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Beyond late gadolinium enhancement: the key role of diffuse myocardial fibrosis in severe aortic stenosis - an Equilibrium Contrast CMR study

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Background

In severe aortic stenosis (AS), hemodynamics and conventional indices do not fully explain symptoms, prognosis or treatment response. We hypothesize that diffuse myocardial fibrosis (DMF) is a key missing factor in AS. This can now be accurately measured non-invasively using equilibrium contrast CMR (EQ-CMR) [1] involving a primed gadolinium infusion, T1 measurement pre- and post-infusion, and direct measure of blood volume of distribution (1-hematocrit). The derived myocardial volume of distribution ($Vd_{(m)}$) correlates strongly with histological diffuse myocardial fibrosisin AS and this calibration can convert $Vd_{(m)}$ to DMF%. Cell volume can be calculated as 1-DMF%*LV mass.

Methods

63 severe AS patients with planned valve replacement underwent baseline and follow up EQ-CMR. Twenty normal controls were included. Baseline and follow-up assessment included NYHA, ECG, echocardiography (for diastolic function and valve area/velocities), BNP and six minute walk test (6MWT). Follow up was at 6-months (2 declined, 4 late deaths, 13 pacemakers,

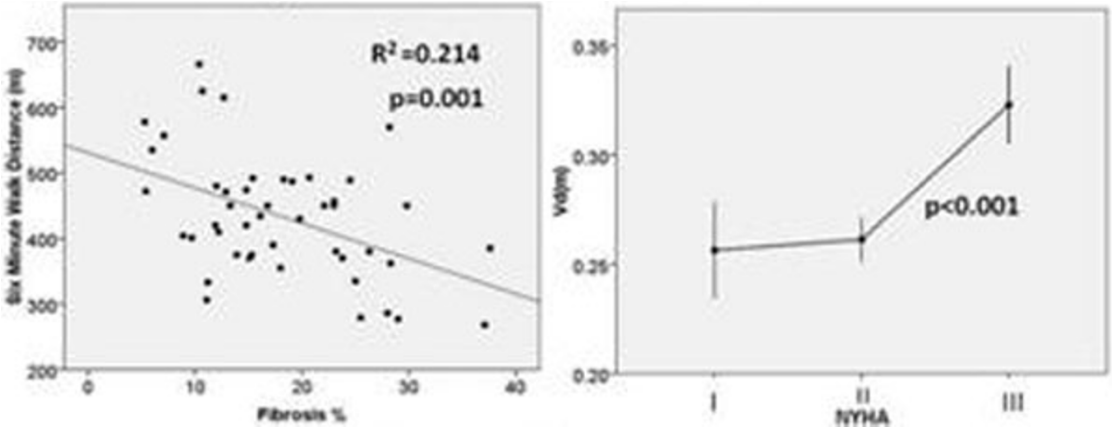

Figure 1 Relationship of DMF with 6MWT and NYHA class.

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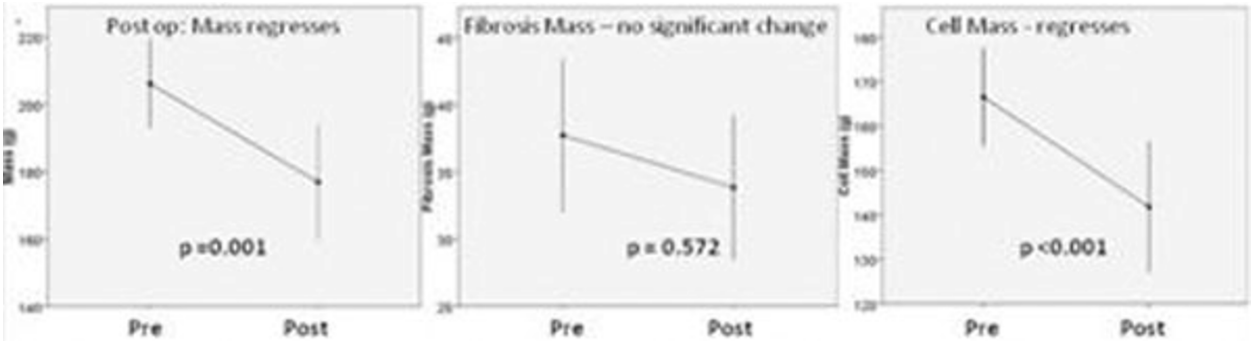

Figure 2 LVH regression redefined by EQ-CMR.

11 outstanding, leaving 33). EQ-CMR results were expressed as $Vd_{(m)}$/DMF% (continuous variable or severity tertiles), or cell volume.

Results

Baseline

AS patients had more fibrosis than controls ($Vd_{(m)}$:0.27± 0.04 vs 0.24±0.04; DMF:17% vs 11%, p = 0.003) with a wide range ($Vd_{(m)}$:0.20-0.39; DMF:4-42%). Breathless patients had more DMF (NYHA class III/IV vs I/II: $Vd_{(m)}$:0.32±0.03 vs 0.26±0.04; DMF:15% vs 27%, p<0.001). DMF correlated with 6MWT (inversely, figure 1, r^2=0.22, p=0.001) and aortic valve area (r^2=0.21, p=0.001). DMF only correlated with EF in patients with LV impairment (n=15, r^2=0.47, p=0.01). Severe DMF patients had worse diastolic function (p=0.029). In a multivariate analysis of all parameters classically associated with 6MWT distance, the only independent predictor was DMF (p=0.04). On univariate analysis there was a weak correlation with BNP and age.

Follow up

Overall, patients improved at follow-up (6MWT, EF, BNP, LV mass, LV volumes). However, only patients with severe fibrosis improved their exercise capacity (p=0.03). LVH regression (202g vs 183g, p=0.002) was shown to be cellular (161g vs. 142g, p<0.001) rather than fibrosis (36g vs 34g p=0.572) resolution, figure 2.

Conclusion

In this first clinical EQ-CMR study of severe AS, DMF is higher when there is LV impairment, diastolic dysfunction and more severe stenosis. DMF is the single best predictor of pre-op exercise capacity and post-op improvement. EQ-CMR shows that at 6-month post valve replacement LVH regression is predominantly reduced cell rather than fibrosis volume. EQ-CMR for the non-invasive measurement of DMF appears to be a significant cardiological advance.

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Reference

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