Role of cytokines of the TGF beta family in the atrial structural remodelling underlying atrial fibrillation in aortic stenosis patients

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Background
Studies on patients and animal models suggest the importance of atrial structural remodelling and fibrosis in the development of atrial fibrillation (AF). The auto-paracrine action of transforming growth factor-βs (TGFβs) on myocardial cells has been suggested to play a role in this process. The TGFβ superfamily of cytokines is composed, among others, of the profibrotic TGFβ and anti-fibrotic bone morphogenetic protein-7 (BMP-7). The role of micro-RNAs (miR) regulated by the TGFβ family in cardiac pathologies, including fibrosis, has been recently recognized.

Purpose
To demonstrate that AF under pressure overload is associated with atrial wall disequilibrium in TGFβ-1/BMP-7-mediated signalling and fibrosis-regulatory miRNAs.

Methods
Patients with aortic stenosis (AS) and AF (n=23) were matched with patients on sinus rhythm (n=23) according to age, gender and left ventricular ejection fraction. Right atrium biopsies were analysed by qPCR and in situ hybridization.

A cohort of patients who underwent cardiac surgery because of non-pressure overload cardiopathies was selected to validate the specificity of our findings.

Results
TGF-β1, COL1A1, COL3A1, FN-1 and lysyl oxidase (LOX) were up-regulated in right atrial wall of AF patients with AS. TGF-β1 positively correlated with COL1A1, COL3A1, FN-1 and LOX. On the other hand, BMP-7 mRNA expression was down-regulated. miR-1, miR-133a, miR-133b and miR-29 expressions were significantly reduced. These changes were not observed in AF patients with non-pressure overload cardiopathies.

Conclusions
The unbalance between pro-fibrotic TGFβ1 and anti-fibrotic BMP-7 facilitates pathological structural remodelling and AF development in AS patients. The increased pro-fibrotic transcriptional activity due to up-
regulation of TGFβ1 expression was related to down-regulation of anti-fibrotic miRNAs (miR-1, miR-133 and miR-29).