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CLINICAL RESEARCH

Alterations in Titin Properties and Myocardial Fibrosis Correlate With Clinical Phenotypes in Hemodynamic Subgroups of Severe Aortic Stenosis

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CME/MOC Objective for This Article: Upon completion of this paper, the reader should be able to: 1) understand the different patterns of myocardial fibrosis and the degree of isoform-expression and phosphorylation changes in cardiomyocyte titin in the different hemodynamic subgroups of aortic stenosis; 2) examine the extent of myocardial remodeling in paradoxical aortic stenosis to help better understand the poor prognosis of these patients; and 3) review the current guidelines and management of severe aortic stenosis, including evaluation focused on hemodynamic subtypes.

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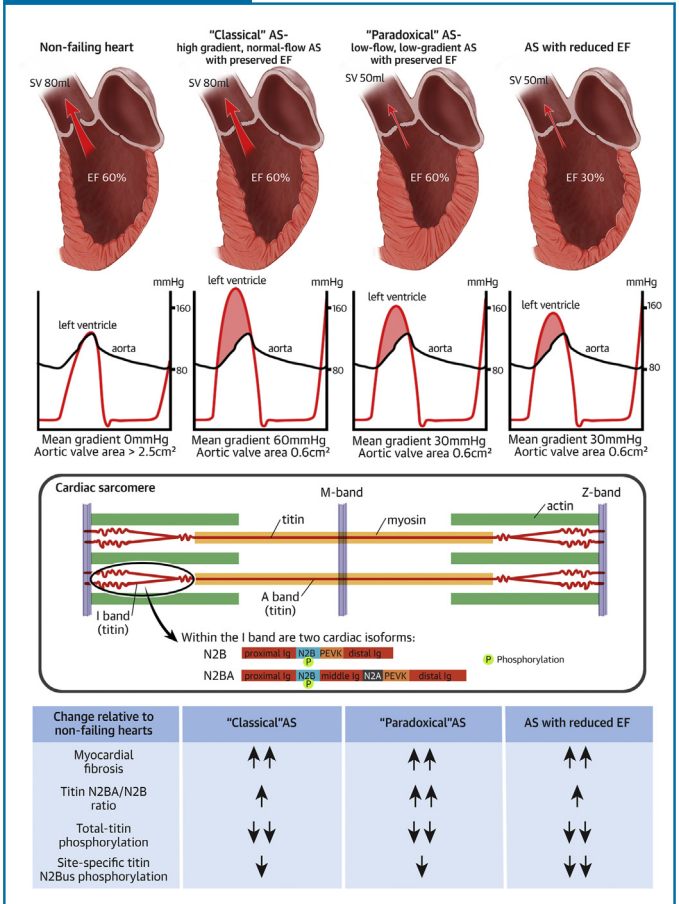
VISUAL ABSTRACT



Change relative to non-failing hearts	"Classical"AS	"Paradoxical"AS	AS with reduced EF
Myocardial fibrosis	↑↑	↑↑	↑↑
Titin N2BA/N2B ratio	↑	↑↑	↑
Total-titin phosphorylation	↓↓	↓↓	↓↓
Site-specific titin N2Bus phosphorylation	↓	↓	↓↓

Gotzmann, M. et al. J Am Coll Cardiol Basic Trans Science. 2018;3(3):335–46.

HIGHLIGHTS

- **The extent of myocardial fibrosis and the degree of isoform-expression and phosphorylation changes in cardiomyocyte titin were unknown in different hemodynamic subgroups of AS, including "paradoxical" low-flow, low-gradient AS with preserved ejection fraction.**
- **Hemodynamic subtypes of AS were found to exhibit increased cardiac fibrosis, titin-isoform transition toward more compliant N2BA variants, and both total and site-specific titin (N2Bus) hypophosphorylation compared with donor heart controls.**
- **A significant shift toward N2BA titin appeared in "paradoxical" AS, whereas alterations in total-titin phosphorylation and cardiac fibrosis were similar in all hemodynamic subtypes of AS, suggesting increased myocardial passive stiffness.**
- **The unfavorable prognosis of "paradoxical" AS could be explained by the pronounced myocardial remodeling, which is no less severe than in other AS subtypes.**

Institute for Clinical Sciences, Biomedical Sciences Institutes, Application Number 201208940-5, WIPO number WO/2014/088516). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.
All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Basic to Translational Science* author instructions page.

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