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Why aortic valve disease may persist after surgery? A joint basic science - Clinical effort

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Background: Diseases of the aortic valve are a common reason for heart surgery. Aortic stenosis (AS) is associated with pressure and aortic regurgitation (AR) with a volume overload of the left ventricle (LV). Over time both pathologies lead to systolic and diastolic heart failure, while progressive downregulation of β-adrenoceptors occurs. While LV re-remodeling occurs in the majority of patients after aortic valve surgery, LV dysfunction persists in one fourth of such patients and leads to a terminal heart failure. We aimed to investigate whether differential remodeling in the protein kinase A (PKA) dependent inotropic response in myocytes and myocardial tissue obtained from patients undergoing aortic valve surgery is associated with the LV re-remodeling after surgery.

Methods: Preoperatively, pro BNP levels were measured and left ventricular strain analysis via echocardiography was performed. Interventricular septal biopsy was obtained intraoperatively in 10 patients who underwent aortic valve surgery. In-vitro contractility was analyzed in myocardial tissue paced with 4 Hz at 37 ℃. Freshly isolated cells were transduced with an adenovirus expressing a cytosolic Förster resonance energy transfer (FRET) based cAMP biosensor (Epac1-camps). After 48 hours of culture, Föster-resonance energy transfer (FRET) was used for the first time to measure cAMP in 60 isolated human ventricular myocytes. Isoprenaline (10 nM – 10 μM) was used for β-adrenoceptor activation and forskolin (10 μmol) to activate adenylyl cyclase directly.

Results: We found a significantly downregulated β-adrenergic sensitivity in cardiomyocytes of patients with aortic valve disease, although contractile response to forskolin was maintained. Furthermore, we found a clear association between reduced sensitivity to isoprenaline (i.e., high EC50 values) and low maximum effect size to isoprenaline in myocardial tissue of patients with aortic valve disease, pointing out relevant β-adrenoceptor dysfunction. There were no significant differences in basal myocardial force between tissue samples of patients with AR and AS.

Conclusion: Collectively, our data show a profound remodelling in the cAMP/PKA pathway in patients with aortic valve disease. These disturbances may have an impact on the postoperative ventricular function and possibly on the long-term LV re-remodelling after aortic valve surgery.