Myocardial work index and myofilament calcium sensitivity: possible hand in hand markers of contractility in aortic valve stenosis patients - a translational study

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Background: In aortic valve stenosis, conventional echocardiographic parameters, such as ejection fraction (EF), are heavily influenced by the increased afterload caused by the valvular disease. Myocardial work index (GWI) quantifies myocardial deformation depending on the momentary LV pressure, potentially serving as a marker of LV contractility independent of loading conditions. Similarly, myofilament Ca2+ sensitivity (pCa50) followed the alterations of LV contractility in a rat model of pressure overload-induced heart failure. Therefore, GWI and pCa50 may also show correlation, as both can be reliable measures of contractility in diseases of chronically elevated LV afterload.

Purpose: Accordingly, our first aim was to assess the association of pCa50 and GWI in a rat model of pressure overload-induced heart failure and sham operated animals. We also aimed to evaluate the changes in GWI after myocardial Ca2+ sensitizing with levosimendan in aortic valve stenosis patients.

Methods: Firstly, on the thoracic aortic banded (n=2) and sham operated (n=3) rats speckle-tracking echocardiography and invasive LV pressure measurements were performed to calculate GWI. Using single permeabilized cardiomyocytes, pCa50 was calculated by myofilament force measurement. Secondly, to test our hypothesis in a clinical setting, 23 severe aortic valve stenosis patients (age 76±9 years, 39% female) were enrolled who received levosimendan therapy. Conventional and advanced echocardiographic measurements were performed before and after a 24-hour intravenous loading dose. We determined global longitudinal strain by speckle-tracking echocardiography, then using LV pressure curves estimated from systolic blood pressure and mean transaortic gradient, we quantified non-invasive global myocardial work index (GWI).

Results: In the animal study, GWI and pCa50 strongly correlated in the rats (r=0.942; p=0.017). In the clinical study, patients with a baseline EF <35% (n=12) had significantly increased GWI after the levosimendan therapy (533±347 vs. 660±419 mmHg%; p=0.004), while those who initially had an EF >35% (n=11) did not show any change (998±342 vs. 1003±275 mmHg%; p=0.788). Also, the pre-levosimendan GWI showed a strong inverse correlation with the relative GWI change after the loading dose (r=-0.708; p=0.003).

Conclusions: We showed in an experimental setting, that GWI and pCa50 correlated in a rat model of pressure overload-induced heart failure and in sham operated controls. In the clinical setting, patients with severely decreased baseline EF and GWI benefited more from the Ca2+ sensitizing therapy, having better LV function after it, while those with better baseline function did not show improvement. Therefore, patients with worse baseline GWI initially might have had decreased Ca2+ sensitivity, which implies a possible correlation between GWI and pCa50 in patients with aortic valve stenosis, resembling the experimental findings.
Correlation of myofilament calcium sensitivity and global myocardial work index in the rat model of pressure overload-induced heart failure and sham operated animals

Correlation of pCa50 - GWI

Correlation of the baseline global myocardial work index and its relative change after the calcium sensitizing therapy in the severe aortic valve stenosis patients

Correlation of GWI - relative GWI change