Objective: Fabry disease, a rare X-linked disorder, can lead to exercise intolerance. In Taiwan, the cardiac variant of Fabry disease has a significantly higher prevalence than the classic variant. The cardiac variant of Fabry disease primarily involves the heart. Enzyme replacement therapy has been used to treat both variants. We aimed to study the impact of enzyme replacement therapy on exercise and cardiac structures between the classic (CL-FD) and cardiac variant (CV-FD) Fabry disease.

Design and methods: Retrospective analysis of 2 groups of patients with Fabry disease (5 patients with the classic variant and 5 with the cardiac variant), who were undergoing enzyme replacement therapy. Patients were assessed annually for 3 years using symptom-limited cycle ergometry and echocardiography.

Results: Subjects were 5 women, mean age 53 (standard deviation (SD) 14.05) years with CL-FD Fabry disease, and 5 men, mean age 65 (SD 2.35) years with CV-FD. The percentage of peak oxygen consumption to predicted value for all included patients was significantly lower (78.78% (SD 12.72)) than 100%. Annual serial measurement showed that peak metabolic equivalent and percentage of peak oxygen consumption decreased significantly over a period of 3 years in patients with CV-FD (p = 0.002, and p =0.004, respectively), but not in those with CL-FD. There were no significant changes in annual serial measurements of left ventricular mass or interventricular septal thickness in patients with either variant of Fabry disease over a period of 3 years.

Conclusion: Peak exercise capacity of the patients with Fabry disease was lower than that of normal peers. Peak exercise capacity decreased over time in patients with CV-FD, but remained the same in patients with CL-FD.

Key words: Fabry disease; enzyme replacement therapy; cardiopulmonary exercise testing; peak oxygen consumption.

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This enzyme deficiency leads to accumulation of glycosphingolipid, primarily globotriaosylceramide (Gb3), which is deposited chiefly in endothelial and vascular smooth-muscle cells. In hemizygous males, FD may present as early as 5 years of age, with characteristic features, such as neuropathic pain, hypohidrosis or anhidrosis, disseminated angiorretoma, cornea verticillata, and microalbuminuria. Over time, male patients with FD develop renal failure, cardiac dysfunction and stroke. This disease phenotype is currently known as classic FD (CL-FD) (3). As many as two-thirds of female carriers may also have clinically significant manifestations of FD, although with a more variable and attenuated phenotype (4). Life expectancy is reduced in both males and females, but this is more apparent in males.

Two variants of FD that have manifestations primarily involving the heart (5, 6) or kidneys (7) have been reported in the last 2 decades. Patients with the cardiac variant (CV-FD) lack the classical symptoms of FD and present in the 5th to 8th decades of life with left ventricular hypertrophy (LVH), arrhythmias, and/or cardiomyopathy (8). CL-FD is very rare; the estimated birth prevalence rate in Western countries is approximately 1/40,000 (9). However, an unexpectedly high prevalence of the CV-FD mutation IVS4+919G->A (IVS4) among both newborns and patients with idiopathic hypertrophic cardiomyopathy (1 in 1,500–1,600 males, 1 in 750–800 females) has been recognized in the Taiwan Chinese population (10, 11).

Patients with FD have decreased exercise tolerance and often report fatigue, even from childhood. The aetiology of this phenomenon is not fully understood. Cardiac and pulmonary involvement had been reported in patients with FD. Up to 36% of male patients with FD with obstructive ventilator defect were found to have pulmonary involvement. Decreased diffusing capacity, haemoptysis, alveolar precipitates and lamellar inclusion bodies have also been described among patients with FD (12, 13). LVH has been shown to occur in as many as 37% of patients with FD and the hypertrophy appears to be related to alteration of the left ventricular structure (14).

Enzyme replacement therapy (ERT) with either agalsidase-alpha or agalsidase-beta has been developed for treatment of FD. ERT may decrease cardiac mass and reduce renal accumulations of Gb3 (15). Trials comparing ERT with placebo show significant improvement with ERT with regard to microvascular endothelial deposits of Gb3 and pain-related quality of life (16). Based on these insights, early initiation of ERT has been advocated. However, to date, no studies have shown convincing clinical evidence for the superiority of agalsidase-alpha or agalsidase-beta (17). The long-term influence of ERT on the risk of morbidity and mortality related to FD is also unknown (16).

FD has multi-factorial effects on the cardiovascular system. Exercise capacity can be used as an integrated measure of cardiovascular function and allows the effects of treatment to be monitored. However, most research has focused on electrocardiographic and echocardiographic parameters. Only a few studies have used cardiopulmonary exercise testing (CPET) to assess patients with FD. One study found decreased exercise tolerance and a precipitous reduction in diastolic blood pressure (DBP) at higher levels of exercise during CPET in patients with FD. It concluded that the significant decrease in DBP in these patients may explain deficits in exercise tolerance (18). Another study found that male patients with FD were unable to attain predicted maximal heart rate during exercise or to achieve normal exercise levels (19). A few small cohort studies using cycle ergometry in CPET also showed that ERT was associated with a small improvement in anaerobic threshold (AT) (19) and exercise tolerance in patients with FD (20).

To the best of our knowledge, no studies have used direct CPET to compare exercise capacity between patients with CL-FD and CL-FD who are undergoing ERT. Since the prevalence of CV-FD is unexpectedly high in Taiwan, we aimed to assess the impact of ERT on exercise tolerance by serial noninvasive CPET in each variant of FD overtime.

METHODS
This retrospective cohort study was performed at a tertiary medical centre in Taiwan.

The study was approved by the Institutional Review Board of the Kaohsiung Veterans General Hospital (number: VGHKS17-CT11-11). Informed consent was obtained from each patient before the study.

Subject characteristics
Inclusion criteria were: patients with FD confirmed by a documented pathogenic mutation in the α-galactosidase A gene, who received regular follow-up with complete transthoracic echocardiographic examination at the cardiology outpatient clinic. The patients were undergoing routine ERT with agalsidase-α (Replagal™, Shire Human Genetic Therapies (HGT), Inc., Cambridge, MA, USA), 0.2 mg/kg every other week, and were referred to the rehabilitation department for serial CPET from June 2015 to October 2017. Informed consent was obtained from each patient during each CPET session.

Exclusion criteria were: significant coronary artery disease; significant arrhythmia; concurrent known pulmonary disease; and age less than 18 years.

Patients’ basic characteristics were recorded, including sex, age, body weight, height, plasma Gb3 level, and plasma lyso-Gb3 level. The study was approved by the Institutional Review Board of Kaohsiung Veterans General Hospital (number VGHKS17-CT11-11).

Cardiopulmonary exercise test
Symptom-limited cycle ergometry was used to measure the subjects’ exercise capacity. The testing system comprised a bicycle, a flow module, a gas analyser, and an electrocardiographic monitor (Metamax 3B, Cortex Biophysik GmbH Co., Germany). The bicycle stress test was performed under the supervision of an experienced physiatrist (K.L.L.). Patients pedalled for 1 min at zero resistance, after which the bicycle ergometer gradually
increased the resistance at a ramp rate of 10 W/min. The test was stopped when the patients demonstrated subjective unbearable symptoms (21). Oxygen consumption (VO₂) and carbon dioxide production (VCO₂) during the exercise test were measured by the breath-by-breath method. In addition, metabolic equivalent (MET), minute ventilation (VE), blood pressure (BP), and heart rate (HR) were measured throughout the exercise test. The AT was determined by the VE/VO₂ and VE/VCO₂ methods (22). VO₂ peak was the maximum oxygen uptake measured at peak exercise. VO₂ peak to predicted value (peakVO₂%) was the percentage compared with the normal standards for cardiopulmonary responses to exercise using a cycle ergometer test among Taiwan adults (23). The change in peakVO₂ in the serial 3 years was defined as ∆peakVO₂% = 100% × [(peakVO₂ of the 2nd or the 3rd year) - (peakVO₂ of the first year)]/ (peakVO₂ of the first year). Comparison of measured and predicted ∆peakVO₂% was performed, with the predicted VO₂ calculated using 2 reference equations. One of the reference equations was the normal standards for CPET using a cycle ergometer test in Taiwan adults (23). The equation was developed for normal standards for VO₂max from a US national registry. The equation was: VO₂max (ml kg⁻¹ min⁻¹) = 45.2 – 0.35*Age – 10.9*Sex (male = 1; female = 2) – 0.15*Weight (pounds) + 0.68*Height (inches) – 0.46*Exercise Mode (treadmill = 1; bike = 2) (R = 0.79, R² = 0.62, standard error of the estimate = 6.6 ml kg⁻¹ min⁻¹). It could be applied to exercise testing using cyclemeter and treadmill. The equation was determined using multiple regression analysis, and comparisons were made with the widely-used Wasserman and equation was determined using multiple regression analysis, and comparisons were made with the widely-used Wasserman and traditional equations, particularly among women and individuals ≥ 60 years old.

**Pulmonary function test**

Pulmonary function testing was performed by spirometry at rest. Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) was measured.

**Echocardiography**

Echocardiographic testing was undertaken according to local protocol and carried out annually in all patients. One experienced cardiologist measured left ventricular end-diastolic diameter (LVEDD), left atrial dimension (LAD), interventricular septal thickness at end-diastole (IVS), and left ventricular posterior wall thickness at end-diastole (LVPW) according to the guidelines of the American Society of Echocardiography and the European Society of Cardiology. Left ventricular (LV) mass was calculated according to the Devereux formula, as follows: LV mass = [1.04 × ((LVEDD + IVS + LVPW)³ – (LVEDD)³) – 13.6] (25). LV mass index (LVMi) (g/m²) was calculated by dividing LV mass by body surface area (BSA) (26) to define the presence of LVH (LVMi > 134/110 g/m² for men/women).

**Statistical analysis**

SPSS for Windows version 19.0 (2010 release, IBM Corp., Armonk, NY, USA) was used for all analyses. Data were expressed as means (standard deviation; SD). Normality and homoscedasticity were checked before each analysis. The χ² test was used to test for differences in distribution between categorized variables. Mann–Whitney U test was used for non-normally distributed variables for comparison between patients with CL-FD and those with CV-FD. Differences in data for CPET and echocardiography among the first, second, and third years of evaluation were analysed by repeated measures 1-way analysis of variance (ANOVA) and a Bonferroni post hoc test. A p-value < 0.05 was considered statistically significant.

**RESULTS**

**Patient characteristics**

Twelve patients met the study inclusion criteria, but 2 dropped out for personal reasons (moving home to other county, and receiving ERT at a different hospital). Therefore, a final total of 10 subjects were included in the study (5 females, mean age 53 years (SD 14.05) in the CL-FD group and 5 males, mean age 65 years (SD 2.35) in the CV-FD group). Mean duration from initiation of ERT to the first year of evaluation for this study was 75.30 months (SD 34.85) in the CL-FD group and 29.70 months (SD 29.09) in the CV-FD group. Six patients were diagnosed with LVH by LVMi; 2 in the CL-FD group, and 4 in the CV-FD group. There were no significant differences between patients with CL-FD and those with CV-FD.

**Table I. Participants’ demographic and baseline characteristics**

| Characteristics | All (n = 10) | CL-FD group (n = 5) | CV-FD group (n = 5) | p-value* |
|-----------------|-------------|---------------------|---------------------|---------|
| Age, years, mean (SD) | 59.00 (11.41) | 53.00 (14.05) | 65.00 (2.35) | 0.151 |
| Height, cm, mean (SD) | 159.72 (1.30) | 153.62 (1.47) | 167.35 (0.40) | 0.111 |
| Weight, kg, mean (SD) | 58.43 (9.79) | 52.06 (5.93) | 66.40 (7.50) | 0.032* |
| BMI, kg/m², mean (SD) | 23.01 (3.67) | 22.51 (4.91) | 23.64 (1.71) | 0.413 |
| Resting SBP, mmHg, mean (SD) | 119.67 (16.58) | 112.40 (7.40) | 128.75 (21.50) | 0.286 |
| Resting DBP, mmHg, mean (SD) | 72.22 (15.62) | 64.40 (14.52) | 82.00 (11.83) | 0.111 |
| Resting HR, bpm, mean (SD) | 66.22 (11.04) | 69.00 (12.10) | 62.75 (10.05) | 0.556 |
| FVC, L, mean (SD) | 2.51 (0.59) | 2.22 (0.55) | 2.88 (0.44) | 0.111 |
| FEV1, % mean (SD) | 83.33 (8.70) | 85.40 (10.29) | 80.75 (6.70) | 0.413 *
| FEV1L, mean (SD) | 1.95 (0.43) | 1.87 (0.53) | 2.06 (0.32) | 0.730 |
| FEV1P, %, mean (SD) | 80.67 (11.90) | 86.60 (9.91) | 73.28 (10.69) | 0.190 |
| Duration of ERT use, mean (SD) | 52.50 (38.65) | 75.30 (34.85) | 29.70 (29.09) | 0.222 |
| Number of patients with LVH, n | 6 (50) | 2 (40) | 4 (80) | 0.197 |

*p < 0.05.*

*Refers to the p-value of a Mann–Whitney U test for continuous variables and χ² test for non-continuous variables between patients with classic Fabry disease and cardiac variant Fabry disease.

*Duration of ERT from first use to the time receiving baseline exercise testing.

CL-FD: classic Fabry disease; CV-FD: cardiac variant Fabry disease; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; ERT: enzyme replacement therapy; HR: heart rate; FVC: functional vital capacity; FEV1P: percentage of predicted forced vital capacity; FEV1: force expiratory volume at 1 min; LVH: left ventricular hypertrophy; SD: standard deviation.
Cardiorespiratory exercise testing and echocardiography
Mean peakVO₂% for all study participants with Fabry disease (FD) in the serial 3 years were all significantly lower than 100%. The 95% confidence interval (95% CI) of peakO₂% of each group was also lower than 100% (Table II).

There were no significant differences in MET at the point of AT (AT MET), Peak power output (W), peak SBP, peak DBP, peak HR, or peak HRR in the serial 3 years in either of the 2 groups over time CL-VD and CV-FD groups. Peak metabolic equivalent (peak MET) and peakVO₂% decreased significantly in the CV-FD group (p = 0.002, p = 0.004, respectively), but not in the CL-FD group in serial measurements over 3 years. In the CV-FD group, post hoc analysis showed significant differences in peak MET (p = 0.028) and peakVO₂% (p = 0.036) between the first and third years of evaluation. Peak respiratory exchange ratio (RER) in the serial 3 years showed significant difference in the CL-FD group. Post hoc analysis found that peak RER in the third year was significantly higher than in the first year (p = 0.005) (Table III).

Although a trend of gradually increasing IVS and LVMI was found in the CV-FD group, no significant differences in IVS, LVMI, or LVM in the serial 3 years were noted in the CL-VD or CV-FD groups (Table III).

### Table II. Descriptive data for peakVO₂% for all study subjects with Fabry disease (FD) at first, second, and third years of evaluation

| Year of evaluation | Patients | peakVO₂%, % Mean (SD) | 95% CI |
|--------------------|----------|------------------------|--------|
| 1                  | Total    | 80.10 (17.16)          | 70.33–90.20 |
|                    | CL-FD    | 77.02 (14.45)          | 64.23–83.27 |
|                    | CV-FD    | 85.97 (21.16)          | 60.57–96.12 |
| 2                  | Total    | 76.89 (14.72)          | 66.54–84.06 |
|                    | CL-FD    | 77.98 (12.97)          | 68.62–86.18 |
|                    | CV-FD    | 78.98 (18.83)          | 58.25–94.85 |
| 3                  | Total    | 78.78 (12.72)          | 71.29–82.65 |
|                    | CL-FD    | 84.75 (5.02)           | 80.93–87.91 |
|                    | CV-FD    | 73.51 (18.15)          | 52.61–87.89 |

peakVO₂%: percentage of measured peak oxygen consumption to predicted value; 95% CI: 95% confidence interval; CL-FD: classic Fabry disease; CV-FD: cardiac variant Fabry disease; SD: standard deviation.

### Table III. Cardiorespiratory exercise testing and echocardiography results at first, second, and third years of evaluation

| Test                  | Group       | First year Mean (SD) | Second year Mean (SD) | Third year Mean (SD) | F value | p-value* |
|-----------------------|-------------|----------------------|-----------------------|----------------------|---------|----------|
| AT MET                | CL-FD       | 3.28 (0.63)          | 3.10 (0.58)           | 3.34 (0.66)          | 0.638   | 0.553    |
|                       | CV-FD       | 4.60 (1.48)          | 4.18 (1.38)           | 3.95 (1.34)          | 6.202   | 0.088    |
| PEAK MET              | CL-FD       | 4.78 (1.22)          | 4.72 (1.03)           | 5.08 (0.97)          | 4.73    | 0.620    |
|                       | CV-FD       | 6.55 (1.70)          | 5.93 (1.50)           | 5.43 (1.43)          | 21.279  | 0.002*   |
| Peak VO₂              | CL-FD       | 0.88 (0.30)          | 0.85 (0.22)           | 0.94 (0.26)          | 0.595   | 0.507    |
|                       | CV-FD       | 1.55 (0.53)          | 1.39 (0.48)           | 1.26 (0.49)          | 12.955  | 0.007*   |
| Peak power output, W  | CL-FD       | 59.40 (19.71)        | 58.00 (17.56)         | 63.40 (16.15)        | 0.316   | 0.613    |
|                       | CV-FD       | 106.00 (45.13)       | 89.00 (22.45)         | 91.25 (30.90)        | 0.424   | 0.673    |
| Peak SBP              | CL-FD       | 134.40 (7.80)        | 140.60 (23.66)        | 147.20 (25.52)       | 0.791   | 0.486    |
|                       | CV-FD       | 151.75 (17.80)       | 153.25 (11.62)        | 159.75 (33.18)       | 0.312   | 0.743    |
| Peak DBP              | CL-FD       | 74.20 (5.22)         | 75.60 (4.10)          | 79.00 (9.82)         | 0.616   | 0.524    |
|                       | CV-FD       | 74.75 (2.06)         | 74.25 (1.89)          | 77.50 (13.18)        | 0.253   | 0.652    |
| Peak HR               | CL-FD       | 129.00 (15.17)       | 109.4 (30.44)         | 108.0 (29.91)        | 1.674   | 0.247    |
|                       | CV-FD       | 118.50 (12.29)       | 121.75 (21.61)        | 113.75 (16.82)       | 0.443   | 0.662    |
| Peak RER              | CL-FD       | 1.02 (0.04)          | 1.04 (0.04)           | 1.10 (0.02)          | 9.416   | 0.008*   |
|                       | CV-FD       | 1.11 (0.02)          | 1.09 (0.03)           | 1.10 (0.02)          | 0.820   | 0.486    |
| Peak HRR              | CL-FD       | 24.80 (14.14)        | 18.6 (13.56)          | 12.40 (14.60)        | 2.559   | 0.138    |
|                       | CV-FD       | 25.75 (13.72)        | 23.75 (11.56)         | 18.75 (16.09)        | 0.264   | 0.777    |
| peakVO₂%              | CL-FD       | 77.02 (14.45)        | 77.98 (12.97)         | 84.75 (5.02)         | 1.040   | 0.397    |
|                       | CV-FD       | 85.97 (21.16)        | 78.98 (18.83)         | 73.51 (18.15)        | 16.547  | 0.004*   |
| IVS (mm)              | CL-FD       | 11.00 (2.00)         | 10.80 (2.28)          | 13.42 (4.85)         | 3.202   | 0.137    |
|                       | CV-FD       | 13.00 (4.08)         | 13.25 (3.95)          | 13.73 (7.37)         | 0.422   | 0.674    |
| LVMI                  | CL-FD       | 152.27 (51.59)       | 139.14 (30.23)        | 169.29 (64.11)       | 1.394   | 0.302    |
|                       | CV-FD       | 169.42 (56.94)       | 178.82 (72.97)        | 178.41 (70.84)       | 0.158   | 0.857    |
| LVM (g)               | CL-FD       | 228.98 (84.76)       | 205.15 (43.92)        | 250.59 (96.11)       | 1.581   | 0.264    |
|                       | CV-FD       | 294.16 (77.98)       | 308.11 (104.61)       | 305.35 (105.58)      | 0.101   | 0.905    |

* p < 0.05.
* aWithin-group difference using repeated measures 1-way analysis of variance (ANOVA).
* bPost hoc analysis using Bonferroni test showed p-value < 0.05 compared with first year.

CL-FD: classic Fabry disease; CV-FD: cardiac variant Fabry disease; AT: anaerobic threshold; MET: metabolic equivalent; AT MET: MET at the point of AT; peak MET: MET at peak exercise; peak VO₂: peak oxygen consumption; peak HR: heart rate at peak exercise; peak RER: respiratory exchange ratio at peak exercise; HRR at 1 min: heart rate reserve at 1 min after termination of the test; peakVO₂%: percentage of measured peak oxygen consumption to predicted value; IVS: interventricular septal thickness at end-diastole; LVMI: left ventricular mass index; LVM: mass of left ventricle; SD: standard deviation.
were noted in LVM and LVMI. There were no significant differences in any CPET and echocardiography data between the second and first years (Table IV).

**DISCUSSION**

To the best of our knowledge this is the first study to compare exercise capacity in patients with CL-FD and CV-FD who are undergoing regular ERT. The main finding of this study was that peak exercise capacity in patients with FD (whether CV-FD or CL-FD) who were undergoing ERT was lower than in their normal peers. Peak exercise capacity decreased over time in patients with CV-FD undergoing ERT, but remained the same in patients with CL-FD undergoing ERT.

There was a significant difference in body weight between the 2 groups, due to the sex of the subjects. Significant positive correlation has been shown between oxygen consumption and body weight in both cycle ergometry and treadmill exercise (27, 28). Therefore, peak MET was chosen to indicate cardiopulmonary fitness in this study. MET is the objective measure of the ratio of the rate at which a person expends energy, relative to their body weight, set by convention at 3.5 ml of oxygen per kg per min (29). Given that peak MET is the peak oxygen consumption relative to body weight, this was used to eliminate the potential bias that derived from body weight.

A number of studies have proven the efficacy of ERT in treatment of cardiac abnormalities in patients with FD. The proven long-term effects of ERT on cardiomyopathy in FD include a significant reduction in left ventricular mass (30, 31), improvement in myocardial function (30, 31), reduction in the accumulation of Gb3 in the heart (16), a lower level of cardiovascular complications (32), and improvement in quality of life (16). However, few studies have evaluated the clinical efficacy of ERT on cardiopulmonary function. In 2006, Bierer et al. (20) conducted a small cohort study, and performed serial CPETs at baseline and every 3 months over a period of at least 18 months. They found that exercise tolerance (VO2 max and oxygen pulse) increased in patients with FD (mean age 32 years) who were receiving ERT. However, there were only 4 patients with FD in their study (20).

Lobo et al. (19) used bicycle stress testing to measure the exercise capacity of patients with FD (mean age 42.8 (SD 11) years). They found that exercise capacity was reduced in patients with FD compared with that predicted from normative population data, which was similar to our result. They also found mild improvement in AT in the first year of ERT, but no consistent further increase beyond the first year (19).

There was no detailed description of the type of FD in patients recruited to these previous studies. Since CV-FD is also called “late-onset FD”, and usually presents in the 5th to 8th decades of life (8), most of the subjects in these studies might have had CL-FD. The mean age of the patients with CV-FD in our study was 65 years (SD 2.35), which was consistent with previous studies. Weidemann et al. (30) found that patients with FD (mean age 42 years
underwent ERT had higher exercise capacity obtained by bicycle stress exercise than those without ERT 3 years after the initiation of ERT (106 W (SD 14) and 122 W (SD 26), respectively; $p = 0.014$) (30). Our results showed that, in patients with CL-FD, AT MET, peak MET, peak $O_2$, Peak power output (W), and peakVO$_2$% were higher in the third year than in the first year of evaluation, but there was no significant difference in the above parameters, except for peak RER ($p = 0.008$), on repeated measures ANOVA. In contrast, in patients with CV-FD, peak exercise capacity gradually became significantly worse in serial measurements over the 3 years. Given that there was a difference in percentage peak oxygen consumption in the serial 3 years between measured and predicted values of peakVO$_2$, for the CV-FD group, the reduction in peakVO$_2$ in CV-FD was due not only to the physiological changes that occur during normal aging, but also to the cardiac involvement of the disease.

Cardiac involvement in both CL-FD and CV-FD begins with hypertrophy, which leads to hypertrophy cardiomyopathy and development of heart failure (33). Of interest, and with no current explanation, patients with CV-FD tend to have mutation-specific cardiac involvement (34). There have been no studies comparing the difference in cardiac involvement between patients with CL-FD and those with CV-FD. One study has shown that significant cardiomyocyte substrate accumulation in patients with IVS4 leads to severe and irreversible cardiac fibrosis prior to the development of LVH or other significant cardiac manifestations (35). In our study, 80% of subjects in the CV-FD group had LVH, and it is possible that they might already have had cardiac fibrosis, which could explain the different efficacy of ERT on peak exercise capacity and LVM between the CL-FD group (in which only 40% of subjects had LVH) and the CV-FD group. This result was also similar to that of Weidemann et al.’s study (30), which found that ERT resulted in a significant reduction in LVM, and a higher exercise capacity in patients with FD without cardiac fibrosis, while patients with FD who did have cardiac fibrosis showed a minor reduction in LVH and no improvement in exercise capacity with ERT (30).

A high RER indicates that predominantly carbohydrates are being metabolized. If peak RER exceeds 1.0, additional energy is supplied anaerobically, during which induced metabolic acidosis occurs (36). Patients with heart failure generally have difficulty reaching RER ≥ 1.0 during exercise tolerance testing (37, 38). In our study the mean peak RER in both groups at the 3 follow-ups were all > 1.0. Thus, it is possible that none of the patients had heart failure, even though LVH was noted on echocardiography in both groups. We also observed that, in the first 2 years, mean peak RER in the CL-FD group was lower than in the CV-FD group. Since all the participants in the CL-FD group were women, this difference could be due sex differences in substrate oxidation during aerobic exercise, which results in men having a higher RER than women (39, 40). There was also a significant increase in peak RER at the third year in the CL-FD group, while it remained the same in the CV-FD group. It is possible that ERT is more beneficial for patients with CL-FD than for those with CV-FD.

Only a few studies have examined the exercise capacity or exercise prescription of patients with FD. Many of these studies found that the lower exercise capacity in patients with FD might result from cardiac abnormalities (19, 20, 41). Refraining from physical exercise has been shown to result in exercise intolerance, in parallel with the evolution of FD (42). Exercise intolerance in patients with FD may be multi-factorial. In 2016, a pilot study by Schmitz et al. (19) showed that a 12-month strength/ circuit exercise training protocol (3 training sessions per week, 30–45 min per session, 90–135 min per week) may help to improve endurance capacity, muscle strength and overall well-being in patients with FD. In addition to ERT, we consider that adequate exercise training is important for patients with FD to ameliorate their exercise capacity.

CL-FD occurs predominantly in males, although some heterozygous females have a more severe phenotype that resembles CL-FD (3, 4). Studies have shown that clinical manifestations in heterozygous females, partly due to skewed X-chromosome inactivation, can vary widely, from no apparent clinical disease to full expression of CL-FD (43).

In Taiwan, CV-FD is the most common form of FD (11). Patients with CV-FD are generally asymptomatic for most of their lives and present in the 5th to 8th decade with LVH, hypertrophic cardiomyopathy, conduction abnormalities, and arrhythmias (8, 14). CL-FD occurs predominantly in males, although some heterozygous females have a more severe phenotype that resembles CL-FD (3, 4). Studies have shown that clinical manifestations in heterozygous females, partly due to skewed X-chromosome inactivation, can vary widely, from no apparent clinical disease to full expression of CL-FD (43).

In our study it was surprising that all of the CL-FD group were female and all of the CV-FD group male. The authors had reviewed all the medical records, including alpha-galactosidase A enzyme activity, cardiac nuclear magnetic resonance imaging, and echocardiography, and confirming the diagnosis of each variant in our participants were correct. However, it was difficult for the authors to explain the difference of the sex distribution in our participants.

Study limitations
The current study has some limitations. First, there were only 5 patients in each group. Although FD is a relatively rare disease worldwide, small numbers of subjects might be more difficult to get a statistically significant difference. Secondly, all of the subjects were recruited from a single medical centre in southern Taiwan and the results might be generalizable only to similar populations. Thirdly, all the patients with FD in this study were already receiving ERT before the first year of evaluation, and
there was no baseline data for their exercise capacity and LVMI prior to commencing ERT. Although the patient profiles for the first year of evaluation in both groups were not significantly different, and there was significant difference in not only the absolute values of peak exercise capacity, but also the relative values compared with the first year of evaluation (as shown in Table IV), the causal relationship between ERT and peak exercise capacity could not be determined directly. Fourthly, although there was no significant difference in the percentage of patients with LVH and LVMI in each group, we did not assess the status of cardiac fibrosis, a factor that has been proven to influence the efficacy of ERT in patients with FD.

Conclusion
This study was the first to compare exercise capacity, measured by direct CPET, and LVMI between patients with CL-FD and those with CV-FD who were undergoing ERT in annual follow-up for 3 consecutive years. The results showed that peak exercise capacity in patients with FD who were undergoing ERT was lower than that of normal peers. This study also found that peak exercise capacity decreased over a period of 3 years in patients with CV-FD who were undergoing ERT, but remained the same in patients with CL-FD who were undergoing ERT.

Larger prospective studies, using more sophisticated imaging, e.g. cardiac magnetic resonance imaging (MRI), and measurement of Gb3 levels, are warranted in order to elucidate the difference in efficacy of ERT in patients with CL-FD and those with CV-FD with regard to cardiac structures and exercise capacity.

The authors have no conflicts of interest to declare.

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