HFPEF – Echo with Strain vs. MRI T1 Mapping

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Disclosures

- Use of gadolinium contrast for cardiac purposes is “off label”
- I have received Prohance contrast donations for research purposes from Bracco Diagnostics
- Research support from the American Heart Association and Pittsburgh Foundation
- Advisory boards for Bayer Healthcare and Merck

Conclusions

- Both ECV and GLS predict outcomes in HFpEF
  - Shah AM, et al. Prognostic importance of impaired systolic function in heart failure with preserved ejection fraction and the impact of spironolactone. Circulation 2015;132:402–14.
  - Schelbert EB, et al. Temporal Relation Between Myocardial Fibrosis and Heart Failure With Preserved Ejection Fraction Association With Baseline Disease Severity and Subsequent Outcome. JAMA Cardiology doi:10.1001/jamacardio.2017.2511
- Both GLS and ECV independently discriminate between hypertensive heart disease and HFpEF and identify patients with prognostically significant functional limitation by CPEX. (Mordi IR et al. J Am Coll Cardiol Img 2017)
- ECV is the best diagnostic discriminatory marker of HFpEF. (Mordi IR et al. J Am Coll Cardiol Img 2017)
- Only ECV identifies a specific pathway for Rx, e.g., spironolactone

Unpublished CMR data (embargoed)

- Overall, GLS by CMR a better predictor than ECV in the entire cohort

- In HFpEF, ECV a stronger predictor than GLS

Background

Strain by now is familiar:

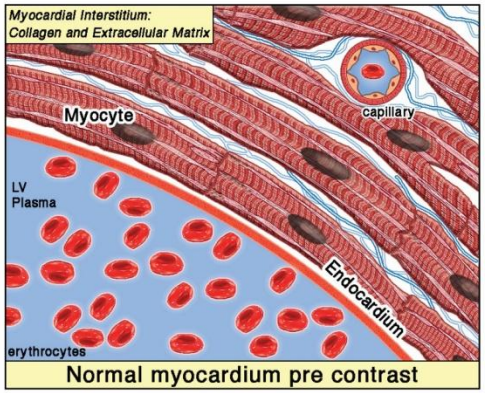
GLS=LV deformation → contractility

What is T1 mapping and ECV?

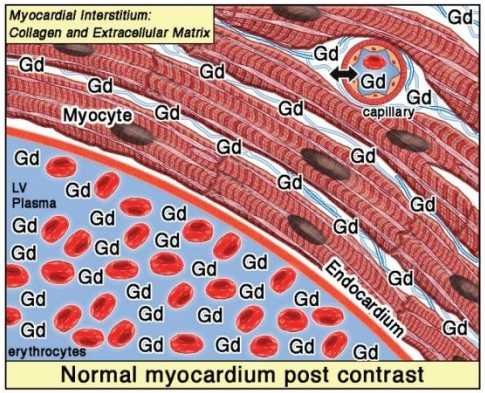
Extra**C**ellular **V**olume fraction (ECV) measures myocardial ***interstitial expansion***

=myocardial Gd uptake relative to plasma (not whole blood measured from images)

Schelbert EB, Fonarow GC, Bonow RO, Butler J, Gheorghiade M. JACC 2014



Normal myocardium pre contrast



Normal myocardium post contrast

Computational Steps for Extracellular Volume Fraction (ECV) measurement

1. Measure: a) myocardial and blood pool T1 values before and after extracellular Gd contrast
   b) the hematocrit

2. Compute $\Delta R1$ for myocardium and blood pool where:

$$\Delta \mathbf{R1} = \mathbf{1/T1}_{\text{post Gd}} - \mathbf{1/T1}_{\text{pre Gd}}$$

Note: $\Delta R1$ linearly relates to the accumulation of Gd in the tissue of interest at a given point in time:
$\Delta R1 = \gamma \cdot [Gd]$ *where γ is defined as the relaxivity of the contrast agent*

3. Compute λ, the partition coefficient for Gd from the Δ**R1** data where:

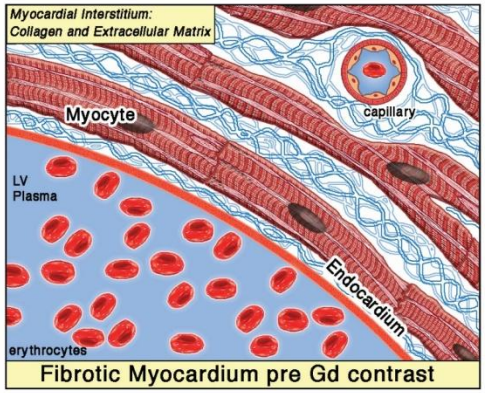
$$\lambda = \Delta \mathbf{R1}_{\text{myocardium}} / \Delta \mathbf{R1}_{\text{blood pool}} = \mathbf{[Gd]}_{\text{myocardium}} / \mathbf{[Gd]}_{\text{blood pool}}$$
$$= (\mathbf{ECV} \cdot \mathbf{[Gd]}_{\text{interstitium}}) / ((\mathbf{1\text{-}hematocrit}) \cdot \mathbf{[Gd]}_{\text{plasma}})$$
$$= \mathbf{ECV} / (\mathbf{1\text{-}hematocrit}) \quad \textit{if equilibration occurs, where:} \ \mathbf{[Gd]}_{\text{interstitium}} = \mathbf{[Gd]}_{\text{plasma}}$$

Note: λ "normalizes" the accumulation Gd in the myocardial interstitium to the concentration of Gd contrast in the blood pool after a bolus

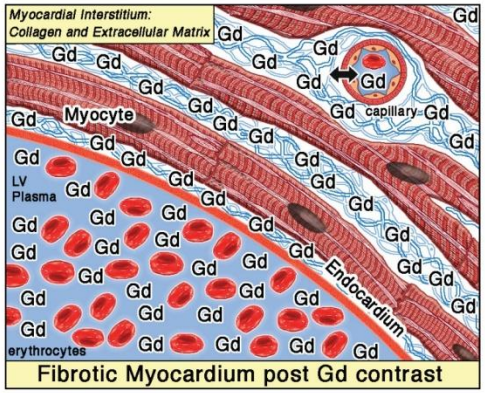
4. Compute the ECV, a unitless measure of the **volume fraction of the myocardial interstitium:**

Extracellular Volume Fraction (ECV) = λ • (1-hematocrit)

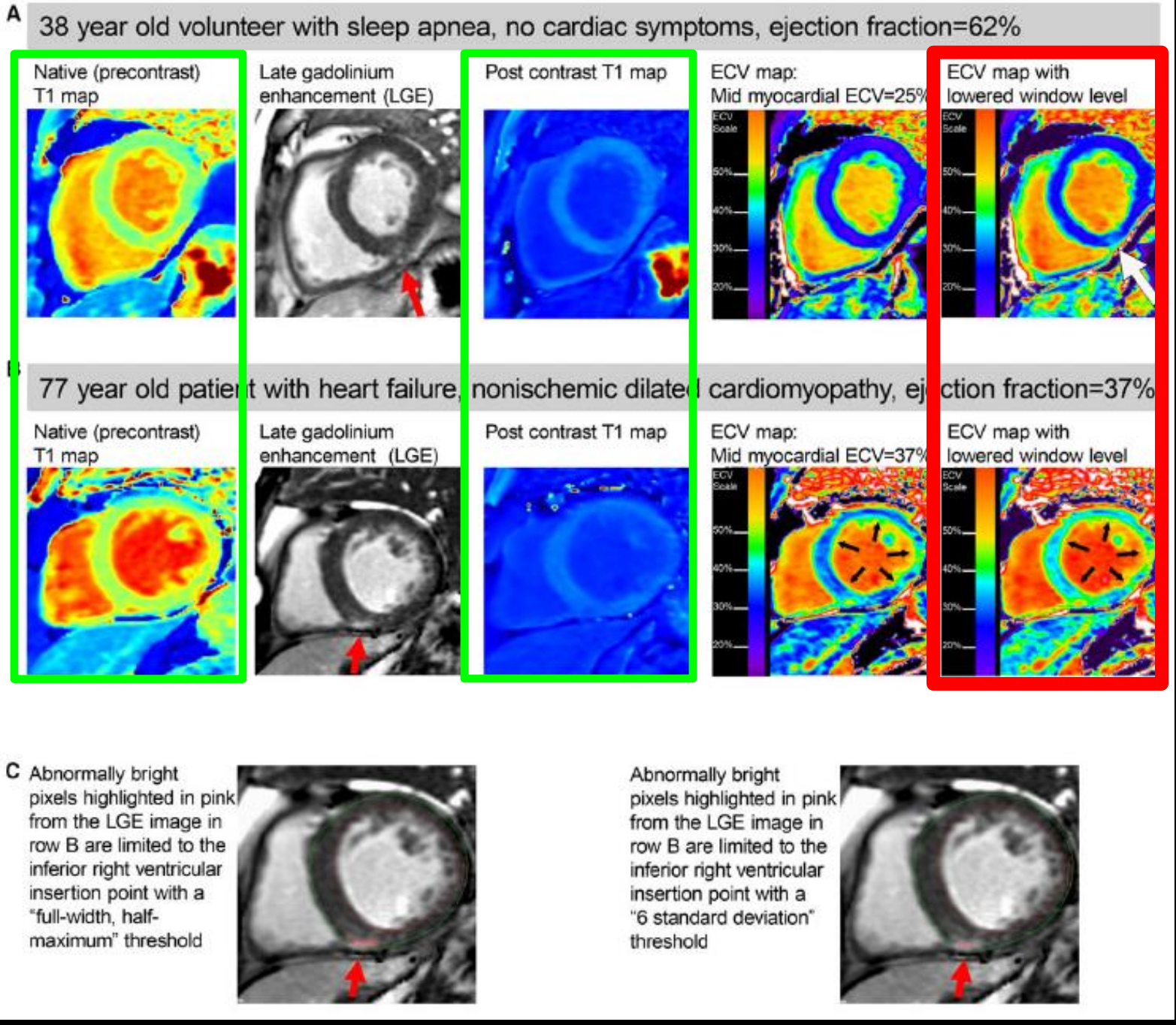
Note: the **(1-hematocrit)** *term adjusts for* ***key variation in the displacement of Gd contrast by the hematocrit*** *which confounds the relationship between ECV and the partition coefficient, λ.*



Fibrotic Myocardium pre Gd contrast



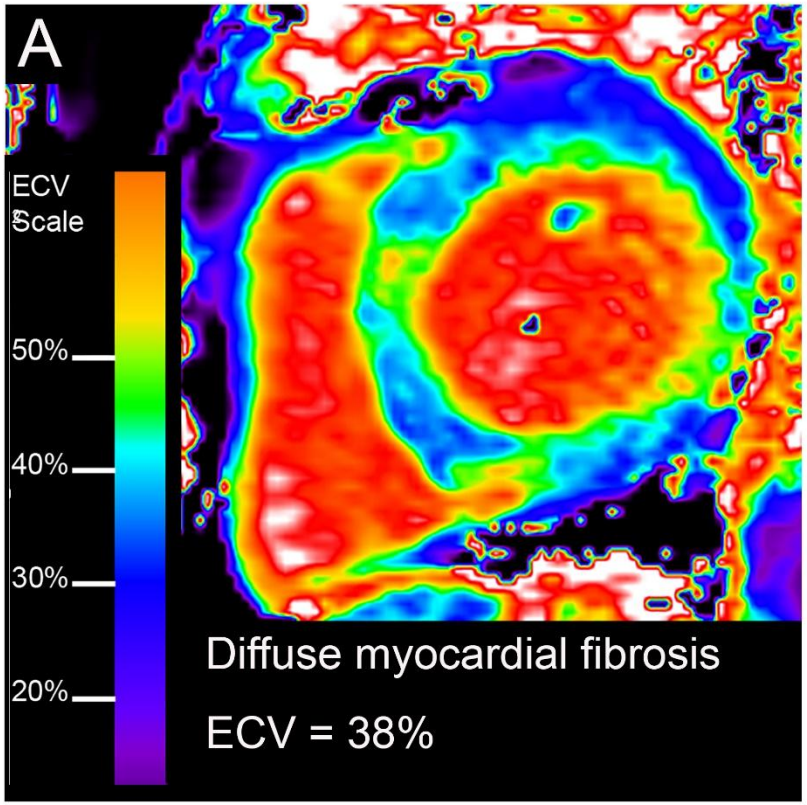
Fibrotic Myocardium post Gd contrast

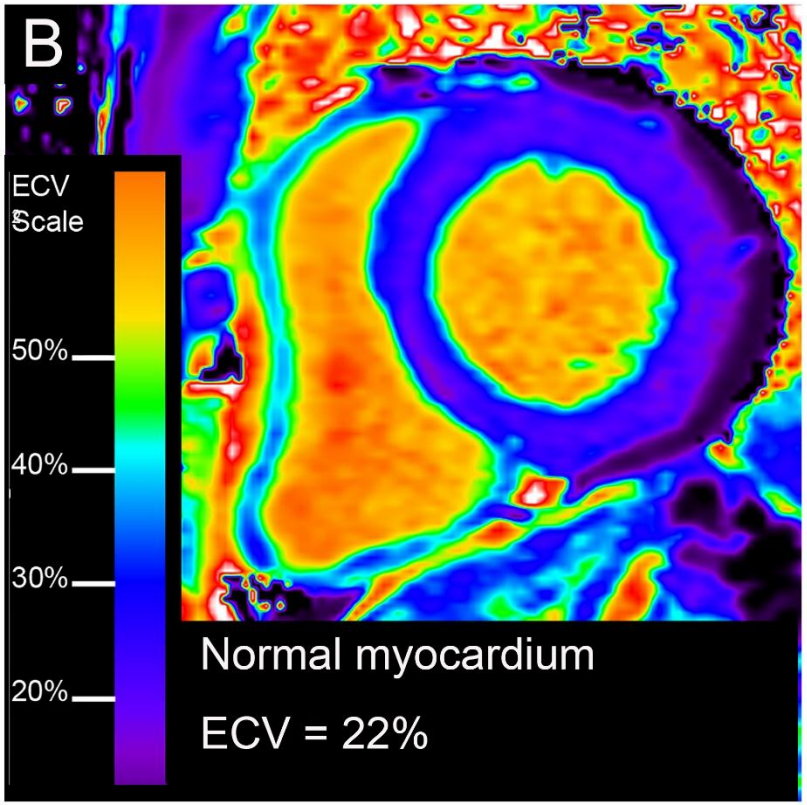


Schelbert EB, et al. J Am Heart Assoc. 2015;4:e002613

Severe diffuse interstitial fibrosis

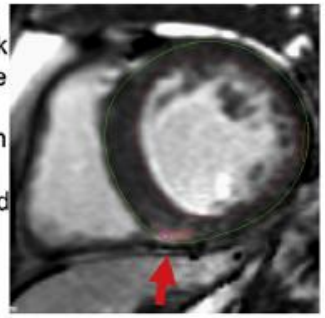
Normal



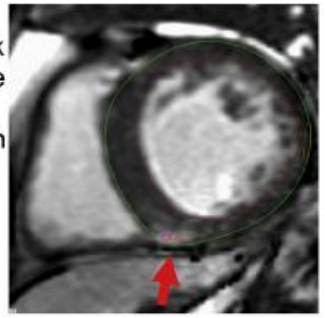


LGE misses the severe diffuse myocardial fibrosis

Abnormally bright pixels highlighted in pink from the LGE image are limited to the inferior right ventricular insertion point with a "full-width, half-maximum" threshold



Abnormally bright pixels highlighted in pink from the LGE image are limited to the inferior right ventricular insertion point with a "6-SD" threshold



Schelbert EB, Fonarow GC, Bonow RO, Butler J, Gheorghiade M. JACC 2014

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Comprehensive Echocardiographic and Cardiac Magnetic Resonance Evaluation Differentiates Among Heart Failure With Preserved Ejection Fraction Patients, Hypertensive Patients, and Healthy Control Subjects

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ABSTRACT

OBJECTIVES The aim of this study was to investigate the utility of a comprehensive imaging protocol including echocardiography and cardiac magnetic resonance in the diagnosis and differentiation of hypertensive heart disease and heart failure with preserved ejection fraction (HFpEF).

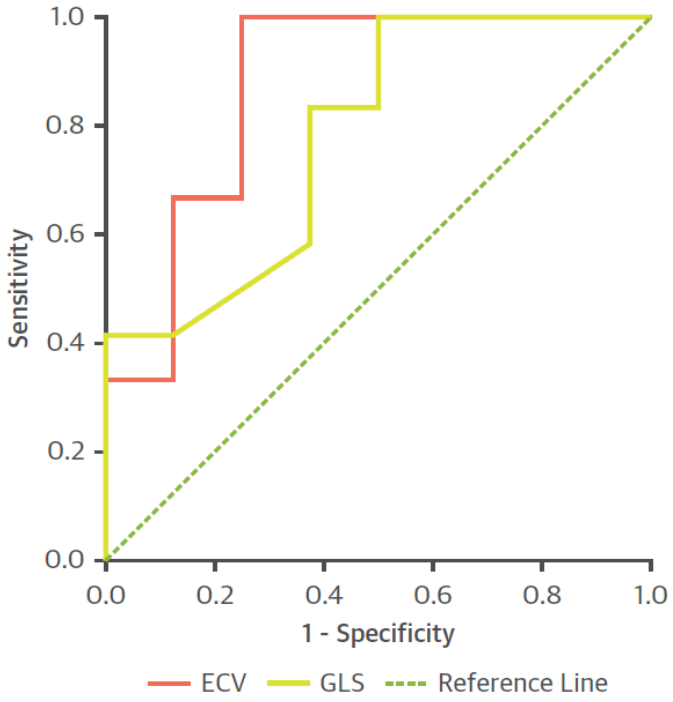
BACKGROUND Hypertension is present in up to 90% of patients with HFpEF and is a major etiological component. Despite current recommendations and diagnostic criteria for HFpEF, no noninvasive imaging technique has as yet shown the ability to identify any structural differences between patients with hypertensive heart disease and HFpEF.

METHODS We conducted a prospective cross-sectional study of 112 well-characterized patients (62 with HFpEF, 22 with hypertension, and 28 healthy control subjects). All patients underwent cardiopulmonary exercise and biomarker testing and an imaging protocol including echocardiography with speckle-tracking analysis and cardiac magnetic resonance including T_1 mapping pre- and post-contrast.

RESULTS Echocardiographic global longitudinal strain (GLS) and extracellular volume (ECV) measured by cardiac magnetic resonance were the only variables able to independently stratify among the 3 groups of patients. ECV was the best technique for differentiation between hypertensive heart disease and HFpEF (ECV area under the curve: 0.88; GLS area under the curve: 0.78; $p < 0.001$ for both). Using ECV, an optimal cutoff of 31.2% gave 100% sensitivity and 75% specificity. ECV was significantly higher and GLS was significantly reduced in subjects with reduced exercise capacity (lower peak oxygen consumption and higher minute ventilation–carbon dioxide production) ($p < 0.001$ for both ECV and GLS).

CONCLUSIONS Both GLS and ECV are able to independently discriminate between hypertensive heart disease and HFpEF and identify patients with prognostically significant functional limitation. ECV is the best diagnostic discriminatory marker of HFpEF and could be used as a surrogate endpoint for therapeutic studies. (J Am Coll Cardiol Img 2017;■:■–■)

FIGURE 2 ROC Curves



Sensitivity and specificity for differentiation of heart failure with preserved ejection fraction and hypertensive patients. ECV **(pink)** gave an area under the curve of 0.88 (95% confidence interval [CI]: 0.70 to 1.00; $p = 0.005$) whereas echocardiographic GLS **(yellow)** gave an area under the curve of 0.78 (95% CI: 0.57 to 0.99; $p = 0.037$). ROC = receiver-operating characteristic; other abbreviations as in Figure 1.

Well-established HFpEF

- HFpEF patients were identified via a large screening program for HFpEF conducted in primary care.
- They were diagnosed on the basis of symptoms and signs consistent with HF, elevated B-type pro-natriuretic peptide (BNP) at the time of diagnosis (>35 pg/ml), normal left ventricular (LV) dimensions with ejection fraction (EF) >50% (12) plus evidence of echocardiographic abnormalities such as left ventricular hypertrophy, left atrial enlargement, or evidence of diastolic dysfunction as per the 2016 European Society of Cardiology guidelines (12).
- Determination of diastolic dysfunction required at least 2 of the following to be present: early mitral inflow velocity/mitral annular early diastolic velocity (E/e') >13; mean septal and lateral mitral annular early diastolic velocity (e') <9 cm/s; or left atrial volume index >34 ml/m2.
- Finally, all patients underwent CPEX in order to confirm the presence of exercise limitation of cardiac etiology by peak oxygen consumption (VO2) <80% predicted and minute ventilation–carbon dioxide production (VE/VCO2) slope >32 (13).
- All patients underwent a symptom-limited protocol and were only included in the study if they were able to achieve a respiratory exchange ratio ≥1.

Evolving concept: ECV can help guide Rx

- ECV provides more than just diagnostics and prognostication

- Disease specific pathway showing interstitial expansion
- →treat the interstitium with RAAS inhibition (assuming no amyloid)

- GLS tells you quite little about underlying pathophysiology
- Even bull's-eye pattern not so accurate for amyloidosis

Supporting evidence for a key role of myocardial fibrosis in HFpEF

ECV describes the structural and functional abnormalities of HFpEF

Heart Failure

Coronary Microvascular Rarefaction and Myocardial Fibrosis in Heart Failure With Preserved Ejection Fraction

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Background—Characterization of myocardial structural changes in heart failure with preserved ejection fraction (HFpEF) has been hindered by the limited availability of human cardiac tissue. Cardiac hypertrophy, coronary artery disease (CAD), coronary microvascular rarefaction, and myocardial fibrosis may contribute to HFpEF pathophysiology.

Methods and Results—We identified HFpEF patients (n=124) and age-appropriate control subjects (noncardiac death, no heart failure diagnosis; n=104) who underwent autopsy. Heart weight and CAD severity were obtained from the autopsy reports. With the use of whole-field digital microscopy and automated analysis algorithms in full-thickness left ventricular sections, microvascular density (MVD), myocardial fibrosis, and their relationship were quantified. Subjects with HFpEF had heavier hearts (median, 538 g; 169% of age-, sex-, and body size–expected heart weight versus 335 g; 112% in controls), more severe CAD (65% with ≥1 vessel with >50% diameter stenosis in HFpEF versus 13% in controls), more left ventricular fibrosis (median % area fibrosis, 9.6 versus 7.1) and lower MVD (median 961 versus 1316 vessels/mm^2) than control (P<0.0001 for all). Myocardial fibrosis increased with decreasing MVD in controls (r=–0.28, P=0.004) and HFpEF (r=–0.26, P=0.004). Adjusting for MVD attenuated the group differences in fibrosis. Heart weight, fibrosis, and MVD were similar in HFpEF patients with CAD versus without CAD.

Conclusions—In this study, patients with HFpEF had more cardiac hypertrophy, epicardial CAD, coronary microvascular rarefaction, and myocardial fibrosis than controls. Each of these findings may contribute to the left ventricular diastolic dysfunction and cardiac reserve function impairment characteristic of HFpEF. (***Circulation***. **2015;131:550–559. DOI: 10.1161/CIRCULATIONAHA.114.009625.)**

CONCLUSIONS

Diffuse myocardial fibrosis, assessed by CMR-derived T1 mapping, independently predicts invasively measured LV stiffness in HFpEF.

Additionally, ECV helps to noninvasively distinguish the role of passive stiffness and hypertensive exercise response with impaired active relaxation.

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Extracellular Volume Fraction for Characterization of Patients With Heart Failure and Preserved Ejection Fraction

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ABSTRACT

BACKGROUND Optimal patient characterization in heart failure with preserved ejection fraction (HFpEF) is essential to tailor successful treatment strategies. Cardiac magnetic resonance (CMR)-derived T_1 mapping can noninvasively quantify diffuse myocardial fibrosis as extracellular volume fraction (ECV).

OBJECTIVES This study aimed to elucidate the diagnostic performance of T_1 mapping in HFpEF by examining the relationship between ECV and invasively measured parameters of diastolic function. It also investigated the potential of ECV to differentiate among pathomechanisms in HFpEF.

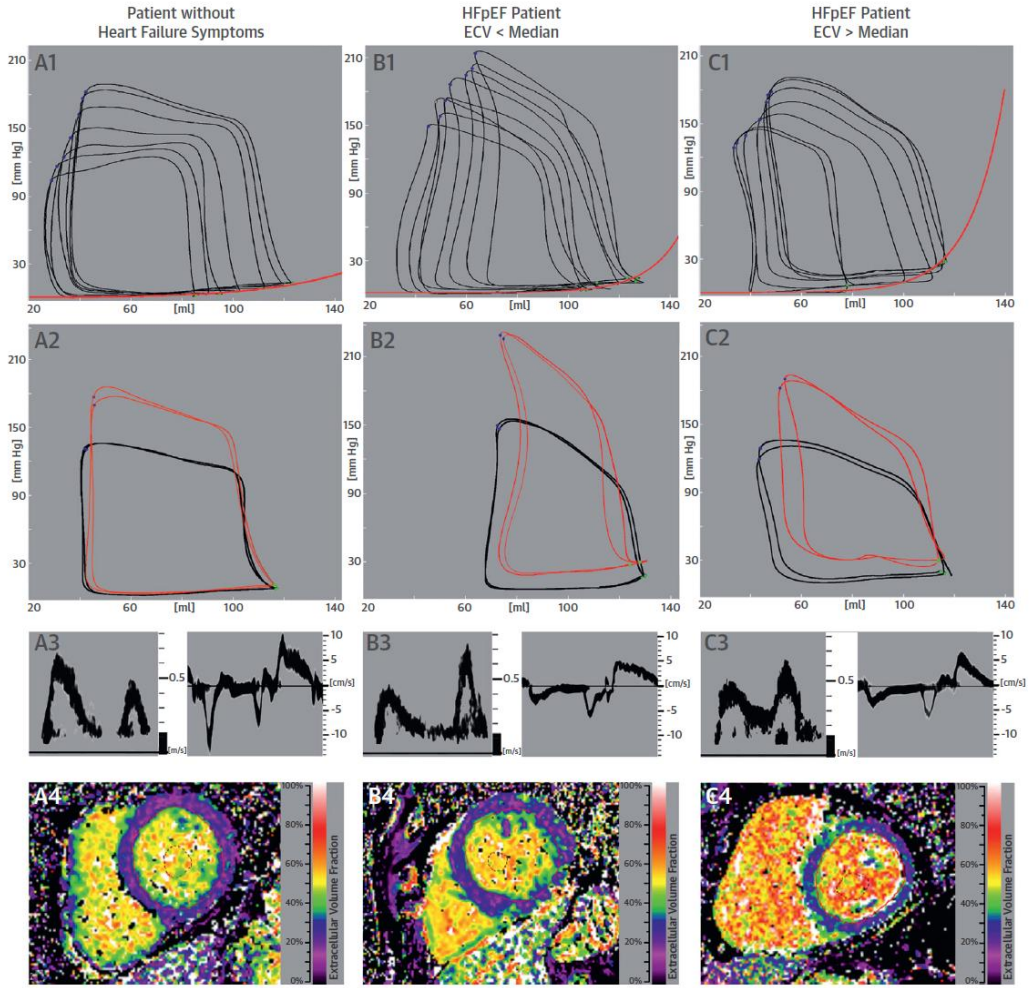
METHODS We performed T_1 mapping in 24 patients with HFpEF and 12 patients without heart failure symptoms. Pressure-volume loops were obtained with a conductance catheter during basal conditions and handgrip exercise. Transient pre-load reduction was used to extrapolate the diastolic stiffness constant.

RESULTS Patients with HFpEF showed higher ECV ($p < 0.01$), elevated load-independent passive left ventricular (LV) stiffness constant (beta) ($p < 0.001$), and a longer time constant of active LV relaxation ($p = 0.02$). ECV correlated highly with beta ($r = 0.75$; $p < 0.001$). Within the HFpEF cohort, patients with ECV greater than the median showed a higher beta ($p = 0.05$), whereas ECV below the median identified patients with prolonged active LV relaxation ($p = 0.01$) and a marked hypertensive reaction to exercise due to pathologic arterial elastance ($p = 0.04$). On multiple linear regression analyses, ECV independently predicted intrinsic LV stiffness ($\beta = 0.75$; $p < 0.01$).

CONCLUSIONS Diffuse myocardial fibrosis, assessed by CMR-derived T_1 mapping, independently predicts invasively measured LV stiffness in HFpEF. Additionally, ECV helps to noninvasively distinguish the role of passive stiffness and hypertensive exercise response with impaired active relaxation. (Left Ventricular Stiffness vs. Fibrosis Quantification by T_1 Mapping in Heart Failure With Preserved Ejection Fraction [STIFFMAP]; NCT02459626) (J Am Coll Cardiol 2016;67:1815–25) © 2016 by the American College of Cardiology Foundation.

Rommel K-P et al. J Am Coll Cardiol 2016;67:1815–25

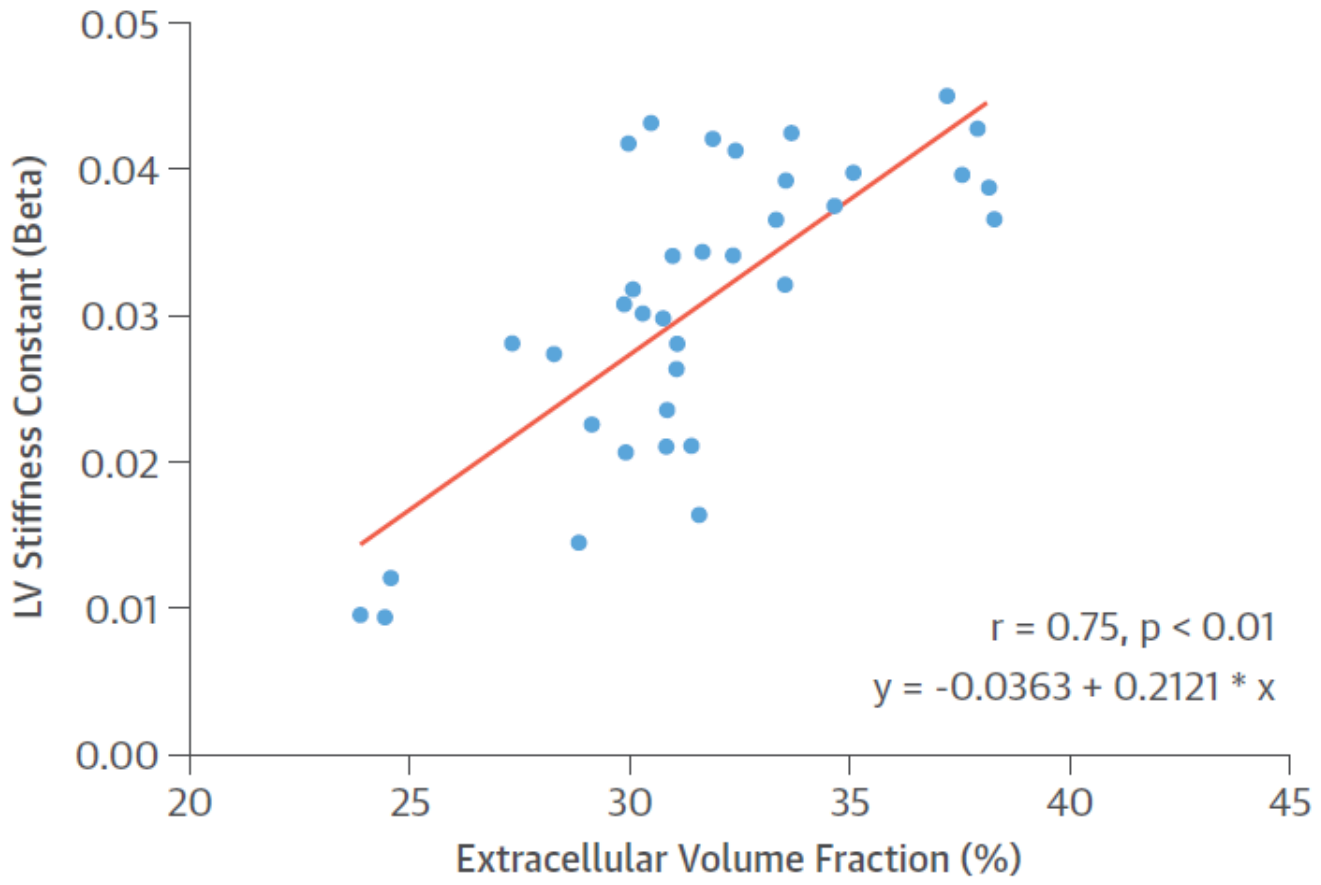
FIGURE 3 Pathomechanisms by ECV Group and Control Subjects



In patients without heart failure symptoms: **(A1)** Pressure-volume (PV) loops under transient pre-load reduction showed a shallow slope of the EDPVR line **(red line)**. **(A2)** PV loops at baseline **(black)** and throughout exercise **(red)** demonstrated a physiological response to exertion and a small change in EDPVR **(green points)**. **(A3)** Echocardiographic mitral valve (MV) inflow pattern **(left)** and septal MV annular velocities **(right)** showed no evidence of diastolic dysfunction. **(A4)** Cardiac magnetic resonance (CMR)-derived extracellular volume map demonstrated a low ECV of 25%. In HFpEF patients with ECV less than the median, **(B1)** PV loops under transient pre-load reduction showed an increased slope of the EDPVR line **(red line)**. **(B2)** PV loops at baseline **(black)** and throughout exercise **(red)** with elevated arterial elastance and marked hypertensive response to exertion resulted in significant changes in EDPVR **(green points)**. **(B3)** Echocardiographic MV inflow pattern **(left)** and septal MV annular velocities **(right)** showed diastolic dysfunction. **(B4)** CMR-derived extracellular volume map demonstrated a normal ECV of 28%. In HFpEF patients with ECV greater than the median: **(C1)** PV loops under transient pre-load reduction showed the steepest slope of the EDPVR line **(red line)**. **(C2)** PV loops at baseline **(black)** and throughout exercise **(red)** showed a significant change in EDPVR **(green points)**. **(C3)**: Echocardiographic MV inflow pattern **(left)** and septal MV annular velocities **(right)** show diastolic dysfunction without notable differences from the other ECV group. **(C4)** CMR-derived extracellular volume map demonstrated an elevated ECV of 36%. Abbreviations as in Figures 1 and 2.

Rommel K-P et al. J Am Coll Cardiol 2016;67:1815–25

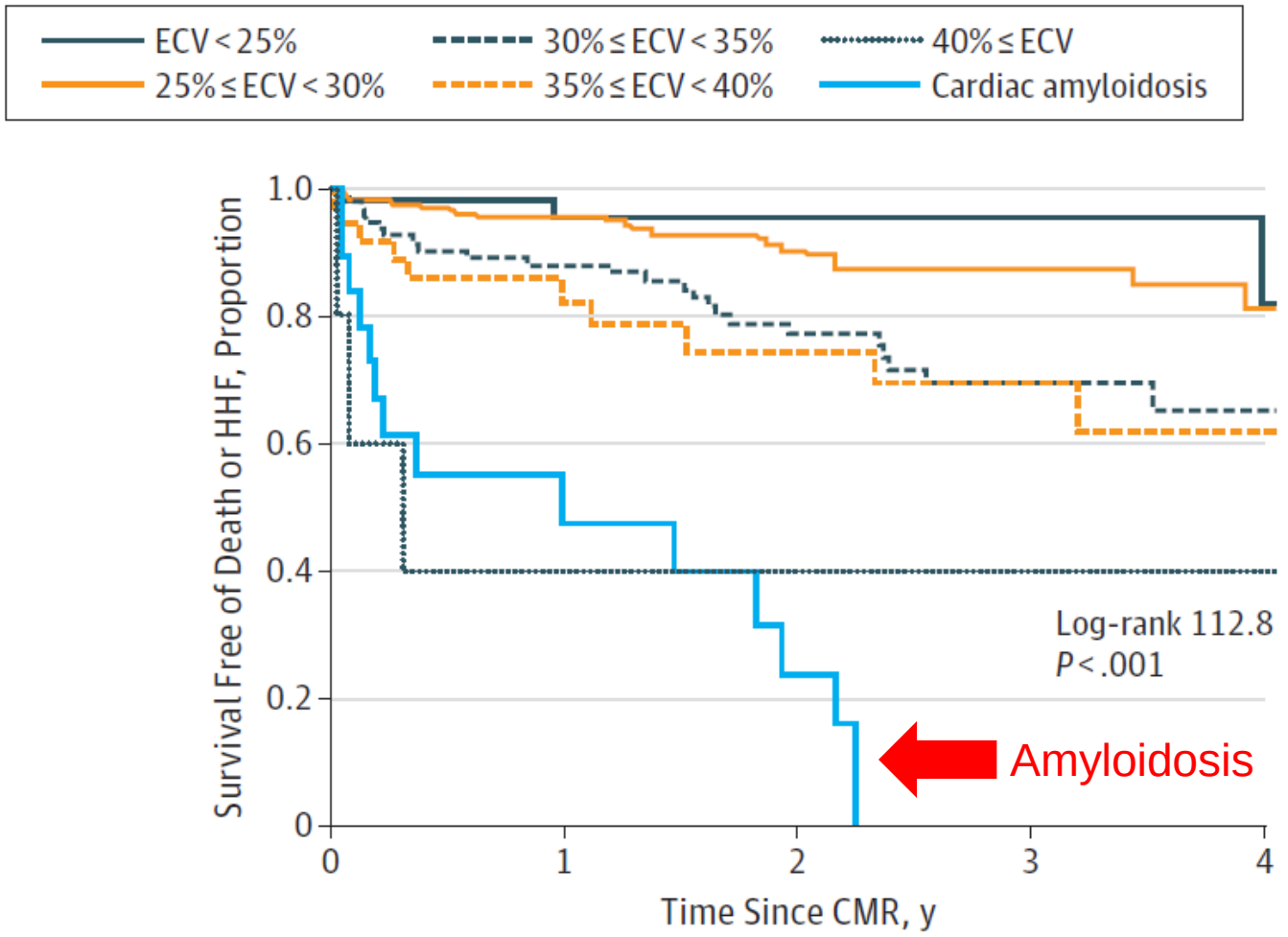
FIGURE 1 Correlation of LV Stiffness Constant and ECV



A significant positive correlation was observed between extracellular volume fraction (ECV) and left ventricular (LV) stiffness constant (beta).

Rommel K-P et al. J Am Coll Cardiol 2016;67:1815–25

B Outcomes according to ECV strata



No. at risk

ECV < 25%	63	36	21	11	6
25% ≤ ECV < 30%	212	157	102	51	20
30% ≤ ECV < 35%	94	73	51	24	12
35% ≤ ECV < 40%	36	23	16	10	4
40% ≤ ECV	5	1	1	1	1

Schelbert EB, et al. JAMA Cardiology 2017

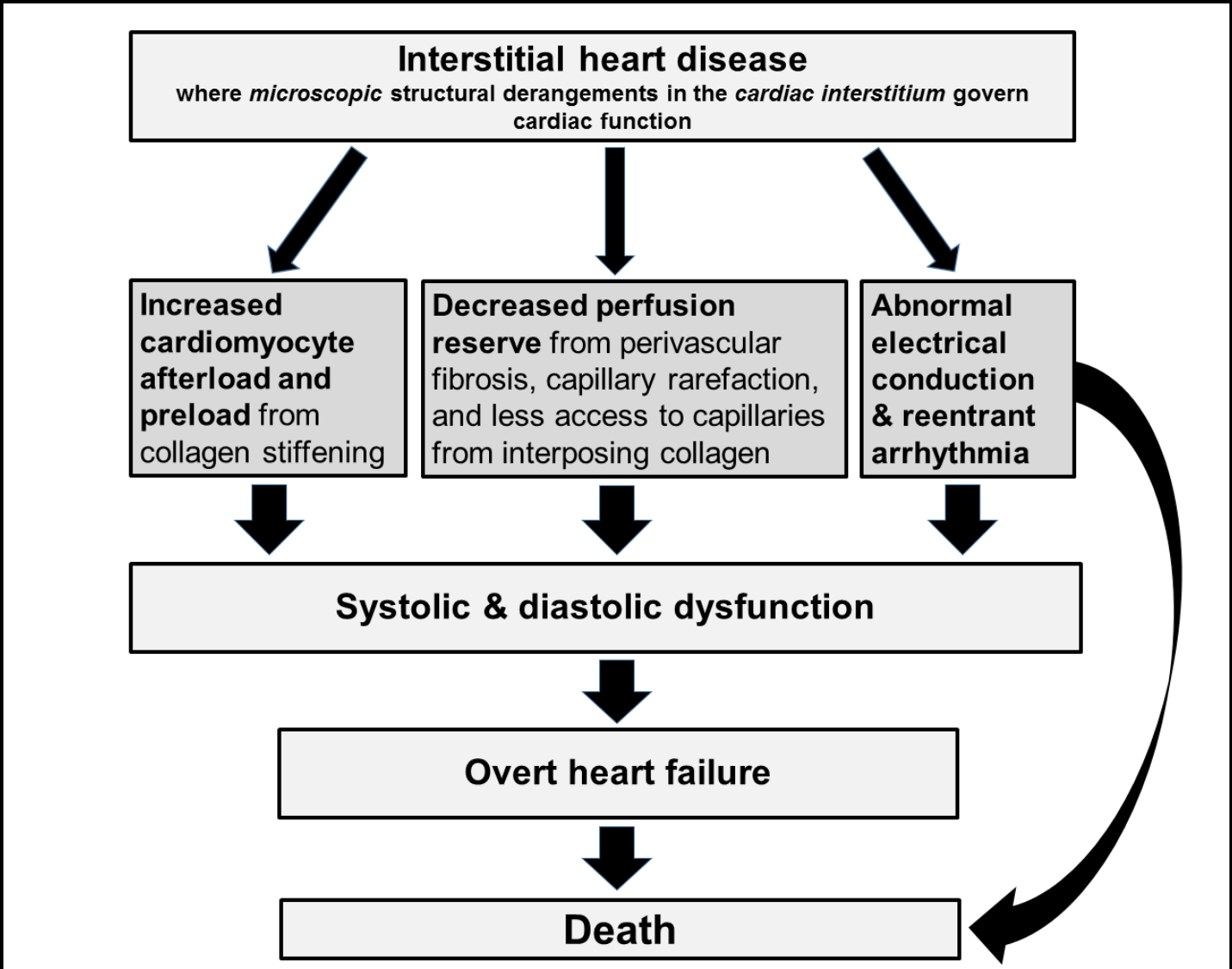
ECV alerts us to the presence of substrate to treat with anti-fibrotic drugs

Table 2. Studies Examining the Extent of Myocardial Fibrosis Reversal by Histological Measures in Human With Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor Blockers, or Mineralocorticoid Receptor Antagonism

Drug	Investigators	Disease	Duration, mo	Collagen Volume Fraction		Relative Percent Change	Absolute Percent Change
				Start	End		
Spironolactone	Izawa et al[16]	Dilated cardiomyopathy	12	4.7	3.4	≈28%	≈1.3%
Lisinopril	Brilla et al[15]	Hypertensive heart disease	6	6.9	6.3	9%	0.6%
Perindopril	Schwartzkopff et al[14]	Hypertensive heart disease	12	5.5	4.3	22%	1.2%
Losartan	Díez et al[17]	Hypertensive heart disease	12	4.32	3.72	14%	0.6%
			Average: 10.5			Average: 18%	Average: 0.93%

Schelbert EB, Sabbah HN, Butler J, Gheorghiade M. Circulation: CV Imaging 2017

CONCEPTUAL MODEL: Inferring cardiomyocyte-ECM interactions by associations with cardiac dysfunction and adverse outcomes



Schelbert EB, Wong TC, Gheorghiade M. JAHA 2015

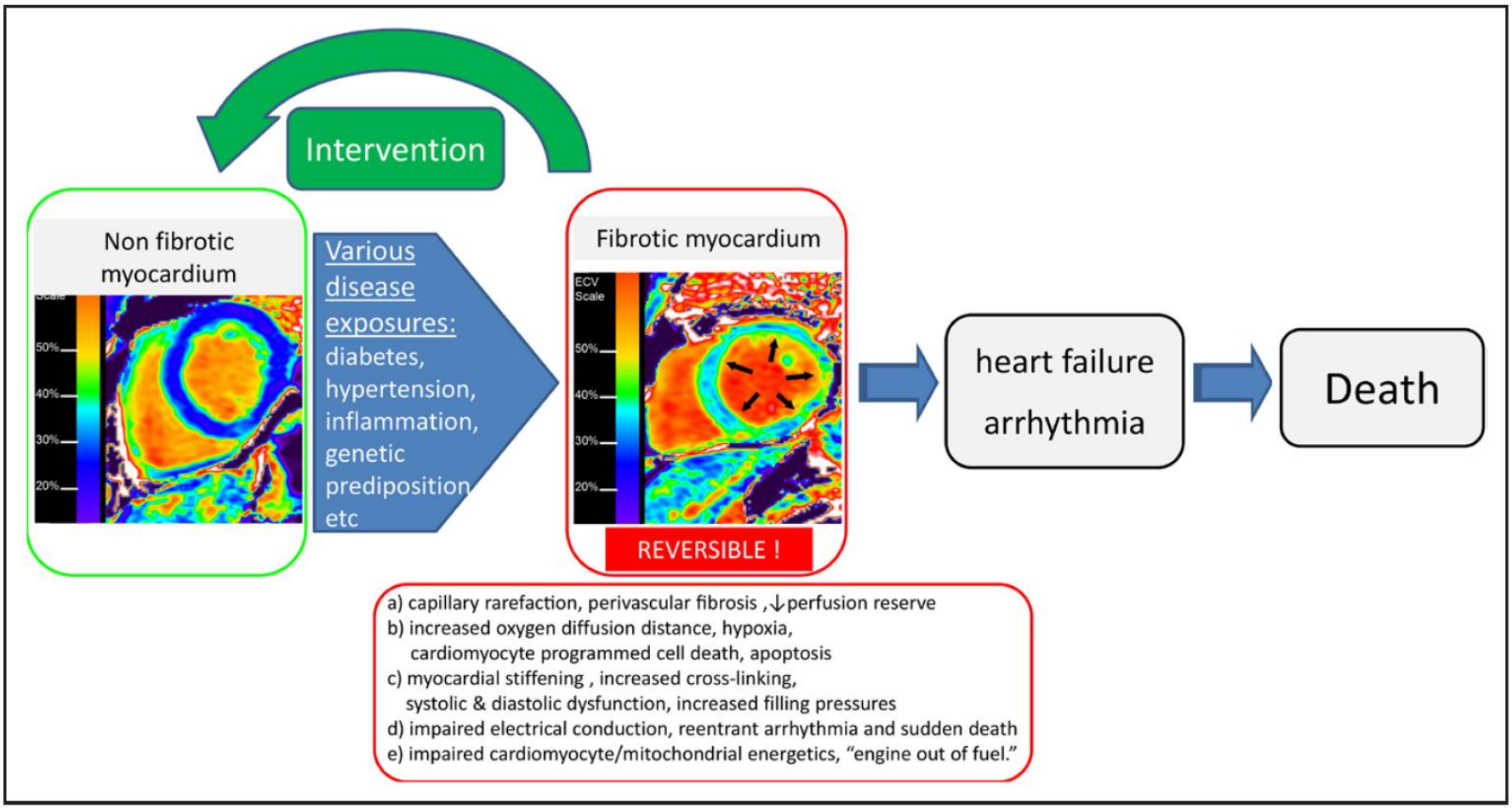


Figure 3. The conceptual model of using extracellular volume (ECV) measures of MF to foster novel therapeutics: MF develops after various exposures that culminate in disruption of normal collagen homeostasis, detectable by ECV. MF confers vulnerability through various interactions listed in the red text box, but these seem reversible, illustrating dysfunctional but viable and salvageable myocardium. Indeed, dysfunctional myocardium often may be salvageable in the absence of large amounts of focal myocardial scarring, and some think there is enormous, untapped cardiac reserve in most hearts. The extent to which conventional (eg, mineralocorticoid receptor antagonists) and novel antifibrotic agents regress myocardial fibrosis, improve function, and improve outcomes requires further study in phase 2 and 3 clinical trials, respectively.

Schelbert EB, Sabbah HN, Butler J, Gheorghiade M. Circulation: CV Imaging 2017

Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial

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Background—Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) patients with heart failure and preserved left ventricular ejection fraction assigned to spironolactone did not achieve a significant reduction in the primary composite outcome (time to cardiovascular death, aborted cardiac arrest, or hospitalization for management of heart failure) compared with patients receiving placebo. In a post hoc analysis, an ≈4-fold difference was identified in this composite event rate between the 1678 patients randomized from Russia and Georgia compared with the 1767 enrolled from the United States, Canada, Brazil, and Argentina (the Americas).

Methods and Results—To better understand this regional difference in clinical outcomes, demographic characteristics of these populations and their responses to spironolactone were explored. Patients from Russia/Georgia were younger, had less atrial fibrillation and diabetes mellitus, but were more likely to have had prior myocardial infarction or a hospitalization for heart failure. Russia/Georgia patients also had lower left ventricular ejection fraction and creatinine but higher diastolic blood pressure (all $P<0.001$). Hyperkalemia and doubling of creatinine were more likely and hypokalemia was less likely in patients receiving spironolactone in the Americas with no significant treatment effects in Russia/Georgia. All clinical event rates were markedly lower in Russia/Georgia, and there was no detectable impact of spironolactone on any outcomes. In contrast, in the Americas, the rates of the primary outcome, cardiovascular death, and hospitalization for heart failure were significantly reduced by spironolactone.

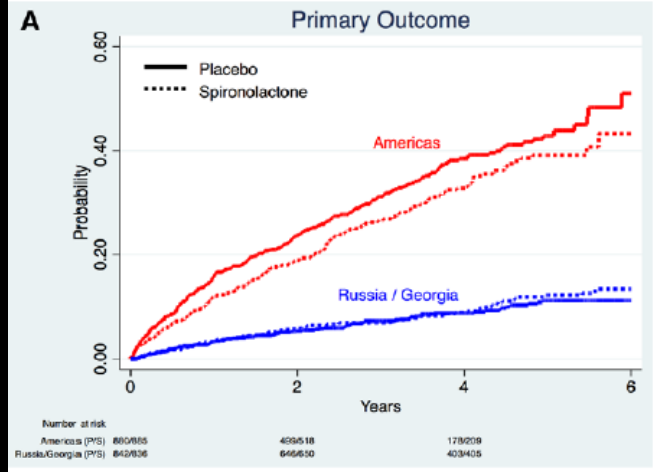
Conclusions—This post hoc analysis demonstrated greater potassium and creatinine changes and possible clinical benefits with spironolactone in patients with heart failure and preserved ejection fraction from the Americas.

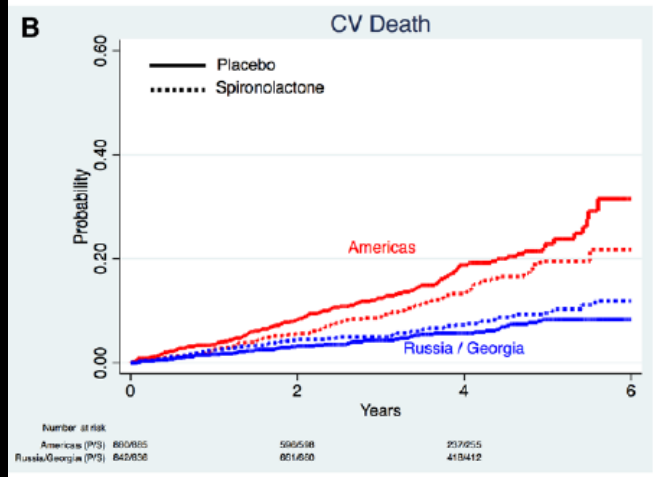
Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00094302.

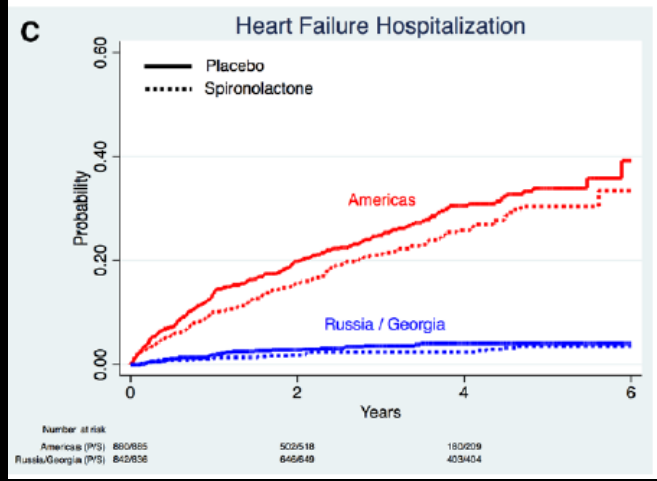
(*Circulation*. 2015;131:34-42. DOI: 10.1161/CIRCULATIONAHA.114.013255.)

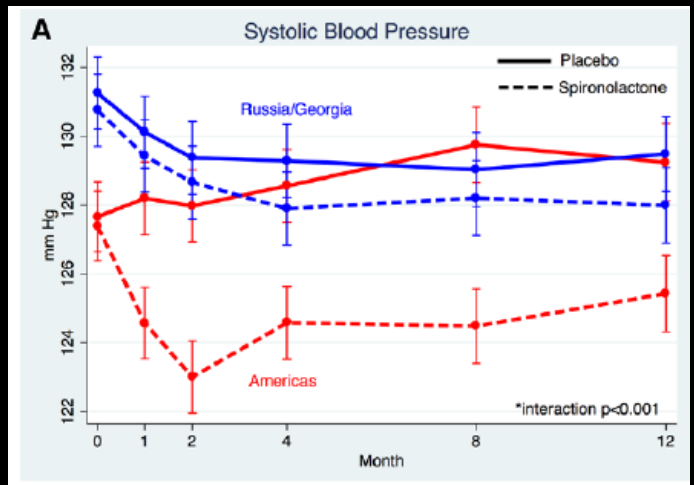
Spironolactone probably worked in HFpEF

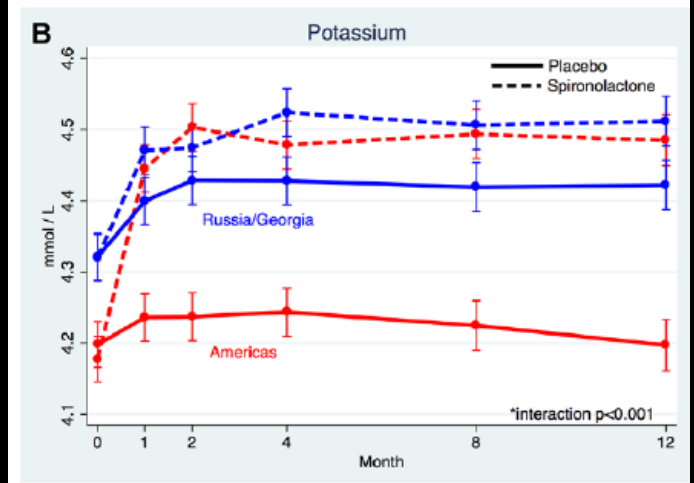
Pfeffer MA, et al. Circulation. 2015; 131:34-42

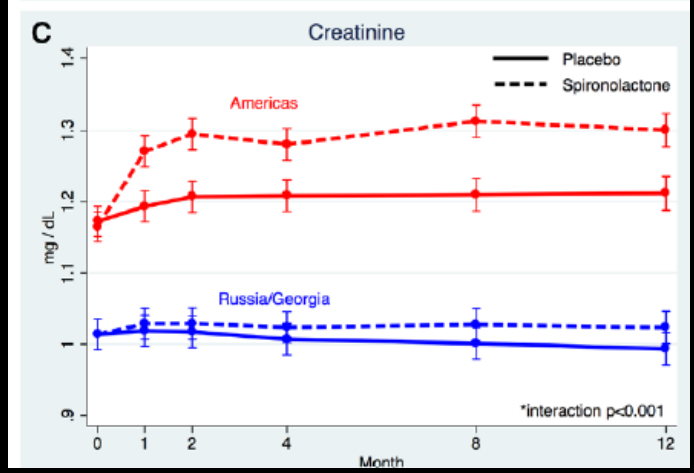












Conclusions

- Both ECV and GLS predict outcomes in HFpEF
  - Shah AM, et al. Prognostic importance of impaired systolic function in heart failure with preserved ejection fraction and the impact of spironolactone. Circulation 2015;132:402–14.
  - Schelbert EB, et al. Temporal Relation Between Myocardial Fibrosis and Heart Failure With Preserved Ejection Fraction Association With Baseline Disease Severity and Subsequent Outcome. JAMA Cardiology doi:10.1001/jamacardio.2017.2511
- Both GLS and ECV independently discriminate between hypertensive heart disease and HFpEF and identify patients with prognostically significant functional limitation by CPEX. (Mordi IR et al. J Am Coll Cardiol Img 2017)
- ECV is the best diagnostic discriminatory marker of HFpEF. (Mordi IR et al. J Am Coll Cardiol Img 2017)
- Only ECV identifies a specific pathway for Rx, e.g., spironolactone

Thanks for your attention!