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Novel magnetic resonance imaging marker of diffuse myocardial fibrosis in hypertensive heart disease: the role of transcytolemmal water-exchange

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Summary

Transcytolemal water exchange and its effect on myocardial T1 relaxation can, if neglected, lead to a significant underestimate of the myocardial extracellular volume fraction, a novel marker of diffuse fibrosis.

Background

LGE may fail to detect diffuse fibrosis in several cardiac conditions. A novel approach uses the myocardial extracellular volume-fraction (MECVF), measured as distribution volume of a gadolinium constrast, as a marker of extracellular expansion. Previous studies have assumed the fast-exchange (FX) limit for the transcytolemal water-exchange, yet the administration of an extracellular-agent can create significant transcytolemal T1-differences, and cause an underestimation of extracellular volume fraction under the FX assumption. We hypothesized that the quantitative measure of MECVF with using a 2-site H-exchange model (2SX-model) correlates positively with the extracellular volume fraction, while the FX approach underestimates extra-cellular matrix expansion in a rodent model of hypertensive heart disease and diffuse myocardial fibrosis created by administration of L-NAME.

Methods

L-NAME(3mg/ml) or placebo was administered respectively to 22(bw=36.9±2.3g) and 15(bw=37.6±2.5g) wild-type mice. Animals were imaged at baseline and 7-weeks after treatment on a 4.7T small-animal MRI-system. T1(#of T1's>5/mouse) was quantified with a modified Look-Locker gradient-echo-cine technique, before and after fractionated Gd-DPTA administration (mean max. R1 in blood post-contrast=5.0±2.26 1/s). MECVF obtained from the T1 measurements with the 2SX and FX-models, and by using blood hematocrit to adjust the partition coefficient. Connective tissue volume fraction (CTVF) was measured using Masson's trichrome.

Results

L-NAME-treated animals demonstrated hypertrophy (weight-indexed LVmass 4.1±0.4 vs. 2.2±0.3 μg/g, p<0.001) and increased CTVF (8.6%±1.5 vs. 2.58%±0.6, P<0.001) as compared to controls. MECVF was substantially higher in L-NAME-treated animals (0.43±0.09 vs, 0.26±0.03, p<0.001 with 2SX-model; 0.20±0.03 vs. 0.20 ±0.05, p=0.82 without TWE with FX assumption). MECVF from 2SX-model showed a good correlation with CTVF and weight-indexed LVmass (both r=0.8, p<0.0001), while MECVF from FX-model did not correlate significantly with CTVF(p=0.44) and LVmass (p=0.80)(fig-1). MECVF from the 2SX model also correlated with the LVEF at 7-weeks(r=0.48, p=0.01). Bland-Altman analysis demonstrated that neglect of the transcytolemal water exchange causes a significant underestimate MECVF expansion(fig-2), which worsens with extracellular matrix expansion and LVH.

Conclusions

CMR MECVF quantification provides a robust measure of myocardial extracellular matrix expansion and interstitial fibrosis, though any break-down of the FX assumption for transcytolemmal exchange can result in a significant

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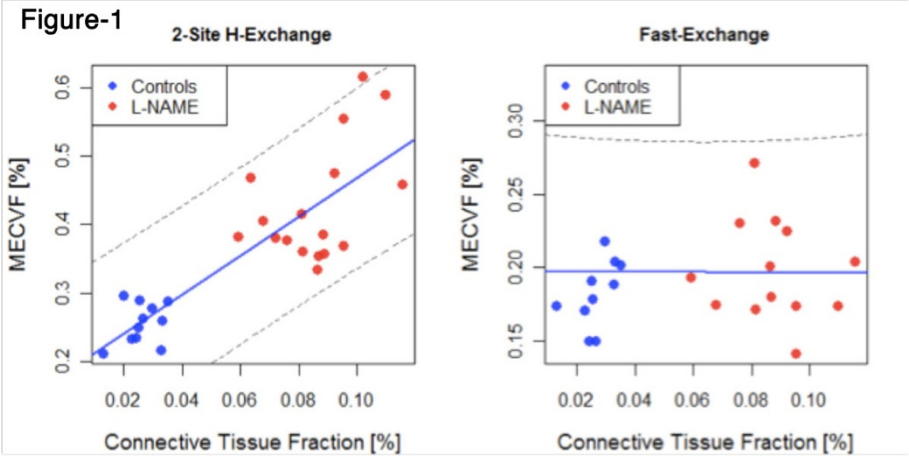

Figure 1 Correlation: MECVF (2-site H-exchange and Fast-exchange) and connective tissue volume fraction

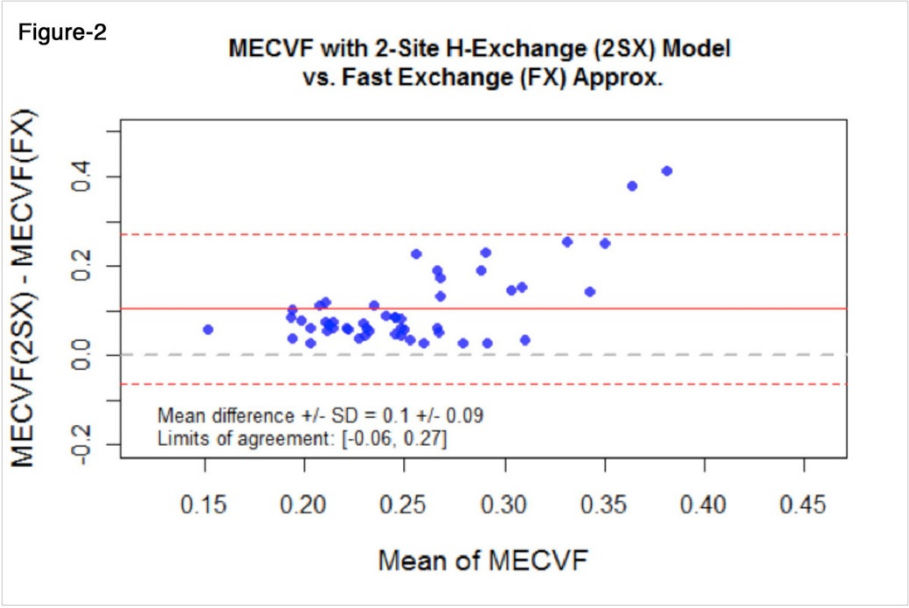

Figure 2 Bland-Altman analysis

underestimation of MECVF. Importantly, underestimates of MECVF due to the FX assumption depend on the degree of cell-hypertrophy, and the maximum T1 in the blood pool. A break-down of the FX assumption cannot be detected with protocols limited to a pair of pre/post-contrast T1 measurements. A generalization of the model for determination of MECVF brings important benefits for an early detection of diffuse fibrosis.

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