>2,7</sup>) or body surface area. However, subjects with FA have abnormal body mass index and height values compared to controls. In addition, in linear regression analyses  $R^2$  values were generally higher when height and weight were included as independent variables rather than using standard corrections. This suggests the abnormal body mass index and height of patients with FA may require that data from echocardiograms be normalized differently from those of controls.

Overall, the present data suggest that hypertrophy, systolic dysfunction, and diastolic dysfunction are not closely related events in FA. Consequently, the present cross-sectional analysis does not facilitate creation of a model of overall cardiomyopathy, limiting the use of echocardiograms as an outcome measurement in FA. This illuminates

the need for a longitudinal analysis of cardiomyopathy in FA. Several features of the present study might obscure the creation of a model. The present retrospective cohort is larger but also younger than that of previous studies in FA and potentially biased.<sup>6,18,19,21</sup> In addition, medication use and presence of clinical symptoms associated with selected studies might influence the ability to discern comprehensive relations. Furthermore, although the present study removes interobserver variability, differences in the variability of collection protocols could emerge (although such variations should be small when using certified technicians performing standard clinical protocols). Moreover, the most severely affected subjects with FA may have been less likely to be included at older ages based on an increased mortality rate from cardiac causes (leading to bias). Nevertheless, given the size of the present cohort and the uniform nature of the protocol for evaluation of each study, such confounders are unlikely to completely obscure simple relations among disease parameters and echocardiographic measurements. In addition, definitively identifying relations between echocardiograph parameters and disease features such as GAA repeat length has been difficult in other cohorts. A longitudinal study analyzing changes over time might allow better discrimination of the relation among hypertrophy, systolic function, and diastolic function in FA and disease-related causative factors.

### Supplementary Data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.amjcard.2011.09.025.

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