Aortic Stenosis: Quantification of Diffuse Fibrosis, Examination of Myocardial Physiology and Response to Ramipril

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Introduction
The physiological response of the myocardium to pressure overload is important in determining outcome in aortic stenosis (AS). It may be modified by inhibition of the renin-angiotensin system. We used cardiac magnetic resonance (CMR) to assess diffuse myocardial fibrosis (DMF), myocardial physiology and the response to Ramipril in AS.

Methods
DMF in AS
24 symptomatic patients with severe AS underwent myocardial biopsy at the time of aortic valve replacement (AVR). 85 asymptomatic AS patients and 33 matched controls were recruited. All subjects underwent CMR scanning at 1.5 for T1 mapping.

Myocardial physiology in moderate AS
31 patients with moderate asymptomatic AS and 12 matched normal controls underwent CMR scanning at 1.5 T for measurement of strain, perfusion and T1 values.

Ramipril in Asymptomatic AS
A double-blinded, placebo-controlled, randomized, prospective trial was carried out.
100 patients with moderate or severe asymptomatic AS and normal LV function were randomized to Ramipril 10 mg od (n=50) or placebo (n=50) for a year.
95 patients underwent CMR scanning (LV mass, function, strain, perfusion, T1 mapping), echocardiography and exercise testing at 0, 6 and 12 months.

Results
DMF in AS
There was a significant correlation between CMR T1 values and collagen vascular fraction (CVF)% (r=0.65, p=0.002) from biopsy. Mean T1 values were significantly longer in all groups with severe AS (972±33 ms in severe asymptomatic, 1014±38 ms in severe symptomatic) than in normal controls (944±16 ms) (p<0.05) (Figure 1). The strongest associations with T1 values were for aortic valve area (r=−0.40, p=0.001) and left ventricular mass index (LVMI) (r=0.36, p=0.008).

Myocardial physiology in moderate AS
There was a significant reduction in perfusion and longitudinal strain (LS) in moderate AS patients compared to normals; myocardial perfusion index 1.9±0.2 in normals, 1.3±0.4 in AS and LS -15±1 in normals, -11±2 in AS. (both p<0.001). There was a moderate correlation between LS and perfusion (r=−0.4 p<0.05).

Ramipril in Asymptomatic AS
Data was available in 78 patients for the primary endpoint (LV mass) at 12 months.
There was reduction in LV mass in the Ramipril compared to placebo group;
−3.96g (CI: −8.55, 0.62) p=0.089 at 6 months and −8.36g (CI: −14.22, −2.51) p=0.006 at 12 months. Figure 2. There was a trend towards reduction in valve area (p=0.067), peak aortic velocity (p=0.056) and fewer deaths in the Ramipril group after completion of the trial (p=0.074).

Conclusion
DMF in AS may be assessed noninvasively using CMR. DMF increases with severity of the AS and LV hypertrophy. Significant changes in perfusion and LS already exist in moderate AS, indicating that significant myocardial changes occur early in the disease process. Ramipril 10 mg over a year led to a significant reduction in LV mass in the treated group. A larger multi-centre clinical outcome trial is required to determine whether this translates into clinical benefit.

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