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Effects of enzyme replacement therapy on cardiac function in classic infantile Pompe disease

L.E. Scheffers [a,b,1,*], R. Kok [a,1], L.E. van den Berg [a,b,f], J.M.P. van den Hout [b], E. Boersma [c], C.I. van Capelle [a], W.A. Helbing [a,d,e], A.T. van der Ploeg [b], L.P. Koopman [a]

[a] Department of Pediatric Cardiology, Erasmus MC - Sophia Children's Hospital, Rotterdam, the Netherlands
[b] Center for Lysosomal and Metabolic Diseases, Erasmus MC - Sophia Children's Hospital, Rotterdam, the Netherlands
[c] Department of Cardiology, Erasmus MC- Sophia children's hospital, Rotterdam, the Netherlands
[d] Department of Pediatrics, division of Cardiology, Radboud umc – Amalia Children's Hospital, Nijmegen, the Netherlands
[e] Department of Radiology, Erasmus MC - Sophia Children's Hospital, Rotterdam, the Netherlands
[f] Department of Orthopaedics and Sports Medicine, Erasmus MC- Sophia Children's hospital, Rotterdam, the Netherlands

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ABSTRACT

Objective: Patients with classic infantile Pompe disease are born with a hypertrophic cardiomyopathy, which resolves after treatment with Enzyme replacement therapy (ERT). We aimed to assess potential deterioration of cardiac function over time using myocardial deformation analysis.
Methods: Twenty-seven patients treated with ERT were included. Cardiac function was assessed at regular time intervals (before and after start with ERT) using conventional echocardiography and myocardial deformation analysis. Separate linear mixed effect models were used to asses temporal changes within the first year and the long-term follow-up period. Echocardiograms of 103 healthy children served as controls.
Results: A total of 192 echocardiograms were analyzed. Median follow-up was 9.9 years (IQR: 7.5–16.3). Mean LVMI before start of ERT was increased 292.3 g/m^2 (95% CI: 202.8–381.8, mean *Z*-score + 7.6) and normalized after 1 year of ERT 87.3 g/m^2 (CI: 67.5–107.1, mean Z-score + 0.8, $p < 0.001$). Mean shortening fraction was within normal limits before start of ERT, up to 22 years of follow-up. Cardiac function measured by RV/LV longitudinal, and circumferential strain was diminished before start of ERT, but normalized (<−16%) within 1 year after start of ERT, and all remained within normal limits during follow-up. Only LV circumferential strain gradually worsened in Pompe patients (+0.24%/year) during follow-up compared to controls. LV longitudinal strain was diminished in Pompe patients, but did not change significantly over time compared to controls.
Conclusion: Cardiac function, measured using myocardial deformation analysis, normalizes after start of ERT, and seems to remain stable over a median follow-up period of 9.9 years.

1. Introduction

Classic infantile Pompe disease is a lysosomal storage disease caused by a deficiency of the enzyme acid-α- glucosidase, needed for the degradation of glycogen in lysosomes [1]. Patients with classic infantile Pompe disease present with a hypertrophic cardiomyopathy and a progressive generalized myopathy shortly after birth [2]. Untreated patients die of cardiac and respiratory failure within the first year of life. Lifelong treatment with enzyme replacement therapy (ERT) with acid-α-glucosidase is central to the multisystem management of Pompe disease, and has shown to improve motor function, cardiac hypertrophy and function, and survival [3]. Despite an initial increase in muscle strength, on the long term most patients develop residual muscle weakness [4,5]. Potentially, this decrease in function can also be detected within the cardiac muscle. A study of our group investigating the effects of ERT on cardiac function beyond an age of three years showed that LVMI had normalized after a median period of 30 weeks since start of treatment with ERT, with sustained effect over the median follow-up period of 4.8

Abbreviations: Enzyme replacement therapy, ERT; Cross reactive immunological material, CRIM; Left ventricular mass index, LVMI; Shortening fraction, SF; Left ventricle, LV; Right ventricle, RV.

* Corresponding author at: Doctor Molewaterplein 40, 3015 GD Rotterdam, Sophia kinderziekenhuis, Sp2430, the Netherlands.
E-mail address: L.scheffers@erasmusmc.nl (L.E. Scheffers).

[1] Shared first authors.

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years since start of ERT [3]. In this study conventional echocardiography was used, as method to assess cardiac response to ERT. It is amenable however that myocardial deformation will be more sensitive to detect subtle changes in in cardiac function that have remained unnoticed so far [6]. In contrast to conventional echocardiographic parameters, like shortening fraction (SF) and ejection fraction (EF), myocardial deformation imaging determines the cardiac function directly at the level of the myocardium [6]. It measures the multidimensional (e.g. longitudinal and circumferential) change in shape of the heart muscle and can be used to detect early subclinical heart failure, even with a preserved EF. In the context of ERT in classic infantile Pompe disease it may therefore be more suitable to detect early signs of cardiac muscle dysfunction. The aim of this study was to investigated long-term effects of ERT on cardiac function of classic infantile Pompe patients by using, for the first time, the more sensitive method of myocardial deformation analyses in addition to conventional echocardiographic measurements.

2. Methods

2.1. Study design and patient cohort

This study was performed at the Erasmus MC University Medical Center, Sophia Children's Hospital, Rotterdam, the Netherlands. The study was approved by the local ethics committee and started in 1999 (trial number: NL.2007.03). Consent was obtained for all patients. In order to be eligible for inclusion, patients needed to have (1) a confirmed diagnosis of classic infantile Pompe disease before the age of 12 months. Classic infantile Pompe disease was defined as a confirmed deficiency of α-glucosidase in leucocytes and/or fibroblasts and/or two pathogenic GAA variants (www.pompevariantdatabase.nl) including a confirmed hypertrophic cardiomyopathy (LVMI *Z*-score $> +2$) on echocardiogram characteristic for classic infantile. (2) [7,8] at least one echocardiogram available for analysis, and (3) patients had to be treated with recombinant human alpha-glucosidase. Doses of ERT applied were 15 or 20 mg/kg/week; 20 mg/kg/2 or 40 mg/kg/wk. After 2008 all but one patient received a dose of 40 mg/kg/week [9,10]. All classic infantile Pompe patients treated with ERT in the Netherlands since 1998 were included in this study. Cardiac function was repeatedly assessed, between 08 and 07-1998 and 01-12-2019, by conventional echocardiography and in retrospect at pre-determined time intervals by myocardial deformation analysis as shown in Fig. 1. Due to low image quality, only echocardiograms performed after 2004 could be analyzed using myocardial deformation. Conventional echocardiography of 14 patients obtained over a time period ranging from 1.1 to 13.9 years after start of ERT, with a median follow-up of 4.8 years, were also described previously [3]. In the current study, follow-up was extended and the population enlarged to 27 patients. In order to compare myocardial deformation parameters of Pompe patients to controls, myocardial deformation analysis were also performed on a previously described cohort of 103 healthy children [11].

2.2. Conventional echocardiography and myocardial deformation analyses

M-mode, two-dimensional echocardiography and Doppler ultrasound of all patients and controls were performed by experienced sonographers using a Philips iE33, Philips EPIC 7C or General Electric Vivid 7 machine. Parameters were compared with normal values using the Boston *Z*-scores [12,13]. LVMI was calculated using the Devereux formula. Left ventricular hypertrophy was defined as a LVMI Z-scores $> +2$. 2D myocardial deformation analyses were performed according to a standard follow-up protocol using the software package TOMTEC, 2D strain cardiac Performance Analyses [14]. All myocardial deformation analyses were performed by one observer (RK) after receiving training given by an echocardiography specialist from TOMTEC. Myocardial deformation analyses were performed on the LV in longitudinal and circumferential direction and on the RV in longitudinal direction. Apical 4-chamber views were used for longitudinal deformation analyses, short-axis view at the level of the papillary muscle was used for LV circumferential deformation. Global myocardial deformation was calculated by dividing the sum of all segments by the number of segments. If the myocardium could not be visualized in a segment, this particular segment was excluded from analyses. For the LV, at least 4 out of 6 segments needed to provide data, in order to be included in the analyses. For the RV the lateral wall was used to calculate global longitudinal strain, and at least 2 out of 3 segments of the RV free wall and the ventricular septum should be measurable. Global myocardial strain > -16 (less negative) for all views was considered abnormal [11,15,16].

2.3. Inter- and intra-observer variability

In order to asses intra- observer variability, 15 echocardiograms were reanalysed in random order after two weeks by the same observer and also independently analyzed by a second observer (LK) to determine inter-observer variability. The coefficient of variation (COV), bias and standard deviation (SD) were calculated and a Bland-Altman analysis was performed.

2.4. Statistical analyses

Normality of continuous variables was evaluated by reviewing histograms and by using Shapiro-Wilk tests. Continuous variables were then described as mean ± one standard deviation (SD) in case normality was plausible, and as median (25th and 75th percentile) otherwise. Categorical variables were described as numbers and percentages. We used linear mixed effect (LME) models, with 'time' as independent variable, to describe temporal changes of LVMI, SF, LV circumferential strain, LV longitudinal strain, and RV longitudinal strain. Capelle et al., demonstrated that most children have LVMI and SF in the normal range at 1 year after the start of ERT [3]. We hypothesised that myocardial deformation might worsen from that 1 year landmark onwards. Therefore, we used separate LME models to describe cardiac function within the first year and the long-term follow-up period thereafter. The long-term model was also used to compare temporal changes in cardiac

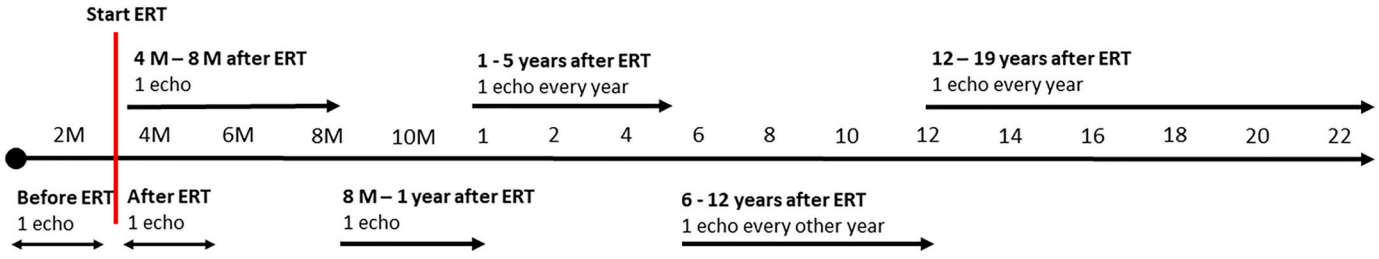

Fig. 1. Predetermined time points of myocardial deformation analyses on echocardiograms.
Enzyme replacement therapy (ERT), months (M).

function between infantile Pompe patients and controls. We transformed the study endpoints into *Z*-scores, and we considered absolute *Z*-scores >+2 as abnormal. Data analyses were performed in R (version 4.0.5, date 2021-03-31), in particular using the lme4 package. Two-sided *p*-values <0.05 were considered statistically significant. Z-scores were calculated as the difference between the measured value and the mean reference value divided by the standard deviation from the reference value. Z-scores >+2 or < −2 were considered abnormal.

3. Results

3.1. Patient characteristics

A total of 27 classic infantile Pompe patients were included of whom 192 echocardiograms were analyzed. Patient characteristics are shown in Table 1. Six patients died during follow up, most common cause of death was respiratory failure. Age at start of ERT ranged from 3 days to 8.3 months (median age 3.2 months). Median follow-up was 9.9 years [IQR: 7.5–16.3], maximum follow-up was 22 years. Data of one patient was only included until the age of 7 years, where after the patient moved to a treatment centre outside of the Netherlands. The data of the Pompe patients was compared to that of 103 children without Pompe disease, age range between 1 and 18 years, with a median age of 10.8 years [IQR: 7.3–14.3]. In the control group 50% of the children were female compared to 59% in the Pompe group [11].

3.2. .Conventional echocardiography

Mean LVMI before the start of ERT was 292.3 g/m^2 (CI: 202.8–381.8, LVMI *Z*-score + 7.6) and had been significantly reduced to 87.3 g/m^2 (CI: 67.5–107.1, LVMI Z-score + 0.8, $p < 0.001$) 1 year after start of ERT. LVMI and SF over time are shown in Fig. 2 and supplement 4 per-patient. At this time point, 21 out of 23 children had a normal LVMI. During follow-up, LMVI remained stable in Pompe patients (−0.56 g/m^2 /yr, $p = 0.15$) and increased in controls (+2.26 g/m^2 /yr compared to pompe patients, $p \leq 0.001$). At the last assessment mean LVMI of patients and controls were both within the normal range (Fig. 2, 65.8 g/m^2 vs 88.8 g/m^2).

Mean SF was normal before start of ERT (mean 36.4%, CI: 29.9–43) and remained within the normal range during the first treatment year. During follow-up, SF in Pompe patients also remained stable and unchanged compared to controls (+0.16%/yr, $p = 0.464$, Fig. 2, SF 35.5 vs 39.3).

Table 1
Patient characteristics.

	Classic infantile Pompe patients (n = 27),
Female, n (%)	16 (59)
Age at diagnose (months)	3.22 [2 days – 7.6 months]
Age at start of ERT (months)	3.53 [3 days – 8.3 months]
Age at study endpoint/ echocardiogram (years)	12 (2−22)
Deaths at study endpoint, n (%)	6 (22)
Age at death (years)	3.5 [0–15]
CRIM Negative, n (%)	6 (22)
Most common mutations	
Homozygous c.525delT	4 (15)
c.525delT & 2481 + 102_2646 + 31del538	2 (7)
Homozygous 2481 + 102_2646 + 31del538	2 (7)
Cardiac Medication recepients (after birth)	
Diuretic, n (%)	6 (22)
Beta-inhibitors, n (%)	8 (30)
ACE-inhibitor, n (%)	1 (4)
Diuretic + Beta-inhibitors, n (%)	2 (7)
Diuretic + ACE-inhibitor, n (%)	2 (7)
Diuretic + dobutamin, n (%)	1 (4)
Diuretic + ACE-inhibitor + Digoxin, n (%)	1 (4)
No cardiac medication, n (%)	6 (22)

Table 1: Data presented are median [range] or mean [SD]. – meant not applicable. Number (n), enzyme replacement therapy (ERT), milligram (mg), kilogram (kg), every other week (eow), cross reactive immunological material (CRIM).

3.3. Myocardial deformation analyses

At baseline, before start of ERT cardiac function measured by myocardial deformation was diminished in every view (normal myocardial strain <−16%). Myocardial deformations outcomes are shown in Fig. 3 and supplement 1 and supplement 5 per-patient. Mean LV circumferential myocardial strain was −12.1% (CI: −14.5 - -9.9, SD ± 4.8), mean LV longitudinal strain was −12.2% (CI: −14.6 - -9.9, SD ± 5.2) and mean RV longitudinal strain was −14.0% (CI: −17.3 - -10.6, SD ± 7.0). Within the first year, mean myocardial deformation normalized in every view and remained within normal limits during follow-up. After the first year of treatment with ERT, cardiac function measured by LV longitudinal strain remained significantly lower but within normal limits in Pompe patients compared to controls (Intercept Pompe: −18.4% vs controls: -21.4%, $P = 0.003$), and did not change significantly over time (−0.04%/yr compared to controls $p = 0.630$). Cardiac function measured by LV circumferential strain in Pompe patients decreased significantly over time compared to the control group during follow-up (+0.24%/yr, $p = 0.019$), but as explained before, remained within normal limits during follow-up. Cardiac function measured by RV longitudinal strain did not significantly differ from the control group (+0.23%/y, $p = 0.277$). Fig. 3 shows the development of myocardial deformation over time, Supplement 1 shows the outcomes of the lme models.

3.4. Observer variability

A total of 15 echocardiograms from the database were analyzed for observer variability. Supplement 2 and 3 show the Bland-Altman plots and numeric outcomes. Coefficient of variation (COV) ranged between 5.3% and − 12.1% for the inter-observer agreement and between −7.4% and − 12.9% for the intra-observer agreement. The COV was the highest for both inter-observer agreement RV longitudinal strain and intra-observer agreement analyses.

4. Discussion

This study shows normalization of cardiac function after start of ERT, measured by both conventional echocardiography and myocardial deformation analyses in 27 patients with classic infantile Pompe disease. After restoration of cardiac function on group level during the first year of treatment, cardiac function seems to remain stable during follow up compared to controls, despite a small decrease in LV circumferential strain. These results are in sharp contrast to the results obtained for skeletal muscle, as decline of muscle function may be observed when patients grow older [17,18]. This study is unique due to the long follow-up time, relatively large cohort, and use of myocardial deformation analyses in patients with classic infantile Pompe disease [3,19].

4.1. Effect of ERT on cardiac function

After the first year of ERT, LVMI had become normal in all but 2 patients. This is in accordance with previously published papers. Both Levine et al., chen et al. and our previous study reported a strikingly fast beneficial response of the cardiac muscle after start of ERT, reflecting rapid reversal of excessive glycogen storage in cardiac muscle cells [3,20,21]. Mean SF, a measure of global left ventricular systolic function correlating with ejection fraction (EF), was also normal in these studies

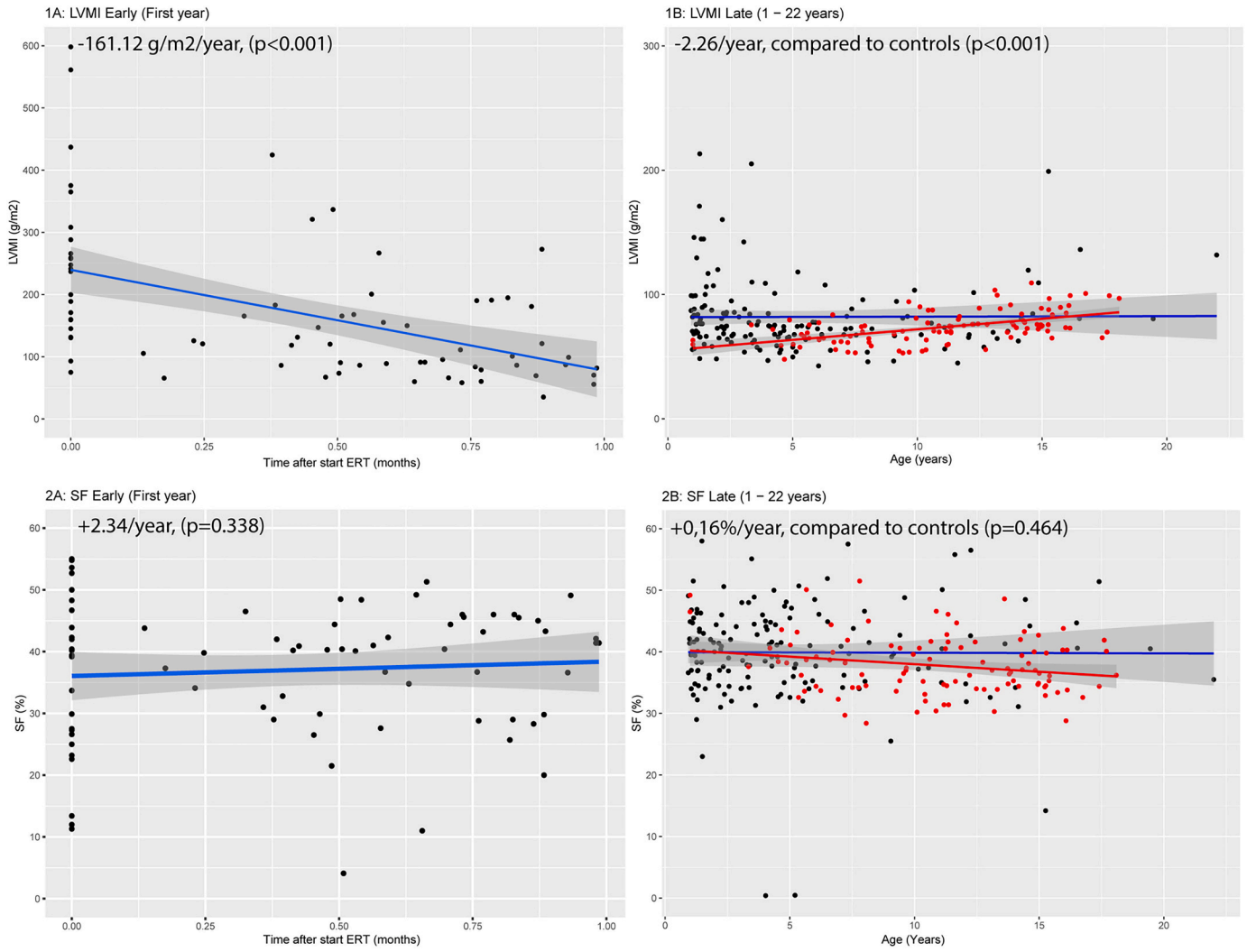

Fig. 2. Conventional echocardiography outcomes of patients with classic infantile Pompe disease and controls over time. 1A: LVMI early (first year), 1B: LVMI late (1–22 years), 2A: SF early (first year), 2B: SF late (1–22 years). Black dots represent measurements in classic infantile patients, red dots in healthy controls. Blue lines represent mean values of all classic infantile Pompe patients, red lines represent healthy controls. Grey area around red and blue lines represents the confidence interval. Left ventricular mass index (LVMI), shortening fraction (SF). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

even before start of ERT, despite severe LV hypertrophy [3,20]. Preserved SF and EF in a heart with severe systolic dysfunction can be explained by the adaptive and compensatory nature of the cardiac muscle [22]. Thus, SF and EF are not sensitive measures to describe subtle ventricular dysfunction, as these parameters of global systolic performance do not adequately reflect regional changes [6]. To overcome these shortcomings in the current study, we measured cardiac function using myocardial deformation analyses in addition to conventional echocardiography [6]. As myocardial deformation represents change in myocardial length from diastolic to systolic state, it allows studying the different components and directions of contractile function of the heart [6]. Up till now, no long term follow up study in classic infantile Pompe patients using this modality has been performed.

In this cohort, mean myocardial deformation analyses showed a decreased cardiac function before start of ERT. Within the first year of treatment, mean myocardial deformation normalized in every view. One study ($n = 8$) and a case-report, used myocardial deformation analyses in classic infantile patients before (only during the first year of treatment), both described a normalization of LV longitudinal strain within the first year after start with ERT [19,21].

During follow up beyond the first year, all parameters LVMI, SF, LV longitudinal and RV longitudinal strain remained stable compared to controls. Only LV circumferential strain gradually worsened in Pompe patients (+0.24%/year) compared to controls. However, this decrease was minimal and mean LV circumferential strain remained within normal ranges during follow-up. Previous studies, detecting subclinical decreased cardiac function in for instance children with metabolic syndrome and adults with systemic hypertension, describe a decreasing longitudinal function, before circumferential function deteriorates [23]. We therefore believe that this finding might not be clinically relevant. Longer follow-up than already performed in our study may help to draw definite conclusions.

4.2. *Effect of ERT on cardiac muscle cell vs skeletal muscle cell*

Skeletal muscles in classic infantile Pompe patients are more prone to escape from treatment effects over time, and patients who initially learned to walk may lose this ability [5,17]. The question arises why cardiac muscle function seems more responsive and remains relatively normal in our cohort during follow up. Especially since the effect of ERT on glycogen in skeletal muscles varies strongly among patients and even within muscle cells, whereas effects of ERT on cardiac muscle cells seem

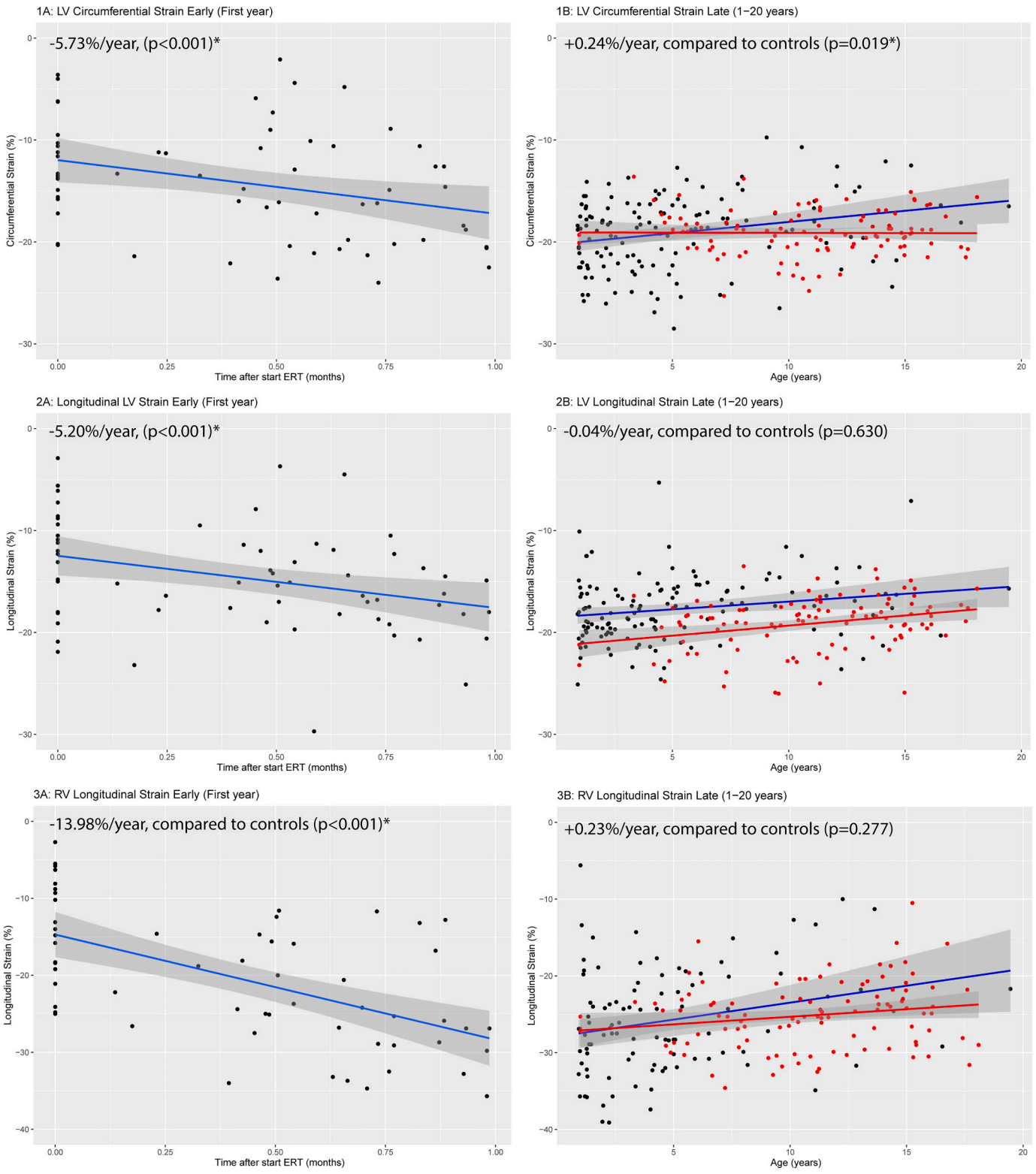

Fig. 3. Myocardial deformation of classic infantile Pompe patients and controls over time. 1A: early left ventricle circumferential myocardial deformation (first year), 1B: late left ventricle circumferential myocardial deformation (1–22 years), 2A: early left ventricle longitudinal myocardial deformation (first year), 2B: late left ventricle longitudinal myocardial deformation (1–22 years), 3A: early right ventricle longitudinal myocardial deformation (first year), 3B: late right ventricle longitudinal myocardial deformation (1–22 years). Black dots represent measurements in classic infantile patients, red dots in healthy controls. Blue lines represent mean values of all classic infantile Pompe patients, red lines represent healthy controls. Grey area around red and blue lines represents the confidence interval. Left ventricle (LV), Right ventricle (RV). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

to be more uniform [24–26]. Skeletal muscle cells show deposition of glycogen-loaded lysosomes between the contractile myofibrils followed by damage by lysosomal rupture, and release of lysosomal enzymes into the cytoplasm, while cardiac muscle cells despite the temporarily glycogen deposition do not seem to show any permanent changes in structure [4,17]. Previous studies in mice show that glycogen accumulation in cardiac muscle cells reverses importantly after start of ERT, whereas skeletal muscle cells shows less response [27–29]. Possibly, this is caused by the lower residual GAA activity, required to prevent glycogen accumulation in the heart. It should be noted that adults with Pompe disease with 10–20% residual GAA activity do not express a cardiac phenotype. Another contributing factor might be the potentially lower amount of mannose 6-phosphate receptors exposed on the skeletal muscle cell surface, required for efficient enzyme uptake and targeting to the lysosomes. In addition, skeletal muscle cells might be harder to reach by ERT as they are more surrounded by endothelium and connective tissue, which potentially hampers adequate uptake of ERT in skeletal muscles more than in cardiac muscle cells [26–28,30].

4.3. Strengths and limitations

Rare diseases are challenging to investigate due to low incidence, our cohort consisted out of 27 patients. For a rare disease like classic infantile Pompe disease, our cohort is large as is the follow-up time. Since the very first treatment worldwide in 1998, our cohort of patients gradually grew over time. As a consequence the follow-up duration per patient differs and the statistical power decreases over time. Therefore results beyond 12 years after start of ERT should be interpreted with some caution, also, we were not able to investigate possible differential effects of ERT dose (15 or 20 mg/kg/week; 20 mg/kg/2 or 40 mg/kg/wk) on cardiac function, due to low patient numbers. Echocardiographic techniques have rapidly improved over time, echocardiograms performed before 2004 could not be analyzed using myocardial deformation due to low image quality. Myocardial deformation analyses were performed using a vendor independent software analyses package (TomTec), normal values for the TOMTEC system of myocardial deformation analyses are not yet established in children, therefor we added a control group to the analyses [11]. This control group was measured cross-sectional, whereas Pompe patients were followed over time, however, median age was comparable. The number of echocardiograms of healthy children younger than one was small, therefore we could not compare myocardial deformation analyses in classic infantile Pompe patients within the first year of ERT with healthy controls. As myocardial deformation analyses could be observer dependent, we added observer variability analyses to this study. The observer was not blinded while doing the myocardial deformation analyses.

4.4. Clinical implications and future research

ERT significantly improved cardiac dimensions and function, and no clinically relevant decline in cardiac function was measured up to 22 years of follow-up. Therefore, cardiac follow-up frequency using echocardiogram can most likely be reduced once cardiac function has normalized. However, low frequency follow-up during adult hood is still warranted. Implementation of myocardial deformation analyses in the follow-up protocol is worthwhile to assess subtle changes of cardiac function earlier and more accurately than conventional echocardiography. As previously published studies show that Pompe patients are known to have arrhythmia's, EKG frequency should not be reduced [31]. Furthermore, more in depth studies on differences in glycogen metabolism and ERT response between cardiac muscle cells and skeletal muscle cells may help to explain the better susceptibility of cardiac muscle to ERT.

5. Conclusion

Cardiac function, measured using both conventional echocardiography and myocardial deformation normalizes on group level within the first year of ERT, and seems to remain stable over a median period of 9.9 years and up to 22 years of follow up in the longest treated patients with classic infantile Pompe disease. These results are unique due to the long follow up period, relatively large cohort, and longitudinal use of myocardial deformation analyses to asses cardiac function. These results suggest that the frequency of echocardiographic studies can be reduced (but not stopped) in the follow-up of classic infantile Pompe patients once the cardiac function has been normalized, as we did not find a clinically relevant decline in cardiac function.

Contributor ship statement

LES, CIC, LK, WAH, JMPH and LEB had the main role in the research protocol design. RK performed the myocardial strain analyses. LES and RK did the statistical analyses under supervision of EB. LES drafted the manuscript. All authors critically revised the manuscript and approved the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Ethics approval

The study was approved by the local ethics committee and started in 1999 (trial number: NL.2007.03).

Patient consent status

Written consent was obtained for all patients. The consent form used had to the same terms outlined as in Wiley's standard consent form.

Funding statement

This specific research project was unfunded. LES is paid by the 'stichting Vrienden van Sophia'.

Declaration of Competing Interest

Prof. dr. Ans T. van der Ploeg and dr. J M.P. (Hannerieke) van den Hout participated in advisory boards and received consultancy fees and/or research grants of Sanofi/Genzyme, Amicus, Denali, Spark Therapeutics, GSK, Biomarin, Takeda and others under agreements between these industries and Erasmus University Medical Center, Rotterdam, The Netherlands.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.03.010.

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