The Heart in Friedreich Ataxia: Definition of Cardiomyopathy, Disease Severity, and Correlation with Neurological Symptoms

Running title: Weidemann et al.; The heart in friedreich ataxia

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Abstract:

**Background** - This cross sectional study provides a practical approach for the clinical assessment of Friedreich ataxia (FA) cardiomyopathy (FA-CM).

**Methods and Results** - A comprehensive cardiac assessment, including standard echocardiography, color Doppler myocardial imaging (CDMI), cardiac magnetic resonance imaging (cMRI), electrocardiography (ECG) and exercise stress testing was performed in 205 FA patients. To assess myocardial hypertrophy in FA-CM, the end-diastolic interventricular septal wall thickness (IVSTd) was found to be the best echocardiographic parameter when compared to cMRI-determined left ventricular mass. Using this parameter, four groups of FA-CM could be defined. Patients with normal values for IVSTd (31.7%) classified as “no FA-CM”. Patients with an IVSTd exceeding the predicted normal IVSTd were classified as “mild FA-CM” (40%) if IVSTd exceeds the normal value by < 18% or as “intermediate FA-CM” (16.1%) if IVSTd exceeds by ≥18%. Patients with ejection fraction (EF) < 50% were classified as “severe FA-CM” (12.2%). Besides increased myocardial mass, severe FA-CM was further characterized by dilatation of the left ventricle, reduced systolic strain-rate of the posterior wall, and ECG abnormalities. Regional myocardial function correlated negatively with FA-CM groups. Younger patients had a tendency for a more advanced FA-CM. Importantly, no clear correlation was found between FA-CM groups and neurological function.

**Conclusions** - We provide and describe a readily applicable clinical grouping of the cardiomyopathy associated with FA based on echocardiographic IVSTd and EF data. As no distinct interrelations between FA-CM and neurological status could be determined, regular follow-up of potential cardiac involvement in FA patients is essential in clinical practice.

**Clinical Trial Registration Information** - Clinicaltrials.gov; ID: NCT00905268.

**Key words:** Friedreich Ataxia, hypertrophic cardiomyopathy, disease severity, imaging
Introduction

Friedreich’s ataxia (FA) is an autosomal recessive neurodegenerative disease caused by a defect in the gene encoding for the mitochondrial protein frataxin. It is a rare disease affecting approximately 1 in 50,000 caucasians.\textsuperscript{1-3} Myocardial involvement in FA is well documented, with concentric (or less frequent) asymmetric left ventricular (LV) hypertrophy as the dominating cardiac finding.\textsuperscript{4-6} Cardiac dysfunction, predisposing to congestive heart failure and supraventricular arrhythmias, was the most frequent cause of death (59\%) in a retrospective study in 99 patients with FA.\textsuperscript{7} Life expectancy in FA patients with cardiac involvement is considerably reduced to 29 - 38 years.\textsuperscript{7-9}

Echocardiography is the routine imaging technique of choice for the evaluation and follow-up of the cardiac involvement in patients diagnosed with FA (FA-CM), although cardiac magnetic resonance imaging (cMRI) has been shown to be more sensitive and accurate in determining the severity of cardiac remodeling in FA patients.\textsuperscript{10} The challenge with echocardiography is two-fold: reliably detecting cardiac involvement and assessing the severity of FA-CM. To meet this challenge, the precise evaluation of the extent of LV hypertrophy is mandatory with LV end-diastolic wall thickness usually being the best acknowledged echocardiographic parameter. However, the clinical phenotypes and patterns of disease progression are highly variable in FA. Therefore, a single cut-off value for the evaluation and definition of FA-CM and the disease progression over time may not suffice.

This is the first study analyzing morphological \textit{and} functional cardiac data from standard echocardiography, color Doppler myocardial imaging (CDMI), cardiac MRI, exercise performance and electrocardiography (ECG) from a large cohort of FA patients with wide ranges in age, neurological symptoms and cardiac involvement.
The aim of this study was therefore to provide a clinical approach for the comprehensive assessment of FA-CM and to determine possible correlations of the degree of FA-CM with neurological disease symptoms and associated genetic factors.

Methods

Study Population

Two hundred and five patients with genetically confirmed FA participating in the MICONOS study (clinicaltrials.gov ID: NCT00905268) were studied. The MICONOS study was conducted between April 2006 and January 2010 and enrolled patients in 13 centers in 6 European countries. For genetic confirmation patients had to present with extended GAA repeat length in the first intron of the frataxin gene on both alleles or with an extended GAA repeat length on one allele and a nonsense mutation on the second allele. Patients were excluded if (i) they had been treated with idebenone or Coenzyme Q10 (CoQ10) within the past month (n=1), (ii) were pregnant and/or breast-feeding, (iii) had clinically significant abnormalities of clinical hematolgy or biochemistry, or (iv) had a past or present history of drug/alcohol abuse. Cardiac data including standard echocardiography, color Doppler myocardial imaging, ECG, cMRI and a bicycle exercise test were acquired within one day during the baseline visit of the MICONOS trial. All patients gave prior written consent for imaging studies including digital data storage and systematic analysis of the data. The MICONOS study was approved by institutional ethics committees and all investigations conformed to the principles outlined in the Declaration of Helsinki.

Standard Echocardiographic Measurements
LV end-diastolic (LVEDD) and end-systolic dimensions (LVESD) and end-diastolic thickness of the posterior wall (Echo-PWTd) and the interventricular septum (Echo-IVSTd) were measured using standard M-mode echocardiographic methods from parasternal LV long axis images. If appropriate, the anatomic M-mode was used. Derived cardiac parameters, including relative wall thickness (RWT), LV myocardial mass (LVM) and ejection fraction (Echo-EF) was calculated as described in **Supplemental Table 1**. Blood pool pulsed Doppler of the mitral valve inflow was used to extract the ratio of early to late diastolic flow velocity (E/A), the deceleration time (DT) and the isovolumic relaxation time (IVRT).

**Color Doppler Myocardial Imaging (CDMI)**

Real time longitudinal 2-dimensional tissue Doppler data were recorded from the interventricular septum, the LV lateral, inferior, anterior, posterior and anteroseptal walls using 4-, 2- and 3-chamber apical views with the wall in the center of the sector. Longitudinal strain rates in the basal, mid and apical segments of each wall were estimated by measuring the spatial velocity gradient. Strain rate profiles were averaged over three consecutive cardiac cycles and integrated over time in order to derive strain profiles using end-diastole as the reference point (Speqle®, K.U.Leuven, Belgium). From the averaged strain rate and strain data, peak systolic strain rate and systolic strain were calculated. The intra-observer variability for peak systolic strain rate of the inferior septal and lateral segments was assessed on 24 CDMI data sets. The correlation coefficient for intra-rater variability was high for both segments (septum: Pearson’s \( r = 0.82 \); lateral: \( r = 0.91 \)). The weighted kappa values for intra-rater variability (septum: \( \kappa = 0.62 \), lateral: \( \kappa = 0.69 \)) indicated satisfying agreement and low intra-rater variability.\(^{11}\)

In addition, the early diastolic velocity of the septal mitral annulus (E’) was extracted to assess the early diastolic transmitral velocity/mitral annular velocity ratio (E/E’). All standard
echocardiography and CDMI data were analyzed centrally in a core laboratory by expert readers blinded to other cardiac data or patient characteristics (St. Georges Hospital, London, UK).

**Cardiac Magnetic Resonance Imaging (cMRI)**

Cine short-axis multi-slice images of the left ventricle were collected using the steady-state free precision (SSFP) technique and analyzed blinded by a central core-lab (BioClinica, Leiden, The Netherlands) using QMassMR software (version 6.1, Medis, Leiden, The Netherlands). Epi- and endocardial convex-shaped contours were drawn manually in the end-diastolic and end-systolic phases of the left ventricle. Papillary muscles and trabeculations were excluded from the calculated LV mass. The density of myocardial tissue was set at 1.05 g/ml. Of note, LV masses analyzed by the SSFP method tend to be ~15% lower than masses recorded by the turbo gradient echo (TGE) method. Both, the exclusion of papillary muscles and trabeculations as well as the SSFP method should be considered when comparing LV masses across studies.

**Bicycle Exercise Test**

Subjects underwent testing on a recumbent exercise bicycle allowing to pedal with either legs or arms (Lode, Groningen, The Netherlands) to assess exercise tolerance. After a 3 minute warm-up phase subjects were instructed to pedal at 50-60 revolutions per minute for arm ergometry and 60-70 revolutions per minute for leg ergometry and to keep pedaling at a constant rate during the test. Following warm-up, the resistance was increased in steps of 10 Watts every minute and the peak exercise workload (in Watts) was recorded. Subjects were advised that they were free to stop whenever they wished but were encouraged to continue for as long as possible. Heart rate (HR) and ECG were recorded during the exercise test for safety reasons and the test would have been discontinued if chest pain, signs of ischemia or arrhythmias developed.
Electrocardiography

Resting ECGs were performed in 191 patients and the following parameters extracted: Heart rate (HR), R-R interval (RR), P-R interval (PR), QRS interval (QRS), Q-T time (QT), Q-T time corrected using Fridericia’s formula (QTcF) or Bazett’s formula (QTcB). In general an abnormal ECG was defined as any of the following: ventricular or supraventricular arrhythmia, atrio- or interventricular conduction delay. All ECGs were analyzed blinded in a central core laboratory by expert readers (ganiMed, Villingen-Schwenningen, Germany).

Assessment of Neurological Function

Neurological function was assessed by the International Cooperative Ataxia Rating Scale (ICARS) by trained raters. The ICARS consists of 19 items addressing oculomotor function, speech, kinetic functions, and posture and gait. Patients who were able to walk at least 10 meters with or without walking aids but without the help of an accompanying person were classified “ambulatory”. For the assessment of the ICARS score in every center a rater and a back-up rater were trained and certified by the study’s Clinical Research Physician, using study-specific training materials (including video training).

Data Analysis

Data are shown as mean with standard deviation (SD), median with quartiles and/or range, or frequency and proportion, as appropriate. Correlations are presented as Spearman’s correlation coefficient rho. Comparisons between groups of no, mild, intermediate and severe FA-CM were done by Kruskal-Wallis test (chi-square test) and, if significant, by group-wise Mann-Whitney U test or chi-square test. No formal adjustment for multiple testing was implemented; to account for the multiple comparisons between FA-CM categories only differences significant at p<0.001 should be considered. Skewed variables were log-normalized before used in multivariable
regression analysis; there, a stepwise model using forward selection followed by backward elimination (p<0.05 used as criteria for entry and grouping in the model). Independent predictors of FA-CM (yes vs. no) were sought by logistic regression using a similar approach.

Results

Two hundred and five patients with genetically confirmed FA were included in this cross-sectional study. The mean (SD) age was 30.6 (13.3; range 8–70) years and 91 patients (44.4%) were female. The median (quartiles) age at diagnosis was 13.5 (9.1; 19.7) years and mean time since diagnosis was 14.6 (9.6) years. The mean ICARS was 48.4 (21.2) points and 51.8% of patients were ambulatory (see Table 1 for patient characteristics).

Friedreich ataxia cardiomyopathy

The primary objective of this study was to identify a readily accessible clinical echocardiography parameter that would allow the sensitive detection and reliable grouping of FA-CM cardiac phenotypes. Since LV hypertrophy is the main cardiac feature in FA, we first correlated a number of standard (i.e. non-derived) echocardiography parameters with LV mass assessed by cMRI, generally accepted as the reference standard to determine myocardial mass (Table 2). The best correlation with cMRI-derived LV mass was seen for the Echo-IVSTd (rho = 0.49; p<0.0001), qualifying this easily accessible parameter as a reliable echocardiographic measure to detect LV hypertrophy in FA.

Using reference values for Echo-IVSTd, correcting for age and body surface area and calculated according to Henry’s nomogram16 (Supplemental Table 1), four groups of FA-CM could be defined:
1. **“no FA-CM”:** patients with normal values for Echo-IVSTd (i.e. not larger than the predicted value calculated by Henry’s nomogram) and MRI ejection fraction ≥ 50%.

2. **“mild FA-CM”:** patients with an Echo-IVSTd exceeding the predicted normal Echo-IVSTd by less than 18% (corresponding to 2 x SD in Henry’s nomogram) and MRI ejection fraction ≥ 50%.

3. **“intermediate FA-CM”:** patients with Echo-IVSTd exceeding the predicted normal Echo-IVSTd by 18% or more and MRI ejection fraction ≥ 50%.

4. **“severe FA-CM”:** patients with MRI ejection fraction < 50% independent of Echo-IVSTd.

Using cMRI data and comparing actual Echo-IVSTd data from this study cohort of FA patients with predicted values according to Henry’s nomogram, there were 65 (31.7%) patients who were classified as no FA-CM. The other patients were thus diagnosed as having cardiac involvement. Of these, 82 (40.0%) had mild FA-CM; 33 (16.1%) intermediate FA-CM and 25 (12.2%) severe FA-CM. The patient characteristics of all FA-CM groups are shown in Table 1.

For comparison, we also grouped patients based on echocardiography data, which resulted in 32.2% of patients with no FA-CM, 41.0% of patients with mild FA-CM, 18.5% with intermediate FA-CM and 8.3% with severe FA-CM. As cMRI is generally considered more reliable than echocardiography we used cMRI-based EF measurements for further analyses.

In general, all patients with a cardiomyopathy had a concentric LV hypertrophy pattern by visual assessment (no patient had a septal or apical hypertrophic cardiomyopathy pattern). Patients in the no FA-CM group were on average older and were included in the study with a longer time since diagnosis than patients with any degree of FA-CM. Interestingly, a higher
proportion of patients presenting with progressing FA-CM was male, i.e. 66% in intermediate
FA-CM and 72% in severe FA-CM stage.

**Echocardiographic characterization of FA-CM groups**

The morphological and functional echocardiographic characteristics of all subjects
studied across all FA-CM groups are shown in **Table 3**. Because FA-CM categories were
defined according to Echo-IVSTd, intermediate FA-CM showed higher values compared to
severe FA-CM. Echo-PWTd was thicker in the mild and intermediate FA-CM groups compared
to no FA-CM, but was thinner in severe FA-CM patients. Interestingly, the Echo-IVSTd was
larger than the Echo-PWTd in the more advanced groups of FA-CM, particularly in the
intermediate and severe FA-CM (2 patients of severe FA-CM and 1 patient of intermediate FA-
CM had an Echo-IVSTd/PWTd> 1.5). When focusing on LV dimensions, both end-diastolic and
end-systolic diameters were larger in severe FA-CM patients and higher values for LV
myocardial mass were evident with more advanced FA-CM. Conventional diastolic
echocardiographic function parameters were not significantly different between the FA-CM
groups. Although Echo-EF was normal and not significantly different between no FA-CM, mild
FA-CM and intermediate FA-CM patients, a trend for a lower values of peak systolic global
longitudinal strain rate, measured as average across all cardiac segments (**Table 3, Figure 1A**),
was detectable. Likewise, significantly lower values for averaged peak systolic global strain in
intermediate and severe FA-CM compared to the no FA-CM group (**Figure 1B**) was observed.
Analysis of peak systolic strain rate for each of the LV cardiac segments showed that the highest
absolute values, i.e. indicating good regional contractility, were found in the septum and the
lowest absolute values, i.e. indicating poor regional contractility, were detected in the posterior
wall (**Figure 1C, D**). Of note, the region with the consistently lowest absolute peak systolic
strain rate in the LV (i.e. functionally worst) was the basal posterior segment in patients with severe FA-CM.

**Electrocardiographic characterization of FA-CM groups**

Resting ECG data was available from 191 patients and showed that the percentage of patients with an abnormal ECG increased with more severe FA-CM groups: 23.4% for no FA-CM, and 26.7%/44.8%/65.2% for mild/intermediate/severe FA-CM, respectively. Patients with severe FA-CM exhibited a higher resting heart rate (Table 4). The QRS duration was normal and not different between FA-CM groups indicating that even patients with severe FA-CM did not tend to develop bundle branch block. Uncorrected and corrected QT intervals were normal and not different between FA-CM groups, implying that these hearts were not very susceptible for malignant ventricular arrhythmias. In parallel to echocardiography findings, intermediate FA-CM patients showed both a higher S wave in V2 and higher R wave in V5 indicating electrocardiographic signs of LV hypertrophy.

**Exercise performance**

Exercise stress test was performed by 191 patients. No stress test had to be stopped early for safety reasons. Peak workload (Watts, median, quartiles) was not different between FA-CM subgroups: 51 W (28; 90) for no FA-CM, 40 W (22; 91) for mild FA-CM, 38 W (26; 64) for intermediate FA-CM, 40 W (27; 91) for severe FA-CM. Interestingly, exercise performance was more closely related to the neurological status than to the FA-CM group. Specifically, peak workload negatively correlated with ICARS for patients using leg (rho = -0.39, p=0.0002) or arm ergometry (rho = -0.52, p<0.0001) (Figure 2). When applying a stepwise regression analysis (using age, age at diagnosis, time since diagnosis, FA-CM group, GAA1 repeat length, arm/leg ergometry and ICARS as possible explanatory factors), the best predictor of exercise
performance was ICARS, accounting for 56% of the variability (p<0.0001). Other independent predictors were GAA1 repeat length (additional 5% of the variability, p=0.0070) and whether the test was performed by arm or leg ergometry (additional 2%, p=0.0462).

Relationship between of FA-CM groups and age, neurological function, and GAA repeat length

When inspecting FA-CM groups by age categories, there was a clear tendency for a higher proportion of patients at young age presenting with intermediate and severe FA-CM (Figure 3A). In fact, 49% of patients below 20 years of age presented with intermediate or severe FA-CM. In contrast, more than two thirds of patients above 40 years had no FA-CM. Patients with an earlier diagnosis (and thus onset) of disease generally also showed more severe cardiac involvement. For example, 37.8% of patients aged less than 14 years at diagnosis presented with intermediate or severe FA-CM, compared to only 17.8% of patients older than 14 years. Interestingly, a total of 46.7% of patients aged more than 14 years at diagnosis were categorized as no FA-CM.

In contrast, no relationship could be found between FA-CM groups and the ICARS score (Table 1). The distribution of FA-CM groups was comparable across all ICARS groups (Figure 3B), indicating that the ICARS is not a predictor for the severity of cardiac involvement in FA. For 85 patients data on GAA repeat lengths was available, and the disease-predicting shorter GAA allele was evaluated for a possible association with FA-CM groups. There was also no clear correlation between GAA repeat length and increasing FA-CM severity (Figure 4).

Multivariate statistical analyses were performed using age, age at diagnosis, time since diagnosis, ICARS score, FA-CM category and GAA1 repeat length as potential explanatory variables. For ICARS (in linear regression), time since FA diagnosis was the best predictor...
(describing 46% of the variability, p<0.0001), followed by age at diagnosis (10%, p<0.0001).

For FA-CM status (logistic regression), age was the best explanatory factor (chi-square = 24.9, p<0.001) and ICARS ranked second (chi-square = 8.6, p<0.0034).

**Discussion**

As cardiac involvement in Friedreich ataxia is commonly described based on data limited to either LV hypertrophy or LV dysfunction or electrical abnormalities, there is still a lack of comprehensive cardiac data sets allowing to develop strategies for the reliable detection and assessment of FA-CM. The present cross-sectional study in more than 200 patients is the hitherto largest in FA presenting data on cardiac morphology and function determined by standard echocardiography, CDMI, cMRI, ECG and exercise testing. In line with emerging diagnostic criteria and standard of care recommendations for FA, the assessment of this heterogeneous patient population with pronounced diversity regarding age, age at diagnosis, duration of disease, genetic status, and neurological symptoms, for the first time allowed a more comprehensive description of FA-CM. Reliable and precise diagnostic and follow-up approaches for FA-CM are needed as cardiac involvement is a major contributor to the increased risk of morbidity and mortality observed in this disease. Specifically, criteria were lacking that allow to assess the severity of cardiac involvement in individual patients according to objective and clinically accessible morphological and functional cardiac parameters. Here we provide comprehensive data that support the grouping of FA-CM based on readily available standard echocardiographic measurements, and describe in detail the clinical presentation of FA-CM phenotypes.

**Friedreich Ataxia Cardiomyopathy**
Like earlier studies\textsuperscript{21} we compared data from our study sample to reference values using Henry’s nomogram\textsuperscript{16} to assess FA-CM. Amongst various standard echocardiographic parameters of cardiac morphology Echo-IVSTd was shown to be a reliable predictor for increased LV mass as measured by the reference cMRI standard. Besides the progression towards LV hypertrophy, a decrease in global LV function also indicates cardiomyopathy. Thus, an additionally reduced MRI-EF (<50\%) was chosen as principal criterion defining severe FA-CM.

With respect to LV morphology we observed that in milder groups of FA-CM the thickness of the LV walls was very homogenous and the LV was not dilated, whereas in patients with severe FA-CM the septum was significantly thicker than the posterior wall. However, the visual impression is that of a homogenous concentric hypertrophy pattern even in severe FA-CM, as these small differences can not be detected by the human eye. In addition, measurement values for both the septum and also the posterior wall thickness were slightly lower in severe FA-CM patients. As the highest myocardial mass was seen in patients with severe FA-CM, the decrease in wall thickness in combination with a dilated LV indicates eccentric LV remodeling in these patients. From autopsy and biopsy studies it is known that FA patients can develop myocardial fibrosis,\textsuperscript{18, 19, 22, 23} which might be responsible for the observed shrinking of the myocardium in severe FA-CM. As the posterior wall was thinner than the septum in these patients it can be speculated that the progression towards fibrosis is more advanced in the posterior cardiac segments. This assumption is supported by the finding that the posterior wall showed also the lowest values for regional longitudinal function. In a recent paper by Mottram et al. reduced longitudinal function was also discussed as a typical functional finding in FA-CM\textsuperscript{6} which is in accordance to our study. The phenomenon of developing fibrosis especially in the
posterior wall is also well known in other genetic cardiomyopathies such as Duchenne muscular
dystrophy and Fabry disease.\textsuperscript{24, 25}  

Our study did not provide evidence for an association between neurological and cardiac
involvement in patients with FA, and further work is needed to better understand the role of
other factors influencing the development of FA-CM. Importantly, exercise capacity of FA
patients was not affected by the severity of FA-CM but rather by the neurological involvement.
Thus, in patients with advanced neurological disease a subclinical cardiomyopathy may be
present despite the absence of exertional symptoms usually observed in patients with myocardial
disease.

**Clinical Implication**

The present study provides guidance how cardiac involvement in FA can be assessed
during routine follow-up as part of the recommended standard of care for FA.\textsuperscript{4} From other
cardiomyopathies it is known that the severity of the disease impacts on treatment strategies.\textsuperscript{26} In
this context, it is clinically important that an observed decrease of posterior wall thickness in FA
during follow-up could represent progression towards an advanced stage of cardiomyopathy
rather than a positive treatment effect, especially in combination with declining EF.

The current data also provides evidence that patients with FA-CM are developing heart
involvement already at early age (i.e., below 40 years of age). Young age appears to better
predict the degree of FA-CM than GAA repeat length, which is in agreement with previous
observations.\textsuperscript{27} This finding is also consistent with a recent study demonstrating that most FA
patients die from cardiac failure aged younger than 40 years.\textsuperscript{7} Our data imply that young patients
in particular should be carefully evaluated for cardiac involvement and routinely checked
thereafter for disease progression; neurological evaluation alone must be considered insufficient to assess cardiac risks.

**Study Limitations**

Cross-sectional studies are not suited to describe the progression of a disease over time. However, two longitudinal studies in FA\(^{18,28}\) suggested a natural course of disease progression from LV hypertrophy to dilated cardiomyopathy similar to our findings. Owing to the comparatively large number of FA patients across a wide range of clinical and diagnostic phenotypes, we consider the present study representative allowing adequate description of the various types of disease severity and organ involvement in FA-CM. Spiroergometry, which is suited best to describe the musculo-cardiac-pulmologic coupling, was not performed in the present study. Hence, a more detailed analysis of the reduced exercise capacity in FA-CM is left for further studies. In addition, a validation of Henry’s nomogram was not performed, which is difficult due to the rare nature of the disease. Because myocardial biopsies were not sampled for ethical reasons we were unable to determine the histological pathology underlying the observed morphological and functional changes.

The preferred approach for grouping FA-CM might be to perform both cMRI and echocardiography at the time when the disease is diagnosed; this would allow setting an accurate baseline for the patient. Later, during follow-up, echocardiographic examinations alone may suffice. However, this issue should be left for future discussion within the format of a guideline/consensus paper.
Conclusions

This cross-sectional study in a large group of FA patients provides a detailed characterization of the morphological, functional and electrocardiographic abnormalities associated with FA-CM and will add to the standard of care for this rare disease.

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Conflict of Interest Disclosures: CR and TM are regular employees of Santhera Pharmaceuticals, the sponsor of the MICONOS study.

References:


Table 1. Patient characteristics of the complete study cohort and for the different groups of FA-CM

<table>
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<tr>
<th></th>
<th>All patients (n= 205)</th>
<th>No FA-CM (n=65)</th>
<th>Mild FA-CM (n=82)</th>
<th>Intermediate FA-CM (n=33)</th>
<th>Severe FA-CM (n=25)</th>
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<td>Age [y]</td>
<td>30.6 ± 13.3 (8-70)</td>
<td>38.8 ± 13.8 (8-68)</td>
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<td>20.4 ± 7.8 **, # (8-42)</td>
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Data is mean ± SD (range).
* and # indicate significance levels for comparisons with “no FA-CM” and “severe FA-CM”, respectively.
* or # indicates p<0.05; ** or ## indicates p<0.001.
a,b: Fisher’s Exact test: p=0.09 (a) and p=0.06 (b) for comparison to “no FA-CM”.
FA-CM = Friedreich ataxia cardiomyopathy.

Table 2. Correlation of different echocardiographic parameters with left ventricular mass as assessed by cMRI

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<thead>
<tr>
<th>Correlation of LV mass (by cMRI) with</th>
<th>Spearman rho</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVSTd</td>
<td>0.49</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>End-diastolic volume</td>
<td>0.46</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LVEDD</td>
<td>0.46</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>PWTd</td>
<td>0.43</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>End-systolic volume</td>
<td>0.37</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LVESD</td>
<td>0.37</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>RWT</td>
<td>0.16</td>
<td>0.026</td>
</tr>
</tbody>
</table>

The evaluated echocardiographic parameters were available in all patients (n=205).
cMRI = cardiac magnetic resonance imaging; IVSTd = end-diastolic wall thickness of the interventricular septum; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; PWTd = end-diastolic thickness of the posterior wall; RWT = relative wall thickness.
Table 3. Morphological and functional echocardiographic and cMRI data for the different groups of FA-CM

<table>
<thead>
<tr>
<th>Echocardiographic parameter</th>
<th>No FA-CM (n=65)</th>
<th>Mild FA-CM (n=82)</th>
<th>Intermediate FA-CM (n=33)</th>
<th>Severe FA-CM (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVSTd [cm]</td>
<td>0.89 ± 0.10</td>
<td>1.11 ± 0.13 **, #</td>
<td>1.38 ± 0.18 **, #</td>
<td>1.24 ± 0.29 **</td>
</tr>
<tr>
<td>PWTd [cm]</td>
<td>0.91 ± 0.15</td>
<td>1.04 ± 0.15 **</td>
<td>1.22 ± 0.21 ** , ##</td>
<td>1.00 ± 0.22</td>
</tr>
<tr>
<td>IVSTd/PWTd</td>
<td>0.99 ± 0.15</td>
<td>1.10 ± 0.21 * , #</td>
<td>1.15 ± 0.19 *</td>
<td>1.27 ± 0.28 **</td>
</tr>
<tr>
<td>LVEDD [cm]</td>
<td>4.35 ± 0.52</td>
<td>4.20 ± 0.50 ##</td>
<td>3.98 ± 0.51 ** , ##</td>
<td>4.72 ± 0.77 *</td>
</tr>
<tr>
<td>LVESD [cm]</td>
<td>2.80 ± 0.47</td>
<td>2.68 ± 0.52 ##</td>
<td>2.55 ± 0.50 ##</td>
<td>3.41 ± 0.76 **</td>
</tr>
<tr>
<td>RWT</td>
<td>0.42 ± 0.08</td>
<td>0.52 ± 0.07 **</td>
<td>0.66 ± 0.12 ** , ##</td>
<td>0.49 ± 0.14 *</td>
</tr>
<tr>
<td>LVM (g) (Devereux)</td>
<td>145.0 ± 40.0</td>
<td>178.7 ± 51.0 *</td>
<td>221.5 ± 63.8 **</td>
<td>233.5 ± 81.3 **</td>
</tr>
<tr>
<td>LVMI (de Simone)</td>
<td>34.1 ± 7.4</td>
<td>43.1 ± 9.5 ** , ##</td>
<td>56.6 ± 11.3 **</td>
<td>56.4 ± 19.5 **</td>
</tr>
<tr>
<td>LVMI (Du Bois)</td>
<td>79.6 ± 16.2</td>
<td>102.6 ± 19.6 ** , ##</td>
<td>139.4 ± 31.6 **</td>
<td>135.6 ± 44.9 **</td>
</tr>
<tr>
<td>EF [%]</td>
<td>65.5 ± 7.4</td>
<td>65.1 ± 10.5 ##</td>
<td>65.9 ± 9.4 ##</td>
<td>53.2 ± 12.1</td>
</tr>
<tr>
<td>FS [%]</td>
<td>36.0 ± 5.6</td>
<td>36.0 ± 8.0 ##</td>
<td>36.2 ± 7.1 ##</td>
<td>28.1 ± 7.2 **</td>
</tr>
<tr>
<td>Peak systolic strain, average [s⁻¹]</td>
<td>-1.33 ± 0.23</td>
<td>-1.30 ± 0.23</td>
<td>-1.21 ± 0.26</td>
<td>-1.19 ± 0.36</td>
</tr>
<tr>
<td>Peak systolic strain, average [%]</td>
<td>-16.4 ± 2.9</td>
<td>-15.3 ± 3.1 #</td>
<td>-13.3 ± 3.4 **</td>
<td>-12.8 ± 3.9 **</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.33 ± 0.47</td>
<td>1.57 ± 0.53 *</td>
<td>1.92 ± 0.73 ** , #</td>
<td>1.47 ± 0.47</td>
</tr>
<tr>
<td>Deceleration time [ms]</td>
<td>163.5 ± 42.7</td>
<td>146.8 ± 45.6</td>
<td>134.8 ± 36.8 *</td>
<td>140.7 ± 43.3</td>
</tr>
<tr>
<td>Isovolumic relaxation time [ms]</td>
<td>88.3 ± 13.7</td>
<td>84.8 ± 13.1</td>
<td>85.1 ± 14.5</td>
<td>91.4 ± 8.3</td>
</tr>
<tr>
<td>E/E' ratio as index of left atrial pressure</td>
<td>9.08 ± 2.95</td>
<td>8.93 ± 2.51</td>
<td>9.16 ± 2.92</td>
<td>8.84 ± 2.48</td>
</tr>
<tr>
<td>cMRI parameter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVM [g]</td>
<td>75.4 ± 22.2</td>
<td>83.9 ± 22.0 #</td>
<td>103.3 ± 34.3 **</td>
<td>106.3 ± 37.7 **</td>
</tr>
<tr>
<td>LVMI (de Simone)</td>
<td>17.7 ± 4.0</td>
<td>20.2 ± 4.1 * , ##</td>
<td>26.3 ± 6.2 **</td>
<td>25.3 ± 7.9 **</td>
</tr>
<tr>
<td>LVMI (Du Bois)</td>
<td>41.4 ± 9.2</td>
<td>48.2 ± 8.9 * , ##</td>
<td>64.6 ± 17.9 **</td>
<td>61.1 ± 19.1 **</td>
</tr>
<tr>
<td>ED Volume [ml]</td>
<td>123.8 ± 29.5</td>
<td>122.2 ± 32.2 ##</td>
<td>122.1 ± 33.4 ##</td>
<td>165.6 ± 55.3 **</td>
</tr>
<tr>
<td>ES Volume [ml]</td>
<td>47.5 ± 15.3</td>
<td>46.9 ± 17.5 ##</td>
<td>47.1 ± 18.1 ##</td>
<td>95.4 ± 43.7 **</td>
</tr>
<tr>
<td>EF [%]</td>
<td>61.9 ± 6.6</td>
<td>62.2 ± 6.2 ##</td>
<td>62.3 ± 6.5 ##</td>
<td>44.0 ± 6.7 **</td>
</tr>
</tbody>
</table>

Values are mean ± SD.  
* and # indicate significance levels for comparisons with “no FA-CM” and “severe FA-CM”, respectively. 
* or # indicates p<0.05; ** or ## indicates p<0.001.

cMRI = cardiac magnetic resonance imaging; ED = end-diastolic; ES = end-systolic; FA-CM = Friedreich ataxia cardiomyopathy; LVM(I) = left ventricular mass (index); IVSTd = end-diastolic wall thickness of the interventricular septum; PWTd = end-diastolic wall thickness of the posterior wall; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; RWT = relative wall thickness; EF = ejection fraction; FS = fractional shortening; E/A = ratio of early to late diastolic transmitral flow; E/E' = ratio of early diastolic transmitral flow to early diastolic velocity of the septal mitral annulus.
Table 4. Resting ECG parameters for the different groups of FA-CM

<table>
<thead>
<tr>
<th>Parameter</th>
<th>no FA-CM (n=64)</th>
<th>mild FA-CM (n=75)</th>
<th>intermediate FA-CM (n=29)</th>
<th>severe FA-CM (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>76 (68; 80)</td>
<td>75 (69; 81)</td>
<td>73 (65; 79)</td>
<td>81 (73; 88)</td>
</tr>
<tr>
<td>RR (ms)</td>
<td>790 (731; 872)</td>
<td>804 (725; 869)</td>
<td>796 (729; 904)</td>
<td>73 (673; 762)</td>
</tr>
<tr>
<td>PR (ms)</td>
<td>134 (125; 154)</td>
<td>132 (121; 146)</td>
<td>126 (120; 134)</td>
<td>130 (115; 140)</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>88 (82; 93)</td>
<td>84 (77; 90)</td>
<td>89 (83; 97)</td>
<td>91 (79; 97)</td>
</tr>
<tr>
<td>QT (ms)</td>
<td>370 (349; 385)</td>
<td>362 (339; 380)</td>
<td>369 (354; 386)</td>
<td>366 (355; 377)</td>
</tr>
<tr>
<td>QTcB (ms)</td>
<td>406 (390; 429)</td>
<td>405 (391; 424)</td>
<td>415 (402; 426)</td>
<td>423 (413; 446)</td>
</tr>
<tr>
<td>QTcF (ms)</td>
<td>394 (382; 410)</td>
<td>390 (374; 413)</td>
<td>400 (385; 416)</td>
<td>408 (393; 418)</td>
</tr>
<tr>
<td>R wave in aVL (mm)</td>
<td>1.9 (1.1; 3.5)</td>
<td>2.3 (1.3; 4.1)</td>
<td>2.2 (1.3; 3.4)</td>
<td>2.0 (1.0; 3.3)</td>
</tr>
<tr>
<td>R wave in V5 (mm)</td>
<td>9.8 (7.1; 12.7)</td>
<td>11.5 (7.2; 15.7)</td>
<td>14.4 (9.0; 19.0)</td>
<td>8.1 (5.7; 11.5)</td>
</tr>
<tr>
<td>S wave in V1 (mm)</td>
<td>6.2 (4.2; 10.6)</td>
<td>9.2 (5.6; 11.8)</td>
<td>9.1 (5.5; 12.5)</td>
<td>6.1 (4.6; 9.9)</td>
</tr>
<tr>
<td>S wave in V2 (mm)</td>
<td>10.1 (7.0; 14.3)</td>
<td>13.8 (9.0; 20.2)</td>
<td>16.8 (11.7; 27.6)*</td>
<td>13.9 (9.9; 23.3)</td>
</tr>
</tbody>
</table>

Values are median (quartiles).

QTcB: QT interval corrected according to Bazett’s formula (QTc=QT/RR^{1/2}); QTcF: QT interval corrected according to Fridericia’s formula (QTc=QT/RR^{1/3}).

* indicates comparison with “no FA-CM” (p<0.001).

FA-CM = Friedreich ataxia cardiomyopathy

Figure Legends:

Figure 1: Box and whisker plots of peak systolic strain rate (A) and peak systolic strain (B) recorded in FA patients with different severity of FA-CM (data averaged across all available segments for each patient [median: 16, range: 3-18 segments]); regional peak systolic strain rate of the septal basal (C) and posterior (D) cardiac segment. The bold horizontal line in panels A, C, D indicates the cut-off for normal values, i.e. values smaller than –1.2. No FA-CM: n=63, mild FA-CM: n=80, intermediate FA-CM: n=32, severe FA-CM: n=25.

FA-CM: Friedreich ataxia cardiomyopathy
**Figure 2:** Scatter plot of peak workload and ICARS score for patients with arm ergometry (red) or leg ergometry (blue). The colored lines indicate the least squared fit for each of the two groups; the black line indicates the least squared fit for the combined group. In general, patients with higher ICARS performed poorer. Leg ergometry essentially is confined to patients with an ICARS < 60.

**Figure 3:** Proportion of patients according to the severity of FA-CM by age (A) or ICARS score (B). Please note that the more severe FA-CM groups were found at younger age (A). In contrast, the severity of the FA-CM was independent of neurological involvement measured by the ICARS score (B). FA-CM: Friedreich ataxia cardiomyopathy

**Figure 4:** Distribution of GAA repeat length (shorter allele) by FA-CM group. Grey lines and bars indicate box and whisker plots. Black lines indicate mean with 95% CI. No FA-CM: n=26, mild FA-CM: n=38, intermediate FA-CM: n=11, severe FA-CM: n=8. FA-CM: Friedreich ataxia cardiomyopathy
The Heart in Friedreich Ataxia: Definition of Cardiomyopathy, Disease Severity, and Correlation with Neurological Symptoms
Frank Weidemann, Christian Rummey, Bart Bijnens, Stefan Störk, Ruta Jasaityte, Jan Dhooge, Aigul Baltabaeva, George Sutherland, Jörg B. Schulz and Thomas Meier

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**SUPPLEMENTAL MATERIAL.**

Supplemental Table I. Derived morphological parameters of the heart

<table>
<thead>
<tr>
<th>Derived parameter</th>
<th>Calculation</th>
<th>unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Wall Thickness (RWT)</td>
<td>(\frac{(PWTd + IVSTd)}{LVEDD})</td>
<td>-</td>
</tr>
<tr>
<td>Ejection Fraction (EF): Modified Simpsons</td>
<td>(\frac{[\text{LV four chamber volume diastole} - \text{LV four chamber volume systole}] \times 100}{\text{LV four chamber volume diastole}})</td>
<td>%</td>
</tr>
<tr>
<td>Left Ventricular Volume, calculated by 2-dimensional method (LVV\textsubscript{2D})</td>
<td>(\frac{5}{6} \times ([\text{diastolic LV short axis total area} \times (\text{diastolic LV four chamber length} + 1)] - \text{diastolic LV short axis cavity area} \times \text{diastolic LV four chamber length}))</td>
<td>ml</td>
</tr>
<tr>
<td>Left Ventricular Mass, calculated by M-mode (LVM) according to Devereux</td>
<td>(1.04\times([PWTd+LVEDD+IVSTd]-LVEDD^3)-13.6)</td>
<td>g</td>
</tr>
<tr>
<td>Prediction of normal IVSTd in dependence of body surface area and age (according to Henry’s nomogram)</td>
<td>IVSTd = 5.44 (BSA\textsuperscript{0.5} + 0.03 (age in y) + 1.5 [BSA = 0.12 (weight in kg\textsuperscript{0.64})])</td>
<td>mm</td>
</tr>
<tr>
<td>Left Ventricular Mass Index using the de Simone formula for body surface area (LVMI-de Simone)</td>
<td>(\frac{\text{LVM}}{\text{patient height in m}^2})</td>
<td>g/m\textsuperscript{2}</td>
</tr>
<tr>
<td>Left Ventricular Mass Index using the Dubois formula for body surface area (LVMI-Dubois)</td>
<td>(\frac{\text{LVM}}{[(0.007184\times\text{patient weight in kg}^{0.425}) \times \text{patient height in cm}^{0.725}])</td>
<td>g/m\textsuperscript{2}</td>
</tr>
</tbody>
</table>

LV = left ventricle; LVM = left ventricular mass; IVSTd = end-diastolic wall thickness of the interventricular septum; LVEDD = left ventricular end-diastolic diameter; PWTd = end-diastolic wall thickness of the posterior wall; BSA = body surface area