

Midwall Fibrosis and 5-Year Outcome In Patients With Moderate and Severe Aortic Stenosis

Brief Title: Midwall fibrosis in aortic stenosis

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Aortic stenosis (AS) is characterized by both progressive narrowing of the valve and the hypertrophic response of the left ventricle that ensues (LV) (1). Whilst initially adaptive, the hypertrophic response ultimately decompensates and patients transition from hypertrophy to heart failure, symptom development and adverse events. Pathology studies have demonstrated that this transition is driven predominantly by progressive myocyte cell death and myocardial fibrosis (2). Using cardiovascular magnetic resonance (CMR), the late gadolinium enhancement (LGE) technique can identify areas of midwall replacement fibrosis in patients with aortic stenosis. Recent studies have demonstrated the association between LGE and other markers of LV decompensation and its presence portends adverse short-term prognosis (3–5). We present the first prospective study investigating the association between midwall LGE and long-term mortality in patients with aortic stenosis.

Patients with moderate and severe AS undergoing CMR with gadolinium contrast at the Royal Brompton Hospital, London, UK from 2003-2008 were included as previously described (4). CMR was undertaken in 143 consecutive patients: age 68 ± 14 years, 97 (68%) male, aortic valve area $1.0 \pm 0.3 \text{cm}^2$, left ventricular ejection fraction (LVEF) $58 \pm 19\%$, 81 (57%) with known coronary artery disease (4). Patients were then followed for a median of five years for all-cause mortality and AS-related mortality (deaths where AS was either the primary cause or a major contributor as assessed by an independent, blinded panel of experts from death certificates and hospital notes).

On CMR, 54 (38%) patients had midwall fibrosis (linear, non-linear, focal, multi-focal or subepicardial (4)), 40 (28%) had subendocardial infarction-pattern LGE and 49 (34%) had no LGE. During a median follow up of 5 years (IQR 2.5, 5), 87 patients (61%) underwent aortic valve replacement (AVR). Forty-four patients (31%) died: 21/54 (39%) in the midwall fibrosis group (4 patients had AVR prior to death), 16/40 (40%) in the subendocardial infarction-pattern group (4 patients had AVR prior to death) and 7/49 (14%) in the no LGE

group (2 patients had AVR prior to death). On univariate analysis both patients with midwall fibrosis [HR 2.55 (95% CI 1.28-5.15, p=0.008)] and subendocardial infarction-pattern LGE [HR 2.71 (95% CI 1.31-5.62, p=0.007)] showed increased all-cause mortality when compared to patients with no LGE (Figure 1A). On multivariate analysis, midwall fibrosis remained an independent predictor of mortality with incremental value to LVEF [HR 2.64 (95% CI 1.07-2.88 p=0.035)] alongside age [HR 1.03 (95% CI 1.00-1.06, p=0.044)], LVEF [HR 0.97 (95% CI 0.94-0.99, p=0.006)] and wall thickness [HR 0.88 (95% CI 0.77-0.99, p=0.026)]. In contrast, subendocardial infarction-pattern LGE did not remain significant suggesting that its effect is mediated via reduced LVEF.

The 23 AS-related deaths followed a similar pattern to all-cause mortality; being more common in patients with midwall 12/54 (22%) and infarction-pattern 8/40 (20%), compared to no LGE 3/49 (6%), both p<0.05. Two patients from the midwall, three from the infarction and one from the no LGE groups had AVR between CMR and death.

Our results demonstrate that midwall fibrosis on CMR LGE is an independent predictor of mortality out to 5 years and of incremental prognostic value to LVEF (Figure 1B). These data would support midwall LGE as a useful marker in the risk stratification of patients with aortic stenosis.

Figure Legend

Figure 1: Midwall fibrosis on CMR is associated with an adverse 5-year prognosis in aortic stenosis of incremental value to ejection fraction.

Panel A, Kaplan-Meier estimator curves for all-cause mortality demonstrating an adverse prognosis in patients with midwall (orange line) compared to no LGE (blue line) and subendocardial infarction-pattern LGE (green line) compared to no LGE. On multivariable analysis midwall fibrosis remained significantly associated with prognosis but subendocardial infarction-pattern did not. The survival pattern was similar when aortic stenosis-related deaths only were considered.

Panel B, Cox proportional hazards model using Ejection Fraction (EF) and midwall LGE presence/absence as predictors of survival. The orange line estimates survival when midwall fibrosis is present and the blue line when absent for a given EF. For example, in a patient with EF=50% and no fibrosis 5-year survival is estimated at 77%, but decreases to 55% in the presence of midwall LGE. The green line indicates survival in patients with infarction fibrosis.

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