

CARDIAC INVOLVEMENT IN POMPE DISEASE: FROM PATHOPHYSIOLOGY TO MULTIMODALITY CARDIOVASCULAR ASSESSMENT AND THERAPEUTIC PERSPECTIVES

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ABSTRACT

Pompe disease, also known as glycogen storage disease type II or acid maltase deficiency, is a rare autosomal recessive lysosomal storage disorder caused by pathogenic variants in the **GAA** gene encoding lysosomal acid α -glucosidase. Deficient enzyme activity results in progressive intralysosomal glycogen accumulation, particularly in skeletal, respiratory, and, in the classic infantile phenotype, cardiac muscle. Cardiac involvement is most prominent in classic infantile-onset Pompe disease, in which severe myocardial hypertrophy, ventricular remodeling, diastolic dysfunction, and electrical abnormalities may develop early in life. In contrast, clinically significant cardiac disease is uncommon in late-onset Pompe disease, although subtle abnormalities have occasionally been identified using sensitive cardiovascular imaging techniques. Cardiovascular assessment therefore needs to be adapted to the clinical phenotype and age of onset. Electrocardiography and echocardiography remain the principal first-line investigations, whereas speckle-tracking echocardiography and cardiac magnetic resonance may provide complementary information in selected patients. Cardiac magnetic resonance allows accurate assessment of ventricular volumes and mass and provides tissue characterization, although current evidence remains limited and heterogeneous. Enzyme replacement therapy has substantially changed the natural history of classic infantile Pompe disease, with regression of myocardial hypertrophy and improvement in cardiac function when treatment is initiated early. The cardiovascular response in late-onset disease appears considerably less pronounced. This review summarizes the mechanisms of cardiac involvement in Pompe disease, its clinical and electrocardiographic manifestations, the contribution of multimodality cardiovascular imaging, practical diagnostic considerations for cardiologists, and current and emerging therapeutic perspectives. Particular emphasis is placed on the role of the cardiologist in recognizing atypical cardiac phenotypes and participating in multidisciplinary long-term management.

KEYWORDS: Pompe disease; glycogen storage disease type II; cardiac involvement; hypertrophic cardiomyopathy; echocardiography; cardiac magnetic resonance; strain imaging; enzyme replacement therapy.

1. INTRODUCTION

Pompe disease is a rare autosomal recessive lysosomal storage disorder caused by deficient activity of lysosomal acid α -glucosidase (GAA), the enzyme responsible for the degradation of glycogen within lysosomes. Progressive glycogen accumulation results in cellular dysfunction and tissue damage, particularly in skeletal and respiratory muscles.

Cardiac involvement varies considerably according to age at onset and residual enzyme activity.^[1–3]

The clinical spectrum ranges from the severe classic infantile phenotype to childhood- and adult-onset forms with slower progression. Classic infantile-onset Pompe disease is characterized by profound hypotonia, generalized muscle weakness, feeding difficulties, respiratory compromise, and prominent hypertrophic cardiomyopathy. Without effective

treatment, the disease may progress rapidly and lead to severe cardiorespiratory failure.^[3,4]

In late-onset Pompe disease, skeletal and respiratory muscle involvement predominates. Significant myocardial hypertrophy, which is a characteristic feature of classic infantile disease, is uncommon. Nevertheless, isolated electrocardiographic, echocardiographic, or cardiac magnetic resonance abnormalities have been reported in a subset of patients.^[5-8]

The introduction of enzyme replacement therapy (ERT) has markedly modified the prognosis of Pompe disease, particularly in patients with classic infantile disease. Early treatment may lead to regression of myocardial hypertrophy, improvement in cardiac function, and prolonged survival.^[9-12]

For cardiologists, Pompe disease is therefore relevant in several clinical situations, particularly unexplained ventricular hypertrophy associated with unusual electrocardiographic findings, skeletal muscle weakness, respiratory muscle involvement, or a multisystem phenotype suggestive of a metabolic disorder.

This review focuses on the mechanisms and clinical expression of cardiac involvement in Pompe disease and discusses the contribution of contemporary cardiovascular imaging to diagnosis and follow-up.

2. Pathophysiology of Cardiac Involvement

The primary molecular defect in Pompe disease is reduced or absent activity of lysosomal acid α -glucosidase. GAA deficiency impairs lysosomal glycogen degradation and results in progressive glycogen accumulation within lysosomes. Enlargement of glycogen-loaded lysosomes progressively disrupts normal cellular architecture.^[1,2]

In cardiomyocytes, glycogen accumulation is associated with lysosomal enlargement, mechanical disruption of the contractile apparatus, altered cellular organization, and abnormalities of intracellular trafficking and autophagy. Impaired autophagic flux may contribute substantially to muscle fiber damage and may also interfere with the delivery and processing of therapeutic enzyme.^[13,14]

The structural consequences in the myocardium include cardiomyocyte enlargement and increased ventricular wall thickness. In classic infantile disease, marked myocardial hypertrophy may result in a small left ventricular cavity and impaired ventricular filling. Dynamic left ventricular outflow tract obstruction has also been described.^[15,16]

The functional consequences initially involve ventricular relaxation and diastolic filling. With disease progression, myocardial remodeling may eventually be accompanied by systolic dysfunction. The severity of cardiac involvement is influenced by the amount of residual GAA activity, genotype, age at onset, and duration of disease.^[1-4]

The pathophysiology can therefore be summarized as follows

GAA deficiency → impaired lysosomal glycogen degradation → glycogen accumulation → lysosomal enlargement and cellular disruption → altered autophagy and contractile machinery → cardiomyocyte hypertrophy and myocardial remodeling → diastolic dysfunction ± systolic dysfunction.

Electrical abnormalities may occur in parallel and include a short PR interval, increased QRS voltage, conduction abnormalities, and arrhythmias.

3. Clinical Phenotypes and Cardiovascular Expression

3.1 Classic infantile-onset Pompe disease

Classic infantile-onset disease generally presents during the first months of life. Severe generalized hypotonia, muscle weakness, feeding difficulties, respiratory impairment, and failure to thrive are typical manifestations. Cardiac disease is particularly prominent and may dominate the clinical presentation.^[3,4]

The characteristic cardiovascular phenotype includes severe hypertrophic cardiomyopathy, increased ventricular wall thickness, a relatively small left ventricular cavity, and diastolic dysfunction. In some patients, left ventricular outflow tract obstruction may contribute to hemodynamic compromise.^[15,16]

Electrocardiographic abnormalities may precede or accompany structural cardiac disease and include a short PR interval and increased QRS voltage.^[17]

3.2 Late-Onset Pompe Disease

Late-onset Pompe disease usually presents with progressive skeletal muscle weakness and respiratory muscle involvement. Cardiac involvement is substantially less frequent than in classic infantile disease. A systematic review of cardiovascular disease in non-classic Pompe disease concluded that cardiac involvement is rare compared with the marked cardiomyopathy of the classic infantile phenotype.^[5]

In a large clinical study of late-onset patients, cardiovascular abnormalities were generally mild. A short PR interval was observed in a minority of patients, while mild abnormalities of left ventricular systolic function or mass were uncommon. Significant

ventricular hypertrophy characteristic of infantile disease was not observed.^[6]

Studies using advanced echocardiographic and CMR techniques have similarly reported largely preserved cardiac structure and function in adults with Pompe disease, although small subsets may demonstrate subtle abnormalities.^[7,8]

Therefore, late-onset Pompe disease should not be regarded as a typical cause of hypertrophic cardiomyopathy. However, individualized cardiovascular assessment remains appropriate when clinical findings suggest possible myocardial involvement.

4. Why Should Cardiologists Recognize Pompe Disease?

Pompe disease may initially come to medical attention outside a neuromuscular clinic. The cardiologist may encounter a patient with ventricular hypertrophy, an unusual ECG phenotype, or unexplained cardiac remodeling before the underlying metabolic diagnosis is established.

Several clinical features should raise suspicion:

- unexplained ventricular hypertrophy, particularly when associated with systemic manifestations;
- severe hypertrophic cardiomyopathy in an infant;
- a short PR interval associated with high QRS voltage;
- skeletal muscle weakness disproportionate to cardiac findings;
- respiratory muscle weakness or unexplained respiratory insufficiency;
- elevated creatine kinase or other muscle enzymes;
- a family history suggestive of an inherited neuromuscular disorder;
- a multisystem phenotype without a clear acquired explanation.

The diagnostic approach should be particularly systematic in infants with hypertrophic cardiomyopathy and hypotonia. In adults with late onset disease, the cardiovascular phenotype is generally less specific and should be interpreted in the context of the neuromuscular presentation.^[1,5,6]

Recognition of Pompe disease is important because the diagnosis has therapeutic implications and because early treatment may substantially modify cardiac disease in the classic infantile phenotype.

5. Cardiovascular Manifestations

Cardiac involvement in Pompe disease can be divided into structural, functional, and electrical abnormalities.

5.1 Myocardial Hypertrophy

Marked ventricular hypertrophy is the characteristic cardiac manifestation of classic infantile Pompe disease. The hypertrophy reflects glycogen accumulation within cardiomyocytes and associated cellular remodeling.^[3,4]

The interventricular septum and left ventricular posterior wall may be substantially thickened, resulting in increased LV mass and reduced ventricular cavity size.

5.2 Diastolic Dysfunction

Severe myocardial hypertrophy and altered myocardial compliance can impair ventricular relaxation and filling. Diastolic dysfunction is therefore an important component of the infantile cardiac phenotype.

5.3 Systolic Dysfunction

Systolic function may initially remain preserved despite marked hypertrophy. With advanced disease, however, myocardial remodeling may lead to impaired ventricular systolic function.

5.4 Left Ventricular Outflow Tract Obstruction

Dynamic LV outflow tract obstruction has been described in severe infantile disease and may contribute to hemodynamic instability. Historical echocardiographic reports documented obstruction associated with marked myocardial hypertrophy.^[15,16]

5.5 Electrical abnormalities

Electrical manifestations include short PR intervals, high QRS voltage, ventricular hypertrophy patterns, repolarization abnormalities, conduction disturbances, and, less frequently, clinically significant arrhythmias.^[17]

6. Electrocardiographic Features

Electrocardiography is a simple and readily available component of cardiovascular assessment.

A characteristic finding in classic infantile Pompe disease is a disproportionately short PR interval associated with increased QRS voltage. These changes reflect alterations in myocardial structure and electrical conduction.^[17]

Other possible findings include

- high QRS voltage;
- electrocardiographic criteria for LV hypertrophy;
- repolarization abnormalities;
- conduction disturbances;
- rhythm abnormalities.

The ECG should not be interpreted in isolation. In particular, an abnormal ECG in an infant with

hypotonia and hypertrophic cardiomyopathy should prompt consideration of metabolic and lysosomal storage disorders.

In late-onset Pompe disease, ECG abnormalities are generally less pronounced. In the late-onset treatment study, a short PR interval was observed in approximately 10% of patients, while significant hypertrophy was not characteristic.^[6]

7. Echocardiographic Assessment

Echocardiography remains the cornerstone of initial cardiac assessment.

A comprehensive study should evaluate:

- interventricular septal thickness;
- left ventricular posterior wall thickness;
- LV end-diastolic and end-systolic dimensions;
- LV mass;
- LV systolic function;
- LV diastolic function;
- left atrial size;
- right ventricular structure and function;
- LV outflow tract gradients;
- valvular abnormalities;
- estimated pulmonary artery pressure when appropriate.

In classic infantile disease, severe concentric LV hypertrophy with a relatively small ventricular cavity is typical. Diastolic dysfunction may be prominent.

Serial echocardiography is particularly useful in treated patients because regression of myocardial hypertrophy can occur after initiation of ERT. Studies of infants receiving alglucosidase alfa have documented substantial cardiac remodeling and improvement in ventricular function.^[9–11]

In late-onset Pompe disease, conventional echocardiography is usually normal or shows only mild abnormalities. In the large late-onset treatment study, increased LV mass was observed in only a small proportion of patients and was generally mild.^[6]

8. Myocardial Strain Imaging

Speckle-tracking echocardiography and myocardial strain analysis may provide additional information regarding myocardial deformation.

In selected patients, strain abnormalities have been reported despite preserved conventional systolic function; however, available studies remain limited and heterogeneous. Strain imaging should therefore be regarded as a complementary technique rather than a validated standalone marker of early cardiac involvement in late-onset Pompe disease.^[7,8]

Global longitudinal strain may provide a more sensitive assessment of myocardial mechanics than conventional ejection fraction in selected settings. Nevertheless, the currently available Pompe disease literature does not support the use of strain imaging as an isolated diagnostic criterion.

Its principal value is therefore complementary, particularly when conventional echocardiographic measurements are inconclusive or when longitudinal assessment of myocardial function is desired.

9. Cardiac Magnetic Resonance

Cardiac magnetic resonance provides accurate and reproducible assessment of ventricular volumes, wall thickness, ventricular mass, and systolic function. It also offers additional tissue characterization capabilities.

Potential CMR parameters include:

- LV and RV volumes;
- LV mass;
- LV and RV ejection fraction;
- myocardial wall thickness;
- late gadolinium enhancement (LGE);
- T1 and T2 mapping;
- extracellular volume fraction (ECV), where available.

In late-onset Pompe disease, CMR studies have generally demonstrated preserved ventricular volumes and systolic function. Nevertheless, a minority of patients may show nonspecific tissue abnormalities, including LGE or elevated ECV.^[8]

A recent systematic review of CMR in Pompe disease identified only a limited number of studies and emphasized substantial heterogeneity in methodology and patient populations. Available data include conventional CMR, LGE, T1/T2 mapping, ECV assessment, and treatment-related imaging studies, but evidence remains insufficient to define a standardized CMR phenotype for all patients with Pompe disease.^[18]

Consequently, CMR should be considered a complementary investigation, particularly when echocardiographic findings are uncertain or when tissue characterization is clinically relevant.

10. When Should Pompe Disease Be Suspected in Cardiology?

The cardiologist should consider Pompe disease when the cardiac phenotype is accompanied by neuromuscular or respiratory features that are difficult to explain by conventional cardiac diagnoses.

Important clinical clues

Cardiac phenotype

- Unexplained hypertrophy
- Small LV cavity
- Diastolic dysfunction
- Unusual ECG abnormalities

Neuromuscular phenotype

- Proximal weakness
- Difficulty climbing stairs
- Difficulty rising from a chair
- Axial weakness
- Progressive exercise intolerance

Respiratory phenotype

- Nocturnal hypoventilation
- Respiratory muscle weakness
- Unexplained restrictive respiratory dysfunction

Laboratory clues

- Elevated CK
- Elevated transaminases of muscular origin
- Other biochemical evidence of muscle injury

When several of these features coexist, a lysosomal storage disorder should be considered.

Importantly, the presence of LV hypertrophy alone is insufficient to diagnose Pompe disease. Differential diagnoses include sarcomeric hypertrophic cardiomyopathy, Fabry disease, Danon disease, mitochondrial disorders, and other metabolic or storage diseases.

11. Biochemical and Genetic Diagnosis

The diagnosis of Pompe disease is based on demonstration of deficient GAA enzyme activity and confirmation of pathogenic variants in the **GAA** gene.

GAA activity can be measured using dried blood spots, leukocytes, or cultured fibroblasts. Dried blood spot testing is particularly useful as an initial screening or diagnostic test because it is minimally invasive and widely accessible.^[19]

However, pseudodeficiency alleles can complicate interpretation, particularly in some populations. Confirmatory testing is therefore important when enzyme activity is reduced or borderline.^[19,20]

Molecular analysis of the **GAA** gene provides confirmation of the diagnosis and assists with genotype characterization. Modern diagnostic strategies increasingly combine enzymatic testing with molecular approaches.^[20]

The diagnostic sequence can therefore be summarized as

Clinical suspicion → GAA enzyme activity → confirmatory biochemical testing when required → GAA gene sequencing → molecular confirmation.

In newborn screening programs, dried blood spot GAA activity is commonly used as the first step, followed by confirmatory biochemical and molecular testing.^[20,21]

12. Cardiovascular Monitoring

Cardiovascular monitoring should be adapted to the disease phenotype, age, clinical status, and treatment. In classic infantile disease, cardiac evaluation should be performed promptly because severe myocardial hypertrophy can be present at diagnosis.

Monitoring should include

- clinical assessment;
- ECG;
- echocardiography;
- assessment of LV systolic and diastolic function;
- assessment of LV mass and wall thickness;
- evaluation for LV outflow tract obstruction;
- rhythm monitoring when clinically indicated.

In late-onset disease, routine cardiovascular assessment should be individualized according to symptoms, clinical phenotype, baseline findings, and comorbid cardiovascular disease.

When abnormalities are detected or when clinical suspicion remains high, advanced imaging such as strain echocardiography or CMR may be considered.

Longitudinal assessment is particularly important in patients receiving ERT because cardiac remodeling may occur over time.

13. Enzyme Replacement Therapy and Cardiac Remodeling

ERT has transformed the prognosis of classic infantile Pompe disease.

Alglucosidase alfa provides recombinant human acid α -glucosidase and aims to restore lysosomal glycogen degradation. In infantile disease, treatment is associated with substantial regression of myocardial hypertrophy and improvement in cardiac function.^[9–12]

Early treatment is particularly important. Studies have demonstrated that early initiation of alglucosidase alfa is associated with improved long-term survival and favorable cardiac outcomes.^[10–12]

Cardiac remodeling may include

- reduction in interventricular septal thickness;
- reduction in LV posterior wall thickness;
- reduction in LV mass;
- enlargement toward a more normal ventricular geometry;
- improvement in ventricular function.

The response to ERT is not necessarily uniform. Factors such as age at treatment initiation, disease severity, genotype, residual enzyme activity, immune response, and CRIM status can influence outcomes.^[12,22]

In late-onset Pompe disease, randomized trials have demonstrated benefits of ERT on selected functional outcomes, but major cardiac remodeling is much less prominent because clinically significant cardiomyopathy is uncommon in this phenotype.^[6,23]

14. Emerging Therapeutic Perspectives

The therapeutic landscape of Pompe disease continues to evolve.

New-generation ERTs have been developed with the objective of improving enzyme delivery and tissue uptake. Avalglucosidase alfa has demonstrated clinical efficacy in late-onset Pompe disease and is now incorporated into therapeutic strategies in several settings.^[24]

Other approaches under investigation include

- next-generation enzyme replacement;
- enzyme modification to enhance lysosomal targeting;
- substrate reduction therapy;
- gene therapy;
- combination therapeutic approaches.

The 2024 European Pompe Consortium recommendations provide updated criteria for starting, switching, and stopping ERT in late-onset disease. The recommendations emphasize clinical symptoms, functional trajectory, treatment response, and individualized shared decision-making.^[25]

Step 1 — Identify the cardiac phenotype

Unexplained ventricular hypertrophy / unusual ECG / unexplained cardiac remodeling



Step 2 — Search for systemic clues

- Skeletal muscle weakness
- Respiratory muscle involvement
 - Exercise intolerance
 - Family history
 - Elevated CK
- Childhood hypotonia or developmental motor difficulties



Step 3 — Perform cardiovascular assessment

These developments may eventually modify the long-term cardiovascular implications of Pompe disease, particularly if earlier diagnosis and more effective systemic enzyme delivery become possible.

15. Long-Term Cardiovascular Follow-Up

Long-term cardiovascular follow-up should focus not only on the presence or absence of hypertrophy but also on changes in ventricular geometry and function over time.

Important parameters include:

- LV wall thickness;
- LV mass;
- LV volumes;
- systolic function;
- diastolic function;
- left atrial size;
- ECG abnormalities;
- rhythm disturbances;
- LV outflow tract gradients when relevant;
- CMR tissue characteristics in selected patients.

The intensity of follow-up should be individualized.

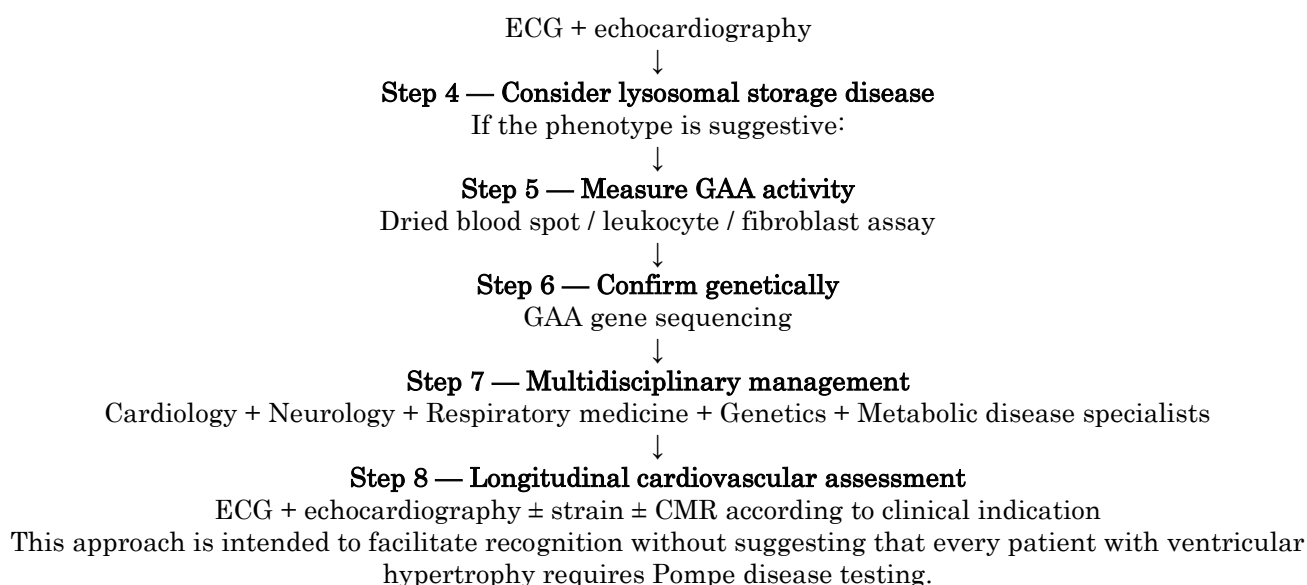
In classic infantile disease, close monitoring is necessary, particularly during the early phase of treatment when substantial reverse remodeling may occur.

In late-onset disease, the cardiovascular follow-up should be driven by the clinical phenotype and baseline cardiovascular findings rather than by the assumption that all patients have clinically significant cardiomyopathy.

A multidisciplinary approach involving cardiology, neurology, respiratory medicine, genetics, metabolic specialists, physiotherapy, and other relevant disciplines is appropriate.

16. Practical Cardiovascular Algorithm

The following algorithm may assist cardiologists confronted with an unexplained cardiac phenotype.



17. Key Messages for Cardiologists

1. Pompe disease is a lysosomal glycogen storage disorder caused by deficient acid α -glucosidase activity.
2. Severe cardiac involvement is a hallmark of classic infantile-onset Pompe disease.
3. Marked myocardial hypertrophy, small LV cavity, diastolic dysfunction, and characteristic ECG abnormalities should raise suspicion in an infant with hypotonia or generalized weakness.
4. Clinically significant cardiac involvement is uncommon in late-onset Pompe disease, although subtle abnormalities may be detected in selected patients.
5. ECG and echocardiography remain the first-line cardiovascular investigations.
6. Strain imaging and CMR provide complementary information but should not currently be regarded as standalone diagnostic tests for cardiac involvement in Pompe disease.
7. The diagnosis requires demonstration of deficient GAA activity and confirmation by molecular testing when appropriate.
8. Early ERT can lead to major regression of myocardial hypertrophy and favorable cardiac remodeling in classic infantile disease.
9. Cardiovascular follow-up should be individualized according to phenotype, age, treatment, and baseline cardiac findings.
Close collaboration between cardiologists and neuromuscular/metabolic specialists is essential.

CONCLUSION

Cardiac involvement in Pompe disease is strongly influenced by the clinical phenotype and age at disease onset. In classic infantile-onset disease, myocardial hypertrophy and ventricular dysfunction represent major components of the clinical phenotype and contribute substantially to morbidity and

mortality. In contrast, clinically significant cardiac disease is uncommon in late-onset Pompe disease, although subtle abnormalities may occasionally be detected using sensitive imaging techniques.

Electrocardiography and echocardiography remain the foundation of cardiovascular assessment. Speckle tracking echocardiography and CMR may provide additional information in selected patients, particularly when conventional imaging is inconclusive. Current evidence supports a complementary rather than universal role for advanced cardiac imaging.

The introduction of ERT has profoundly changed the prognosis of classic infantile Pompe disease, particularly when treatment is initiated early. Regression of myocardial hypertrophy and improvement in cardiac function demonstrate the potential reversibility of glycogen-mediated myocardial injury.

For the cardiologist, recognizing the association between an unusual cardiac phenotype and neuromuscular or respiratory manifestations is essential. A structured diagnostic pathway combining clinical assessment, GAA enzyme testing, genetic confirmation, and multidisciplinary follow-up can facilitate timely diagnosis and appropriate treatment.

Future developments in enzyme delivery, gene therapy, substrate reduction, and combination strategies may further modify the natural history of Pompe disease. Continued cardiovascular characterization will be important to define the role of advanced imaging and to optimize long-term cardiac surveillance across the disease spectrum.

Conflict of interest: None declared.

Table 1: Cardiovascular manifestations across the clinical spectrum of Pompe disease.

Feature	Classic infantile-onset disease	Late-onset disease
Myocardial hypertrophy	Marked and characteristic	Uncommon
LV cavity	Often small	Usually preserved
LV mass	Markedly increased	Usually normal or mildly increased
Diastolic dysfunction	Common	Usually absent or mild
Systolic dysfunction	May occur in advanced disease	Uncommon
LV outflow tract obstruction	Reported	Rare
Short PR interval	Characteristic	May occur
High QRS voltage	Common	Less prominent
Conduction abnormalities	Possible	Occasional
Clinically significant arrhythmias	Possible	Uncommon
CMR abnormalities	Variable	Usually subtle and uncommon
Major cardiac response to ERT	Well documented	Less prominent

Table 2: Recommended Cardiovascular Assessment in Pompe Disease.

Assessment	Main objective	Suggested role
Clinical examination	Identify cardiac and systemic manifestations	All patients
ECG	Detect conduction and repolarization abnormalities	Baseline and follow-up
Echocardiography	Assess structure and function	First-line cardiac imaging
Doppler assessment	Evaluate filling and outflow obstruction	When indicated
Speckle-tracking strain	Assess myocardial deformation	Selected patients
Cardiac MRI	Volumes, mass, function, tissue characterization	Selected patients
Holter monitoring	Detect clinically relevant arrhythmias	Symptomatic/selected patients
Serial assessment	Monitor remodeling and treatment response	According to phenotype

Table 3: Clinical clues Suggesting Pompe Disease in Cardiology.

Domain	Findings that may raise suspicion
Cardiac	Unexplained hypertrophy, small LV cavity, diastolic dysfunction
ECG	Short PR, high QRS voltage, conduction abnormalities
Skeletal muscle	Proximal weakness, axial weakness, exercise intolerance
Respiratory	Respiratory muscle weakness, restrictive dysfunction
Laboratory	Elevated CK or muscle enzymes
Family history	Inherited neuromuscular phenotype
Pediatric presentation	Hypotonia + hypertrophic cardiomyopathy
Multisystem presentation	Cardiac + skeletal/respiratory involvement

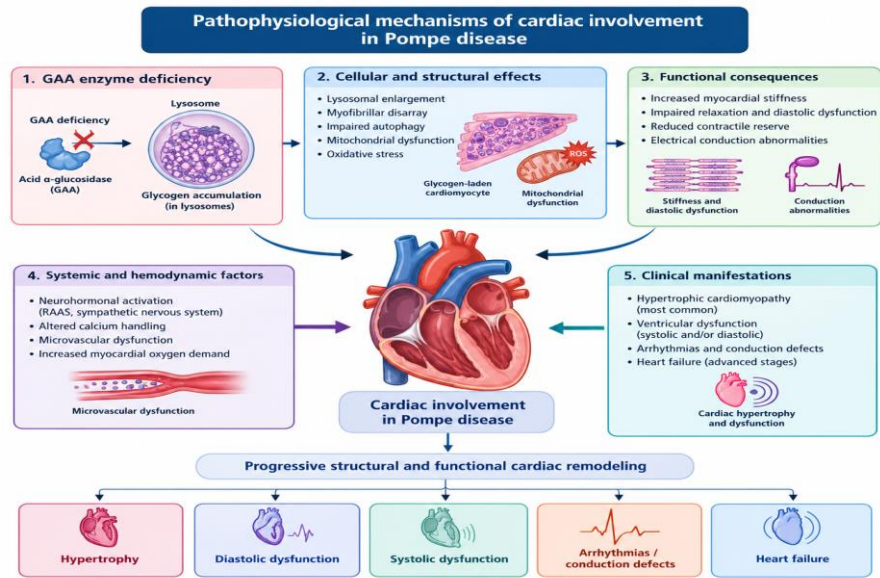


Figure 1. Pathophysiological Mechanisms of Cardiac Involvement in Pompe Disease.

Deficient lysosomal acid α -glucosidase activity results in impaired glycogen degradation and progressive glycogen accumulation within cardiomyocytes. Lysosomal enlargement, cellular disorganization, altered autophagy, and disruption of the contractile machinery contribute to myocardial hypertrophy and

remodeling. These abnormalities may lead to diastolic dysfunction and, in advanced disease, systolic impairment. Electrical consequences may include a short PR interval, increased QRS voltage, conduction abnormalities, and arrhythmias.

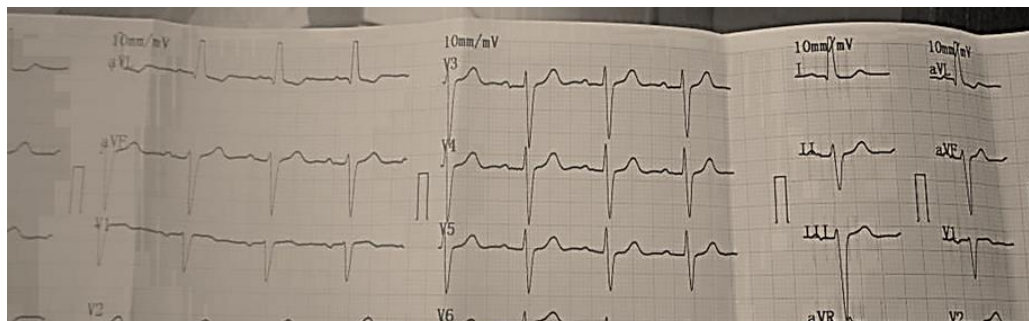


Figure 2: Electrocardiographic features may include a short PR interval, increased QRS voltage, a left ventricular hypertrophy pattern, repolarization abnormalities, and conduction disturbances as shown in the figure above.

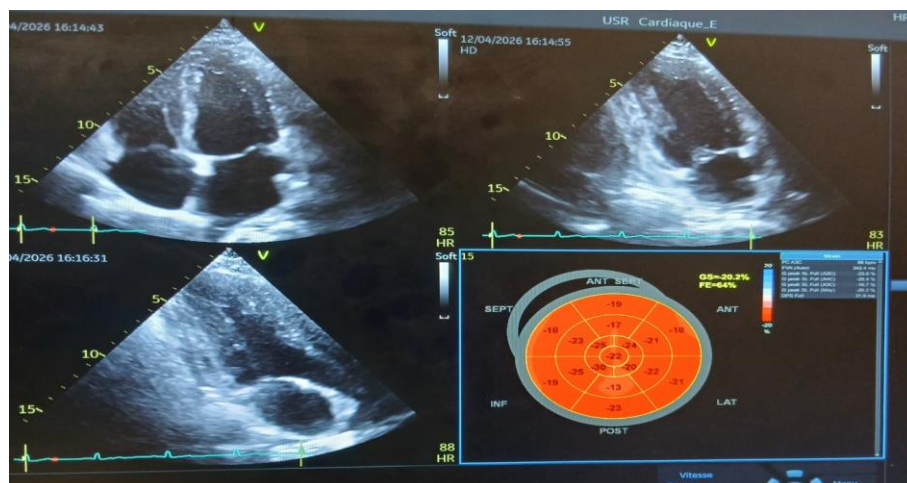


Figure 1. A 20-year-old patient presents with left ventricular hypertrophy with preserved GLS. MRI showed fatty infiltration with a decrease in muscle mass. The enzyme assay is consistent with Pompe disease.

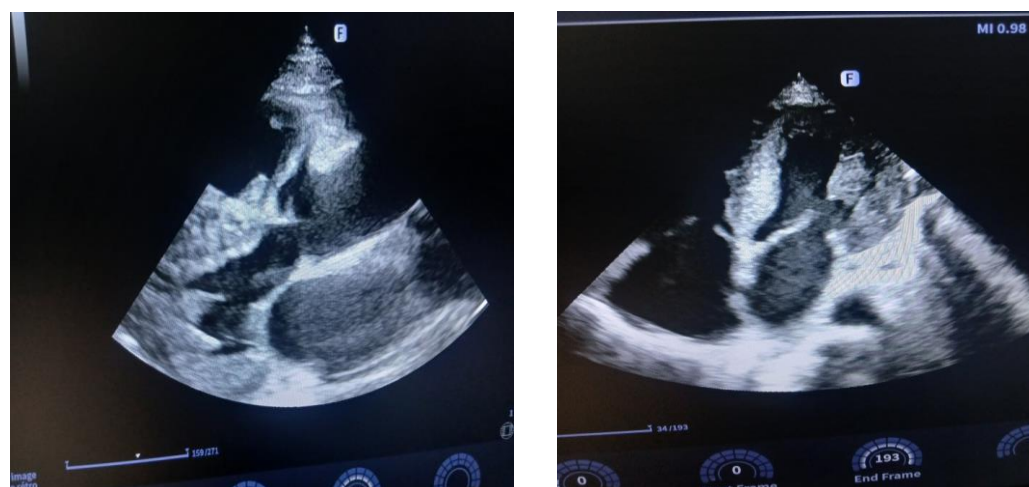


Figure 3. Echocardiographic manifestations may include increased ventricular wall thickness, increased left ventricular mass, a relatively small left ventricular cavity, diastolic dysfunction, and, in selected patients with severe hypertrophy, left ventricular outflow tract obstruction.

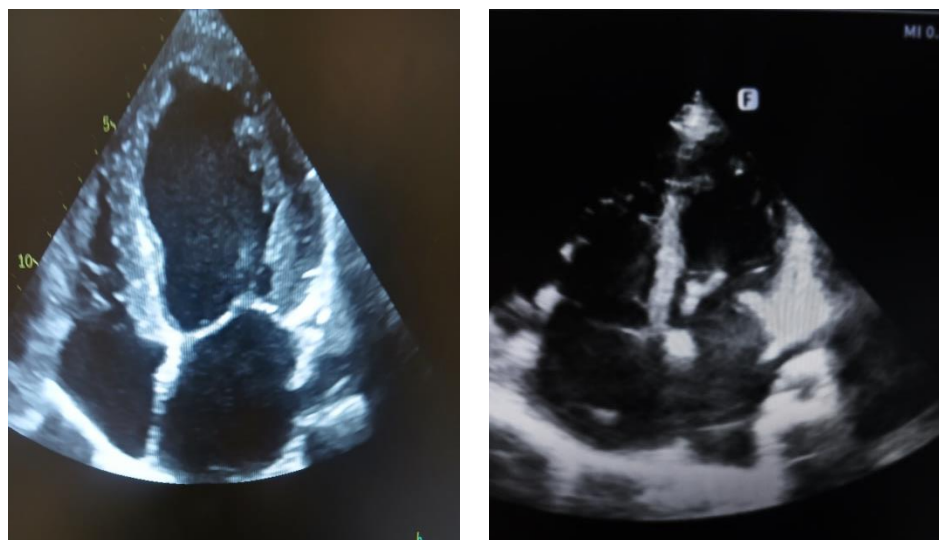


Figure 4. Cardiovascular impact of enzyme replacement therapy in Pompe disease.

Restoration of lysosomal enzyme activity promotes glycogen clearance and may result in regression of myocardial hypertrophy and favorable cardiac remodeling, particularly when treatment is initiated early in classic infantile-onset disease. The magnitude of cardiac response may depend on disease phenotype, age at treatment initiation, disease burden, immune factors, and treatment duration.

Abbreviations

CMR: cardiac magnetic resonance
CRIM: cross-reactive immunologic material
ECG: electrocardiography/electrocardiogram
ECV: extracellular volume
ERT: enzyme replacement therapy
GAA: acid α -glucosidase gene/protein
LGE: late gadolinium enhancement
LOPD: late-onset Pompe disease
LV: left ventricle/left ventricular
LVH: left ventricular hypertrophy
NBS: newborn screening
PD: Pompe disease
RV: right ventricle/right ventricular

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