

Age-related changes in cardiomyopathic phenotype in patients with Barth syndrome

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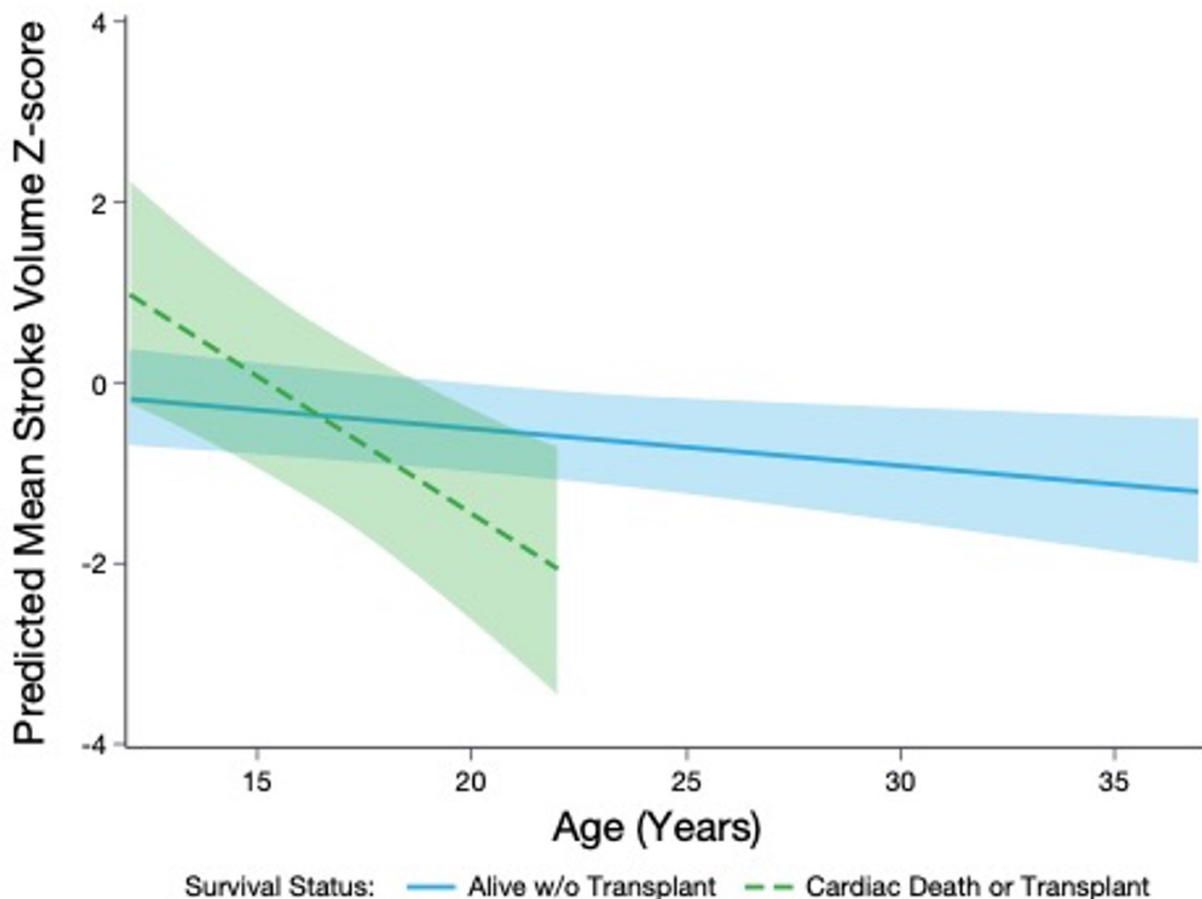


Figure 1. Left ventricular stroke volume relationship to morbidity and mortality in patients ≥ 12 -years-old

With current treatment options for BTHS cardiomyopathic phenotype focused predominantly on alleviating symptoms, Dr Hani N. Sabbah, Director of Cardiovascular Research at Henry Ford Health, explores the potential of more targeted treatment approaches

Barth syndrome (BTHS) is a rare, X-linked disease caused by defects in the TFAZZIN gene encoding an acyltransferase responsible for the remodeling/maturation of cardiolipin (critical to mitochondrial structure/function).⁽¹⁾ The most common clinical manifestation of BTHS is cardiomyopathy (~90% of BTHS patients) with a wide range of phenotypical presentations.^(2,3) Mechanisms contributing to BTHS cardiomyopathy pathophysiology include abnormal mitochondrial structure/function,⁽⁴⁾ defective mitochondrial calcium

uptake,⁽⁵⁾ a mismatch between ATP supply and demand,⁽⁶⁾ and altered lipid/glucose metabolism.⁽⁷⁾ The BTHS cardiomyopathic phenotypes appear to evolve with advancing age, which may be useful in treatment selection.

Natural history of BTHS cardiomyopathy

BTHS cardiomyopathic phenotypes include dilated cardiomyopathy (DCM), left ventricular (LV) noncompaction (LVNC), endocardial fibroelastosis, and hypertrophic cardiomyopathy (HCM). Presenting in infancy, DCM is characterized by decreased LV systolic function and increased LV mass, LV end-diastolic dimension (LVEDD), and LV end-systolic dimension (LVESD).^(3,8,9) Similarly, a French study (N=22 BTHS patients) showed LV chamber size, LV mass, and LVEDD were increased, and LV ejection fraction (LVEF) was decreased during the first six months of life.⁽¹⁰⁾

In contrast, HCM is typically observed in adolescent/adult patients with BTHS and is characterized by thickened, stiff cardiac walls that prevent proper myocardial relaxation, resulting in reduced LV filling and stroke volume (LVSV),⁽²⁾ a phenotype similar to heart failure with preserved ejection fraction (HFpEF). Consistent with the HCM phenotype and indicative of impaired LV diastolic function, negative LVSV z-scores were observed in patients 12 years of age and older in a subgroup analysis from a recently published cardiac natural history (NH) study in BTHS patients (Figure 1).⁽¹¹⁾

Furthermore, a gradual decline in LVSV, and therefore in cardiac output, has been demonstrated in NH cohorts.⁽¹²⁾ With findings suggesting an evolving cardiomyopathic phenotype, a recent longitudinal study in BTHS demonstrated: significant worsening of septal E:e'; LV global longitudinal strain and right ventricular fractional area of change; reduction in LV size/LVSV; and no change in LVEF over time.⁽¹³⁾

Echocardiography in BTHS consistently demonstrates that LV shortening fraction and LVEF are only mildly abnormal outside of infancy.⁽¹⁴⁾ These findings support a temporal evolution of the cardiomyopathic phenotype in BTHS patients with advancing age from a DCM during infancy to one consistent with an HCM resembling HFpEF.

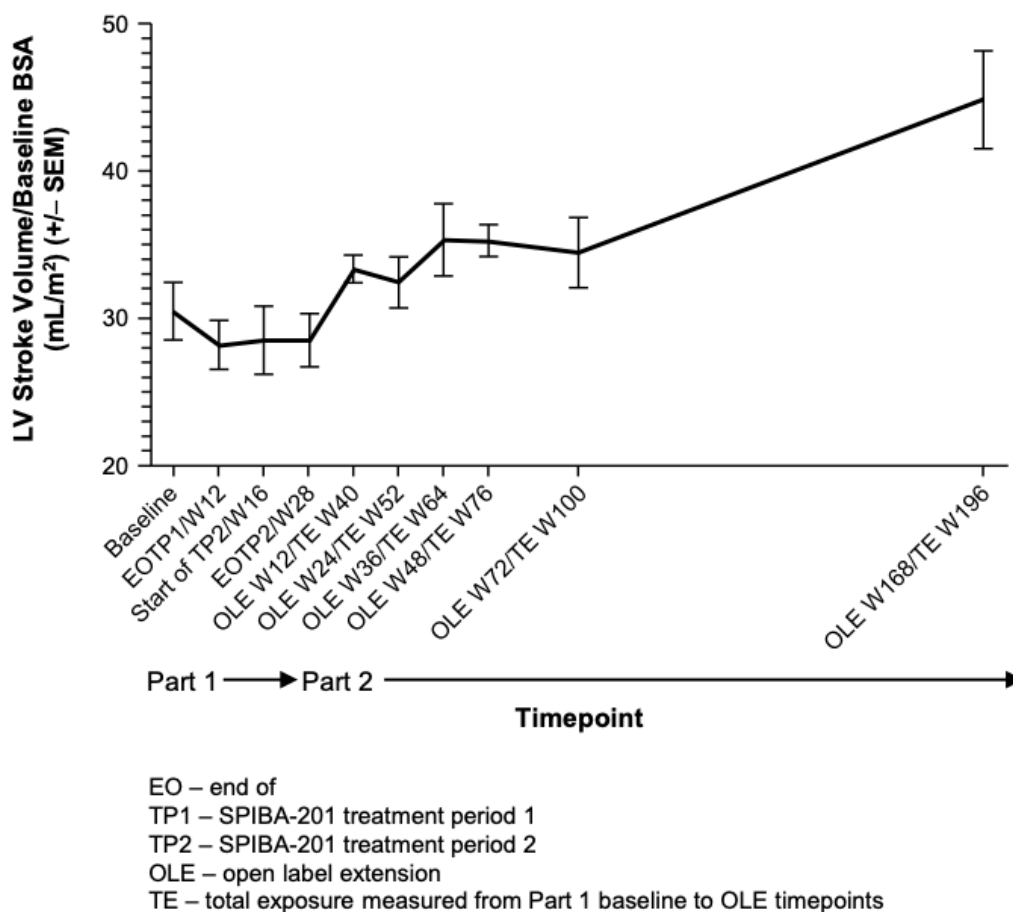


Figure 2. Mean left ventricular stroke volume indexed to the baseline body surface area in the TAZPOWER trial and open label extension

Therapeutic approach to cardiomyopathy in BTHS patients

The current approach to treating BTHS cardiomyopathy is primarily directed at alleviating symptoms, not targeting the underlying disease pathophysiology. Given the age-related-changing phenotype, a more logical therapeutic approach in BTHS adolescents/adults would be to treat as if the phenotype were that of HFpEF, focusing on improving LV relaxation and filling. The reduced LV volume and ensuing inadequate LV filling observed in HCM and HFpEF leads to decreased LVSV, an integral component of overall cardiac performance.⁽²⁾ In the HFpEF phenotype, the LV must expand through improved LV relaxation to allow for adequate LV filling in order to increase LVSV.

Therefore, increased LV volumes and LVSV are appropriate goals for treating HCM of BTHS. In preclinical and clinical studies in heart failure (HF) and BTHS models, the mitochondria-targeting peptide, elamipretide, increases LVSV, LVEDV, and LVESV, making it a promising treatment option for HCM in BTHS.⁽²⁾ Elamipretide readily penetrates and transiently localizes to the inner mitochondrial membrane (IMM), where it interacts with cardiolipin to improve IMM stability, enhance ATP synthesis, and reduce reactive oxygen species (ROS) production.⁽¹⁵⁻²¹⁾ Cardiolipin is a logical therapeutic target because the primary defect underlying BTHS is altered cardiolipin content. Elamipretide is

well-suited for BTHS because it interacts with the membrane bilayer, independent of the cardiolipin side chain composition, and interacts with accumulated monolysocardiolipin in a similar ratio.⁽²¹⁾

TAZPOWER phase 2 clinical trial

TAZPOWER evaluated the efficacy/safety of 12-week treatment with daily subcutaneous elamipretide in BTHS patients 12 years of age and older, followed by a 168-week open label extension (OLE) on elamipretide.⁽²²⁾ Similar to NH and longitudinal studies, the observed cardiac phenotype demonstrated poor LV active and passive filling, leading to reduced LVSV; small LVED and LVES volumes (both below the eighth percentile z-scores); low cardiac index (mean 2.3); and normal LVEF, all resembling the HFpEF type of LV failure.⁽²⁾

During the OLE portion, significant improvements in functional and cardiac outcomes were observed after elamipretide compared to baseline.⁽²²⁾ Elamipretide treatment resulted in a 16% improvement (30.5mL/m² to 35.3mL/m²) and >45% improvement (mean 14.4mL; p=0.007) in LVSV indexed to body surface area (BSA) at 36 weeks and 168 weeks, respectively (Figure 2).⁽²²⁾ Significant improvements in LVED and LVES volumes indexed to baseline BSA were seen at all OLE time points.

Comparing TAZPOWER and OLE elamipretide-treated subjects, and a NH-study cohort of BTHS patients, it was demonstrated that the LVSV index increased significantly in elamipretide-treated patients versus NH controls.⁽¹²⁾ Collectively, the TAZPOWER results support that long-term treatment with elamipretide may improve overall cardiac function, quality of life, and the long-term disease trajectory of BTHS.

Conclusions and future considerations

NH and longitudinal studies suggest the cardiomyopathic phenotype in BTHS transforms from DCM with reduced LVEF in infancy to HCM with preserved LVEF, similar to HFpEF, in adolescence and adulthood.^(12,13,25) Treatment strategies and agents that improve LV relaxation, such as elamipretide, may be beneficial for use in adolescent and adult patients with BTHS considering the unique HCM phenotype. Understanding the temporal change in HF phenotypes in BTHS will enable the use of targeted treatments at the appropriate stages of the disease to improve cardiac performance and quality of life while preventing, or at the very least, retarding progression of the disease toward intractable end HF.

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