Valvular and Myocardial Fibroblast Activation in Aortic Stenosis
A Prospective Positron Emission Tomography Study

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Activated fibroblasts drive leaflet thickening and left ventricular decompensation in aortic stenosis. Gallium-68 Fibroblast Activation Protein Inhibitor (^{68}Ga-FAPI) binds to these key effector cells, and provides a readout of fibroblast activation. We aimed to describe the role of activated fibroblasts in patients with aortic stenosis *in vivo* using ^{68}Ga-FAPI.

In a prospective observational study, patients with aortic stenosis and control subjects underwent echocardiography, ^{68}Ga-FAPI PET, CT, and MRI. Valvular and myocardial ^{68}Ga-FAPI uptake was quantified using maximal standardised uptake values (SUVmax), and target-to-background ratio (TBRmax). Aortic stenosis severity was measured by peak velocity on echocardiography and the CT calcium score. Myocardial fibrosis was quantified by late gadolinium enhancement (LGE) on MRI.

86 patients with aortic valve disease (72±11 years, 68% male) plus 9 matched control subjects (72±9 years, 67%% male) participated. Increased ^{68}Ga-FAPI uptake was observed in the aortic valves of patients with aortic stenosis compared with controls ($p<0.001$). ^{68}Ga-FAPI TBRmax correlated with peak velocity ($r=0.532$, $p<0.0010$) and calcium score ($r = 0.577$, $p<0.001$). 54 patients (69%) had myocardial ^{68}Ga-FAPI uptake, of whom 30 (38%) also had LGE corresponding to the region of 68Ga-FAPI uptake. Myocardial ^{68}Ga-FAPI uptake correlated with increased indexed left ventricular mass ($r=0.429$, $p<0.001$) and indexed Extracellular Volume ($r=0.404$, $p<0.001$).

For the first time, we have described valvular and myocardial fibroblast activation in patients with aortic stenosis *in vivo*. Valvular fibroblast activation is increased in patients with aortic stenosis, correlating with increased disease severity. Myocardial fibroblast activation is seen in the majority of patients with aortic stenosis in areas with and without established fibrosis, and is associated with adverse left ventricular remodelling. ^{68}Ga-FAPI PET can visualise the key effector cell driving aortic valve disease, and may have a role in monitoring disease modifying treatments, as well as identifying patients at high risk of myocardial decompensation.

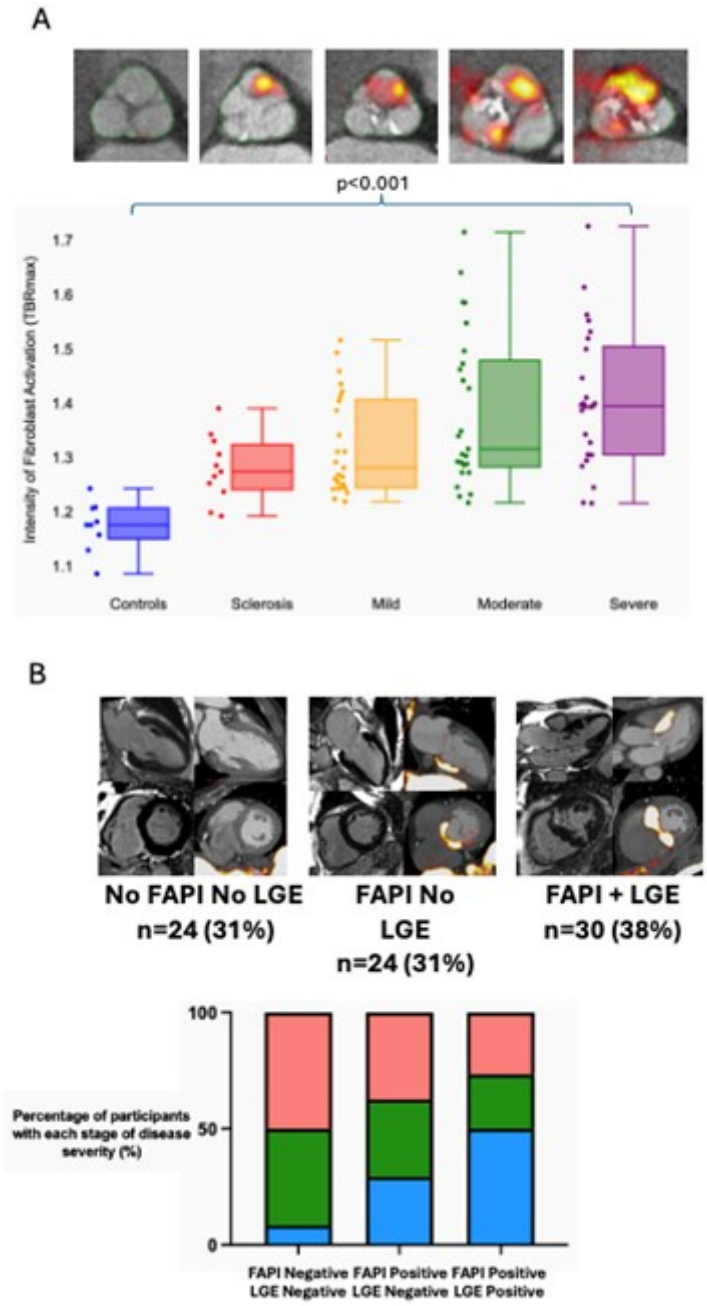

Figure. 1 Valvular and Myocardial Fibroblast Activation in Aortic Stenosis Panel A: Valvular ^{68}Ga-FAPI uptake is increased in patients with aortic stenosis compared with age and sex-matched controls. There was a positive correlation between valvular ^{68}Ga-FAPI uptake and both peak aortic jet velocity on echocardiography and the CT Calcium Score. Panel B: Myocardial ^{68}Ga-FAPI uptake was seen in 69% of patients with aortic stenosis, of whom the majority had moderate to severe disease. ^{68}Ga-FAPI uptake was present whenever and wherever established fibrosis was seen, but was also present in nearly 1/3 of patients who did not have established fibrosis. Myocardial ^{68}Ga-FAPI uptake correlated with measures of left ventricular adverse remodelling.