European Heart Journal – Cardiovascular Imaging (2015) **16**, 1129–1136
doi:10.1093/ehjci/jev057

Normal left-atrial structure and function despite concentric left-ventricular remodelling in a cohort of patients with Anderson–Fabry disease

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Received 21 October 2014; accepted after revision 18 February 2015; online publish-ahead-of-print 6 March 2015

Aims Anderson–Fabry Disease (AFD) is an important cause of cardiomyopathy characterized by concentric left-ventricular hypertrophy (LVH). We evaluated the extent of left-atrial (LA) structural and functional remodelling in this group of patients given that LA remodelling is a marker of adverse outcomes in the presence of LVH.

Methods and results Clinical profiles were obtained and cardiac MRI was performed in cohorts of patients with AFD ($n = 31$), healthy controls ($n = 23$), and a positive control cohort with known concentric remodelling and LVH (CR/H, $n = 21$). Of patients with AFD, 58% were on enzyme-replacement therapy (ERT), 84% were on renin–angiotensin system antagonism, and 65% were on statins. Despite a similar increase in LV mass index in the AFD when compared with the CR/H cohort, mean LA volumes for the AFD group were similar to those seen in the healthy control group. Following from this, we observed that the percentage contribution to LV stroke volume due to elastic/passive and active LA emptying was similar in the AFD and healthy control groups, while passive emptying was significantly lower in the CR/H group. The consequences of LVH in the AFD cohort were manifested in atrioventricular uncoupling, whereby the extent of elastic/passive and active LA emptying was not a function of the extent of longitudinal movement of the mitral annular plane, as it was in healthy control subjects.

Conclusion Left-atrial structure and function were relatively normal in our cohort of patients with AFD, who were also judiciously treated with a contemporary strategy that includes renin–angiotensin system antagonism, statins, and ERT.

Keywords Anderson-Fabry disease • Left atrium • Cardiomyopathy • Left ventricular hypertrophy classification

Introduction

Anderson–Fabry disease (AFD) is a lysosomal storage disorder caused by genetic deficiency of the enzyme encoded by the alpha-galactosidase A gene (α-Gal A) enzyme located on the X-chromosome (Xq22.1).[1] This causes progressive, widespread intracellular accumulation of globotriaosylceramide (Gb3) and other sphingolipids throughout the body. Initial clinical manifestations of AFD are non-specific, and are often mistakenly attributed to other disorders, leading to missed or delayed diagnoses, by which time end-organ damage may be irreversible. Presently, the most common cause of mortality in patients with AFD is cardiomyopathy, which is characterized by concentric left-ventricular hypertrophy (LVH), valvular deterioration, and arrhythmias.[2] Furthermore, mutations associated with variant forms AFD, such as those with principally cardiac manifestations, were found to be much more prevalent than historically predicted, which identifies AFD as a small, but significant, contributor to cardiomyopathies associated with concentric LVH.

Increased left atrial (LA) size and volume are accepted markers of adverse cardiovascular outcomes across a wide spectrum of patients.[3–7] Left-atrial volume also has incremental prognostic value as it increases.[8] In addition, LA functional parameters are clinically relevant: LA strain and strain rate are useful as surrogates for LA fibrosis and stiffness, for predicting onset of heart failure with preserved

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ejection fraction, as surrogates for exercise capacity in heart failure, and for predicting recurrence of atrial fibrillation.[9] As described earlier, Anderson–Fabry cardiomyopathy is well characterized by LV hypertrophy (LVH) and functional changes characteristic of extensive concentric remodelling and hypertrophy (CR/H).[10–12] On the other hand, the extent of LA structural and functional remodelling in AFD is not well known, and, consequently, the clinical utility of these measures is not established in this population. Multimodality imaging, which includes cardiac MRI (CMR), could be useful for generating new knowledge regarding cardiac remodelling in AFD.[13] Using CMR, which offers precise volume measurements through high-resolution images, we therefore studied the nature of structural and functional remodelling of the LA in patients with AFD. We compared the structural and functional remodelling in these patients with a healthy control reference group, and patients that have an acquired CR/H phenotype to serve as a positive control group. We hypothesized that patients with AFD would exhibit LA structural and functional remodelling similar to patients with CR/H.

Methods

Patient recruitment

Patients with diagnosed AFD ($n = 31$) were recruited for participation in this study through metabolic clinics in Edmonton and Calgary, Alberta, Canada. As part of a larger study on AFD, patients were studied using cardiac magnetic resonance imaging (CMR) and detailed medical history review. The clinical diagnosis was based on clinical features consistent with AFD,[2] plasma α-galactosidase activity, and α-galactosidase A gene mutations as previously described[14] and we determined the Mainz Severity Score Index (MSSI) for patients with AFD based upon clinical characteristics, which was scored from 0 to 76.[15] Healthy controls ($n = 23$) and positive controls, selected on the basis of echocardiographic or MRI-derived evidence of CR/H ($n = 21$), were included from the Alberta Heart Failure Etiology and Analysis Research Team (HEART) project as previously described.[16–18] All study subjects gave informed consent, and this study conforms to the most recent ratification of the Declaration of Helsinki.[19]

Cardiac magnetic resonance imaging

Each subject (controls and AFD patients) underwent a comprehensive CMR scan on a 1.5 T magnet (Sonata, Siemens, Erlangen, Germany). Imaging sequences included localizers, steady-state free precession (SSFP) cine imaging in long-axis and short-axis projections to determine right- and left-ventricular volumes and function, as well as late-gadolinium enhancement imaging with 0.15 mmol/kg of gadolinium contrast to assess for the presence of myocardial scar. Typical imaging parameters for SSFP included a 380 × 300 mm field of view, 256 × 162 matrix, 8 mm slice thickness, TE 1.24 ms, TR 2.48 ms, flip angle 51°, 14 views/segment, and 30 phases/cardiac cycle, and for LGE imaging included a 380 × 285 mm field of view, 256 × 173 matrix, 8 mm slice thickness, TE 4.2 ms, TR 14.7 ms, flip angle 25°, and inversion time of 300 ms. Cine images were acquired using electrocardiogram gating, whereby ventricular depolarization (selected as ventricular end diastole by default) triggered the onset of imaging with a temporal resolution of ~30 ms, which is sufficient to produce a cine image of 30 frames over the complete cardiac cycle. The high graphical resolution of CMR combined with the temporal resolution of ECG gating allows unequivocal assessment of cardiac phases: ventricular end diastole, ventricular end systole, and diastasis. Left-ventricular end systole was determined visually as the frame before mitral-valve opening, while diastasis was determined visually as the frame before the initiation of left-atrial contraction. Left-ventricular volumes were traced from short-axis SSFP cines and were indexed to height using commercially available software (Syngo Argus, Siemens, Erlangen, Germany). Subjects with findings of severe mitral or aortic valvular lesions on CMR were excluded from this study.

Left-atrial tracings were performed using two-chamber and four-chamber views of the heart. Custom MATLAB software (version R2012a, MathWorks, Natick, MA, USA) was used to trace LA areas and lengths in order to compute volume based on the highly reproducible biplane area–length method,[8,20] which is standard in echocardiography[21] and which correlates well with the gold-standard multiple slice method that requires a full short-axis scan through the LA.[22] Length tracings were made from the mitral annular plane to the LA base. Area tracings were made along the inner border of the LA, excluding wall tissue, pulmonary vein inlets, and LA appendage and were terminated at the plane of the mitral annulus. Left-atrial volumes were calculated at three phases of the cardiac cycle: LV end diastole, diastasis, and LV end systole. For the measurement in end systole, the area from the plane of the mitral annulus to the point of leaflet coaptation was also excluded, as diastasis and end-diastole measurements were made with an open mitral valve, which necessitated defining the border of the LA to be the mitral annulus. Left-atrium volumes were indexed to body height, measured in metres, to control for the significant adiposity in the CR/H positive control group, which is a technique that has been shown to be at least as robust as indexing to body surface area.[4] Left atrium or ventricle volumes at end diastole, diastasis, and end systole indexed to height are denoted as EDVI, DiVI, and ESVI, respectively. As noted earlier, volumes at end diastole and end systole are defined relative to LV phase in this manuscript, such that LA ESVI is the LA volume at the end of LV systole.

Functional analyses

From measured cardiac chamber volumes, we determined basic functional volumes indexed to height. For the LA, we calculated the elastic/passive emptying volume index (LA PEVI = LA ESVI − LA DiVI), active emptying volume index (LA AEVI = LA DiVI − LA EDVI), and total emptying volume index (LA TEVI = LA ESVI − LA EDVI).[23] Left-atrial PEVI is a reflection of the reservoir capacity of the LA, while LA AEVI is a reflection of the active contractility of the LA. For the LV, we calculated stroke volume index (SVI = LV EDVI − LV ESVI) and also measured LVEF. Using SVI, we also indirectly calculated the LV filling due to pulmonary venous flow through the LA as a conduit (PVFI = SVI − LA TEVI). From LA EEVI, LA AEVI, LA TEVI, and PVFI, we calculated the reservoir (elastic), booster pump (active), total LA, and pulmonary venous contributions to LV SV, expressed as percentage.

Statistical analysis

All statistical analyses were conducted in using SPSS software version 21 (IBM, Armonk, NY, USA). Categorical data are expressed as counts. Continuous data are expressed as mean ± standard deviation. Comparisons between categorical variables were made using Fisher's exact test, while one-way ANOVA with Tukey tests for *post-hoc* analyses were used to compare continuous variables between the study groups. Linear regressions were used to evaluate linear relationships between continuous variables. Continuous data compared by study group shown in graphs display the mean (horizontal line) and standard deviation (vertical line). Scatterplots are used to graphically represent comparisons made using linear regression analyses.

Results

Study participants

All subject groups were of similar average height and sex distribution, but the CR/H group was significantly older ($P < 0.01$) and heavier ($P < 0.01$) than either the healthy control or AFD group (*Table 1*). Systolic blood pressure (SBP) was much higher in the CR/H group than either the AFD ($P < 0.01$) or healthy control groups ($P < 0.01$; *Table 1*), which is an important component of increased afterload that contributes to concentric remodelling. The AFD cohort was well treated with ACEi/ARB (84%) and statins (65%), and, according to treatment guidelines, eligible patients (58%) were started as early as possible on ERT (*Table 2*).[2] The CR/H group was also treated with ACEi/ARB (82%) and statins (55%); however, as noted earlier, large differences existed in mean SBP. Despite differences in blood pressure, age, and body weight, there were no differences in heart rates between the groups (*Table 2*). The Mainz Severity Score Index (MSSI),[15] in our cohort with AFD is consistent with a moderate severity of illness (*Table 2*), and, as previously reported, the burden of LGE-positive areas was 6.0 ± 4.2% with a prevalence of 45%,[16] which is consistent with other studies in patients with AFD.[24]

Cardiac structural findings

As we included the CR/H group as a positive control for cardiac remodelling, we hypothesized that LA volumes would be significantly increased compared with healthy controls. We found this was the case for LA EDVI ($P < 0.01$); however, contrary to our hypothesis, LA EDVI was not significantly different in the AFD group compared with healthy controls (*Table 3*). Similarly, LA DiVI was similar between the AFD group and healthy controls, but was significantly larger in the CR/H group than either healthy controls or the AFD group ($P < 0.01$ for both), while LA ESVI was not significantly different between the study groups (*Table 3*). We evaluated whether the difference in LA EDVI between study groups could be partly explained by the difference in SBP, but found no significant relationship ($r = 0.14$, $P = 0.24$).

Table 1 Baseline clinical profile by study group

	HC	AFD	CR/H	*P*-value
Number	23	31	21	–
Sex (M/F)	11/12	15/16	12/9	0.78
Age (years)	42 ± 15	41 ± 12	64 ± 11	<0.01
Height (m)	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	0.97
BMI (kg/m^2)	24 ± 5	25 ± 5	31 ± 6	<0.01
SBP (mmHg)	122 ± 9	114 ± 15	140 ± 19	<0.01
DBP (mmHg)	78 ± 11	70 ± 11	76 ± 15	0.07
MABP (mmHg)	93 ± 10	85 ± 12	97 ± 13	<0.01
Heart rate (bpm)	64 ± 7	63 ± 10	63 ± 10	0.94

HC, healthy control; AFD, Anderson-Fabry Disease; CR/H, concentric remodelling/hypertrophy; M, male; F, female, BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MABP, mean arterial blood pressure. *P*-value represents one-way ANOVA or Fisher's exact test where appropriate.

Similar to the LA, mean LV maximum volumes did not differ between study groups, but mean LV minimum volumes did: LV ESVI was similar between the AFD group and healthy controls, but was significantly higher in the CR/H group than controls ($P < 0.05$; *Table 3*). Nonetheless, both the AFD ($P < 0.01$ for both) and CR/H ($P < 0.01$ for both) groups exhibited increased LV mass index and posterior wall thickness to height ratio in comparison to healthy controls (*Table 3*). The divergence of phenotypes between healthy control, AFD and CR/H subjects is apparent in two- and four-chamber images representative of the average LA volume and LV mass for each group (*Figure 1*).

Cardiac functional findings

We compared the LA emptying volumes due to passive and active processes between study groups, and found that mean LA PEVI was significantly lower in the CR/H group (*Figure 2A*). Likewise, LA AEVI was lower in AFD compared with the CR/H group (*Figure 2B*). We also evaluated the effect of SBP on LA PEVI and LA AEVI, wherein we found no relationship for LA PEVI ($r = -0.11$, $P = 0.37$) but a weak, barely significant relationship for LA AEVI ($r = 0.24$, $P = 0.05$). Left-ventricular EF was significantly increased in AFD patients compared with the CR/H group, but all subjects were characterized by preserved LVEF (*Figure 2C*) and preserved LV SVI (*Figure 2D*). The reduction of LA PEVI in the context of preserved LV SVI was offset in the CR/H by a larger proportion of LV filling attributed to LA contraction and pulmonary venous flow (*Table 3*). Despite preserved ejection fraction, the effect of concentric remodelling on LV longitudinal function was seen in both the AFD and CR/H groups with reduced mitral annular systolic and diastolic excursion (MASE and MADE, respectively) when compared with healthy controls (*Figure 2E* and *F*; *Table 3*). Left-ventricular lengths in our study groups were not significantly different: AFD (98 ± 9 mm), healthy controls (95 ± 8 mm), and CR/H (96 ± 8 mm; $P = 0.35$) and therefore our MASE values were not corrected for LV lengths.

When expressed as a percentage of LV stroke volume, the elastic component of LA emptying volume was significantly lower in the CR/H group when compared with either the healthy control or AFD groups (*Figure 3A*). However, the active component was similar in all groups with a non-significant increase in the CR/H group (*Figure 3B*). Similarly, the percentage of filling attributed to pulmonary venous flow was non-significantly elevated to offset the reduction in elastic contribution in the CR/H group (66 ± 10%) when compared with the control (58 ± 11%) and AFD (61 ± 14%) groups ($P = 0.11$). Atrioventricular coupling of mitral annular excursion and LA volume change was apparent in the hearts of healthy controls (*Figure 3C* and *E*), but was not apparent in the AFD and CR/H groups (*Figure 3D* and *F*).

Discussion

Assessment of LA structure and function is an important component of the evaluation of patients with heart disease.[6,25] In this analysis, we made comparisons to healthy individuals, whom served as the reference for normal cardiac structure and function, and patients with concentric remodelling/hypertrophy, whom served as a positive control for cardiac remodelling. As hypothesized, we detected significant differences in LA phasic volumes, LV mass, LV end systolic

Table 2 An individual summary for each subject in the AFD group

Mutation	ERT	Age at start of ERT (years)	Length of ERT (years)	ACEi/ARB	Statin	MSSI
R227X	Yes	43	9.5	Yes	Yes	39
Y134S	Yes	26	8.5	Yes	No	22
A143P	Yes	40	8.5	Yes	No	47
Y134S	Yes	26	9	Yes	No	42
Q386X	No	N/A	N/A	Yes	No	26
R112C	Yes	42	9.5	No	Yes	30
Y134S	Yes	62	6.5	Yes	Yes	47
S345P	Yes	41	6.5	Yes	Yes	33
Q321R	Yes	46	5	Yes	Yes	22
G43V	Yes	26	9	Yes	Yes	25
W349X	Yes	25	5.5	Yes	Yes	27
N215S	No	N/A	N/A	No	No	19
N215S	No	N/A	N/A	Yes	Yes	24
S345P	No	N/A	N/A	Yes	Yes	19
S345P	No	N/A	N/A	No	No	17
S345P	No	N/A	N/A	Yes	No	22
S345P	No	N/A	N/A	Yes	Yes	19
E338K	No	N/A	N/A	Yes	No	21
E338K	Yes	36	10 months	Yes	No	26
S345P	Yes	42	8.5	Yes	Yes	47
E338K	Yes	53	9	Yes	Yes	49
R220X	Yes	53	2	Yes	Yes	37
G261V	No	N/A	N/A	Yes	Yes	19
R227Q	Yes	36	4.5	Yes	Yes	37
R227Q	No	N/A	N/A	No	No	15
S345P	No	N/A	N/A	Yes	Yes	24
S345P	Yes	33	1 month	Yes	Yes	29
N215S	Yes	64	2	Yes	Yes	36
R220X	No	N/A	N/A	No	No	13
S345P	No	N/A	N/A	Yes	Yes	22
Q386X	Yes	31	4	Yes	Yes	35
Summary	18Y/13N	40 ± 12 years	6 ± 3 years	26Y/5N	20Y/11N	29 ± 10

Mutation strings use the standard one-letter amino acid code.
ERT, enzyme replacement therapy; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; Y, yes; N, no; MSSI, Mainz Severity Score Index (Whybra C *et al.*, 2004).

volume, and LV posterior wall thickness to height ratio between healthy controls and the CR/H group. These results are in agreement with previous studies in individuals with a concentric hypertrophy phenotype, either due to a genetic disorder, such as hypertrophic cardiomyopathy, or a systemic condition, such as hypertension, that have found LA enlargement, and decreased LA function.[7] Surprisingly, the group with AFD exhibited characteristics similar to both the healthy and CR/H groups. In our AFD cohort, LA phasic volumes were similar to those of healthy controls despite their ~50% larger LV by mass. We reported findings and analysis for minimum LA volume (LA EDVI) in this study, as LA EDVI may have just as much or more clinical utility than maximum LA volume (LA ESVI).[26] In line with our finding of normal LA phasic volumes in the AFD cohort, we also found preserved LA function that was similar to healthy individuals, whereby passive and active changes in LA volume contributed approximately equivalently to LV SV. In the CR/H group on the other hand, elastic LA contribution was significantly reduced with commensurate, however, non-significant, increases in active contribution and conduit flow through the LA from the pulmonary veins. Our findings are consistent with previous reports, which indicate that active LA contribution increases in the early stages of cardiac dysfunction.[27,28] We reported all findings as indexed to body height rather than body surface area. Indexing chamber dimensions to body height has been shown to be at least as robust as indexing to body surface area,[4] and we showed that left ventricle mass index (LVMI) calculated either using height or body surface area[29] based on ideal body weight,[30] which is another previously published correction method,[16] are very similar (*Table 3*).

Table 3 Heart rates and cardiac structural and functional metrics by study group

	HC	AFD	CR/H	*P*-value
Left atrium				
LA EDVI (mL/m)	18 ± 6	23 ± 11	30 ± 21	0.01
LA DiVI (mL/m)	28 ± 9	32 ± 14	42 ± 18	0.01
LA ESVI (mL/m)	40 ± 11	44 ± 16	48 ± 21	0.28
LA PEVI (mL/m)	12 ± 6	12 ± 7	6 ± 5	0.07
LA AEVI (mL/m)	10 ± 4	9 ± 5	13 ± 3	0.04
LA TEVI (mL/m)	22 ± 7	21 ± 8	18 ± 7	0.17
PVFI (mL/m)	31 ± 11	34 ± 11	34 ± 12	0.59
Mitral annulus				
MASE (mm)	17 ± 3	13 ± 4	12 ± 2	<0.01
MADE (mm)	13 ± 3	10 ± 3	9 ± 2	<0.01
Left ventricle				
LV EDVI (mL/m)	82 ± 20	82 ± 19	86 ± 21	0.66
LV ESVI (mL/m)	29 ± 8	27 ± 9	35 ± 12	0.01
LVMI (g/m)[a]	63 ± 17	94 ± 30	86 ± 19	<0.01
LVMI (g/m^2)[b]	62 ± 17	92 ± 28	85 ± 17	<0.01
T:H Ratio (mm/m)	3.6 ± 0.5	4.8 ± 1.1	4.5 ± 0.5	<0.01

HC, healthy control; AFD, Anderson–Fabry Disease; CR/H, concentric remodelling/hypertrophy; LA, left atrium; LV, left ventricle; EDVI, end-diastolic volume indexed to height; DiVI, diastasis volume indexed to height; ESVI, end-systolic volume indexed to height; PEVI, passive emptying volume indexed to height; AEVI, active emptying volume indexed to height; TEVI, total emptying volume indexed to height; PVFI, pulmonary venous flow indexed to height; MASE, mitral annular systolic excursion; MADE, mitral annular diastolic excursion; LVMI, LV mass index; T:H ratio, LV posterior wall thickness indexed to height.
P-value represents one-way ANOVA.
[a]Indexed to height.
[b]Indexed to body surface area (Du Bois and Du Bois[29]) based on ideal bodyweight (Robinson *et al.*[30]).

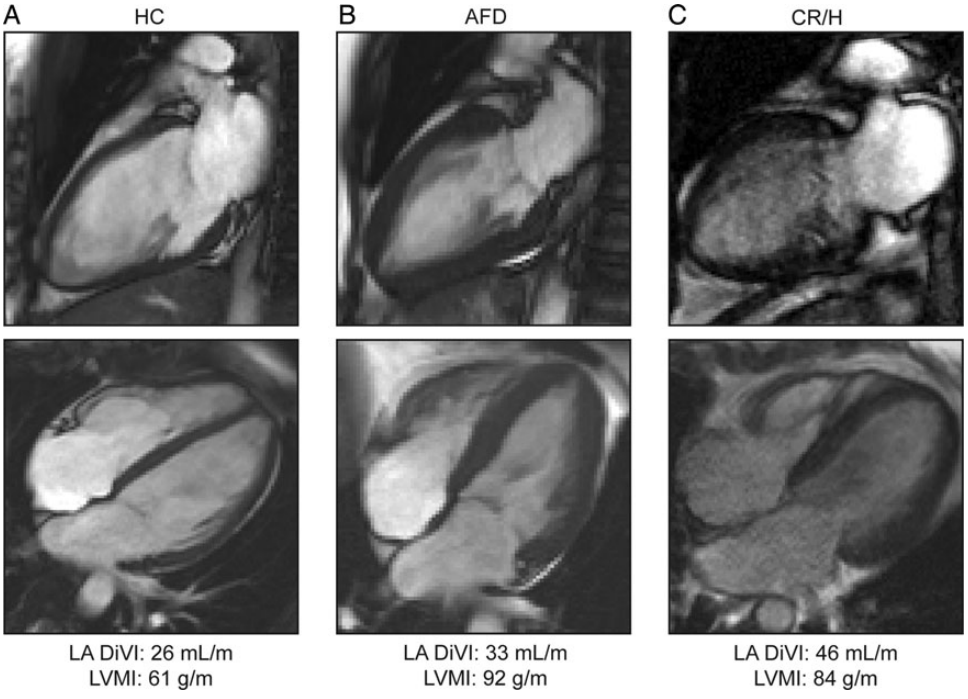

Figure 1 Representative two- (top) and four-chamber (bottom) cardiac MRI images at diastasis from healthy control (HC, *A*), Anderson–Fabry Disease (AFD, *B*), and (CR/H, *C*) subjects, respectively, illustrating differential left-atrial (LA) and left-ventricular (LV) remodelling. LA DiVI, LA diastasis volume indexed to height, and LVMI, LV mass indexed to height, are shown for each of the subjects selected and can be compared with group means in *Table 3*.

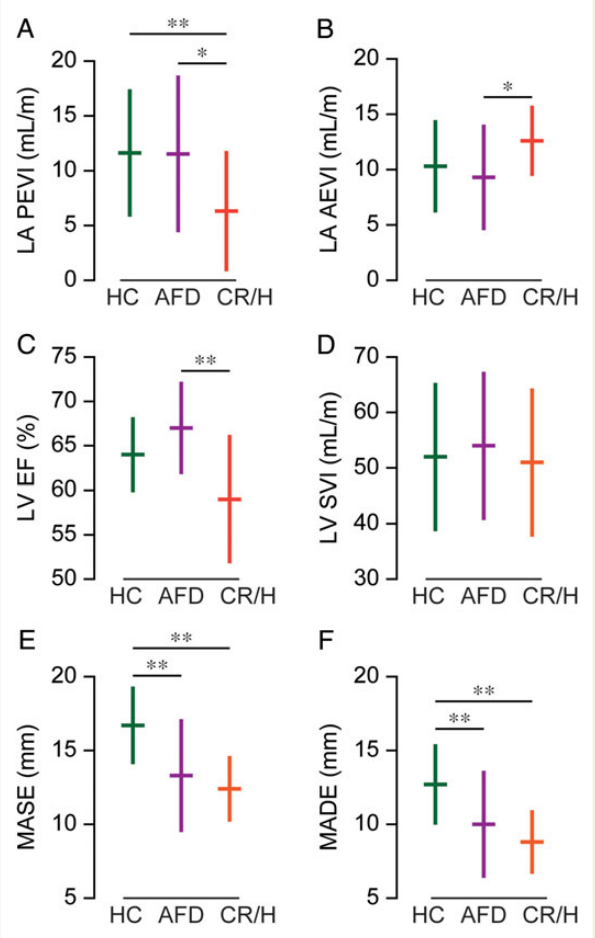

Figure 2 Assessment of left-atrial (LA) and left-ventricular (LV) function in the healthy controls (HC, green), Anderson–Fabry disease (AFD, purple) and concentric remodelling/hypertrophy (CR/H, orange) cohorts shown as mean (horizontal bar) ± standard deviation (vertical bar). LA PEVI, LA passive emptying volume indexed to height; LA AEVI, LA active emptying volume indexed to height; LV EF, LV ejection fraction; LV SVI, LV stroke volume indexed to height; MASE, mitral annular plane systolic excursion; MADE, mitral annular plane diastolic excursion. *$P < 0.05$ and **$P < 0.01$.

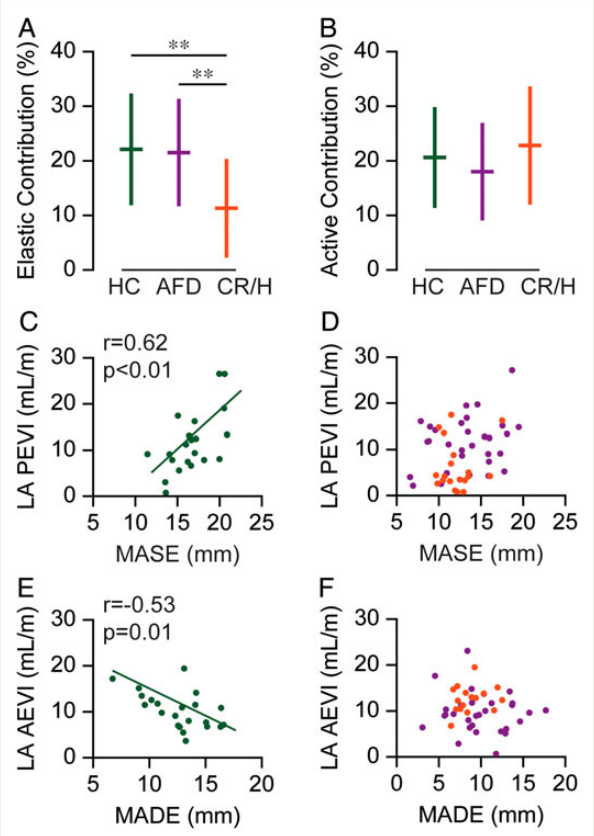

Figure 3 Assessment of left-atrial (LA) function in relation to left-ventricular (LV) function. (*A* and *B*) LA elastic (*A*) and active (*B*) emptying fractions as percent of LV stroke volume compared as mean (horizontal bar) ± standard deviation (vertical bar) in healthy controls (HC, green), Anderson–Fabry Disease (AFD, purple) and concentric remodelling/hypertrophy (CR/H, orange) subjects. (*C*–*F*) Scatterplots to explore the extent of LA–LV coupling in HC (green), AFD (purple), and CR/H subjects (orange). Effect size and significance level are shown for the scatterplots in HC subjects (*C* and *E*), where significant relationships were found. LA PEVI, LA passive emptying volume indexed to height; LA AEVI, LA active emptying volume indexed to height; MASE, mitral annular plane systolic excursion; MADE, mitral annular plane diastolic excursion. *$P < 0.05$ and **$P < 0.01$.

The type, rather than the extent, of LV remodelling impacts the degree of LA remodelling and LA enlargement.[31] The unique aetiology of the AFD LV hypertrophy, including the relatively young age of onset, appears not to result in early LA functional or structural changes. However, the significantly advanced age of the CR/H group could be a determining factor for differential LA volumes. While age alone is not a determinant for LA volume,[32] exposure to stressors, such as hypertension, through ageing may have driven the LA enlargement in the CR/H group. There is considerable variation in cardiac structural and functional change in AFD, some of which appears to occur with age.[33] This potential outcome is cause for further judicious prospective follow-up of patients who have AFD. Furthermore, the difference in LA AEVI between the AFD and CR/H groups may be partly due to the pronounced difference in SBP, although it is interesting to note that we did not find any effect of SBP on LA PEVI. The effect of SBP alone on LA function appears to be small, but it may nonetheless be a worthwhile metric to control in patients with AFD, especially as they advance in age, in order to preserve LA structure and function.

Interestingly, there were apparent consequences with respect to atrioventricular coupling from the concentric LV remodelling and hypertrophy observed in both the AFD and CR/H groups. In the hearts of healthy individuals, longitudinal motion of the LV was a determinant of the extent of LA volumetric change. We observed a strong, significant, positive association between mitral annular plane excursion during LV systole and LA passive emptying volume in healthy individuals. On the other hand, we found that LA active emptying volume was strongly, significantly, and negatively associated

with mitral annular plane excursion during LV diastole in healthy individuals. In contrast, we did not observe these relationships in either the AFD or CR/H groups, which suggest that there was some uncoupling of LA and LV function, at least in the longitudinal plane, due to concentric LV remodelling and hypertrophy, although peri-annular infiltration in the AFD group may also contribute to these functional alterations. In the AFD group, whose LA function resembled that of normal individuals, compensatory mechanisms maintain LA filling and subsequent passive and active emptying despite a reduction in mitral annular motion in the longitudinal direction. Previous reports indicate that circumferential strain is proportionally less reduced than longitudinal strain across various types of LVH,[34] so circumferential LV motion may therefore take on a larger role in the preservation of LA filling in the setting of reduced longitudinal motion. Previous reports by our group on this patient population found significantly increased CMR-derived circumferential global fractional shortening of the endocardium in the AFD group when compared with healthy controls,[35] and found non-significantly increased echocardiographically derived circumferential LV strain and rate.[12] These findings are consistent with the principle that circumferential LV motion is involved in the preservation of systolic function in the setting of concentric hypertrophy due to hypertrophic cardiomyopathy[36] and in the context of diastolic dysfunction illustrated by a reduction of strain rate during isovolumic relaxation (SR_{IVR}) and increased mitral E velocity and average E/E' ratio, in AFD patients relative to healthy controls.[12]

While we did observe slightly elevated LA phasic volumes in the AFD group relative to controls, there is clearly a lack of significant adverse LA remodelling in these patients. These findings, when compared with the findings of Boyd *et al.*,[37] which reported LA enlargement in non-ERT-treated AFD patients with or without LVH, suggest that a contemporary treatment strategy that involves ERT, renin–angiotensin system antagonism through the use of ACEi or ARBs, and statins may be sufficient to arrest or delay the onset of deleterious LA remodelling. The thin myocardium of the LA may allow better penetration of ERT in contrast to the LV, for which low penetration and tissue bioavailability has been reported.[38] Nonetheless, ERT is associated with abrogation of LVH and improvement in regional myocardial function in patients with AFD,[39–41] which may reduce remodelling stimuli on the LA, especially if it is initiated early on.[42] Furthermore, combining the blood pressure control and anti-hypertrophic effects of renin–angiotensin system antagonism and statins with ERT may have added benefit in terms of the preservation of normal LA volumes and function in the AFD group.

In addition to the obvious benefit of preserving normal cardiac function in patients with AFD, the preservation of normal LA volume and function may reduce the incidence of atrial fibrillation in patients with AFD. Enlarged LA are good substrate for the development of electrophysiological abnormalities, so maintaining normal LA volume may preserve LA function and prevent the development of atrial arrhythmias.[6,43] As arrhythmias are significant contributors to cardiovascular morbidity in patients with AFD, preventing them is important.[44] In conclusion, in a contemporary cohort of patients with AFD, we observed LA phasic volumes and function that were similar to healthy controls, despite LV remodelling and atrioventricular uncoupling similar to a group of patients with CR/H. The current contemporary treatment strategy that involves ERT, renin–angiotensin system antagonism and statins,[2] may be effective at mitigating adverse LA remodelling; however, more work will be required to confirm whether this is the case, and to determine what other factors contribute to LA remodelling in patients with AFD.

Limitations

The study we have presented herein has several limitations. The patient group with AFD and the group with CR/H were significantly different in mean age, and, although noted above that age alone is not a determinant of LA size,[32] the difference is nonetheless worth noting. As relates to our hypothesis that a contemporary treatment strategy that includes ERT, renin–angiotensin system antagonism, and statins could be contributing to mitigating adverse LA remodelling, we do not have any longitudinal data to test this. Our data provide a cross-sectional comparison of two patient groups with LVH and differential LA remodelling in comparison to healthy individuals. Studies with a longitudinal component will identify the efficacy of the current treatment strategy on global cardiac remodelling. We were also limited technically, as we were not able to evaluate the extent of LA fibrosis,[45] which is a component of declining LA function and the development of atrial fibrillation.

Acknowledgements

We would like to thank the Alberta HEART study for providing access to subjects to form the reference groups. We would also like to thank all participants in the study for their time and commitment.

Funding

This research was supported by the University of Alberta Hospital Foundation, HSFC, CIHR, and AI-HS. B.N.P. was partially supported by an Alberta HEART STEADI-HF Training Program stipend.

Conflict of interest: none declared.

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