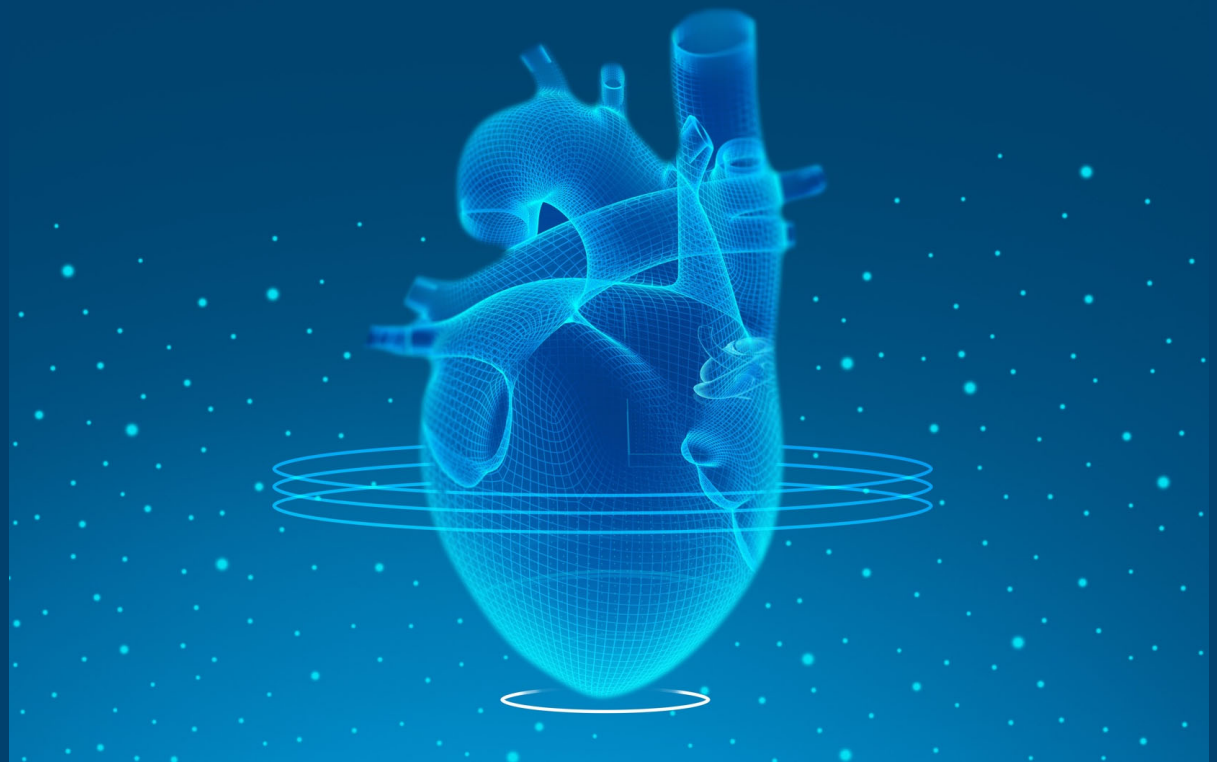
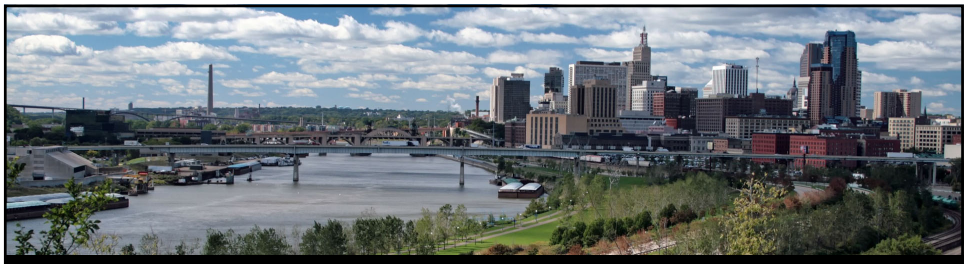
Minneapolis Heart Institute Foundation®

GRAND ROUNDS





Myocardial fibrosis as a therapeutic target

Erik Schelbert, MD MS
Minneapolis Heart Institute® at United Hospital

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Disclosures

- Research support from a) the American Heart Association and b) The Pittsburgh Foundation
- Current Scientific Advisory Board for Haya Therapeutics
- Consultant for PureTech LYT 100

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Background: Several knowledge gaps in cardiology

- Heart Failure epidemic…
  - Increasing in prevalence
  - Costly
  - Incompletely understood
  - Not just sequelae of CAD with huge infarcts
  - "Conceptual homogenization of myocardium"—rather than considering components separately:
    - cardiomyocyte
    - Interstitium
    - microvasculature
- What is vulnerable remodeling…?
  - Among myriad changes in myocardium, what are the key components that really matter?
  - What are the causes and what are the effects?

3

Focus on Myocardial fibrosis

- Consider: the heart may be like other organs:
  - Lung → pulmonary fibrosis,
  - Liver → cirrhosis,
  - Kidney → glomerular fibrosis
- where disruption of its architecture through interstitial expansion leads to organ dysfunction and vulnerability to the patient
- "*Amyloid-light*"

4

Leveraging over a decade of CMR investigation
Association of myocardial fibrosis with outcomes → vulnerability

http://static.guim.co.uk/sys-images/Guardian/Pix/pictures/2013/1/30/1359549064145/Crowd-of-people-008.jpg

5

Apt Quote

When you can measure what you are speaking about and summarize it in numbers, you know something about it.

And when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind. It may be the beginning of knowledge, but you have scarcely in your thought advanced to the stage of science, whatever the matter may be.

—Lord Kelvin, Popular Lectures and Addresses Vol 1 (1889) Electrical Units of measurement delivered 3 May 1883.

6

WE now have to the tools to measure and follow myocardial fibrosis (and amyloidosis)

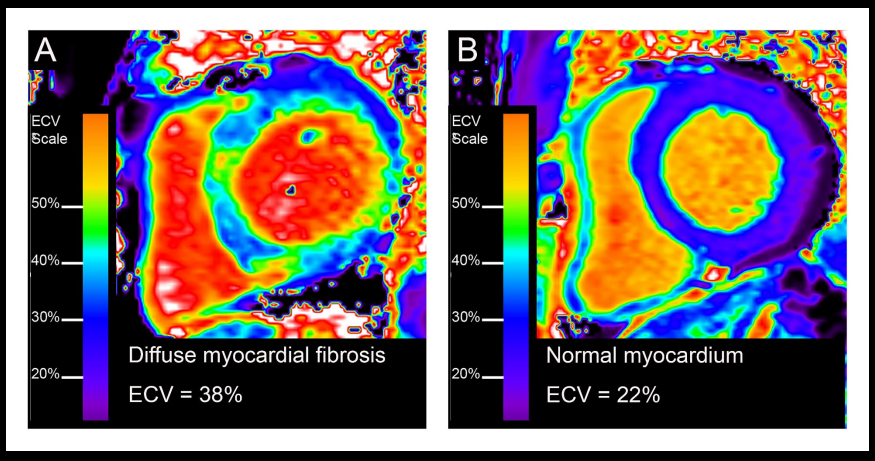
ECV

ExtraCellular Volume

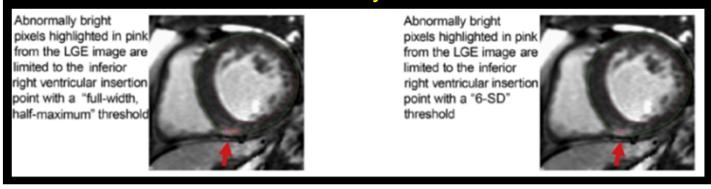
7

Severe diffuse interstitial fibrosis

Normal



LGE misses the severe diffuse myocardial fibrosis



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

8

Conclusions

- Interstitial expansion from myocardial fibrosis likely causes:
  - Mechanical dysfunction (i.e., diastolic)
    - Systolic function and ECV are mostly independent
  - Microvascular dysfunction (↓ perfusion reserve, capillary rarefaction)
  - Electrical dysfunction (reentry)

  and the increases risks of death, hospitalization for HF, arrhythmia
- Similar strength of association with adverse outcomes between ECV and EF and/or GLS → Myocardial fibrosis likely causal
- CMR (and CCT) measure interstitial expansion with ECV reliably
- Anti-fibrotic Rx under development promise to reverse cardiac dysfunction & improve outcomes.
- ECV is critical for serial monitoring of disease progression / regression

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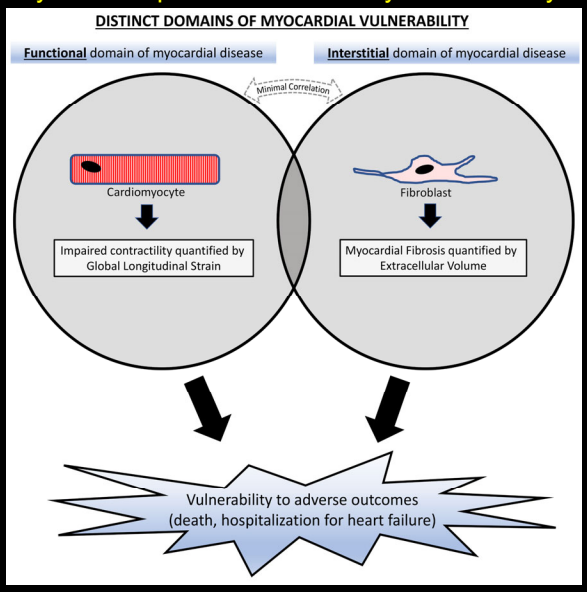
Key outcomes data → Conceptual model

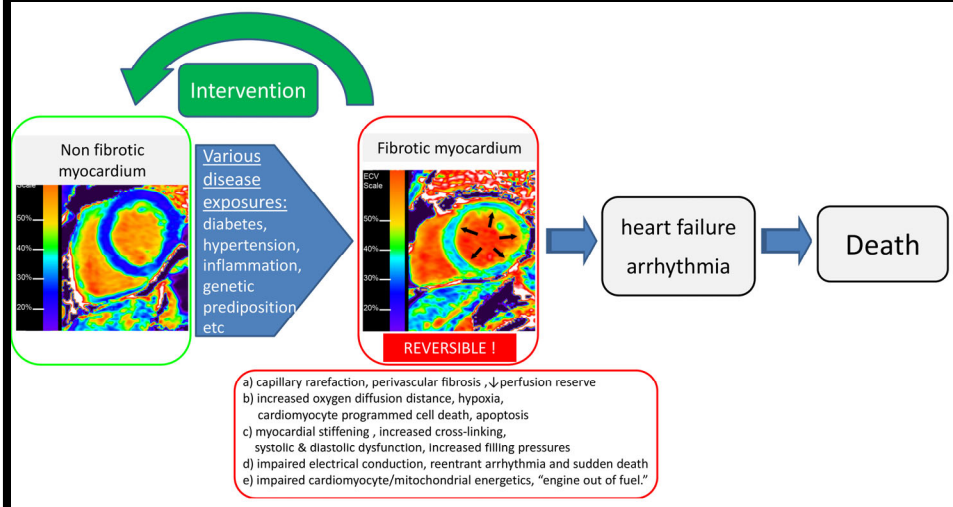
A new taxonomy to conceptualize vulnerability related to myocardial disease



Fröjdh F, Fukui M, Cavalcante JL,....Ugander M, Schelbert EB. Extracellular Volume and Global Longitudinal Strain Both Associate With Outcomes But Correlate Minimally. *JACC Imaging 2020*

10

Potential for therapy to REVERSE myocardial fibrosis



- Renin angiotensin aldosterone inhibitors
- Other agents in development

Schelbert, EB, et al. Circ Cardiovasc Imaging. 2017;10:e005619. DOI: 10.1161/CIRCIMAGING.116.005619

11

A new age for understanding the role of the cardiac interstitium

- more than 30 phase 2 trials and observational ongoing studies leveraging *change in ECV* as an endpoint

Schelbert EB, Butler J, Diez J. Why Clinicians Should Care About the Cardiac Interstitium. JACC Cardiovasc Imaging. 2019 Nov;12(11 Pt 2):2305-2318.

12

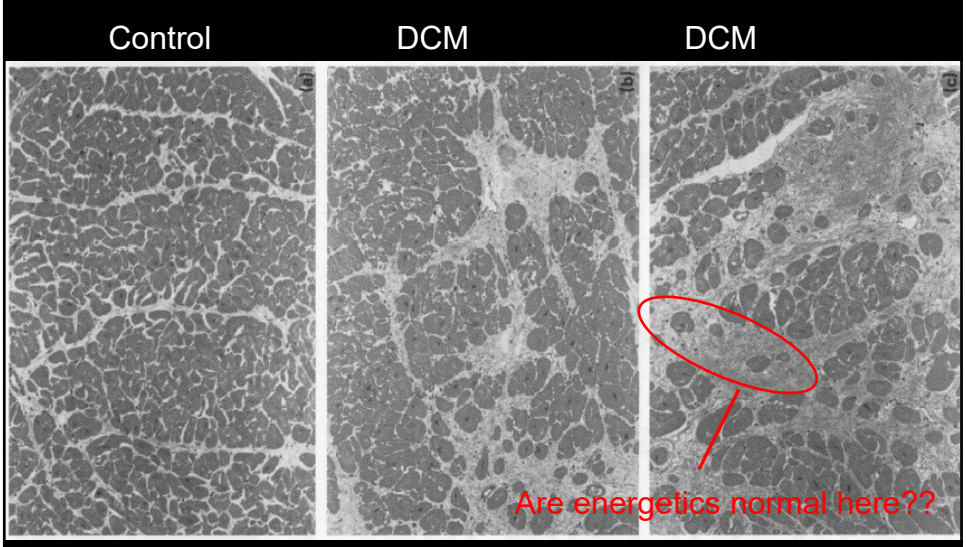
The story starts with histopathology:

ECM expansion from diffuse fibrosis seems ubiquitous in diseased myocardium at autopsy

distortion of micro-architecture

13

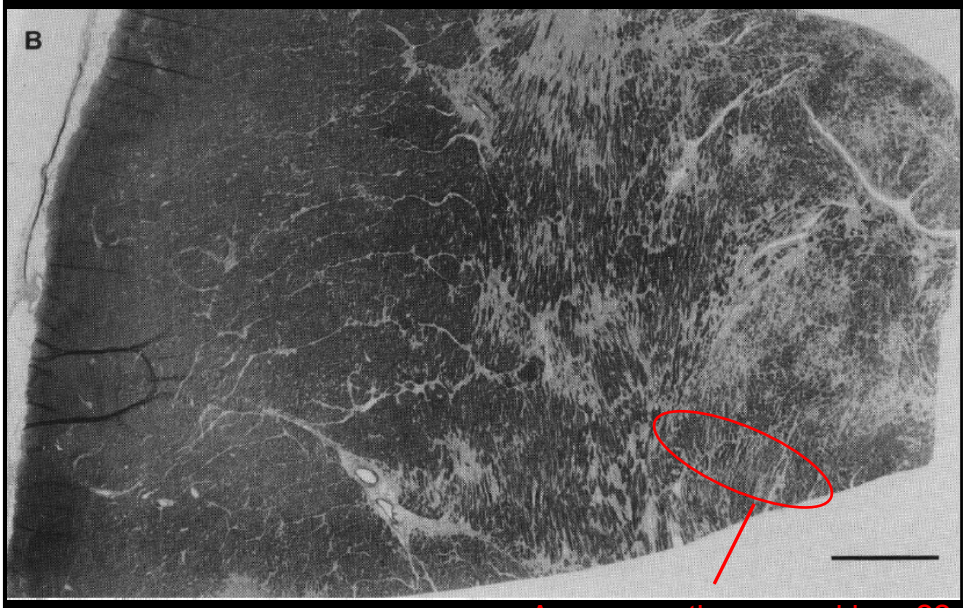
Nonischemic dilated cardiomyopathy



Beltrami C, et al. J Moll Cell Cardiol 1995

14

Remote, non-infarcted myocardium in Ischemic CM

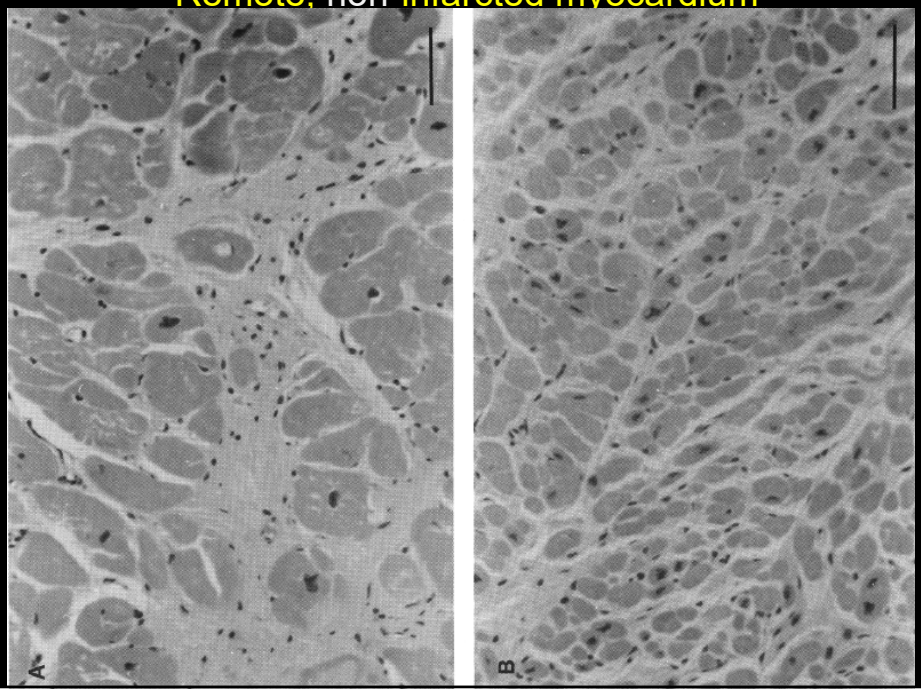


Beltrami C, et al. Circulation 1994

Are energetics normal here??

15

Remote, non-infarcted myocardium



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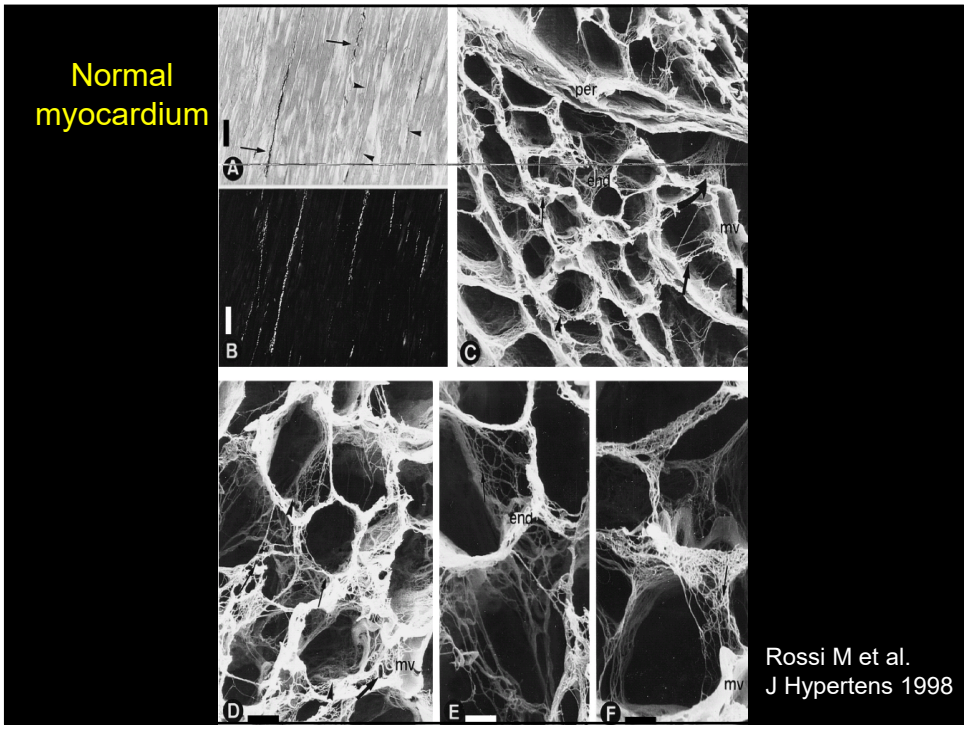
Normal myocardium
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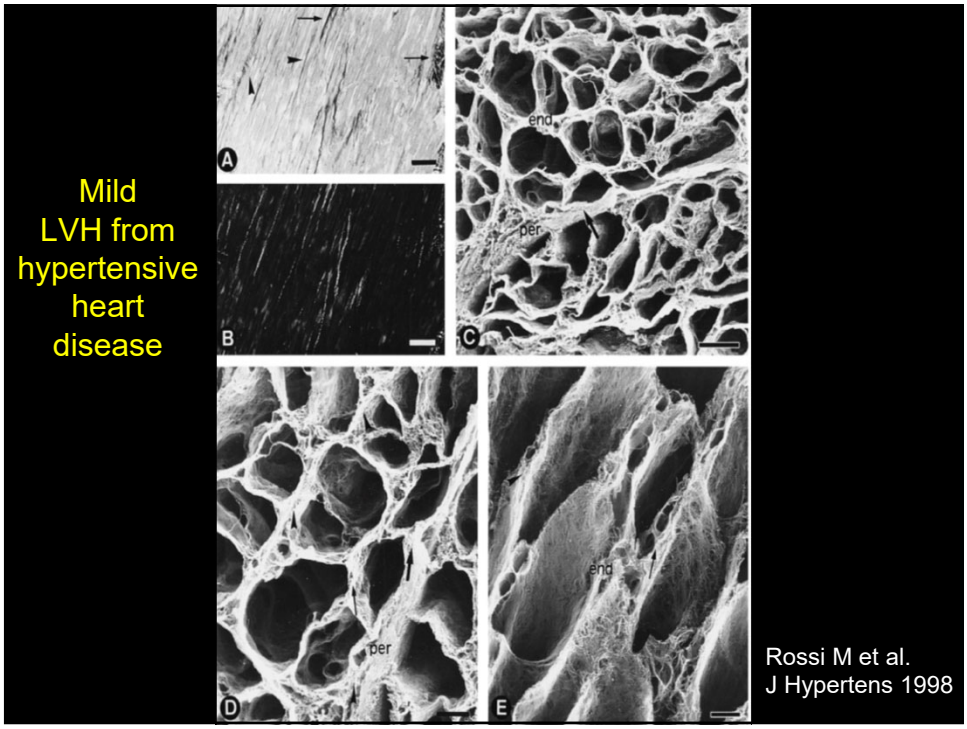
Rossi M et al.
J Hypertens 1998

17


Mild LVH from hypertensive heart disease
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D
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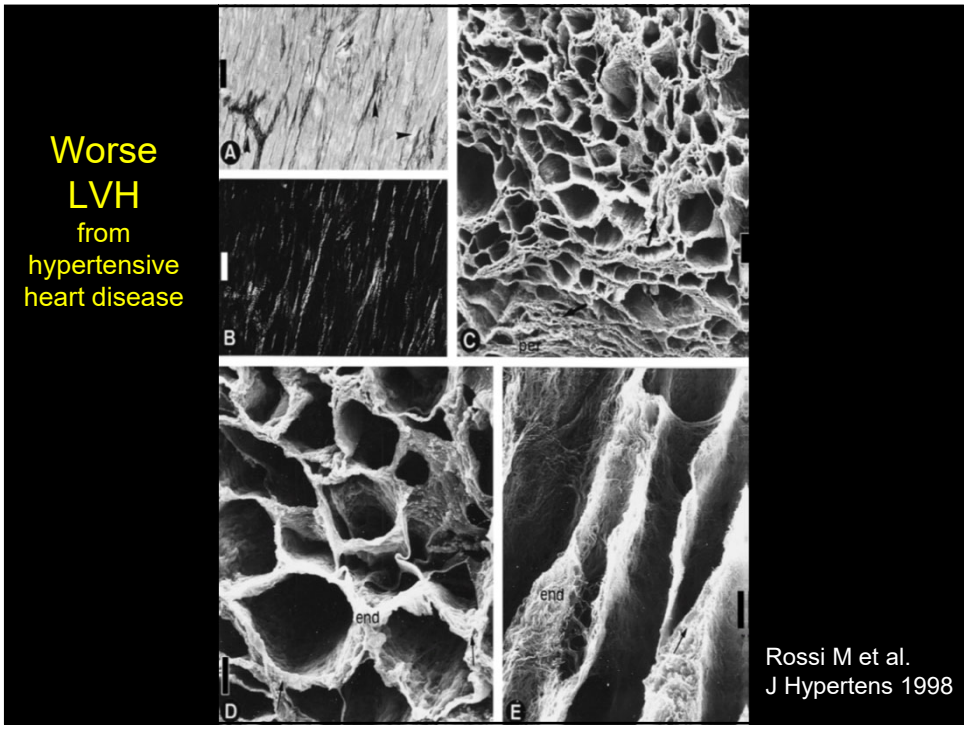
Rossi M et al.
J Hypertens 1998

18


Worse
LVH
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Rossi M et al.
J Hypertens 1998

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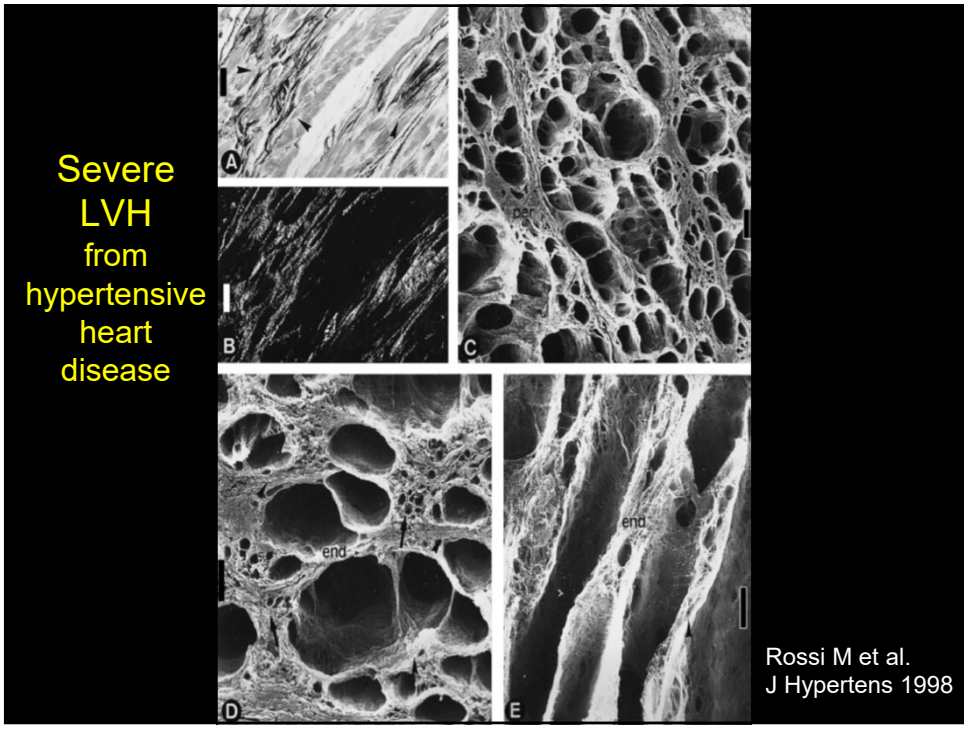
Severe
LVH
from
hypertensive
heart
disease
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per
end
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end
E
Rossi M et al.
J Hypertens 1998

20

"Cardiac/myocardial cirrhosis" in hypertensive diabetic CM

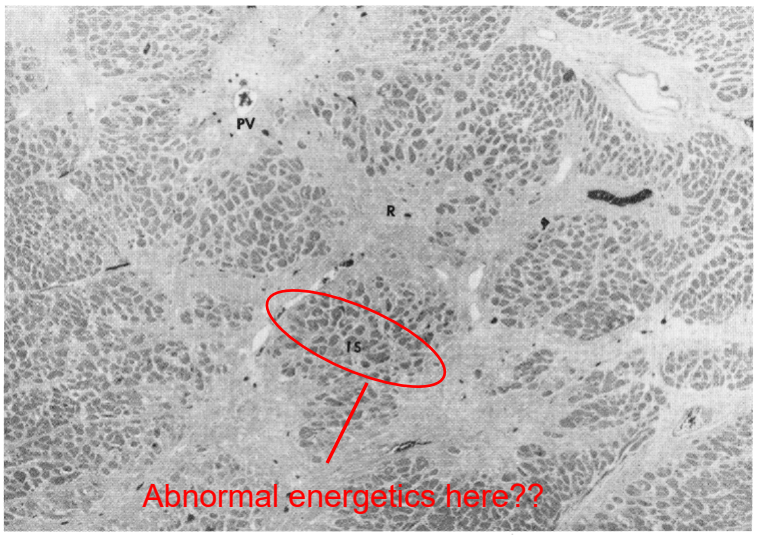

FIGURE 1. *In this histological section from the heart of a patient with hypertension and diabetes, +3 interstitial fibrosis (IS), +2 perivascular fibrosis (PV), and large areas of replacement fibrosis (R) are present. Total microscopic fibrosis score is +8. Extensive scarring has resulted in a peculiar nodularity of the myocardial architecture, reminiscent of cirrhosis at low power. Hematoxylin-eosin stain; original magnification, ×50.*

van Hoeven and Factor, Circulation 1990

21

Mechanisms for myocardial fibrosis to cause vulnerability

- Capillary rarefaction and perivascular fibrosis that limit perfusion reserve

Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Maleszewski JJ, Redfield MM. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction.Circulation. 2015; 131:550–559. doi: 10.1161/CIRCULATIONAHA.114.009625.

Kato S, Saito N, Kirigaya H, Gyotoku D, Iinuma N, Kusakawa Y, Iguchi K, Nakachi T, Fukui K, Futaki M, Iwasawa T, Kimura K, Umemura S. Impairment of coronary flow reserve evaluated by phase contrast cine-magnetic resonance imaging in patients with heart failure with preserved ejection fraction.J Am Heart Assoc. 2016; 5:e002649. doi: 10.1161/JAHA.115.002649.

Brilla CG, Janicki JS, Weber KT. Cardioreparative effects of lisinopril in rats with genetic hypertension and left ventricular hypertrophy.Circulation. 1991; 83:1771–1779.

22

Mechanisms for myocardial fibrosis to cause vulnerability

- Increased space between the capillary and collagen-encircled cardiomyocyte, increasing the oxygen diffusion distance and rendering the cardiomyocyte prone to hypoxia, an important trigger of cardiomyocyte-programmed cell death or apoptosis, potentially promoting progressive MF

Sabbah HN, Sharov VG, Lesch M, Goldstein S. Progression of heart failure: a role for interstitial fibrosis.Mol Cell Biochem. 1995; 147:29–34.CrossrefMedlineGoogle Scholar

Sabbah HN. Apoptotic cell death in heart failure.Cardiovasc Res. 2000; 45:704–712.

23

Mechanisms for myocardial fibrosis to cause vulnerability

- Myocardial stiffening from titin and collagen expansion with increased cross-linking in MF that leads to systolic and especially ***diastolic dysfunction*** and increased filling pressures

Rommel KP, von Roeder M, Latuscynski K, Oberueck C, Blazek S, Fengler K, Besler C, Sandri M, Lücke C, Gutberlet M, Linke A, Schuler G, Lurz P. Extracellular volume fraction for characterization of patients with heart failure and preserved ejection fraction.J Am Coll Cardiol. 2016; 67:1815–1825. doi: 10.1016/j.jacc.2016.02.018.

Zile MR, Baicu CF, Ikonomidis JS, Stroud RE, Nietert PJ, Bradshaw AD, Slater R, Palmer BM, Van Buren P, Meyer M, Redfield MM, Bull DA, Granzier HL, LeWinter MM. Myocardial stiffness in patients with heart failure and a preserved ejection fraction: contributions of collagen and titin.Circulation. 2015; 131:1247–1259. doi: 10.1161/CIRCULATIONAHA.114.013215.

Brilla CG, Janicki JS, Weber KT. Cardioreparative effects of lisinopril in rats with genetic hypertension and left ventricular hypertrophy.Circulation. 1991; 83:1771–1779

Brilla CG, Funck RC, Rupp H. Lisinopril-mediated regression of myocardial fibrosis in patients with hypertensive heart disease.Circulation. 2000; 102:1388–1393.

Díez J, Querejeta R, López B, González A, Larman M, Martínez Ubago JL. Losartan-dependent regression of myocardial fibrosis is associated with reduction of left ventricular chamber stiffness in hypertensive patients.Circulation. 2002; 105:2512–2517.

Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system.Circulation. 1991; 83:1849–1865.

24

Mechanisms for myocardial fibrosis to cause vulnerability

- Impaired electric conduction from disarray in the collagen network architecture that predisposes to reentrant arrhythmia and sudden death

Tamarappoo BK, John BT, Reinier K, Teodorescu C, Uy-Evanado A, Gunson K, Jui J, Chugh SS. Vulnerable myocardial interstitium in patients with isolated left ventricular hypertrophy and sudden cardiac death: a postmortem histological evaluation.J Am Heart Assoc. 2012; 1:e001511. doi: 10.1161/JAHA.112.001511.

Banypersad SM, Moon JC, Whelan C, Hawkins PN, Wechalekar AD. Updates in cardiac amyloidosis: a review.J Am Heart Assoc. 2012; 1:e000364. doi: 10.1161/JAHA.111.000364.

J.M. McLenachan, H.J. Dargie. Ventricular arrhythmias in hypertensive left ventricular hypertrophy. Relationship to coronary artery disease, left ventricular dysfunction, and myocardial fibrosis. Am J Hypertens, 3 (1990), pp. 735-740

T. Kawara, R. Derksen, J.R. de Groot, et al. Activation delay after premature stimulation in chronically diseased human myocardium relates to the architecture of interstitial fibrosis. Circulation, 104 (2001), pp. 3069-3075

K.P. Anderson, R. Walker, P. Urie, P.R. Ershler, R.L. Lux, S.V. Karwandee. Myocardial electrical propagation in patients with idiopathic dilated cardiomyopathy. J Clin Invest, 92 (1993), pp. 122-140

25

Mechanisms for myocardial fibrosis to cause vulnerability

- Final culmination of all of these insults:

- Likely impaired cardiomyocyte/mitochondrial energetics if interposing excess collagen isolates cardiomyocytes from capillaries in the setting of decreased perfusion reserve, arrhythmia, and myocardial stiffening, culminating in an engine out of fuel.

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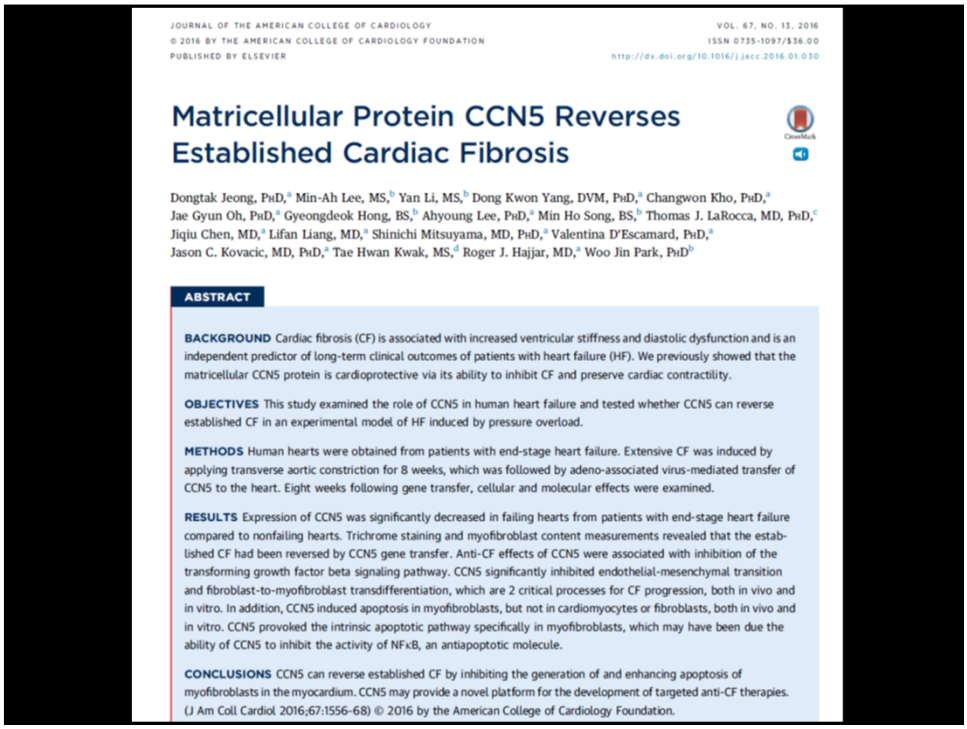

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Matricellular Protein CCN5 Reverses Established Cardiac Fibrosis

Dongtak Jeong, PhD,[a] Min-Ah Lee, MS,[b] Yan Li, MS,[b] Dong Kwon Yang, DVM, PhD,[a] Changwon Kho, PhD,[a] Jae Gyun Oh, PhD,[a] Gyeongdeok Hong, BS,[b] Ahyoung Lee, PhD,[a] Min Ho Song, BS,[b] Thomas J. LaRocca, MD, PhD,[c] Jiqiu Chen, MD,[a] Lifan Liang, MD,[a] Shinichi Mitsuyama, MD, PhD,[a] Valentina D'Escamard, PhD,[a] Jason C. Kovacic, MD, PhD,[a] Tae Hwan Kwak, MS,[d] Roger J. Hajjar, MD,[a] Woo Jin Park, PhD[b]

ABSTRACT

BACKGROUND Cardiac fibrosis (CF) is associated with increased ventricular stiffness and diastolic dysfunction and is an independent predictor of long-term clinical outcomes of patients with heart failure (HF). We previously showed that the matricellular CCN5 protein is cardioprotective via its ability to inhibit CF and preserve cardiac contractility.

OBJECTIVES This study examined the role of CCN5 in human heart failure and tested whether CCN5 can reverse established CF in an experimental model of HF induced by pressure overload.

METHODS Human hearts were obtained from patients with end-stage heart failure. Extensive CF was induced by applying transverse aortic constriction for 8 weeks, which was followed by adeno-associated virus-mediated transfer of CCN5 to the heart. Eight weeks following gene transfer, cellular and molecular effects were examined.

RESULTS Expression of CCN5 was significantly decreased in failing hearts from patients with end-stage heart failure compared to nonfailing hearts. Trichrome staining and myofibroblast content measurements revealed that the established CF had been reversed by CCN5 gene transfer. Anti-CF effects of CCN5 were associated with inhibition of the transforming growth factor beta signaling pathway. CCN5 significantly inhibited endothelial-mesenchymal transition and fibroblast-to-myofibroblast transdifferentiation, which are 2 critical processes for CF progression, both in vivo and in vitro. In addition, CCN5 induced apoptosis in myofibroblasts, but not in cardiomyocytes or fibroblasts, both in vivo and in vitro. CCN5 provoked the intrinsic apoptotic pathway specifically in myofibroblasts, which may have been due the ability of CCN5 to inhibit the activity of NFκB, an antiapoptotic molecule.

CONCLUSIONS CCN5 can reverse established CF by inhibiting the generation of and enhancing apoptosis of myofibroblasts in the myocardium. CCN5 may provide a novel platform for the development of targeted anti-CF therapies.
(J Am Coll Cardiol 2016;67:1556-68)

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4 human histology studies showing fibrosis is *reversible*:

28

Lisinopril-Mediated Regression of Myocardial Fibrosis in Patients With Hypertensive Heart Disease

Christian G. Brilla, MD, PhD; Reinhard C. Funck, MD; Heinz Rupp, PhD

Background—In arterial hypertension, left ventricular hypertrophy (LVH) includes myocyte hypertrophy and fibrosis, which leads to LV diastolic dysfunction and, finally, heart failure. In spontaneously hypertensive rats, myocardial fibrosis was regressed and LV diastolic function was improved by treatment with the angiotensin-converting enzyme inhibitor lisinopril. Whether this holds true for patients with hypertensive heart disease was addressed in this prospective, randomized, double-blind trial.

Methods and Results—A total of 35 patients with primary hypertension, LVH, and LV diastolic dysfunction were treated with either lisinopril (n=18) or hydrochlorothiazide (HCTZ; n=17). At baseline and after 6 months, LV catheterization with endomyocardial biopsy, Doppler echocardiography with measurements of LV peak flow velocities during early filling and atrial contraction and isovolumic relaxation time, and 24-hour blood pressure monitoring were performed. Myocardial fibrosis was measured by LV collagen volume fraction and myocardial hydroxyproline concentration. With lisinopril, collagen volume fraction decreased from 6.9±0.6% to 6.3±0.6% ($P<0.05$ versus HCTZ) and myocardial hydroxyproline concentration from 9.9±0.3 to 8.3±0.4 μg/mg of LV dry weight ($P<0.00001$ versus HCTZ); this was associated with an increase in the early filling and atrial contraction LV peak flow velocity ratio from 0.72±0.04 to 0.91±0.06 ($P<0.05$ versus HCTZ) and a decrease in isovolumic relaxation time from 123±9 to 81±5 ms ($P<0.00002$ versus HCTZ). Normalized blood pressure did not significantly change in either group. No LVH regression occurred in lisinopril-treated patients, whereas with HCTZ, myocyte diameter was reduced from 22.1±0.6 to 20.7±0.7 μm ($P<0.01$ versus lisinopril).

Conclusions—In patients with hypertensive heart disease, angiotensin-converting enzyme inhibition with lisinopril can regress myocardial fibrosis, irrespective of LVH regression, and it is accompanied by improved LV diastolic function. (***Circulation***. **2000;102:1388-1393.**)

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Losartan-Dependent Regression of Myocardial Fibrosis Is Associated With Reduction of Left Ventricular Chamber Stiffness in Hypertensive Patients

Javier Díez, MD, PhD; Ramón Querejeta, MD, PhD; Begoña López, BSc; Arantxa González, BSc; Mariano Larman, MD; José L. Martínez Ubago, MD

Background—This study was designed to investigate whether myocardial collagen content is related to myocardial stiffness in patients with essential hypertension.

Methods and Results—The study was performed in 34 patients with hypertensive heart disease. Nineteen of these patients were also evaluated after 12 months of treatment with losartan. Transvenous endomyocardial biopsies of the interventricular septum were performed to quantify collagen volume fraction (CVF). Left ventricular (LV) chamber stiffness (K_{LV}) was determined from the deceleration time of the early mitral filling wave as measured by Doppler echocardiography. Histological analysis at baseline revealed the presence of 2 subgroups of patients: 8 with severe fibrosis and 26 with nonsevere fibrosis. Values of CVF and K_{LV} were significantly higher in the 2 subgroups of hypertensives than in normotensives. In addition, compared with patients with nonsevere fibrosis, patients with severe fibrosis exhibited significantly increased values of CVF and K_{LV}. After treatment, CVF and K_{LV} decreased significantly in patients with severe fibrosis (n=7). None of these parameters changed significantly after treatment in patients with nonsevere fibrosis (n=12). CVF was directly correlated with K_{LV} ($r=0.415$, $P<0.02$) in all hypertensives.

Conclusions—These findings show a strong association between myocardial collagen content and LV chamber stiffness in patients with essential hypertension. Our results also suggest that the ability of losartan to induce regression of severe myocardial fibrosis is associated with diminution of myocardial stiffness in hypertensive patients. (***Circulation***. **2002; 105:2512-2517.**)

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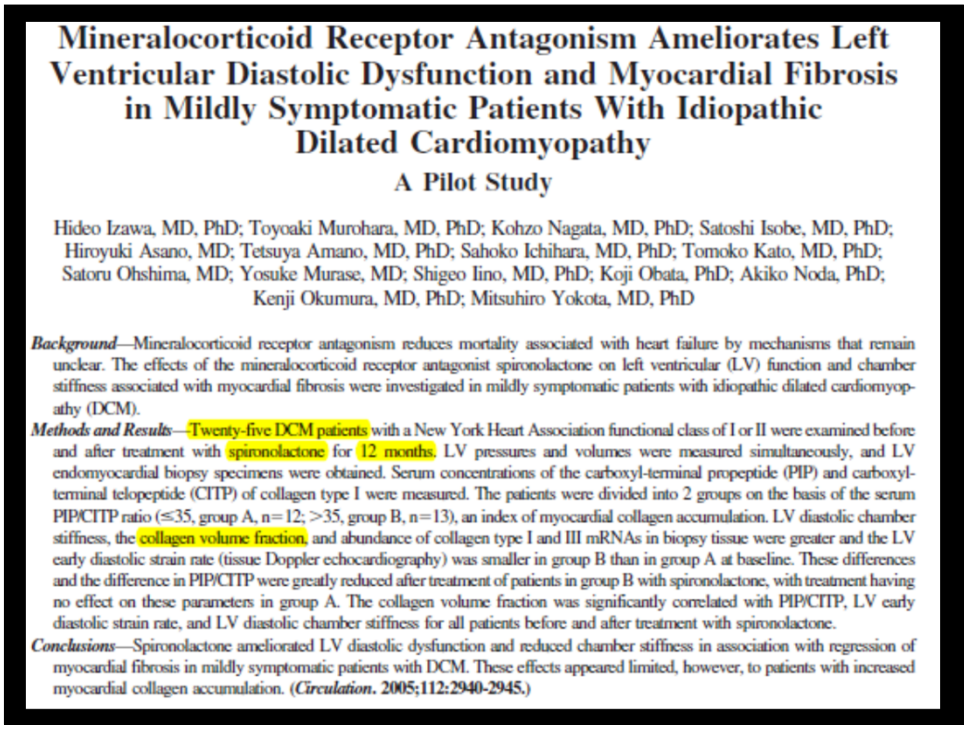

Mineralocorticoid Receptor Antagonism Ameliorates Left Ventricular Diastolic Dysfunction and Myocardial Fibrosis in Mildly Symptomatic Patients With Idiopathic Dilated Cardiomyopathy

A Pilot Study

Hideo Izawa, MD, PhD; Toyoaki Murohara, MD, PhD; Kohzo Nagata, MD, PhD; Satoshi Isobe, MD, PhD; Hiroyuki Asano, MD; Tetsuya Amano, MD, PhD; Sahoko Ichihara, MD, PhD; Tomoko Kato, MD, PhD; Satoru Ohshima, MD; Yosuke Murase, MD; Shigeo Iino, MD, PhD; Koji Obata, PhD; Akiko Noda, PhD; Kenji Okumura, MD, PhD; Mitsuhiro Yokota, MD, PhD

Background—Mineralocorticoid receptor antagonism reduces mortality associated with heart failure by mechanisms that remain unclear. The effects of the mineralocorticoid receptor antagonist spironolactone on left ventricular (LV) function and chamber stiffness associated with myocardial fibrosis were investigated in mildly symptomatic patients with idiopathic dilated cardiomyopathy (DCM).

Methods and Results—Twenty-five DCM patients with a New York Heart Association functional class of I or II were examined before and after treatment with spironolactone for 12 months. LV pressures and volumes were measured simultaneously, and LV endomyocardial biopsy specimens were obtained. Serum concentrations of the carboxyl-terminal propeptide (PIP) and carboxyl-terminal telopeptide (CITP) of collagen type I were measured. The patients were divided into 2 groups on the basis of the serum PIP/CITP ratio (≤35, group A, n=12; >35, group B, n=13), an index of myocardial collagen accumulation. LV diastolic chamber stiffness, the collagen volume fraction, and abundance of collagen type I and III mRNAs in biopsy tissue were greater and the LV early diastolic strain rate (tissue Doppler echocardiography) was smaller in group B than in group A at baseline. These differences and the difference in PIP/CITP were greatly reduced after treatment of patients in group B with spironolactone, with treatment having no effect on these parameters in group A. The collagen volume fraction was significantly correlated with PIP/CITP, LV early diastolic strain rate, and LV diastolic chamber stiffness for all patients before and after treatment with spironolactone.

Conclusions—Spironolactone ameliorated LV diastolic dysfunction and reduced chamber stiffness in association with regression of myocardial fibrosis in mildly symptomatic patients with DCM. These effects appeared limited, however, to patients with increased myocardial collagen accumulation. (***Circulation***. **2005;112:2940-2945.**)

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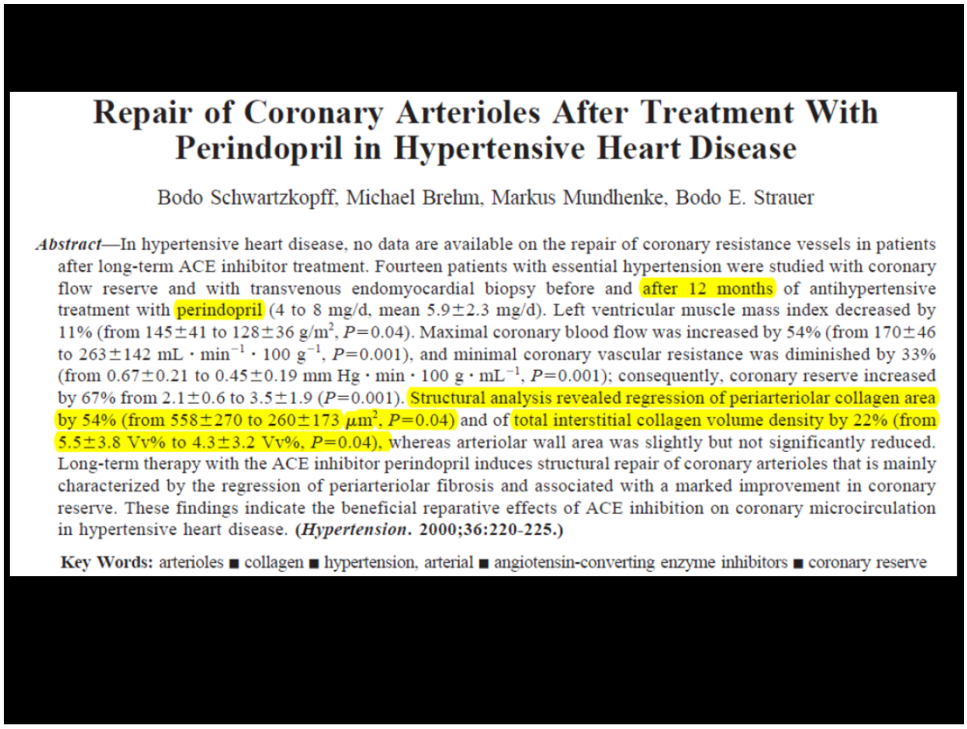

Repair of Coronary Arterioles After Treatment With Perindopril in Hypertensive Heart Disease

Bodo Schwartzkopff, Michael Brehm, Markus Mundhenke, Bodo E. Strauer

Abstract—In hypertensive heart disease, no data are available on the repair of coronary resistance vessels in patients after long-term ACE inhibitor treatment. Fourteen patients with essential hypertension were studied with coronary flow reserve and with transvenous endomyocardial biopsy before and after 12 months of antihypertensive treatment with perindopril (4 to 8 mg/d, mean 5.9±2.3 mg/d). Left ventricular muscle mass index decreased by 11% (from 145±41 to 128±36 g/m^2, P=0.04). Maximal coronary blood flow was increased by 54% (from 170±46 to 263±142 mL · min^{-1} · 100 g^{-1}, P=0.001), and minimal coronary vascular resistance was diminished by 33% (from 0.67±0.21 to 0.45±0.19 mm Hg · min · 100 g · mL^{-1}, P=0.001); consequently, coronary reserve increased by 67% from 2.1±0.6 to 3.5±1.9 (P=0.001). Structural analysis revealed regression of periarteriolar collagen area by 54% (from 558±270 to 260±173 μm^2, P=0.04) and of total interstitial collagen volume density by 22% (from 5.5±3.8 Vv% to 4.3±3.2 Vv%, P=0.04), whereas arteriolar wall area was slightly but not significantly reduced. Long-term therapy with the ACE inhibitor perindopril induces structural repair of coronary arterioles that is mainly characterized by the regression of periarteriolar fibrosis and associated with a marked improvement in coronary reserve. These findings indicate the beneficial reparative effects of ACE inhibition on coronary microcirculation in hypertensive heart disease. (***Hypertension***. **2000;36:220-225.**)

Key Words: arterioles ■ collagen ■ hypertension, arterial ■ angiotensin-converting enzyme inhibitors ■ coronary reserve

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But only very modest changes with renin-angiotensin-aldosterone inhibition, ~1% absolute Δ

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	Dilated cardiomyopathy	12	4.7	3.4	≈28%	≈1.3%
Lisinopril	Brilla et al	Hypertensive heart disease	6	6.9	6.3	9%	0.6%
Perindopril	Schwartzkopff et al	Hypertensive heart disease	12	5.5	4.3	22%	1.2%
Losartan	Díez et al	Hypertensive heart disease	12	4.32	3.72	14%	0.6%
			Average: 10.5			Average: 18%	Average: 0.93%

Erik B. Schelbert, Hani N. Sabbah, Javed Butler, and Mihai Gheorghiade.
https://doi.org/10.1161/CIRCIMAGING.116.005619Circulation: Cardiovascular Imaging. 2017;10:e005619

33

2 more interesting fibrosis studies in HF

34

HFpEF vs. HFrEF
…collagen volume fraction is equally elevated…

Heart Failure

Myocardial Structure and Function Differ in Systolic and Diastolic Heart Failure

Loek van Heerebeek, MD; Attila Borbély, MD; Hans W.M. Niessen, MD, PhD; Jean G.F. Bronzwaer, MD, PhD; Jolanda van der Velden, PhD; Ger J.M. Stienen, PhD; Wolfgang A. Linke, PhD; Gerrit J. Laarman, MD, PhD; Walter J. Paulus, MD, PhD

Background—To support the clinical distinction between systolic heart failure (SHF) and diastolic heart failure (DHF), left ventricular (LV) myocardial structure and function were compared in LV endomyocardial biopsy samples of patients with systolic and diastolic heart failure.

Methods and Results—Patients hospitalized for worsening heart failure were classified as having SHF (n=22; LV ejection fraction (EF) 34±2%) or DHF (n=22; LVEF 62±2%). No patient had coronary artery disease or biopsy evidence of infiltrative or inflammatory myocardial disease. More DHF patients had a history of arterial hypertension and were obese. Biopsy samples were analyzed with histomorphometry and electron microscopy. Single cardiomyocytes were isolated from the samples, stretched to a sarcomere length of 2.2 μm to measure passive force ($F_{passive}$), and activated with calcium-containing solutions to measure total force. Cardiomyocyte diameter was higher in DHF (20.3±0.6 versus 15.1±0.4 μm, $P<0.001$), but collagen volume fraction was equally elevated. Myofibrillar density was lower in SHF (36±2% versus 46±2%, $P<0.001$). Cardiomyocytes of DHF patients had higher $F_{passive}$ (7.1±0.6 versus 5.3±0.3 kN/m^2; $P<0.01$), but their total force was comparable. After administration of protein kinase A to the cardiomyocytes, the drop in $F_{passive}$ was larger ($P<0.01$) in DHF than in SHF.

Conclusions—LV myocardial structure and function differ in SHF and DHF because of distinct cardiomyocyte abnormalities. These findings support the clinical separation of heart failure patients into SHF and DHF phenotypes. (***Circulation*. 2006;113:1966-1973.**)

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Degree of Cardiac Fibrosis and Hypertrophy at Time of Implantation Predicts Myocardial Improvement During Left Ventricular Assist Device Support

Brian A. Bruckner, MD,[a] Peter Razeghi, MD,[b] Sonny Stetson, BS,[c] Larry Thompson, MD,[a] Javier Lafuente, MD,[a] Mark Entman, MD,[a] Matthias Loebe, MD, PhD,[a] George Noon, MD,[a] Heinrich Taegtmeyer, MD, PhD,[b] O. H. Frazier, MD,[b] and Keith Youker, PhD[a]

Background: There have been increasing reports of cardiac improvement in heart failure patients supported by left ventricular assist devices (LVADs i.e.), including a number of patients who have tolerated removal of the device without the benefit of cardiac transplant. In the current study, we retrospectively investigated echocardiographic and histologic changes in patients supported by LVADs (n = 18). The goal of our study was to determine if the degree of cardiac fibrosis and myocyte size in pre-implant biopsies could predict myocardial improvement as assessed by improvements in ejection fraction (EF) during LVAD support.

Methods: We determined total collagen content in myocardial biopsy specimens by a semi-quantitative analysis of positive Picro-Sirius Red–stained areas and myocyte size measurements by computerized edge detection software.

Results: During LVAD support, 9 of the 18 patients (Group A) were distinguished by significant improvement in ejection fraction (pre <20% vs unloaded 34 ± 5%). In addition, Group A patients had significantly less fibrosis and smaller myocytes than their Group B counterparts, whose EF did not improve. There was an inverse correlation between pre-implant biopsy collagen levels and myocyte size with increases in EF during LVAD unloading.

Conclusions: We found that the patients who demonstrated the greatest improvements in EF during support had less fibrosis and smaller myocytes at the time of device implantation. We propose that tissue profiling a patient's pre-implant biopsy for fibrosis and myocyte size may allow stratification in Stage IV heart failure and may predict myocardial improvement during LVAD support. J Heart Lung Transplant 2004;23: 36–42.

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Histology suggests adverse associations between myocardial fibrosis and morbidity and mortality

Myocardial fibrosis is clearly ubiquitous in diseased myocardium, regardless of 'stimulus' or etiology

How do leverage this information clinically??

→ ECV !

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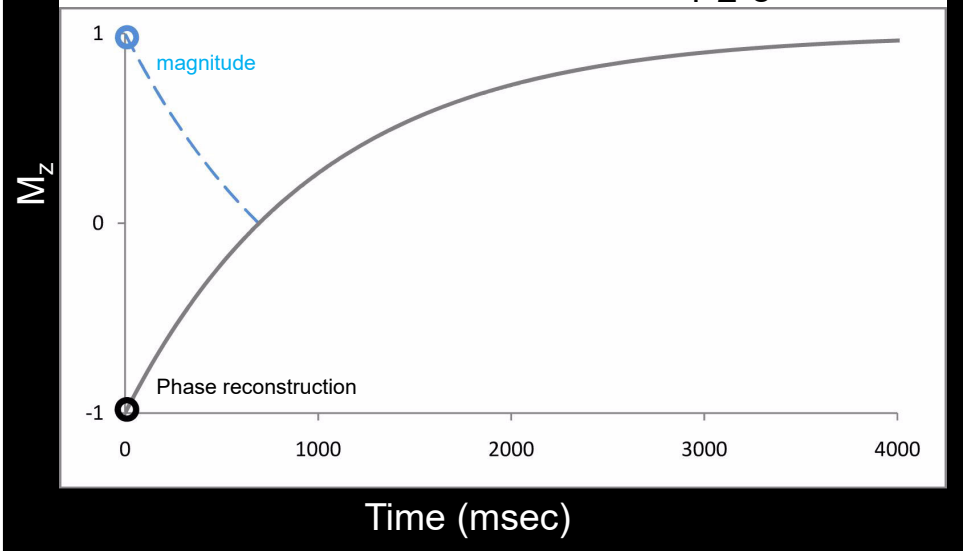
CMR ECV requires T1 or R1 measurement…exponentiated time constant

Signal intensity (magnetization) $= 1-2 \cdot e^{(-\text{time} / \mathbf{T1})}$
$= 1-2 \cdot e^{(-\text{time} \cdot \mathbf{R1})}$



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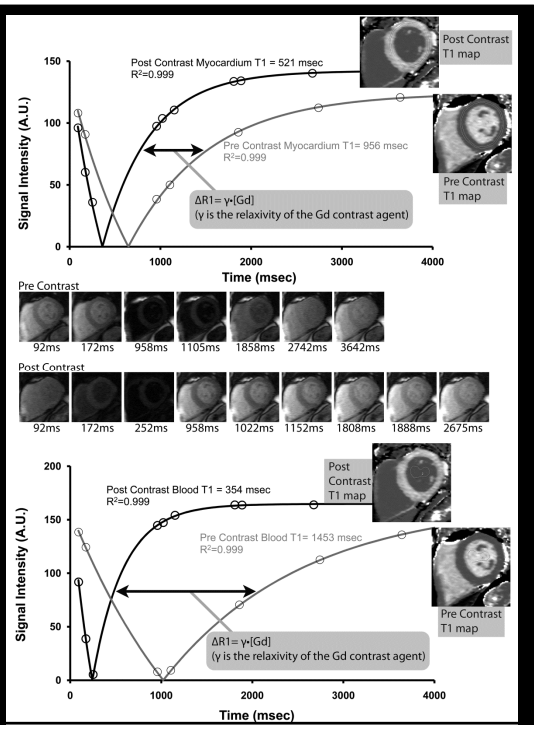
"MOLLI"

developed by Daniel Messroghli

permits pixelwise T1 maps since component images after an RF inversion pulse are acquired at same point in the cardiac cycle



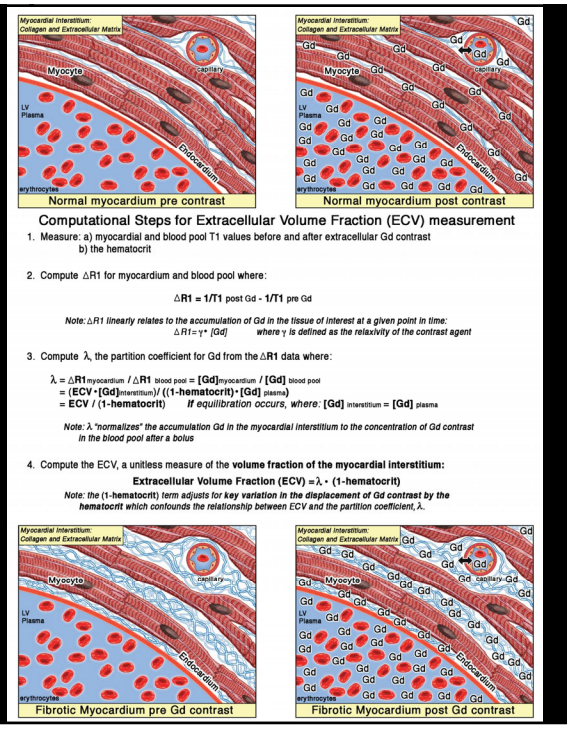
Messroghli DR, et al. J Magn Reson Imaging. 2007;26:1081-1086

Wong TC, et al. Circulation. 2012;126:1206-1216

39

ExtraCellular Volume fraction (ECV) measures myocardial interstitial expansion

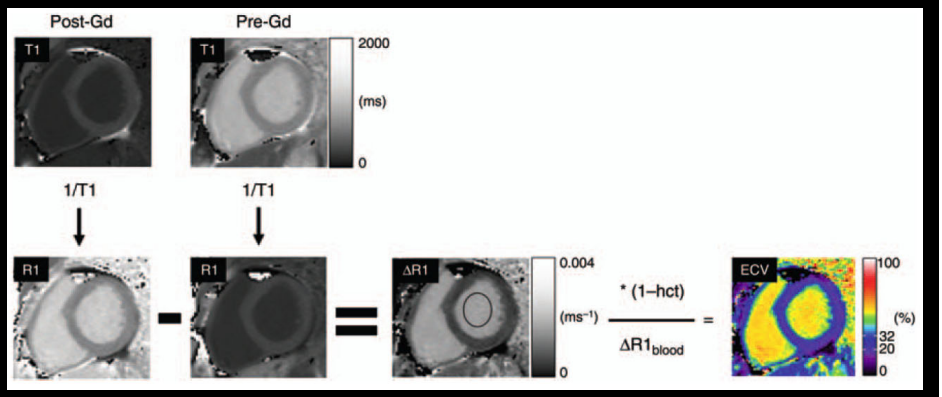
= myocardial Gd uptake relative to plasma (not whole blood measured from images)



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

40

Imaging the interstitial space with Extracellular Volume Fraction (ECV)



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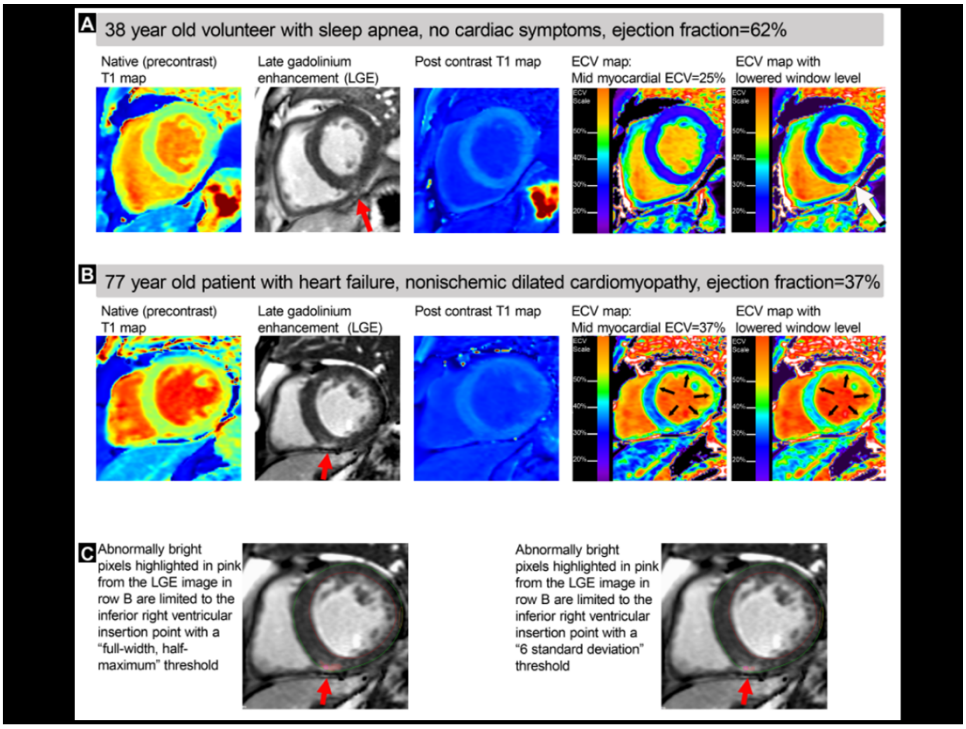

42

ECV is validated against collagen volume fraction in human myocardium (many centers, many papers)

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Generally high R2 values, despite the potential for 1) *spatial heterogeneity of myocardial fibrosis*, and 2) *destructive histologic processing* to introduce error

1. R2= 0.893
2. R2=0.796
3. R2=0.767
4. R2=0.72
5. R2=0.69
6. R2=0.685
7. R2=0.608
8. R2=0.56

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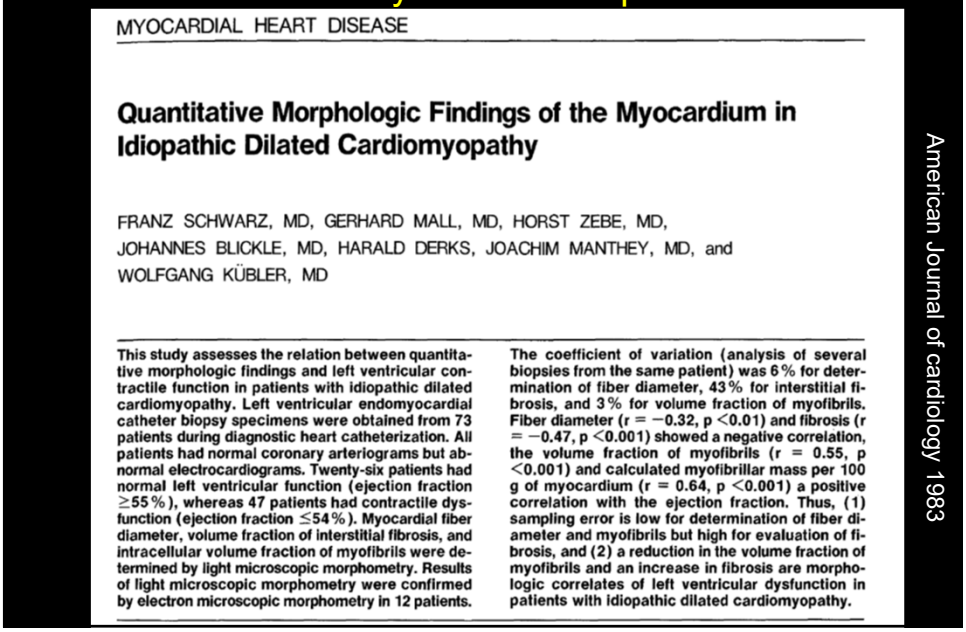
Spatial variation plagues needle and endomyocardial biospies



MYOCARDIAL HEART DISEASE

Quantitative Morphologic Findings of the Myocardium in Idiopathic Dilated Cardiomyopathy

FRANZ SCHWARZ, MD, GERHARD MALL, MD, HORST ZEBE, MD, JOHANNES BLICKLE, MD, HARALD DERKS, JOACHIM MANTHEY, MD, and WOLFGANG KÜBLER, MD

This study assesses the relation between quantitative morphologic findings and left ventricular contractile function in patients with idiopathic dilated cardiomyopathy. Left ventricular endomyocardial catheter biopsy specimens were obtained from 73 patients during diagnostic heart catheterization. All patients had normal coronary arteriograms but abnormal electrocardiograms. Twenty-six patients had normal left ventricular function (ejection fraction ≥55%), whereas 47 patients had contractile dysfunction (ejection fraction ≤54%). Myocardial fiber diameter, volume fraction of interstitial fibrosis, and intracellular volume fraction of myofibrils were determined by light microscopic morphometry. Results of light microscopic morphometry were confirmed by electron microscopic morphometry in 12 patients.

The coefficient of variation (analysis of several biopsies from the same patient) was 6% for determination of fiber diameter, 43% for interstitial fibrosis, and 3% for volume fraction of myofibrils. Fiber diameter ($r = -0.32$, $p < 0.01$) and fibrosis ($r = -0.47$, $p < 0.001$) showed a negative correlation, the volume fraction of myofibrils ($r = 0.55$, $p < 0.001$) and calculated myofibrillar mass per 100 g of myocardium ($r = 0.64$, $p < 0.001$) a positive correlation with the ejection fraction. Thus, (1) sampling error is low for determination of fiber diameter and myofibrils but high for evaluation of fibrosis, and (2) a reduction in the volume fraction of myofibrils and an increase in fibrosis are morphologic correlates of left ventricular dysfunction in patients with idiopathic dilated cardiomyopathy.

American Journal of cardiology 1983

45

Diffuse fibrosis is not homogeneous
(Coefficient of variation=SD/mean)

- Left ventricular endomyocardial catheter biopsies from 73 patients with idiopathic dilated cardiomyopathy
- The coefficient of variation (several biopsies from the same patient) was:
  - 6% for determination of fiber diameter,
  - 43% for interstitial fibrosis,
  - 3% for volume fraction of myofibrils.
- Sampling error is high for evaluation of fibrosis,
- A reduction in the volume fraction of myofibrils and an increase in fibrosis are morphologic correlates of left ventricular dysfunction in patients with idiopathic dilated cardiomyopathy.

Schwarz F, Mall G, Zebe H et al. Quantitative morphologic findings of the myocardium in idiopathic dilated cardiomyopathy. Am J Cardiol 1983;51:501-6.

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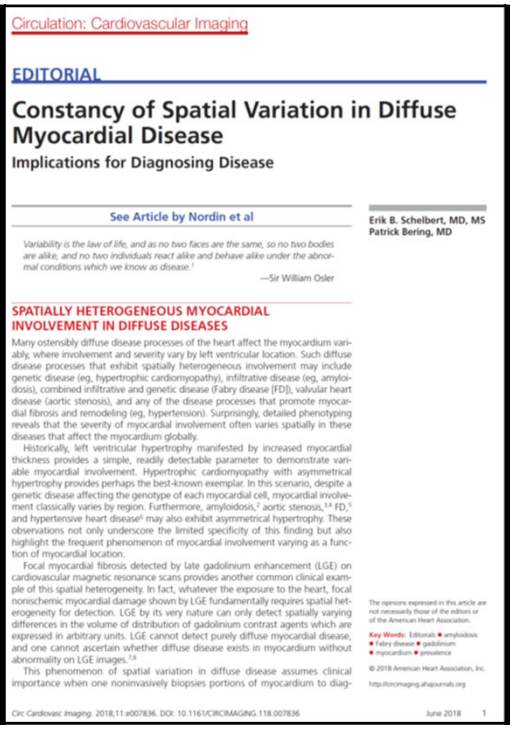
Diffuse ≠ homogenous

Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions which we know as disease.

—Sir William Osler

Analogous to HCM, amyloid, etc



Circulation: Cardiovascular Imaging

EDITORIAL

Constancy of Spatial Variation in Diffuse Myocardial Disease

Implications for Diagnosing Disease

See Article by Nordin et al

Erik B. Schelbert, MD, MS
Patrick Bering, MD

Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions which we know as disease.[1]

—Sir William Osler

SPATIALLY HETEROGENEOUS MYOCARDIAL INVOLVEMENT IN DIFFUSE DISEASES

Many ostensibly diffuse disease processes of the heart affect the myocardium variably, where involvement and severity vary by left ventricular location. Such diffuse disease processes that exhibit spatially heterogeneous involvement may include genetic disease (eg, hypertrophic cardiomyopathy), infiltrative disease (eg, amyloidosis), combined infiltrative and genetic disease (Fabry disease [FD]), valvular heart disease (aortic stenosis), and any of the disease processes that promote myocardial fibrosis and remodeling (eg, hypertension). Surprisingly, detailed phenotyping reveals that the severity of myocardial involvement often varies spatially in these diseases that affect the myocardium globally.

Historically, left ventricular hypertrophy manifested by increased myocardial thickness provides a simple, readily detectable parameter to demonstrate variable myocardial involvement. Hypertrophic cardiomyopathy with asymmetrical hypertrophy provides perhaps the best-known exemplar. In this scenario, despite a genetic disease affecting the genotype of each myocardial cell, myocardial involvement classically varies by region. Furthermore, amyloidosis,[2] aortic stenosis,[3,4] FD,[5] and hypertensive heart disease[6] may also exhibit asymmetrical hypertrophy. These observations not only underscore the limited specificity of this finding but also highlight the frequent phenomenon of myocardial involvement varying as a function of myocardial location.

Focal myocardial fibrosis detected by late gadolinium enhancement (LGE) on cardiovascular magnetic resonance scans provides another common clinical example of this spatial heterogeneity. In fact, whatever the exposure to the heart, focal nonischemic myocardial damage shown by LGE fundamentally requires spatial heterogeneity for detection. LGE by its very nature can only detect spatially varying differences in the volume of distribution of gadolinium contrast agents which are expressed in arbitrary units. LGE cannot detect purely diffuse myocardial disease, and one cannot ascertain whether diffuse disease exists in myocardium without abnormality on LGE images.[7,8]

This phenomenon of spatial variation in diffuse disease assumes clinical importance when one noninvasively biopsies portions of myocardium to diag-

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

Key Words: Editorials ■ amyloidosis ■ Fabry disease ■ gadolinium ■ myocardium ■ prevalence

http://circimaging.ahajournals.org

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ECV in the clinical setting

HFpEF

48

On multivariate linear regression analyses including ECV, E/E', and left atrial volume index as the noninvasive imaging parameters potentially informing on LV stiffness, ECV emerged as the only independent predictor for intrinsic LV stiffness ($ß_{standardized}$ = 0.75; $ß_{nonstandardized}$ = 0.21; p< 0.01).

Echo probably too load dependent…

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

Karl-Philipp Rommel, MD,[a] Maximilian von Roeder, MD,[a] Konrad Latuscynski, BSc,[a] Christian Oberueck, BSc,[a] Stephan Blazek, MD,[a] Karl Fengler, MD,[a] Christian Besler, MD,[a] Marcus Sandri, MD,[a] Christian Lücke, MD,[b] Matthias Gutberlet, MD,[b] Axel Linke, MD,[a] Gerhard Schuler, MD,[a] Philipp Lurz, MD, PhD[a]

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 ($ß = 0.75$; $p < 0.01$).

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.

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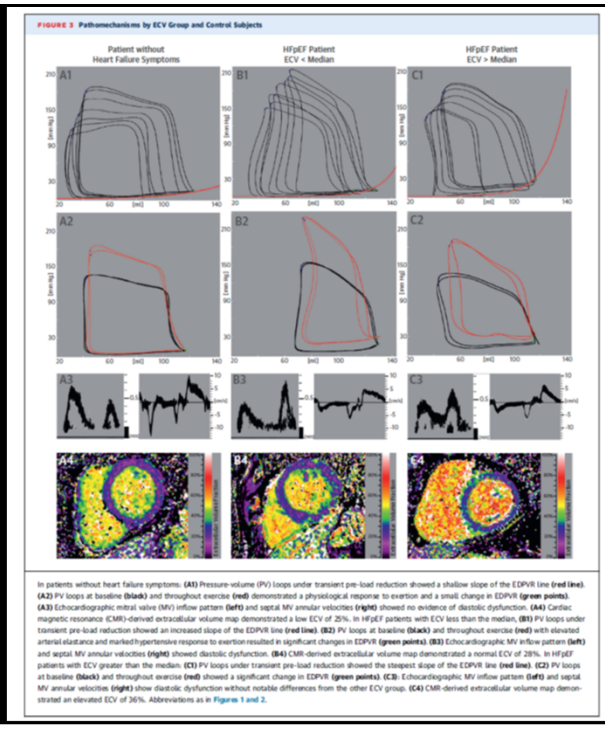

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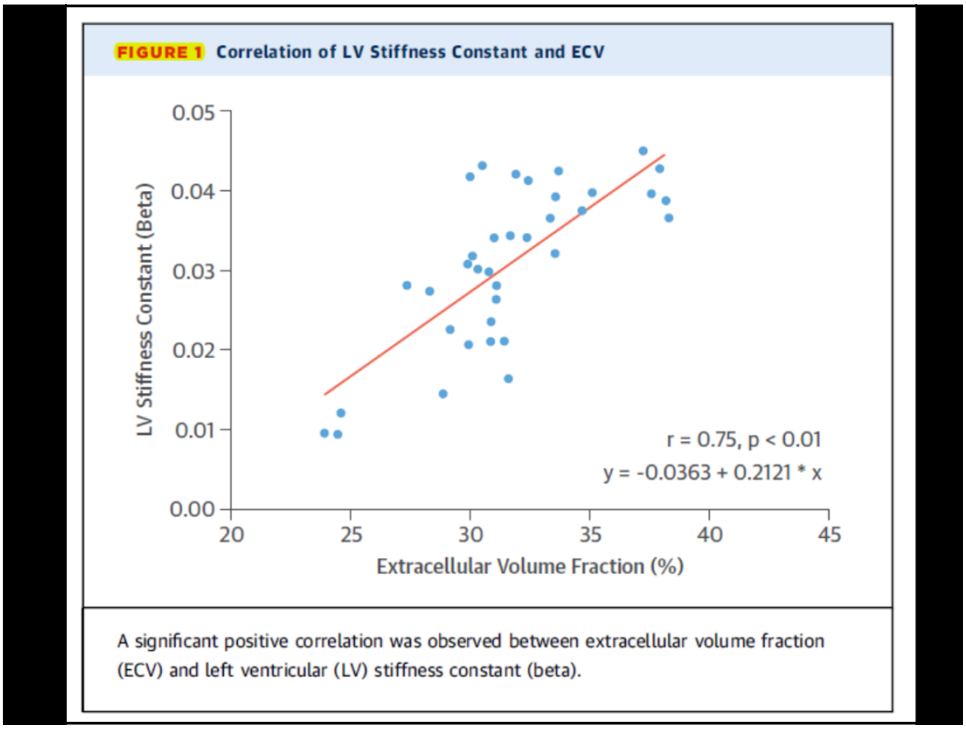

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ECV better agrees with EDPVR than echo indices (too load dependent)

- ECV was significantly higher in patients with HFpEF
- HFpEF patients had higher LV EDPs at baseline and during exercise as well as amore pronounced increase in EDPVR in response to physical exertion (Δ EDPVR)
- On multivariate linear regression analyses including ECV, E/E', and left atrial volume index predicting LV stiffness, ECV was the only independent predictor for intrinsic LV stiffness ($p < 0.01$)

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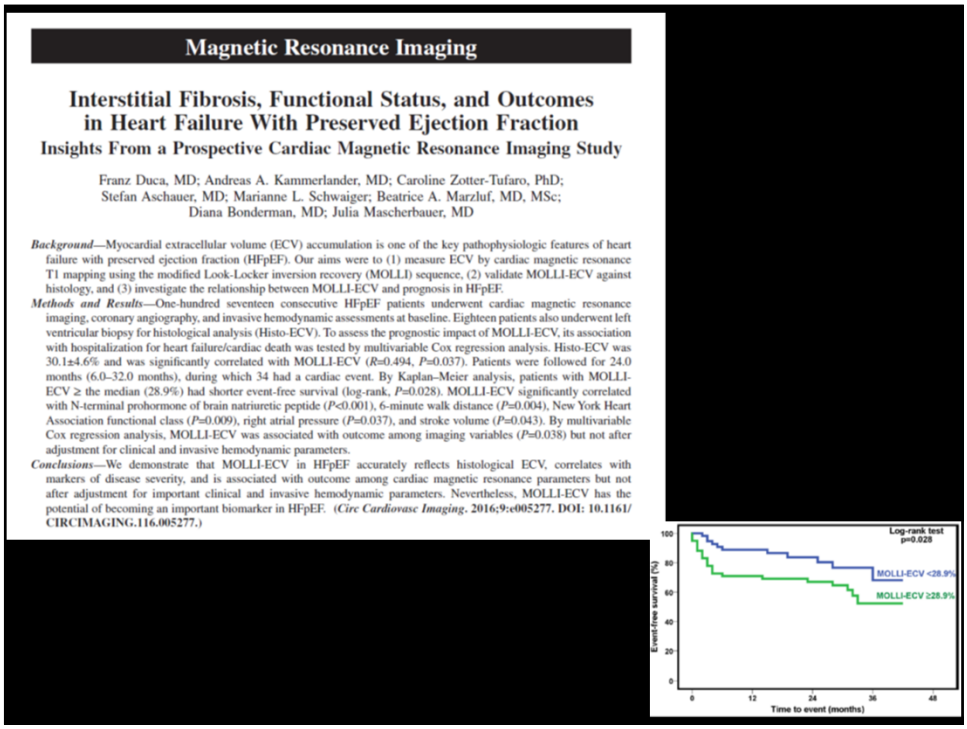

Magnetic Resonance Imaging

Interstitial Fibrosis, Functional Status, and Outcomes in Heart Failure With Preserved Ejection Fraction

Insights From a Prospective Cardiac Magnetic Resonance Imaging Study

Franz Duca, MD; Andreas A. Kammerlander, MD; Caroline Zotter-Tufaro, PhD; Stefan Aschauer, MD; Marianne L. Schwaiger; Beatrice A. Marzluf, MD, MSc; Diana Bonderman, MD; Julia Mascherbauer, MD

Background—Myocardial extracellular volume (ECV) accumulation is one of the key pathophysiologic features of heart failure with preserved ejection fraction (HFpEF). Our aims were to (1) measure ECV by cardiac magnetic resonance T1 mapping using the modified Look-Locker inversion recovery (MOLLI) sequence, (2) validate MOLLI-ECV against histology, and (3) investigate the relationship between MOLLI-ECV and prognosis in HFpEF.

Methods and Results—One-hundred seventeen consecutive HFpEF patients underwent cardiac magnetic resonance imaging, coronary angiography, and invasive hemodynamic assessments at baseline. Eighteen patients also underwent left ventricular biopsy for histological analysis (Histo-ECV). To assess the prognostic impact of MOLLI-ECV, its association with hospitalization for heart failure/cardiac death was tested by multivariable Cox regression analysis. Histo-ECV was 30.1±4.6% and was significantly correlated with MOLLI-ECV (R=0.494, P=0.037). Patients were followed for 24.0 months (6.0–32.0 months), during which 34 had a cardiac event. By Kaplan–Meier analysis, patients with MOLLI-ECV ≥ the median (28.9%) had shorter event-free survival (log-rank, P=0.028). MOLLI-ECV significantly correlated with N-terminal prohormone of brain natriuretic peptide (P<0.001), 6-minute walk distance (P=0.004), New York Heart Association functional class (P=0.009), right atrial pressure (P=0.037), and stroke volume (P=0.043). By multivariable Cox regression analysis, MOLLI-ECV was associated with outcome among imaging variables (P=0.038) but not after adjustment for clinical and invasive hemodynamic parameters.

Conclusions—We demonstrate that MOLLI-ECV in HFpEF accurately reflects histological ECV, correlates with markers of disease severity, and is associated with outcome among cardiac magnetic resonance parameters but not after adjustment for important clinical and invasive hemodynamic parameters. Nevertheless, MOLLI-ECV has the potential of becoming an important biomarker in HFpEF. (*Circ Cardiovasc Imaging*. 2016;9:e005277. DOI: 10.1161/CIRCIMAGING.116.005277.)

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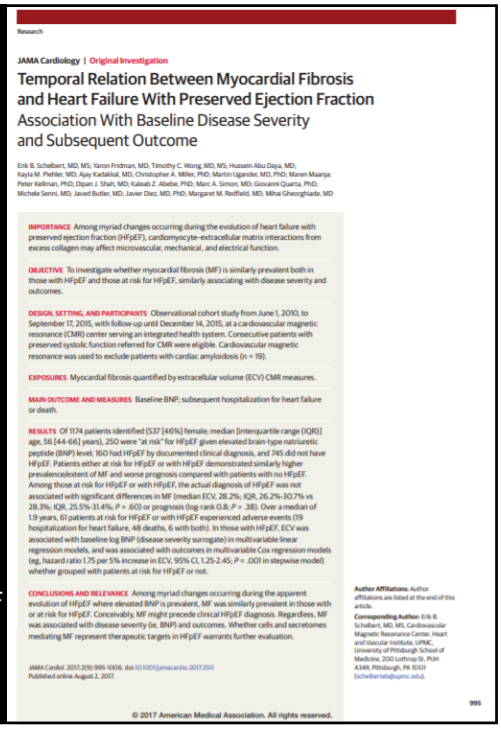
Among myriad changes occurring during the apparent evolution of HFpEF where elevated BNP is prevalent, MF was similarly prevalent in those with or at risk for HFpEF

Conceivably, MF might precede clinical HFpEF diagnosis.

Regardless, MF was associated with disease severity (ie, BNP) and outcomes.

Whether cells and secretomes mediating MF represent therapeutic targets in HFpEF warrants further evaluation



Research

JAMA Cardiology | Original Investigation

Temporal Relation Between Myocardial Fibrosis and Heart Failure With Preserved Ejection Fraction

Association With Baseline Disease Severity and Subsequent Outcome

Erik B. Schelbert, MD, MS; Yaron Fridman, MD; Timothy C. Wong, MD, MS; Hussein Abu Daya, MD; Kayla M. Piehler, MD; Ajay Kadakkal, MD; Christopher A. Miller, PhD; Martin Ugander, MD, PhD; Maren Maanja; Peter Kellman, PhD; Dipan J. Shah, MD; Kaleab Z. Abebe, PhD; Marc A. Simon, MD; Giovanni Quarta, PhD; Michele Senni, MD; Javed Butler, MD; Javier Diez, MD, PhD; Margaret M. Redfield, MD; Mihai Gheorghiade, MD

IMPORTANCE Among myriad changes occurring during the evolution of heart failure with preserved ejection fraction (HFpEF), cardiomyocyte-extracellular matrix interactions from excess collagen may affect microvascular, mechanical, and electrical function.

OBJECTIVE To investigate whether myocardial fibrosis (MF) is similarly prevalent both in those with HFpEF and those at risk for HFpEF, similarly associating with disease severity and outcomes.

DESIGN, SETTING, AND PARTICIPANTS Observational cohort study from June 1, 2010, to September 17, 2015, with follow-up until December 14, 2015, at a cardiovascular magnetic resonance (CMR) center serving an integrated health system. Consecutive patients with preserved systolic function referred for CMR were eligible. Cardiovascular magnetic resonance was used to exclude patients with cardiac amyloidosis (n = 19).

EXPOSURES Myocardial fibrosis quantified by extracellular volume (ECV) CMR measures.

MAIN OUTCOME AND MEASURES Baseline BNP; subsequent hospitalization for heart failure or death.

RESULTS Of 1174 patients identified (537 [46%] female, median [interquartile range (IQR)] age, 56 [44-66] years), 250 were "at risk" for HFpEF given elevated brain-type natriuretic peptide (BNP) level; 160 had HFpEF by documented clinical diagnosis, and 745 did not have HFpEF. Patients either at risk for HFpEF or with HFpEF demonstrated similarly higher prevalence/extent of MF and worse prognosis compared with patients with no HFpEF. Among those at risk for HFpEF or with HFpEF, the actual diagnosis of HFpEF was not associated with significant differences in MF (median ECV, 28.2%; IQR, 26.2%-30.7% vs 28.3%; IQR, 25.5%-31.4%; P = .60) or prognosis (log-rank 0.8; P = .38). Over a median of 1.9 years, 61 patients at risk for HFpEF or with HFpEF experienced adverse events (19 hospitalization for heart failure, 48 deaths, 6 with both). In those with HFpEF, ECV was associated with baseline log BNP (disease severity surrogate) in multivariable linear regression models, and was associated with outcomes in multivariable Cox regression models (eg, hazard ratio 1.75 per 5% increase in ECV, 95% CI, 1.25-2.45; P = .001 in stepwise model) whether grouped with patients at risk for HFpEF or not.

CONCLUSIONS AND RELEVANCE Among myriad changes occurring during the apparent evolution of HFpEF where elevated BNP is prevalent, MF was similarly prevalent in those with or at risk for HFpEF. Conceivably, MF might precede clinical HFpEF diagnosis. Regardless, MF was associated with disease severity (ie, BNP) and outcomes. Whether cells and secretomes mediating MF represent therapeutic targets in HFpEF warrants further evaluation.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Erik B. Schelbert, MD, MS, Cardiovascular Magnetic Resonance Center, Heart and Vascular Institute, UPMC, University of Pittsburgh School of Medicine, 200 Lothrop St, PUH A349, Pittsburgh, PA 15213 (schelberteb@upmc.edu).

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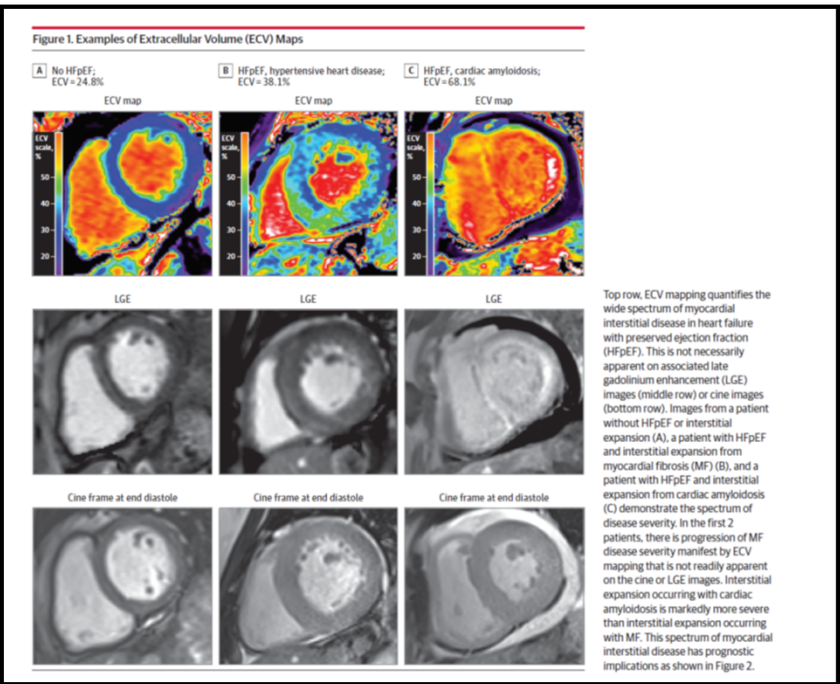

Figure 1. Examples of Extracellular Volume (ECV) Maps

A No HFpEF; ECV = 24.8%
B HFpEF, hypertensive heart disease; ECV = 38.1%
C HFpEF, cardiac amyloidosis; ECV = 68.1%

ECV map
LGE
Cine frame at end diastole

Top row, ECV mapping quantifies the wide spectrum of myocardial interstitial disease in heart failure with preserved ejection fraction (HFpEF). This is not necessarily apparent on associated late gadolinium enhancement (LGE) images (middle row) or cine images (bottom row). Images from a patient without HFpEF or interstitial expansion (A), a patient with HFpEF and interstitial expansion from myocardial fibrosis (MF) (B), and a patient with HFpEF and interstitial expansion from cardiac amyloidosis (C) demonstrate the spectrum of disease severity. In the first 2 patients, there is progression of MF disease severity manifest by ECV mapping that is not readily apparent on the cine or LGE images. Interstitial expansion occurring with cardiac amyloidosis is markedly more severe than interstitial expansion occurring with MF. This spectrum of myocardial interstitial disease has prognostic implications as shown in Figure 2.

Schelbert EB, et al. JAMA Cardiology. 2017; doi:10.1001/jamacardio.2017.2511

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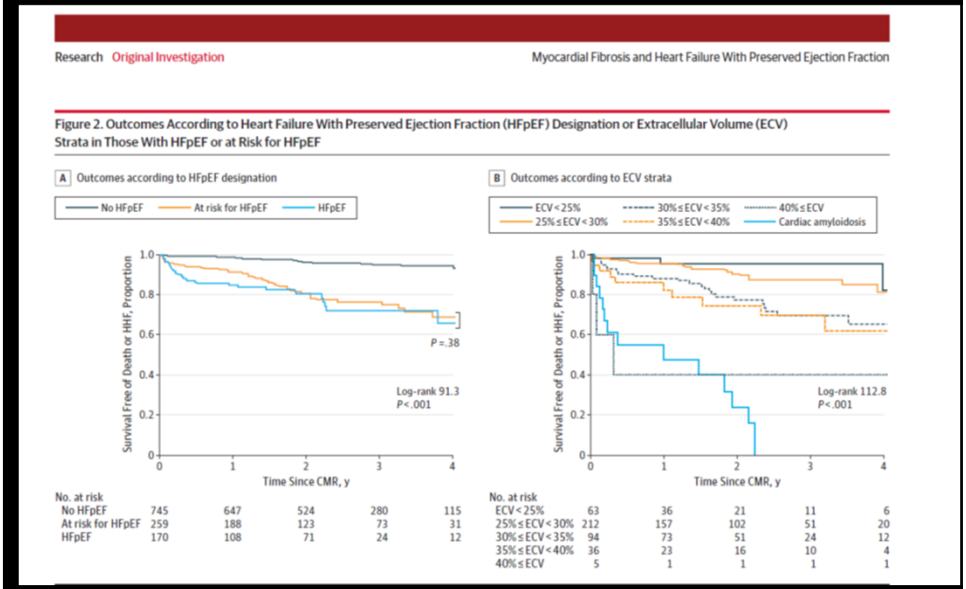
Outcomes in HFpEF (TOPCAT-like definition)



Research Original Investigation — Myocardial Fibrosis and Heart Failure With Preserved Ejection Fraction

Figure 2. Outcomes According to Heart Failure With Preserved Ejection Fraction (HFpEF) Designation or Extracellular Volume (ECV) Strata in Those With HFpEF or at Risk for HFpEF

A Outcomes according to HFpEF designation
No HFpEF; At risk for HFpEF; HFpEF
Survival Free of Death or HHF, Proportion
P = .38
Log-rank 91.3 P < .001
Time Since CMR, y

No. at risk					
No HFpEF	745	647	524	280	115
At risk for HFpEF	259	188	123	73	31
HFpEF	170	108	71	24	12

B Outcomes according to ECV strata
ECV < 25%; 25% ≤ ECV < 30%; 30% ≤ ECV < 35%; 35% ≤ ECV < 40%; 40% ≤ ECV; Cardiac amyloidosis
Survival Free of Death or HHF, Proportion
Log-rank 112.8 P < .001
Time Since CMR, y

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; doi:10.1001/jamacardio.2017.2511

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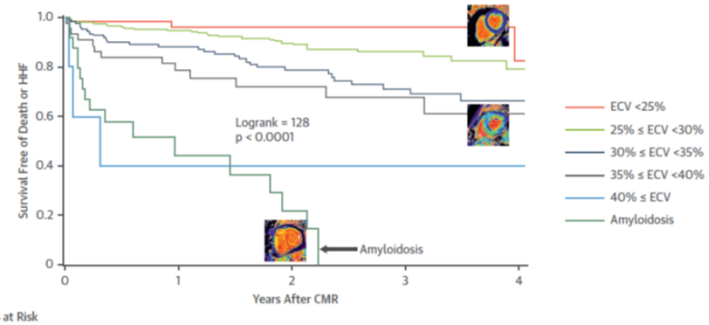
JACC: CARDIOVASCULAR IMAGING, VOL. 12, NO. 11, 2019
NOVEMBER 2019:2305–18

FIGURE 1 The Extent of Interstitial Expansion as Quantified by ECV Associated With Future Adverse Events



Numbers at Risk					
ECV <25%	69	39	23	11	6
25% ≤ ECV <30%	252	187	126	60	23
30% ≤ ECV <35%	123	92	66	36	18
35% ≤ ECV <40%	45	28	19	11	4
40% ≤ ECV	5	1	1	1	1
Amyloidosis	25	6	3	0	0

In a single-center sample of 519 consecutive patients referred for cardiovascular magnetic resonance with ejection fraction ≥45%, the extent of interstitial expansion as quantified by extracellular volume (ECV) associated with future adverse events, such as hospitalization for heart failure or all-cause mortality. The **inset images** demonstrate representative ECV maps (normal, myocardial fibrosis, cardiac amyloidosis **[arrow]**). CMR = cardiovascular magnetic resonance; HHF = hospitalization for heart failure.

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ECV in the clinical setting

Aortic Stenosis

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In patients with severe aortic stenosis scheduled for aortic valve intervention,

an increased ECV% is a measure of left ventricular decompensation and a powerful independent predictor of mortality.

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 75, NO. 3, 2020

Extracellular Myocardial Volume in Patients With Aortic Stenosis

Russell J. Everett, MD, PhD,[a] Thomas A. Treibel, MD, PhD,[b] Miho Fukui, MD,[c] Heesun Lee, MD,[d] Marzia Rigolli, MD, DPhil,[e] Anvesha Singh, MD, PhD,[f] Petra Bijsterveld, MA,[g] Lionel Tastet, MSc,[h] Tarique Al Musa, MD,[g] Laura Dobson, MD,[g] Calvin Chin, MD, PhD,[f] Gabriella Captur, MD, PhD,[j] Sang Yong Om, MD,[k] Stephanie Wiesemann, MD,[l] Vanessa M. Ferreira, MD, DPhil,[e] Stefan K. Piechnik, PhD,[e] Jeanette Schulz-Menger, MD,[l] Erik B. Schelbert, MD,[c] Marie-Annick Clavel, DVM, PhD,[h] David E. Newby, MD, PhD,[a] Saul G. Myerson, MD,[f] Phillipe Pibarot, DVM, PhD,[h] Sahmin Lee, MD,[k] João L. Cavalcante, MD,[c] Seung-Pyo Lee, MD, PhD,[d] Gerry P. McCann, MD,[f] John P. Greenwood, MD, PhD,[g] James C. Moon, MD,[b] Marc R. Dweck, MD, PhD[a]

ABSTRACT

BACKGROUND Myocardial fibrosis is a key mechanism of left ventricular decompensation in aortic stenosis and can be quantified using cardiovascular magnetic resonance (CMR) measures such as extracellular volume fraction (ECV%). Outcomes following aortic valve intervention may be linked to the presence and extent of myocardial fibrosis.

OBJECTIVES This study sought to determine associations between ECV% and markers of left ventricular decompensation and post-intervention clinical outcomes.

METHODS Patients with severe aortic stenosis underwent CMR, including ECV% quantification using modified Look-Locker inversion recovery-based T1 mapping and late gadolinium enhancement before aortic valve intervention. A central core laboratory quantified CMR parameters.

RESULTS Four-hundred forty patients (age 70 ± 10 years, 59% male) from 10 international centers underwent CMR a median of 15 days (IQR: 4 to 58 days) before aortic valve intervention. ECV% did not vary by scanner manufacturer, magnetic field strength, or T1 mapping sequence (all $p > 0.20$). ECV% correlated with markers of left ventricular decompensation including left ventricular mass, left atrial volume, New York Heart Association functional class III/IV, late gadolinium enhancement, and lower left ventricular ejection fraction ($p < 0.05$ for all), the latter 2 associations being independent of all other clinical variables ($p = 0.035$ and $p < 0.001$). After a median of 3.8 years (IQR: 2.8 to 4.6 years) of follow-up, 52 patients had died, 14 from adjudicated cardiovascular causes. A progressive increase in all-cause mortality was seen across tertiles of ECV% (17.3, 31.6, and 52.7 deaths per 1,000 patient-years; log-rank test; $p = 0.009$). Not only was ECV% associated with cardiovascular mortality ($p = 0.003$), but it was also independently associated with all-cause mortality following adjustment for age, sex, ejection fraction, and late gadolinium enhancement (hazard ratio per percent increase in ECV%: 1.10; 95% confidence interval [1.02 to 1.19]; $p = 0.013$).

CONCLUSIONS In patients with severe aortic stenosis scheduled for aortic valve intervention, an increased ECV% is a measure of left ventricular decompensation and a powerful independent predictor of mortality. (J Am Coll Cardiol 2020;75:304-16) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation.

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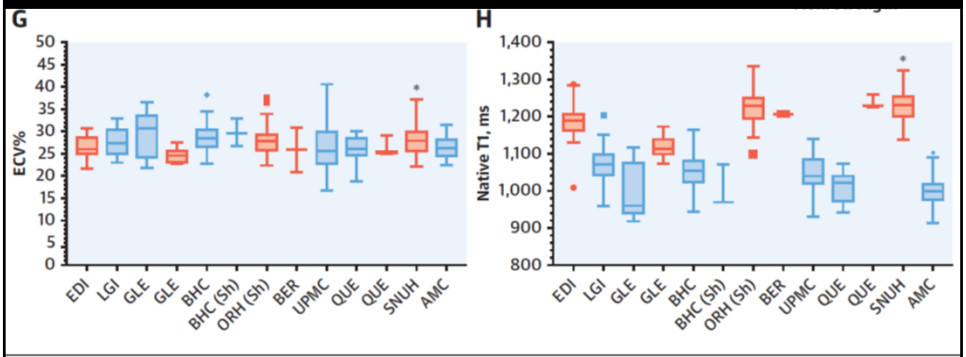
Similar ECV distributions across 13 centers, 440 pts not so for native T1 (all over the “map”)



Everett RJ, Treibel TA, Fukui M et al. Extracellular Myocardial Volume in Patients With Aortic Stenosis. J Am Coll Cardiol 2020;75:304-316.

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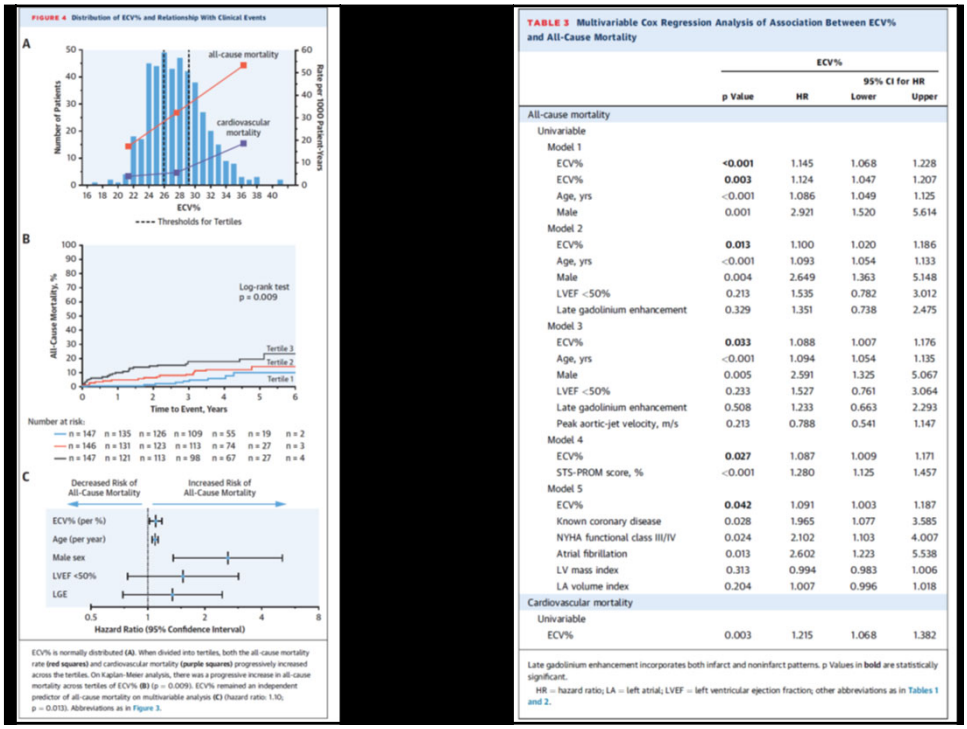

FIGURE 4 Distribution of ECV% and Relationship With Clinical Events

ECV% is normally distributed (**A**). When divided into tertiles, both the all-cause mortality rate (**red squares**) and cardiovascular mortality (**purple squares**) progressively increased across the tertiles. On Kaplan-Meier analysis, there was a progressive increase in all-cause mortality across tertiles of ECV% (**B**) ($p = 0.009$). ECV% remained an independent predictor of all-cause mortality on multivariable analysis (**C**) (hazard ratio: 1.10; $p = 0.013$). Abbreviations as in Figure 3.

TABLE 3 Multivariable Cox Regression Analysis of Association Between ECV% and All-Cause Mortality

	ECV%			
			95% CI for HR	
	p Value	HR	Lower	Upper
All-cause mortality				
Univariable				
Model 1				
ECV%	**<0.001**	1.145	1.068	1.228
ECV%	**0.003**	1.124	1.047	1.207
Age, yrs	<0.001	1.086	1.049	1.125
Male	0.001	2.921	1.520	5.614
Model 2				
ECV%	**0.013**	1.100	1.020	1.186
Age, yrs	<0.001	1.093	1.054	1.133
Male	0.004	2.649	1.363	5.148
LVEF <50%	0.213	1.535	0.782	3.012
Late gadolinium enhancement	0.329	1.351	0.738	2.475
Model 3				
ECV%	**0.033**	1.088	1.007	1.176
Age, yrs	<0.001	1.094	1.054	1.135
Male	0.005	2.591	1.325	5.067
LVEF <50%	0.233	1.527	0.761	3.064
Late gadolinium enhancement	0.508	1.233	0.663	2.293
Peak aortic-jet velocity, m/s	0.213	0.788	0.541	1.147
Model 4				
ECV%	**0.027**	1.087	1.009	1.171
STS-PROM score, %	<0.001	1.280	1.125	1.457
Model 5				
ECV%	**0.042**	1.091	1.003	1.187
Known coronary disease	0.028	1.965	1.077	3.585
NYHA functional class III/IV	0.024	2.102	1.103	4.007
Atrial fibrillation	0.013	2.602	1.223	5.538
LV mass index	0.313	0.994	0.983	1.006
LA volume index	0.204	1.007	0.996	1.018
Cardiovascular mortality				
Univariable				
ECV%	0.003	1.215	1.068	1.382

Late gadolinium enhancement incorporates both infarct and noninfarct patterns. p Values in **bold** are statistically significant.

HR = hazard ratio; LA = left atrial; LVEF = left ventricular ejection fraction; other abbreviations as in Tables 1 and 2.

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J Am Coll Cardiol. 2021 Aug 10;78(6):545-558. doi: 10.1016/j.jacc.2021.05.047.

Markers of Myocardial Damage Predict Mortality in Patients With Aortic Stenosis

Soongu Kwak [1], Russell J Everett [2], Thomas A Treibel [3], Seokhun Yang [1], Doyeon Hwang [1], Taehoon Ko [4], Michelle C Williams [2], Rong Bing [2], Trisha Singh [2], Shruti Joshi [2], Heesun Lee [1], Whal Lee [5], Yong-Jin Kim [1], Calvin W L Chin [6], Miho Fukui [7], Tarique Al Musa [8], Marzia Rigolli [9], Anvesha Singh [10], Lionel Tastet [11], Laura E Dobson [8], Stephanie Wiesemann [12], Vanessa M Ferreira [9], Gabriella Captur [13], Sahmin Lee [14], Jeanette Schulz-Menger [12], Erik B Schelbert [15], Marie-Annick Clavel [11], Sung-Ji Park [16], Tobias Rheude [17], Martin Hadamitzky [18], Bernhard L Gerber [19], David E Newby [2], Saul G Myerson [9], Phillipe Pibarot [11], João L Cavalcante [15], Gerry P McCann [10], John P Greenwood [8], James C Moon [3], Marc R Dweck [20], Seung-Pyo Lee [21]

- Conclusions:
- **Machine learning** identified myocardial fibrosis (**ECV**) and biventricular remodeling markers as the top predictors of survival in AS and highlighted their nonlinear association with mortality.

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ECV in the clinical setting

Degenerative Chronic Mitral regurgitation

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Valvular Heart Disease

Quantification of Left Ventricular Interstitial Fibrosis in Asymptomatic Chronic Primary Degenerative Mitral Regurgitation

Nicola C. Edwards, PhD; William E. Moody, MBChB; Mengshi Yuan, MBBS; Peter Weale, BSc; Desley Neal, MD; Jonathan N. Townend, MD; Richard P. Steeds, MA, MD

Background—The optimum timing of surgery in asymptomatic patients with chronic severe primary degenerative mitral regurgitation (MR) remains controversial, and further markers are needed to improve decision-making. There are limited data that wall stress is increased in MR and may result in ventricular fibrosis. We investigated the hypothesis that chronic volume overload in MR is a stimulus for myocardial fibrosis using T1-mapping cardiac MRI.

Methods and Results—A cross-sectional study of 35 patients (age 60±14 years) with asymptomatic moderate and severe primary degenerative MR (mean effective regurgitant orifice area, 0.45±0.25 cm)^2 with no class I indication for surgery were compared with age and sex controls. Subjects were studied with cardiopulmonary exercise testing, echocardiography, and cardiac MRI. Longitudinal and circumferential myocardial deformation was reduced with MR when left ventricular ejection fraction (67%±10%) and N-terminal pro B Natriuretic peptide (126 [76–428] ng/L) were within the normal range. Myocardial extracellular volume was increased (0.32±0.07 versus 0.25±0.02, P<0.01) and was associated with increased left ventricular end-systolic volume index (r=0.62, P<0.01), left atrial volume index (r=0.41, P<0.05) but lower left ventricular ejection fraction (r=–0.60, P<0.01), longitudinal function (mitral annular plane systolic excursion, r=–0.46, P<0.01), and peak $VO_{2\,max}$ (r=–0.51, P<0.05). In a multivariable regression model, left ventricular end-systolic volume index and left atrial volume index were independent predictors of extracellular volume (r^2=0.42, P<0.01).

Conclusions—Patients with asymptomatic MR demonstrate a spectrum of myocardial fibrosis associated with reduced myocardial deformation and reduced exercise capacity. Future work is warranted to investigate whether left ventricle fibrosis affects clinical outcomes. **(*Circ Cardiovasc Imaging*. 2014;7:946-953.)**

Key Words: magnetic resonance imaging ■ mitral valve regurgitation ■ myocardial fibrosis

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ECV associates with various disease severity metrics in chronic Mitral Regurgitation

- ECV was increased (0.32±0.07 versus 0.25±0.02, P<0.01)
- ECV associated with:
  - increased left ventricular end-systolic volume index (r=0.62, P<0.01),
  - left atrial volume index (r=0.41, P<0.05)
  - lower left ventricular ejection fraction (r=−0.60, P<0.01),
  - longitudinal function (mitral annular plane systolic excursion, r=−0.46, P<0.01), and
  - peak VO2 max (r=−0.51, P<0.05).
- In a multivariable regression model, LV-ESVindex and LA Vol index were independent predictors of ECV (r2=0.42, P<0.01).

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ECV in the clinical setting

All comers

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JACC: CARDIOVASCULAR IMAGING, VOL. ■, NO. ■, 2020
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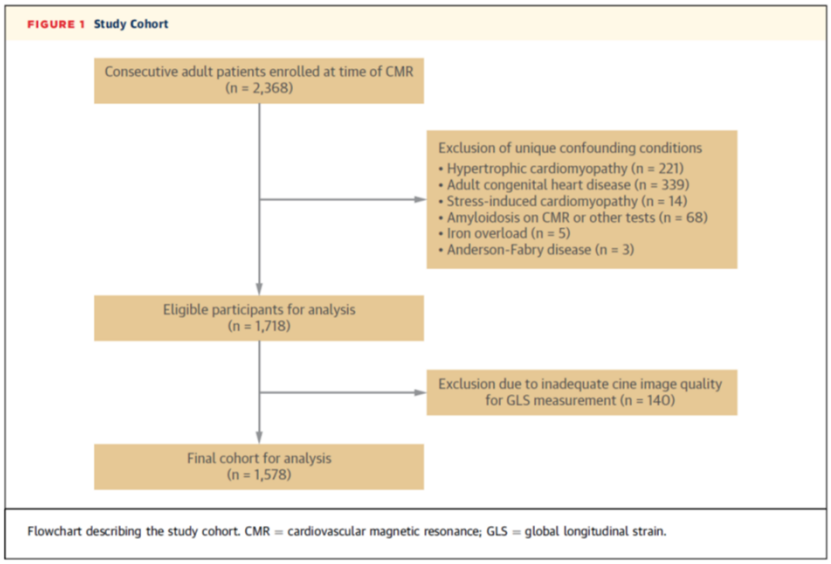

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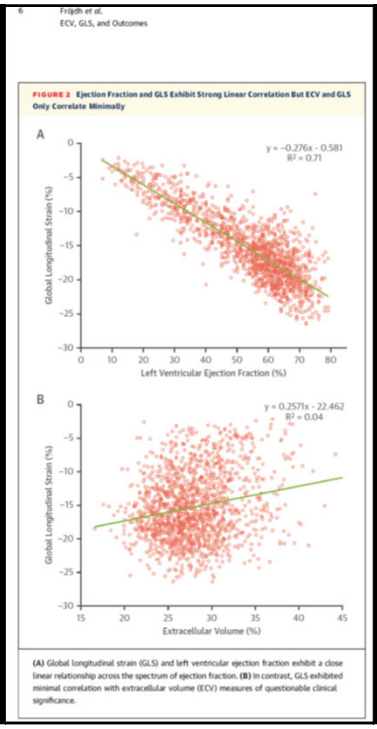
- GLS linearly related to EF
- GLS far more associated with outcomes compared to EF
- ECV and GLS are barely related (R2=0.04)



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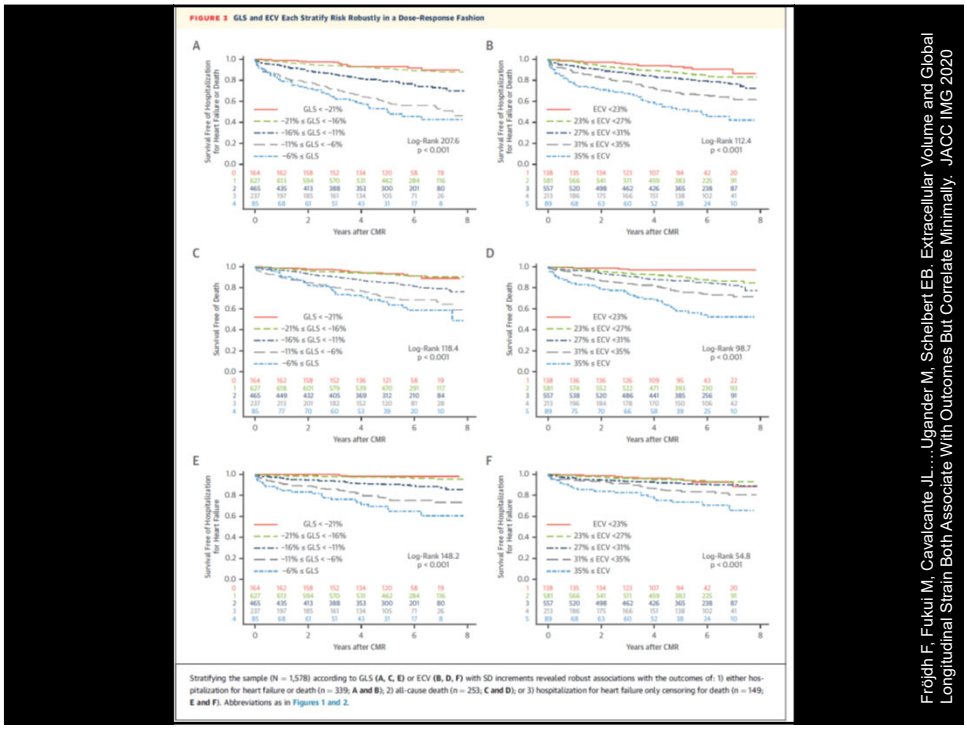

Fröjdh F, Fukui M, Cavalcante JL….Ugander M, Schelbert EB. Extracellular Volume and Global Longitudinal Strain Both Associate With Outcomes But Correlate Minimally. JACC IMG 2020

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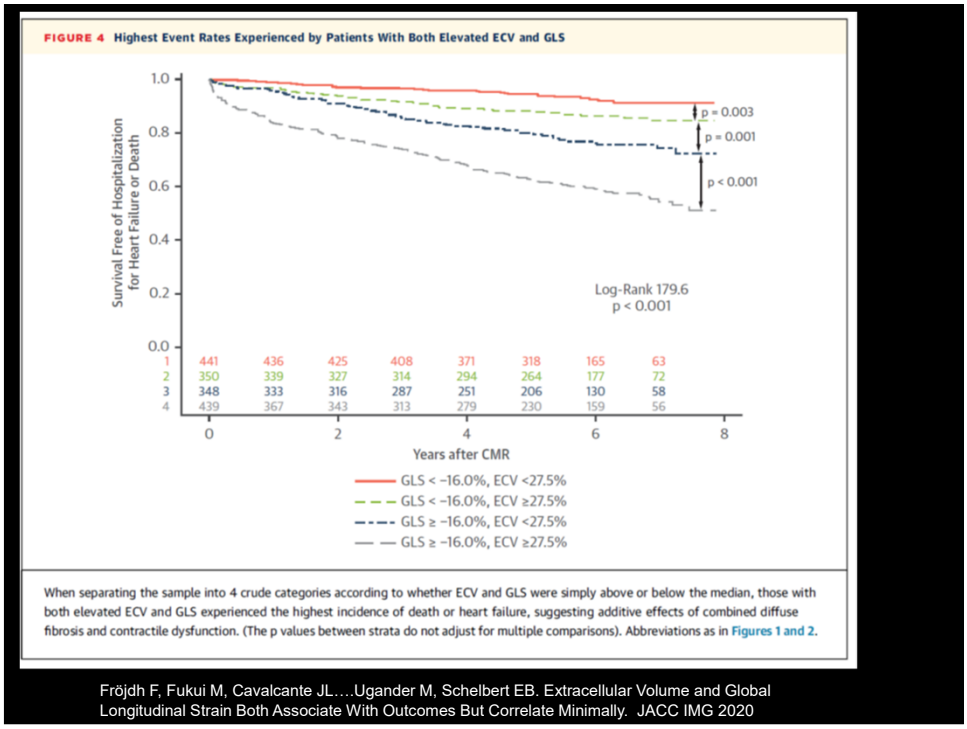

Fröjdh F, Fukui M, Cavalcante JL….Ugander M, Schelbert EB. Extracellular Volume and Global Longitudinal Strain Both Associate With Outcomes But Correlate Minimally. JACC IMG 2020

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Multivariable modeling adjusting for every variable we collected

TABLE 2 Univariable and Stepwise Multivariable Cox Regression Models for Outcomes of Either Death or Hospitalization for Heart Failure (n = 339) in the Entire Cohort (N = 1,578)

	Univariable Model			Multivariable Model Without Stratification for Heart Failure Stage			Multivariable Model With Stratification for Heart Failure Stage		
	Chi-Square Value	HR (95% CI)	p Value	Chi-Square Value	HR (95% CI)	p Value	Chi-Square Value	HR (95% CI)	p Value
GLS (per 5% increment)	188.7	2.07 (1.86-2.29)	<0.001	55.6	1.56 (1.39-1.76)	<0.001	25.1	1.42 (1.24-1.62)	<0.001
LVEF (per 15% decrement)	141.5	1.74 (1.59-1.91)	<0.001					-	
ECV (per 4% increment)	114.9	1.66 (1.51-1.82)	<0.001	36.3	1.39 (1.25-1.54)	<0.001	30.3	1.36 (1.22-1.52)	<0.001
Age (per 15-yr increment)	108.9	1.89 (1.68-2.13)	<0.001	28.5	1.46 (1.27-1.68)	<0.001	27.6	1.45 (1.26-1.67)	<0.001
LV mass index (per 21 g/m^2)	80.6	1.45 (1.34-1.57)	<0.001						
Diabetes mellitus, type 2	77.7	2.71 (2.17-3.37)	<0.001	12.8	1.54 (1.21-1.94)	<0.001	10.5	1.48 (1.17-1.87)	0.001
MI	69.3	2.53 (2.04-3.16)	<0.001						
Hypertension	62.5	2.54 (2.02-3.20)	<0.001	9.7	1.49 (1.16-1.92)	0.002	8.7	1.48 (1.14-1.92)	0.003
Glomerular filtration rate, (per 24 ml/min/1.73 m^2 decrement)	55.7	1.57 (1.40-1.77)	<0.001	5.6	1.15 (1.02-1.29)	0.018	3.2	1.11 (0.99-1.25)	0.073
Previous CABG	50.8	2.84 (2.13-3.78)	<0.001	4.1	1.37 (1.01-1.86)	0.042	3.3	1.33 (0.98-1.79)	0.068
Percentage of MI mass (per 9% increment)	49.8	1.30 (1.21-1.40)	<0.001					-	
End-diastolic volume index (per 33 ml/m^2)	48.8	1.34 (1.23-1.45)	<0.001						
Significant mitral regurgitation	28.1	2.80 (1.91-4.10)	<0.001						
Previous percutaneous coronary intervention	17.7	1.78 (1.36-2.32)	<0.001						
Nonischemic scar on LGE	16.3	1.67 (1.30-2.12)	<0.001						
Current cigarette smoking	13.6	1.64 (1.26-2.14)	<0.001	8.7	1.55 (1.16-2.08)	0.003	9.5	1.58 (1.18-2.12)	0.002
Atrial fibrillation	13.4	1.75 (1.30-2.36)	<0.001	4.5	1.39 (1.03-1.89)	0.033	4.6	1.40 (1.03-1.90)	0.032
Moderate or severe aortic stenosis	13.0	2.59 (1.54-4.35)	<0.001						
Nonischemic scar mass (per 3% increment)	12.3	1.16 (1.07-1.26)	<0.001					-	
Dyslipidemia	11.6	1.45 (1.17-1.80)	<0.001						
Previous cigarette smoking	10.1	1.43 (1.15-1.79)	0.002	4.8	1.31 (1.03-1.68)	0.028	4.4	1.30 (1.02-1.66)	0.036
White race	4.1	0.74 (0.55-0.99)	0.044	3.0	0.76 (56-1.04)	0.084			
Female	4.0	0.80 (0.64-1.00)	0.046						

The chi-square values permit comparisons of strength of associations with outcomes. Hazard ratios (HRs) were modeled as continuous variables but scaled to 1 SD increments (which does not affect p values or chi-square values). We created multivariable models stratified according to hospitalization status, and additional models were further stratified according to heart failure stage, a variable strongly associated with GLS (Supplemental Table 2).

CABG = coronary artery bypass grafting; CI = confidence interval; LVEF = left ventricular ejection fraction; other abbreviations as in Table 1.

Fröjdh F, Fukui M, Cavalcante JL,...Ugander M, Schelbert EB. Extracellular Volume and Global Longitudinal Strain Both Associate With Outcomes But Correlate Minimally. JACC IMG 2020

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Supplemental Table 3. Comparison of GLS and ECV in their associations with outcomes in various clinically relevant subgroups using univariable and multivariable Cox regression models stratified by hospitalization status.

Subgroup	Variable	Univariable Cox Model			Stepwise Multivariable Cox Model			Covariates
		χ2 value	HR (95% CI)	p value	χ2 value	HR (95% CI)	p value	
LVEF≥55% (n=947; 129 events)	GLS (per 5% increment)	32.4	2.21 (1.68-2.90)	<0.001	11.3	1.56 (1.20-2.03)	<0.001	age, hypertension, atrial fibrillation
	ECV (per 4% increment)	42.1	1.67 (1.43-1.94)	<0.001	29.4	1.53 (1.31-1.78)	<0.001	
LVEF<55% (n=631; 210 events)	GLS (per 5% increment)	62.7	2.03 (1.70-2.42)	<0.001	22.6	1.62 (1.33-1.98)	<0.001	age, diabetes, glomerular filtration, coronary bypass, current smoking, race
	ECV (per 4% increment))	45.2	1.52 (1.34-1.71)	<0.001	10.5	1.26 (1.10-1.45)	0.001	
Heart failure with LVEF≥55% (n=130; 42 events)	GLS (per 5% increment)	3.4	1.51 (0.98-2.35)	0.064	-	-	-	gender
	ECV (per 4% increment))	11.1	1.50 (1.18-1.90)	<0.001	5.5	1.33 (1.05-1.70)	0.018	
Heart failure with LVEF<55% (n=341; 153 events)	GLS (per 5% increment)	11.8	1.46 (1.18-1.81)	<0.001	4.5	1.30 (1.02-1.66)	0.033	age, diabetes, glomerular filtration, coronary bypass, current smoking, atrial fibrillation, race
	ECV (per 4% increment))	19.3	1.42 (1.21-1.66)	<0.001	4.56	1.21 (1.02-1.44)	0.033	
Myocardial infarction present (n=345; 130 events)	GLS (per 5% increment)	37.0	1.93 (1.56-2.38)	<0.001	19.4	1.66 (1.33-2.09)	<0.001	age, diabetes, glomerular filtration, race
	ECV (per 4% increment)	37.0	1.69 (1.43-2.01)	<0.001	11.2	1.39 (1.15-1.69)	<0.001	
Myocardial infarction absent (n=1233; 209 events)	GLS (per 5% increment)	102.2	1.96 (1.72-2.23)	<0.001	19.6	1.41 (1.21-1.65)	<0.001	age, diabetes, hypertension, nonischemic scar, current smoking, atrial fibrillation
	ECV (per 4% increment)	69.2	1.64 (1.46-1.84)	<0.001	26.4	1.40 (1.23-1.59)	<0.001	
Diabetes present (n=315; 124 events	GLS (per 5% increment)	38.4	1.87 (1.54-2.28)	<0.001	15.8	1.53 (1.24-1.89)	<0.001	glomerular filtration, coronary bypass
	ECV (per 4% increment)	23.9	1.57 (1.31-1.87)	<0.001	7.9	1.32 (1.09-1.60)	0.005	
Diabetes absent (n=1263; 215 events)	GLS (per 5% increment)	125.4	2.06 (1.81-2.33)	<0.001	28.2	1.49 (1.28-1.72)	<0.001	age, hypertension, nonischemic scar, current smoking, atrial fibrillation, ex-smoker, lipid disorder, moderate or severe aortic stenosis
	ECV (per 4% increment)	75.7	1.66 (1.48-1.86)	<0.001	27.6	1.40 (1.24-1.59)	<0.001	
Any evidence of obstructive coronary artery disease (n=463; 162 events)	GLS (per 5% increment)	40.8	1.74 (1.47-2.06)	<0.001	23.1	1.57 (1.31-1.89)	<0.001	age, diabetes, hypertension, glomerular filtration, coronary bypass, lipid disorder
	ECV (per 4% increment)	36.8	1.57 (1.36-1.82)	<0.001	14.6	1.37 (1.17-1.62)	<0.001	
No evidence of obstructive coronary artery disease (n=1115; 177 events)	GLS (per 5% increment)	104.7	2.08 (1.81-2.39)	<0.001	14.6	1.38 (1.17-1.64)	<0.001	age, diabetes, hypertension, mitral regurgitation, nonischemic scar, current smoking, atrial fibrillation
	ECV (per 4% increment)	68.5	1.70 (1.50-1.92)	<0.001	24.6	1.43 (1.24-1.65)	<0.001	

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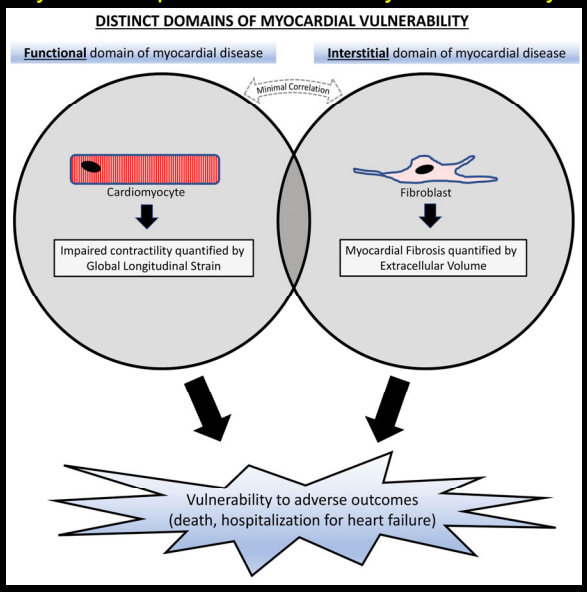
Key outcomes data → Conceptual model

A new taxonomy to conceptualize vulnerability related to myocardial disease



Fröjdh F, Fukui M, Cavalcante JL,….Ugander M, Schelbert EB. Extracellular Volume and Global Longitudinal Strain Both Associate With Outcomes But Correlate Minimally. *JACC Imaging 2020*

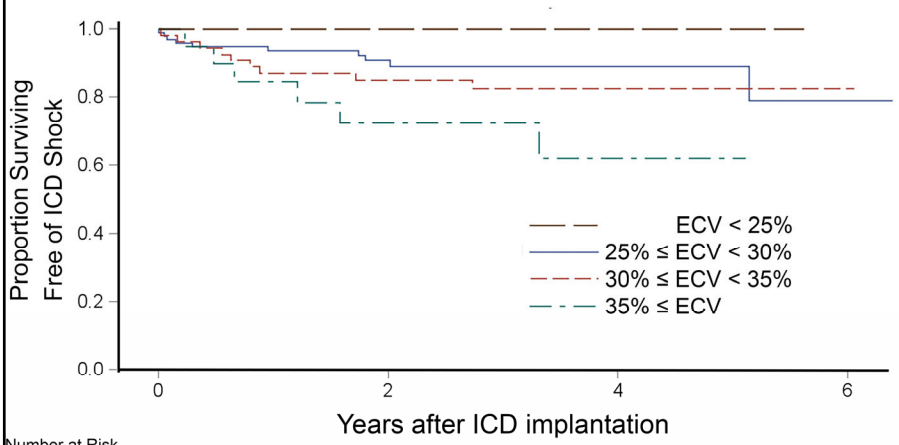
73

ECV in the clinical setting

Incident ventricular arrhythmia requiring ICD Rx

74

ECV predicts serious ventricular arrhythmia (appropriate ICD shock)



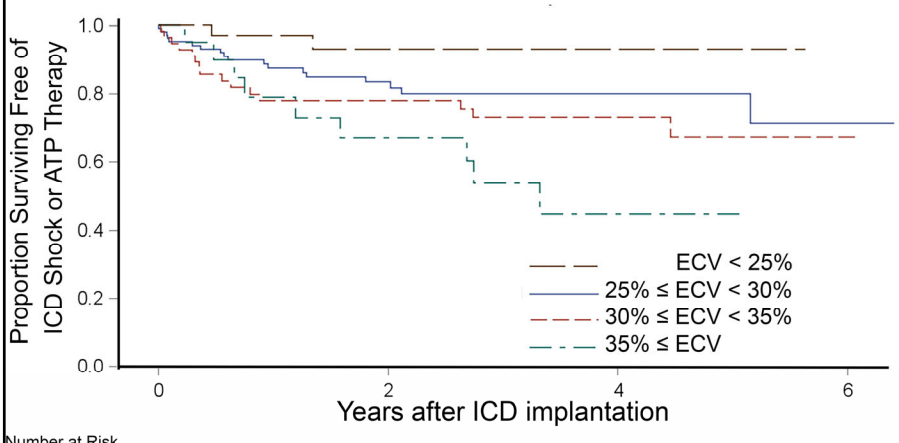
Number at Risk

ECV<25%	38	29	19	12	6	4
25%≤ECV<30%	102	73	54	37	26	9
30%≤ECV<35%	55	45	41	33	20	8
35%≤ECV	20	14	11	8	3	1

ACC 2018 "Diffuse myocardial fibrosis measured by extracellular volume associates with incident ventricular arrhythmia in implantable cardioverter defibrillator recipients more than focal fibrosis

75

Shock or anti-tachycardia pacing



Number at Risk

ECV<25%	38	28	18	11	5	3
25%≤ECV<30%	102	69	51	35	26	9
30%≤ECV<35%	55	40	38	30	18	6
35%≤ECV	20	13	11	7	2	1

ACC 2018 "Diffuse myocardial fibrosis measured by extracellular volume associates with incident ventricular arrhythmia in implantable cardioverter defibrillator recipients more than focal fibrosis

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ECV and ICD shock

- In multivariable Cox models, ECV remained associated with ICD shock HR 2.17 (95%CI 1.17-4.00) for every 5% increase in ECV, adjusted for:
  - age,
  - ejection fraction (EF),
  - myocardial infarction,
  - nonischemic scar on LGE,
  - ICD indication (primary prevention) and
  - ischemic cardiomyopathy

  whereas myocardial infarction and focal fibrosis by LGE did not.

77

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Vulnerable Myocardial Interstitium in Patients With Isolated Left Ventricular Hypertrophy and Sudden Cardiac Death: A Postmortem Histological Evaluation

Balaji K. Tamarappoo, MD, PhD; Benjamin T. John, MD; Kyndaron Reinier, PhD, MPH; Carmen Teodorescu, MD, PhD; Audrey Uy-Evanado, MD; Karen Gunson, MD; Jonathan Jui, MD, MPH; Sumeet S. Chugh, MD

Background—Concentric left ventricular hypertrophy (LVH) is independently associated with increased risk of sudden cardiac death (SCD). Some animal models of LVH display specific alterations of the myocardial interstitium that could increase myocardial vulnerability to ventricular arrhythmias, but these merit evaluation in humans with LVH and SCD.

Methods and Results—Twelve consecutive patients with isolated LVH and SCD (LVH+SCD) in the absence of hypertrophic cardiomyopathy, coronary disease, or other cardiac structural abnormality were ascertained in the Oregon Sudden Unexpected Death Study. Detailed postmortem comparisons were conducted with 18 controls who had isolated LVH and unnatural deaths (Control Group A) and 6 controls who had structurally normal hearts and unnatural deaths (Control Group B). Postmortem left ventricular myocardial sections were obtained for measurement of collagen volume fraction, characterization of gap junctions, and quantification of collagen subtypes. Heart weight normalized to body weight was higher in LVH+SCD cases (6.9±1.2 g/kg) than in Control Group A (5.3±1.4 g/kg) and Control Group B (4.2±0.3 g/kg); *P*=0.001. Collagen volume fraction was also higher in LVH+SCD cases (3.1±0.4) than in Control Group A (2.3±0.4) and Control Group B (1.6±0.3); *P*=0.0002. The relative amount of collagen III was significantly higher in LVH+SCD cases (33.0±4.4%) than in Control Group A (20.9±4.3%) and Control Group B (13.4±3.5%); *P*=0.0001. There was an overall increase in the number of connexin 43–labeled gap junctions with increasing myocyte size. No subject was found to have high-risk hypertrophic cardiomyopathy mutations.

Conclusions—In addition to the expected increase in myocardial mass and overall collagen content, SCD with isolated LVH was associated with relative abundance of type III collagen, a novel finding that warrants further mechanistic evaluation. (***J Am Heart Assoc.*** **2012;1:e001511 doi: 10.1161/JAHA.111.001511.)**

78

Effect of *Spironolactone* on Ventricular Arrhythmias in Congestive Heart Failure Secondary to Idiopathic Dilated or to Ischemic Cardiomyopathy

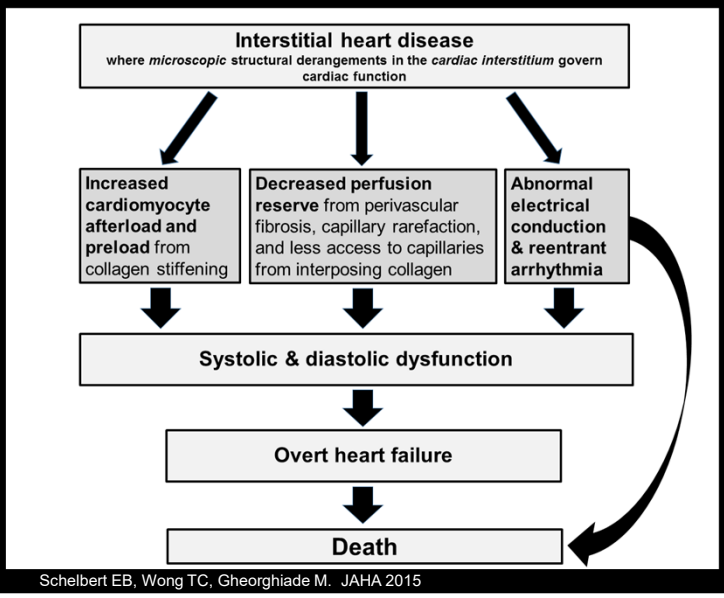
Felix J.A. Ramires, MD, Antonio Mansur, MD, Otavio Coelho, MD, Mario Maranhão, MD, Cesar J. Gruppi, MD, Charles Mady, MD, and José A.F. Ramires, MD

Epidemiologic studies have shown an important increase in the high mortality of patients with congestive heart failure (CHF) despite optimal medical management. Ventricular arrhythmia was recognized as the most common cause of death in this population. Electrolyte imbalance, myocardial fibrosis, left ventricular dysfunction, and inappropriate neurohumoral activation are presumed responsible for sudden cardiac death. In this study, we focused on the deleterious effects of the overproduction of aldosterone that occurs in patients with CHF. Secondary hyperaldersteronism can be part of several factors thought to be responsible for sudden cardiac death. We randomized 35 patients (32 men, aged 48 ± 9 years) with systolic dysfunction (ejection fraction 33 ± 5%) and New York Heart Association class III CHF secondary to dilated or ischemic cardiomyopathy into 2 groups. The treatment group received spironolactone, an aldosterone receptor antagonist, along with standard medical management using furosemide, angiotensin-converting enzyme inhibitors, and digoxin. The control group received only the standard medical treatment. Holter monitoring was used to assess the severity of ventricular arrhythmia. After 20 weeks, patients who received spironolactone had a reduced hourly frequency of ventricular premature complexes (VPCs) (65 ± 18 VPCs/hour at week 0 and 17 ± 9 VPCs/hour at week 16) and episodes of nonsustained ventricular tachycardia (VT) (3.0 ± 0.8 episodes of VT/24-hour period at week 0, and 0.6 ± 0.3 VT/24-hour period at week 16). During monitored treadmill exercise, a significant improvement in ventricular arrhythmia was found in the group receiving spironolactone (39 ± 10 VPCs at week 0, and 6 ± 2 VPCs at week 16). These findings suggest that aldosterone may contribute to the incidence of ventricular arrhythmia in patients with CHF, and spironolactone helps reduce this complication.

(Am J Cardiol 2000;85:1207–1211)

79

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



Schelbert EB, Wong TC, Gheorghiade M. JAHA 2015

80

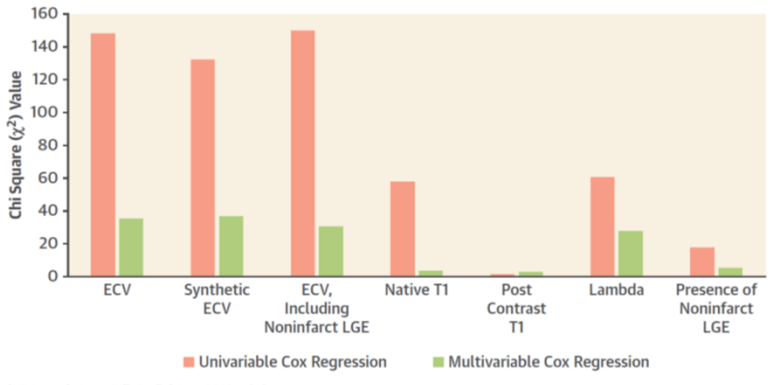
Most robust measure for myocardial fibrosis?

81

JACC: CARDIOVASCULAR IMAGING, VOL. ■, NO. ■, 2019
■ 2019:■-■

CENTRAL ILLUSTRATION **ECV Exhibits More Robust Risk Stratification Than Other T1-Based Measures of MF**

Strength of Association with Outcomes as Measured by Chi Square (χ^2) Values in Cox Regression Models



Treibel, T.A. et al. J Am Coll Cardiol Img. 2019;■(■):■-■.

ECV = extracellular volume fraction; MF = myocardial fibrosis.

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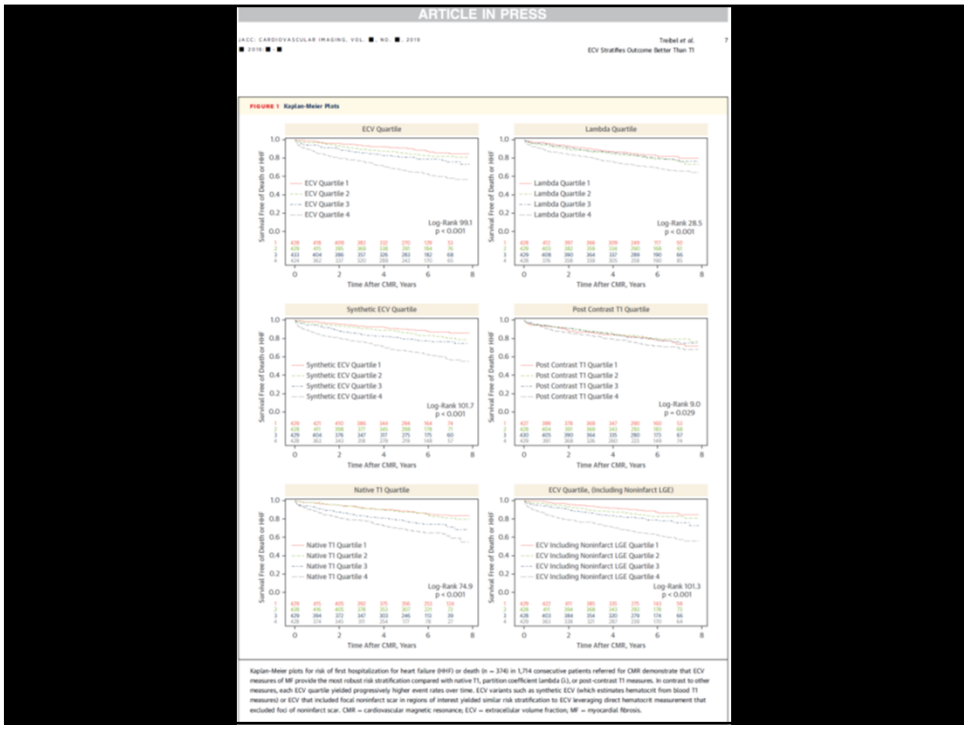

83

ECV in the clinical setting

Athletic Heart

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JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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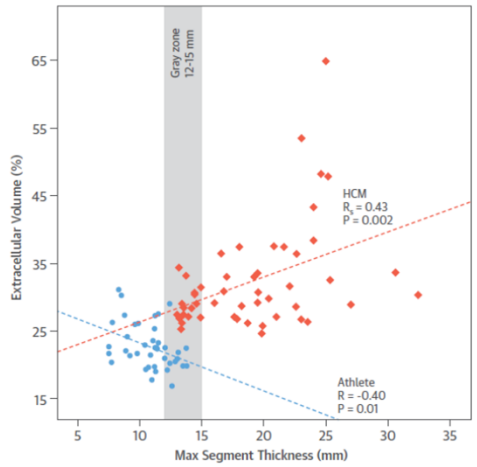
VOL. 67, NO. 18, 2016
ISSN 0735-1097/$36.00

Letters

Assessing Myocardial Extracellular Volume by T1 Mapping to Distinguish Hypertrophic Cardiomyopathy From Athlete's Heart

FIGURE 1 Segmental Thickness and ECV



Scatter plot shows maximal segmental thickness and ECV of the same segment for HCM subjects **(orange)** and athletes **(blue)**. The **gray area** highlights the indeterminate zone of 12 to 15 mm. ECV = extracellular volume; HCM = hypertrophic cardiomyopathy.

85

Ventricular Structure and Function

OPEN

Athletic Cardiac Adaptation in Males Is a Consequence of Elevated Myocyte Mass

Adam K. McDiarmid, MD*; Peter P. Swoboda, MBBS*; Bara Erhayiem, BMBS; Rosalind E. Lancaster, PhD; Gemma K. Lyall, MSc; David A. Broadbent, BSc; Laura E. Dobson, MBChB; Tarique A. Musa, MBBS; David P. Ripley, MBChB; Pankaj Garg, MD; John P. Greenwood, PhD; Carrie Ferguson, PhD; Sven Plein, PhD

Background—Cardiac remodeling occurs in response to regular athletic training, and the degree of remodeling is associated with fitness. Understanding the myocardial structural changes in athlete's heart is important to develop tools that differentiate athletic from cardiomyopathic change. We hypothesized that athletic left ventricular hypertrophy is a consequence of increased myocardial cellular rather than extracellular mass as measured by cardiovascular magnetic resonance.

Methods and Results—Forty-five males (30 athletes and 15 sedentary age-matched healthy controls) underwent comprehensive cardiovascular magnetic resonance studies, including native and postcontrast T1 mapping for extracellular volume calculation. In addition, the 30 athletes performed a maximal exercise test to assess aerobic capacity and anaerobic threshold. Participants were grouped by athleticism: untrained, low performance, and high performance (VO_{2max} <60 or>60 mL/kg per min, respectively). In athletes, indexed cellular mass was greater in high- than low-performance athletes 60.7±7.5 versus 48.6±6.3 g/m²; P<0.001), whereas extracellular mass was constant (16.3±2.2 versus 15.3±2.2 g/m²; P=0.20). Indexed left ventricular end-diastolic volume and mass correlated with VO_{2max} (r=0.45, P=0.01; r=0.55, P=0.002) and differed significantly by group (P=0.01; P<0.001, respectively). Extracellular volume had an inverse correlation with VO_{2max} (r=−0.53, P=0.003 and left ventricular mass index (r=-0.44, P=0.02).

Conclusions—Increasing left ventricular mass in athlete's heart occurs because of an expansion of the cellular compartment while the extracellular volume becomes relatively smaller: a difference which becomes more marked as left ventricular mass increases. Athletic remodeling, both on a macroscopic and cellular level, is associated with the degree of an individual's fitness. Cardiovascular magnetic resonance ECV quantification may have a future role in differentiating athlete's heart from change secondary to cardiomyopathy. **(*Circ Cardiovasc Imaging*. 2016;9:e003579. DOI: 10.1161/CIRCIMAGING.115.003579.)**

Key Words: athlete's heart ■ cardiovascular magnetic resonance imaging ■ ECV ■ exercise physiology ■ hypertrophy/remodeling ■ T1 mapping

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ORIGINAL ARTICLE

Regression of Left Ventricular Mass in Athletes Undergoing Complete Detraining Is Mediated by Decrease in Intracellular but Not Extracellular Compartments

BACKGROUND: Athletic cardiac remodeling can occasionally be difficult to differentiate from pathological hypertrophy. Detraining is a commonly used diagnostic test to identify physiological hypertrophy, which can be diagnosed if hypertrophy regresses. We aimed to establish whether athletic cardiac remodeling assessed by cardiovascular magnetic resonance is mediated by changes in intracellular or extracellular compartments and whether this occurs by 1 or 3 months of detraining.

METHODS: Twenty-eight athletes about to embark on a period of forced detraining due to incidental limb bone fracture underwent clinical assessment, ECG, and contrast-enhanced cardiovascular magnetic resonance within a week of their injury and then 1 month and 3 months later.

RESULTS: After 1 month of detraining, there was reduction in left ventricular (LV) mass (130±28 to 121±25 g; $P<0.0001$), increase in native T1 (1225±30 to 1239±30 ms; $P=0.02$), and extracellular volume fraction (24.5±2.3% to 26.0±2.6%; $P=0.0007$) with no further changes by 3 months. The decrease in LV mass was mediated by a decrease in intracellular compartment volume (94±22 to 85±19 mL; $P<0.0001$) with no significant change in the extracellular compartment volume. High LV mass index, low native T1, and low extracellular volume fraction at baseline were all predictive of regression in LV mass in the first month.

CONCLUSIONS: Regression of athletic LV hypertrophy can be detected after just 1 month of complete detraining and is mediated by a decrease in the intracellular myocardial compartment with no change in the extracellular compartment. Further studies are needed in athletes with overt and pathological hypertrophy to establish whether native T1 and extracellular volume fraction may complement electrocardiography, echocardiography, cardiopulmonary exercise testing, and genetic testing in predicting the outcome of detraining.

Peter P. Swoboda, MBBS, PhD
Pankaj Garg, MD, PhD
Eylem Levelt, MBBS, DPhil
David A. Broadbent, PhD
Ashkun Zolfaghari-Nia, BSc
A. James R. Foley, MBChB, MD
Graham J. Fent, MBChB, MD
Pei G. Chew, MBChB
Louise A. Brown, MBChB
Christopher E. Saunderson, MBChB
Erica Dall'Armellina, MD, PhD
John P. Greenwood, PhD
Sven Plein, PhD

Key Words: athletes ■ magnetic resonance imaging ■ hypertrophy ■ sports

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Swoboda et al; Regression of Myocardial Mass on Detraining

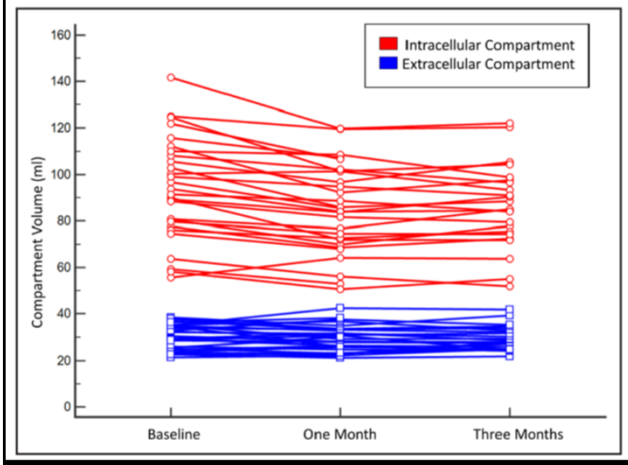

Figure 3. Change in cardiac compartment volumes on complete detraining. Individual participant data showing volumes of intracellular (red) and extracellular (blue) compartments at baseline and then after 1 and 3 months of detraining.

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Novel therapeutics for myocardial fibrosis on the horizon

- Mineralocorticoid antagonists
- RNA therapeutics (long non-coding)
- Pirfenidone - an oral antifibrotic agent without hemodynamic effect

89

ORIGINAL ARTICLE

Finerenone, a Novel Selective Nonsteroidal Mineralocorticoid Receptor Antagonist Protects From Rat Cardiorenal Injury

Peter Kolkhof, PhD, Martina Delbeck, PhD,* Axel Kretschmer, PhD,† Wolfram Steinke, PhD,‡ Elke Hartmann, PhD,§ Lars Bärfacker, PhD,¶ Frank Eitner, MD,* Barbara Albrecht-Küpper, PhD,* and Stefan Schäfer, MD†*

- J Cardiovasc Pharmacol 2014;64:69–78)

90

Aldosterone blockage without the hyperkalemia

or

renal dysfunction!

European Heart Journal (2013) 34, 2453–2463
doi:10.1093/eurheartj/eht187

FASTTRACK CLINICAL RESEARCH

Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial

Bertram Pitt[1†*], Lars Kober[2], Piotr Ponikowski[3], Mihai Gheorghiade[4], Gerasimos Filippatos[5], Henry Krum[6], Christina Nowack[7], Peter Kolkhof[8], So-Young Kim[9], and Faiez Zannad[10†]

[1]University of Michigan School of Medicine, Ann Arbor, MI, USA; [2]Heart Centre, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [3]Medical University, Clinical Military Hospital, Wroclaw, Poland; [4]Center for Cardiovascular Innovation, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [5]Heart Failure Unit, Department of Cardiology, Attikon University Hospital, Athens, Greece; [6]Department of Epidemiology and Preventive Medicine, Centre of Cardiovascular Research and Education in Therapeutics, Monash University, Melbourne, VIC, Australia; [7]Global Clinical Development, Bayer Pharma AG, Wuppertal, Germany; [8]Cardiology Research, Global Drug Development, Bayer Pharma AG, Wuppertal, Germany; [9]Bayer Vital GmbH, Bayer HealthCare, Leverkusen, Germany; and [10]INSERM, Centre d'Investigation clinique 9501 and Unit 961, CHU Department of Cardiology, Université de Lorraine, Nancy, France

Received 28 March 2013; revised 17 April 2013; accepted 10 May 2013; online publish-ahead-of-print 27 May 2013

See page 2426 for the editorial comment on this article (doi:10.1093/eurheartj/eht235)

Aims Mineralocorticoid receptor antagonists (MRAs) improve outcomes in patients with heart failure and reduced left ventricular ejection fraction (HFrEF), but their use is limited by hyperkalaemia and/or worsening renal function (WRF). BAY 94-8862 is a highly selective and strongly potent non-steroidal MRA. We investigated its safety and tolerability in patients with HFrEF associated with mild or moderate chronic kidney disease (CKD).

Methods and results This randomized, controlled, phase II trial consisted of two parts. In part A, the safety and tolerability of oral BAY 94-8862 [2.5, 5, or 10 mg once daily (q.d.)] was assessed in 65 patients with HFrEF and mild CKD. In part B, BAY 94-8862 (2.5, 5, or 10 mg q.d., or 5 mg twice daily) was compared with placebo and open-label spironolactone (25 or 50 mg/day) in 392 patients with HFrEF and moderate CKD. BAY 94-8862 was associated with significantly smaller mean increases in serum potassium concentration than spironolactone (0.04–0.30 and 0.45 mmol/L, respectively, $P < 0.0001$–0.0107) and lower incidences of hyperkalaemia (5.3 and 12.7%, respectively, $P = 0.048$) and WRF. BAY 94-8862 decreased the levels of B-type natriuretic peptide (BNP), amino-terminal proBNP, and albuminuria at least as much as spironolactone. Adverse events related to BAY 94-8862 were infrequent and mostly mild.

Conclusion In patients with HFrEF and moderate CKD, BAY 94-8862 5–10 mg/day was at least as effective as spironolactone 25 or 50 mg/day in decreasing biomarkers of haemodynamic stress, but it was associated with lower incidences of hyperkalaemia and WRF.

Keywords Aldosterone • Antagonist • Chronic kidney disease • Heart failure • Mineralocorticoid receptor

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ARTICLE

https://doi.org/10.1038/s41467-020-14349-2 OPEN

Preclinical development of a miR-132 inhibitor for heart failure treatment

Ariana Foinquinos[1,10], Sandor Batkai[1,2,10], Celina Genschel[1,2], Janika Viereck[1,2], Steffen Rump[2], Mariann Gyöngyösi[3], Denise Traxler[3], Martin Riesenhuber[3], Andreas Spannbauer[3], Dominika Lukovic[3], Natalie Weber[4], Katrin Zlabinger[3], Ena Hašimbegović[3], Johannes Winkler[3], Jan Fiedler[1], Seema Dangwal[1], Martin Fischer[5], Jeanne de la Roche[5], Daniel Wojciechowski[5], Theresia Kraft[4], Rita Garamvölgyi[6], Sonja Neitzel[7], Shambhabi Chatterjee[1], Xiaoke Yin[8], Christian Bär[1], Manuel Mayr[8], Ke Xiao[1] & Thomas Thum[1,2,9*]

Despite proven efficacy of pharmacotherapies targeting primarily global neurohormonal dysregulation, heart failure (HF) is a growing pandemic with increasing burden. Treatments mechanistically focusing at the cardiomyocyte level are lacking. MicroRNAs (miRNA) are transcriptional regulators and essential drivers of disease progression. We previously demonstrated that miR-132 is both necessary and sufficient to drive the pathological cardiomyocytes growth, a hallmark of adverse cardiac remodelling. Therefore, miR-132 may serve as a target for HF therapy. Here we report further mechanistic insight of the mode of action and translational evidence for an optimized, synthetic locked nucleic acid antisense oligonucleotide inhibitor (antimiR-132). We reveal the compound's therapeutic efficacy in various models, including a clinically highly relevant pig model of HF. We demonstrate favourable pharmacokinetics, safety, tolerability, dose-dependent PK/PD relationships and high clinical potential for the antimiR-132 treatment scheme.

Histological assessment of fibrosis revealed a significant dose-dependent reduction of interstitial fibrosis suggesting improvements in the overall cardiac remodeling in the antimiR132-treated groups

92

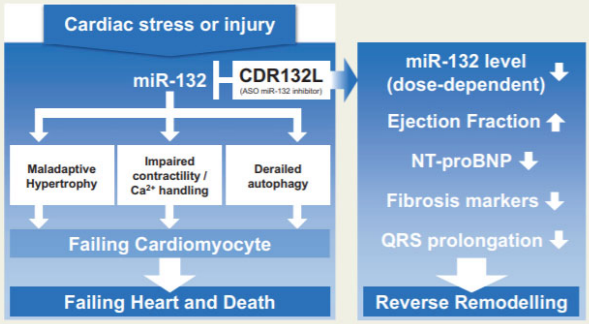
ESC European Society of Cardiology
European Heart Journal (2021) 42, 178–188
doi:10.1093/eurheartj/ehaa898

CLINICAL RESEARCH
Heart failure and cardiomyopathies

Novel antisense therapy targeting microRNA-132 in patients with heart failure: results of a first-in-human Phase 1b randomized, double-blind, placebo-controlled study

Jörg Täube
Sandor Ba
Celina Ger
Johann Bau

Graphical Abstract



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FIERCE Biotech

BIOTECH RESEARCH CRO MEDTECH TREND

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Fierce Biotech's JPM 2022 coverage all in one place
Dealmaking, R&D updates and biotech trends: Follow our coverage of the virtual JPM 2022

Biotech

Bristol-backed Cardior gets $75M to run midphase antisense heart failure trial

by Nick Paul Taylor | Aug 25, 2021 8:25am

- Cardior Pharmaceuticals has a bigger goal—and has persuaded investors to commit €64 million ($75 million) to support its ambitions.
- Cardior expects to have phase 2 data in the second half of 2024

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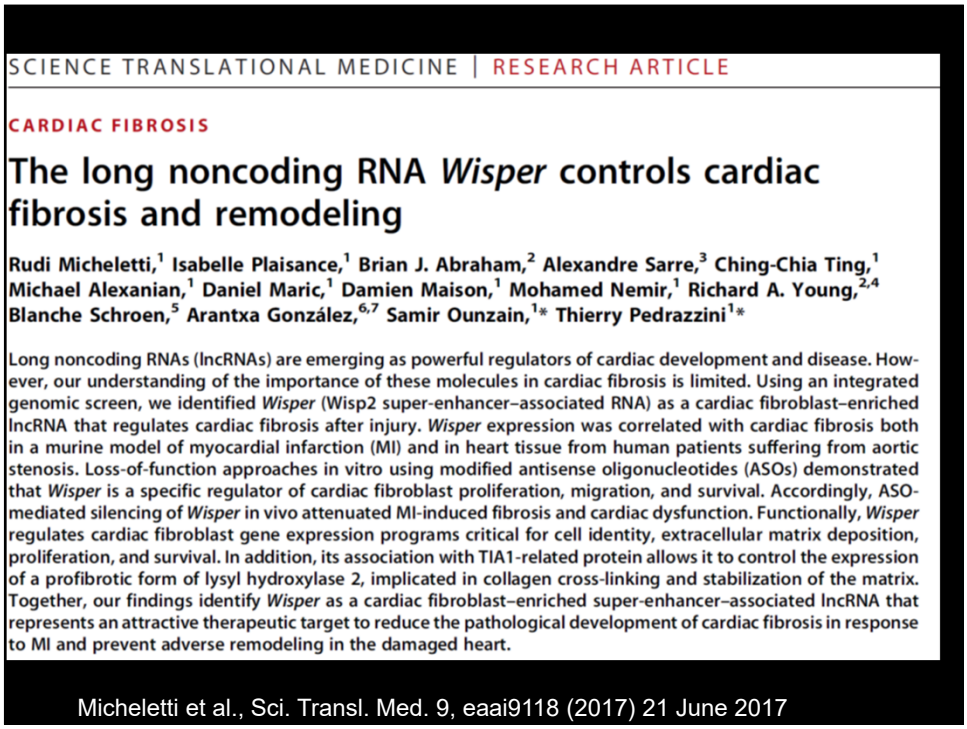


SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CARDIAC FIBROSIS

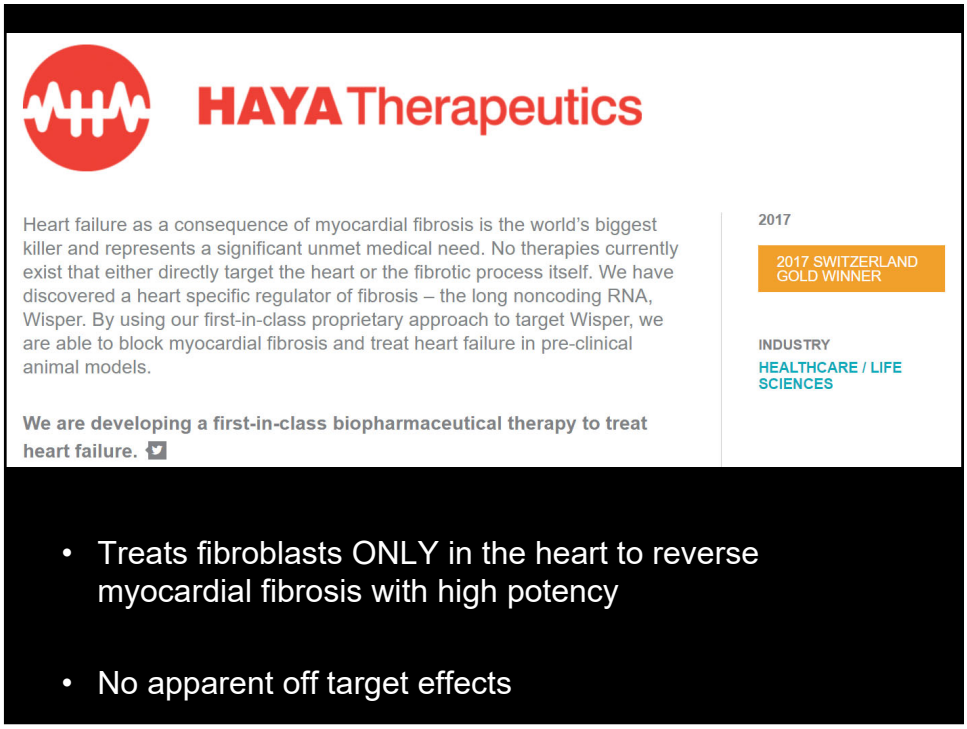
The long noncoding RNA *Wisper* controls cardiac fibrosis and remodeling

Rudi Micheletti,[1] Isabelle Plaisance,[1] Brian J. Abraham,[2] Alexandre Sarre,[3] Ching-Chia Ting,[1] Michael Alexanian,[1] Daniel Maric,[1] Damien Maison,[1] Mohamed Nemir,[1] Richard A. Young,[2,4] Blanche Schroen,[5] Arantxa González,[6,7] Samir Ounzain,[1]* Thierry Pedrazzini[1]*

Long noncoding RNAs (lncRNAs) are emerging as powerful regulators of cardiac development and disease. However, our understanding of the importance of these molecules in cardiac fibrosis is limited. Using an integrated genomic screen, we identified *Wisper* (Wisp2 super-enhancer–associated RNA) as a cardiac fibroblast–enriched lncRNA that regulates cardiac fibrosis after injury. *Wisper* expression was correlated with cardiac fibrosis both in a murine model of myocardial infarction (MI) and in heart tissue from human patients suffering from aortic stenosis. Loss-of-function approaches in vitro using modified antisense oligonucleotides (ASOs) demonstrated that *Wisper* is a specific regulator of cardiac fibroblast proliferation, migration, and survival. Accordingly, ASO-mediated silencing of *Wisper* in vivo attenuated MI-induced fibrosis and cardiac dysfunction. Functionally, *Wisper* regulates cardiac fibroblast gene expression programs critical for cell identity, extracellular matrix deposition, proliferation, and survival. In addition, its association with TIA1-related protein allows it to control the expression of a profibrotic form of lysyl hydroxylase 2, implicated in collagen cross-linking and stabilization of the matrix. Together, our findings identify *Wisper* as a cardiac fibroblast–enriched super-enhancer–associated lncRNA that represents an attractive therapeutic target to reduce the pathological development of cardiac fibrosis in response to MI and prevent adverse remodeling in the damaged heart.

Micheletti et al., Sci. Transl. Med. 9, eaai9118 (2017) 21 June 2017

95



HAYA Therapeutics

Heart failure as a consequence of myocardial fibrosis is the world's biggest killer and represents a significant unmet medical need. No therapies currently exist that either directly target the heart or the fibrotic process itself. We have discovered a heart specific regulator of fibrosis – the long noncoding RNA, Wisper. By using our first-in-class proprietary approach to target Wisper, we are able to block myocardial fibrosis and treat heart failure in pre-clinical animal models.

We are developing a first-in-class biopharmaceutical therapy to treat heart failure.

2017

2017 SWITZERLAND GOLD WINNER

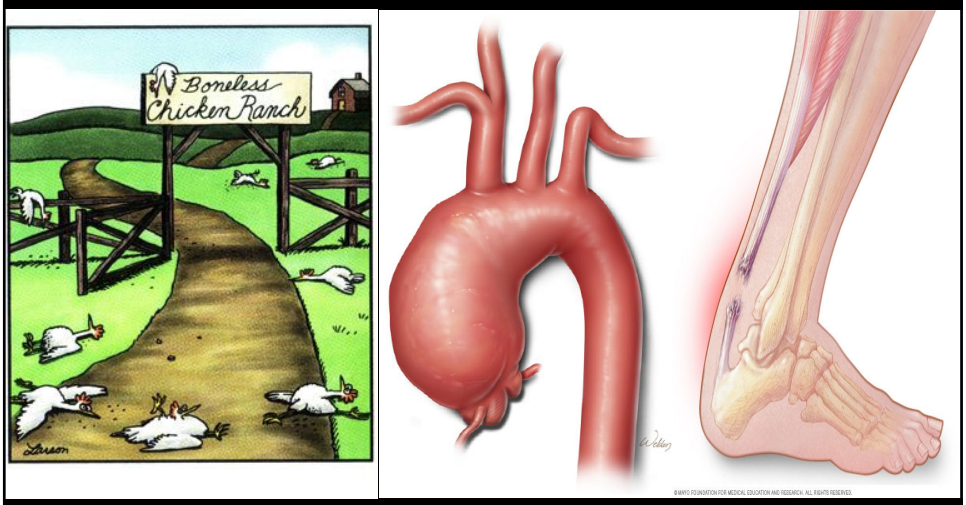
INDUSTRY

HEALTHCARE / LIFE SCIENCES

- Treats fibroblasts ONLY in the heart to reverse myocardial fibrosis with high potency
- No apparent off target effects

96

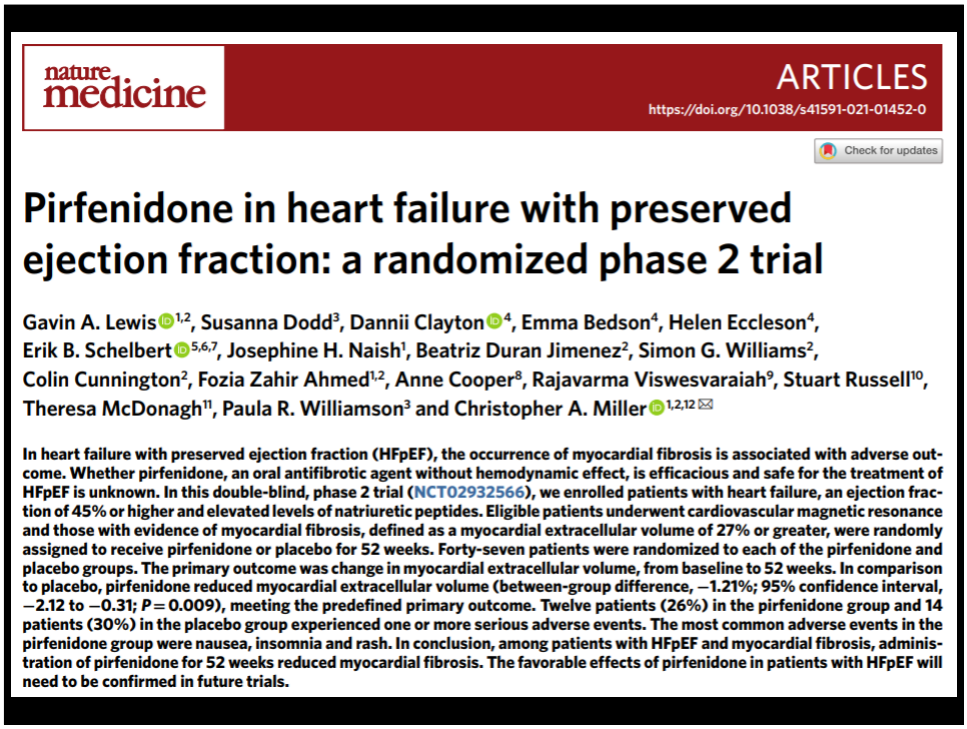
Undesirable off target effects



97

First Randomized Controlled doble blinded Phase 2 trial to reverse myocardial fibrosis

98



nature medicine

ARTICLES

https://doi.org/10.1038/s41591-021-01452-0

Check for updates

Pirfenidone in heart failure with preserved ejection fraction: a randomized phase 2 trial

Gavin A. Lewis[1,2], Susanna Dodd[3], Dannii Clayton[4], Emma Bedson[4], Helen Eccleson[4], Erik B. Schelbert[5,6,7], Josephine H. Naish[1], Beatriz Duran Jimenez[2], Simon G. Williams[2], Colin Cunnington[2], Fozia Zahir Ahmed[1,2], Anne Cooper[8], Rajavarma Viswesvaraiah[9], Stuart Russell[10], Theresa McDonagh[11], Paula R. Williamson[3] and Christopher A. Miller[1,2,12] ✉

In heart failure with preserved ejection fraction (HFpEF), the occurrence of myocardial fibrosis is associated with adverse outcome. Whether pirfenidone, an oral antifibrotic agent without hemodynamic effect, is efficacious and safe for the treatment of HFpEF is unknown. In this double-blind, phase 2 trial (NCT02932566), we enrolled patients with heart failure, an ejection fraction of 45% or higher and elevated levels of natriuretic peptides. Eligible patients underwent cardiovascular magnetic resonance and those with evidence of myocardial fibrosis, defined as a myocardial extracellular volume of 27% or greater, were randomly assigned to receive pirfenidone or placebo for 52 weeks. Forty-seven patients were randomized to each of the pirfenidone and placebo groups. The primary outcome was change in myocardial extracellular volume, from baseline to 52 weeks. In comparison to placebo, pirfenidone reduced myocardial extracellular volume (between-group difference, −1.21%; 95% confidence interval, −2.12 to −0.31; *P* = 0.009), meeting the predefined primary outcome. Twelve patients (26%) in the pirfenidone group and 14 patients (30%) in the placebo group experienced one or more serious adverse events. The most common adverse events in the pirfenidone group were nausea, insomnia and rash. In conclusion, among patients with HFpEF and myocardial fibrosis, administration of pirfenidone for 52 weeks reduced myocardial fibrosis. The favorable effects of pirfenidone in patients with HFpEF will need to be confirmed in future trials.

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Pirfenidone in heart failure with preserved ejection fraction: a randomized phase 2 trial

- enrolled patients with heart failure, an ejection fraction of 45% or higher and elevated levels of natriuretic peptides, myocardial ECV ≥ 27%
- randomly assigned to receive pirfenidone (n=47) or placebo (n=47) for 52 weeks.
- In comparison to placebo, pirfenidone reduced myocardial ECV (−1.21%; 95% CI, −2.12 to −0.31; P = 0.009).
- 12 patients (26%) in the pirfenidone group and 14 patients (30%) in the placebo group experienced serious adverse events. The most common adverse events in the pirfenidone group were nausea, insomnia and rash.

Lewis GA, Dodd S, Clayton D et al. Pirfenidone in heart failure with preserved ejection fraction: a randomized phase 2 trial. Nat Med 2021;27:1477-1482.

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Pirfenidone in heart failure with preserved ejection fraction: a randomized phase 2 trial

- **Pirfenidone was associated with a reduction in log NT-proBNP** compared to placebo (P=0.02)
- the effect seen by week 13 (the reduction in median NT-proBNP from baseline to week 13 with pirfenidone was 415ng/L versus 326ng/L with placebo;

Lewis GA, Dodd S, Clayton D et al. Pirfenidone in heart failure with preserved ejection fraction: a randomized phase 2 trial. Nat Med 2021;27:1477-1482.

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Pirfenidone in heart failure with preserved ejection fraction: a randomized phase 2 trial

- among patients with HFpEF and myocardial fibrosis, administration of pirfenidone for 52 weeks reduced myocardial fibrosis −1.21%;
- “The favorable effects of pirfenidone in patients with HFpEF will need to be confirmed in future trials” (e.g., phase 3).

Lewis GA, Dodd S, Clayton D et al. Pirfenidone in heart failure with preserved ejection fraction: a randomized phase 2 trial. Nat Med 2021;27:1477-1482.

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Future Directions

- Assess how cardiomyocyte and interstitial/fibroblast domains of vulnerability change with interventions
  - Pharmacologic
  - Procedural (percutaneous, surgical)
- Understand the efficacy of these interventions on each domain as they both important
- Define high-ECV enriched populations without reliance on CMR/CCT for Phase 3 trials
  - (there definitely is a way to do this! — unpublished data)

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Conclusions

- Interstitial expansion from myocardial fibrosis likely causes:
  - Mechanical dysfunction (i.e., diastolic)
    - Systolic function and ECV are mostly independent
  - Microvascular dysfunction (↓ perfusion reserve, capillary rarefaction)
  - Electrical dysfunction (reentry)

  and the increases risks of death, hospitalization for HF, arrhythmia
- Similar strength of association with adverse outcomes between ECV and EF and/or GLS → Myocardial fibrosis likely causal
- CMR (and CCT) measure interstitial expansion with ECV reliably
- Anti-fibrotic Rx under development promise to reverse cardiac dysfunction & improve outcomes.
- ECV is critical for serial monitoring of disease progression / regression

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- Eric Olausson, MD, Karolinska Institutet
- Kayla Piehler, MD
- Martin Ugander, MD, PhD, Karolinska Institutet
- Timothy Wong, MD, MS

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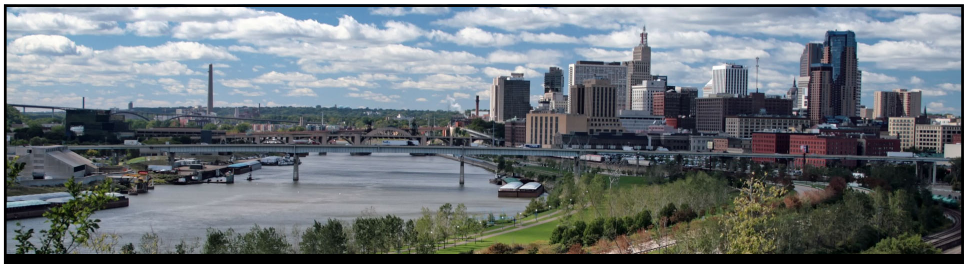

Thank you

Minneapolis Heart Institute

Allina Health

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ORIGINAL RESEARCH

American Heart Association.

Myocardial Effects of Aldosterone Antagonism in Heart Failure With Preserved Ejection Fraction

Adam K. McDiarmid, MD; Peter P. Swoboda, PhD; Bara Erhayiem, BMBS; Katrina A. Bounford, BSc; Petra Bijsterveld, MA; Keith Tyndall, RN; Graham J. Fent, MBChB; Pankaj Garg, MD; Laura E. Dobson, MD; Tarique A. Musa, PhD; James R. J. Foley, MBChB; Klaus K. Witte, MD; Mark T. Kearney, MD; John P. Greenwood, PhD; Sven Plein, PhD

Background—Spironolactone may have prognostic benefit in selected patients with heart failure with preserved ejection fraction. This study assessed the myocardial tissue effects of spironolactone in heart failure with preserved ejection fraction.

Methods and Results—A 1:1 randomized controlled study of 6 months of spironolactone versus control in heart failure with preserved ejection fraction. The primary outcome was change in myocardial extracellular volume fraction by cardiovascular magnetic resonance as a surrogate of diffuse fibrosis. Of 55 randomized patients, 40 (20 women; age, 75.2±5.9 years) completed follow-up (19 treatment, 21 control). A significant change in extracellular volume over the study period was not seen (treatment, 28.7±3.7% versus 27.7±3.4% [P=0.14]; controls, 27.6±3.4% versus 28.3±4.4% [P=0.14]); however, the rate of extracellular volume expansion was decreased by spironolactone (−1.0±2.4% versus 0.8±2.2%). Indexed left ventricular mass decreased with treatment (104.4±26.6 versus 94.0±20.6 g/m^2; P=0.001) but not in controls (101.4±29.4 versus 104.0±32.8 g/m^2; P=0.111). Extracellular mass decreased by 13.8% (15.1±4.8 versus 13.0±3.4 g/m^2; P=0.003), and cellular mass decreased by 8.3% (37.6±10.0 versus 34.3±7.9 g/m^2; P=0.001) with spironolactone, but was static in controls.

Conclusions—Spironolactone did not lead to significant change in extracellular volume. However, spironolactone did decrease rate of extracellular expansion, with a decrease in the mass of both cellular and extracellular myocardial compartments. These data point to the mechanism of action of spironolactone in heart failure with preserved ejection fraction, including a direct tissue effect with a reduction in rate of myocardial fibrosis. (***J Am Heart Assoc.*** **2020;9:e011521. DOI: 10.1161/JAHA.118.011521.)**

Key Words: cardiovascular magnetic resonance • extracellular volume • heart failure • heart failure with preserved ejection fraction

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Omnipresent issue in research: Cause vs. Effect

Among cascading derangements in diseased myocardium:

- which “domains” confer vulnerability and are truly causal?
- which abnormalities simply represent downstream, noncausal effects of the above?
- How do we conceptualize these changes?

https://www.virginia.org/listings/OutdoorsAndSports/CascadesNationalRecreationTrail/

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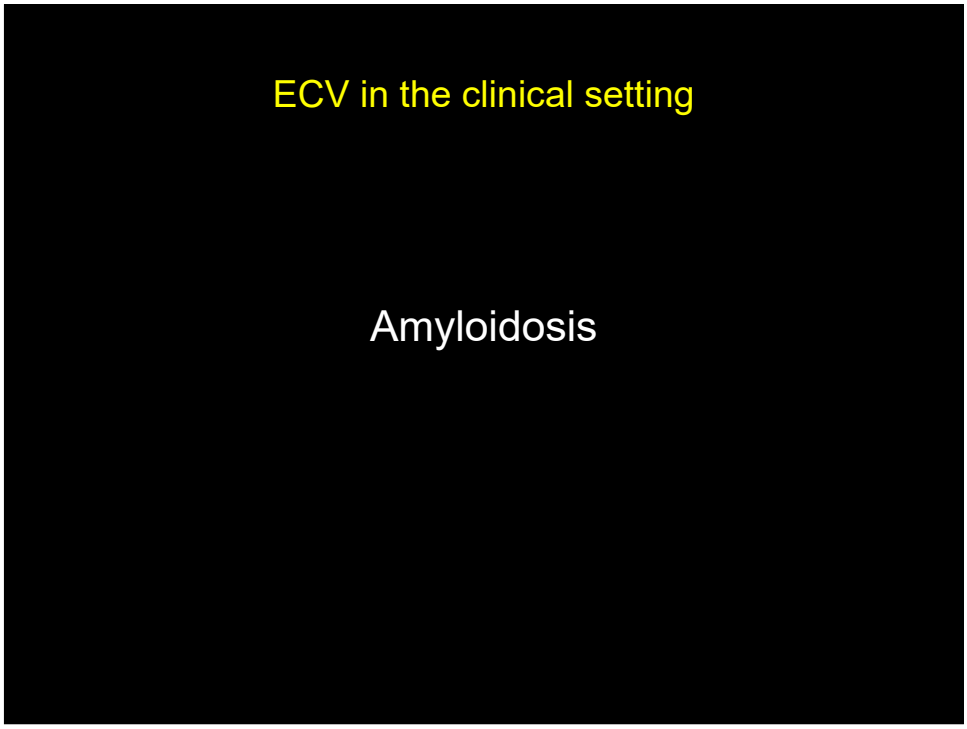

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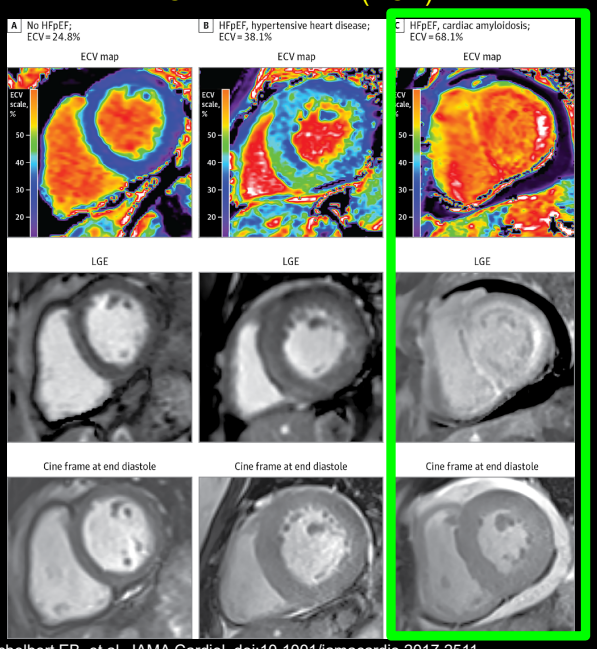
Different story for Late Gadolinium Enhancement (LGE) and ExtraCellular Volume (ECV) cardiac MR



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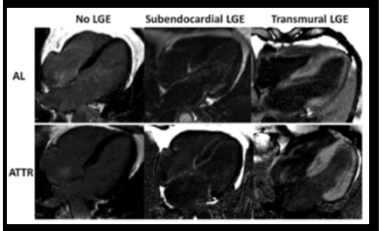
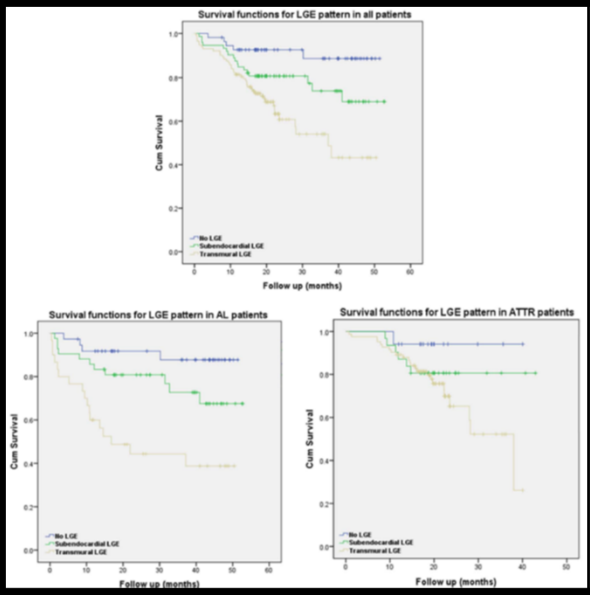
Prognostic Value of Late Gadolinium Enhancement (LGE) Cardiovascular Magnetic Resonance (CMR) in Both types of Cardiac Amyloidosis



LGE is crude burden of disease measure



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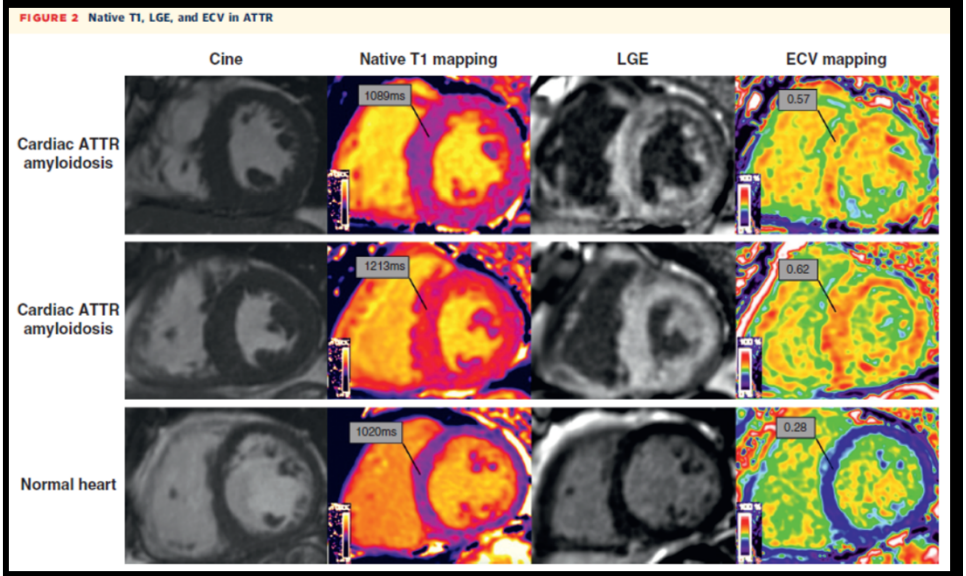
Cardiac MR for ATTR diagnosis

LGE (qualitative) + ECV (quantitative measure of interstital volume)



Martinez-Naharro M, et al. J Am Coll Cardiol Img 2019;12:810–9 https://doi.org/10.1016/j.jcmg.2018.02.006

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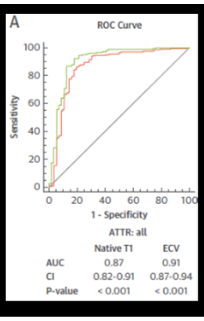
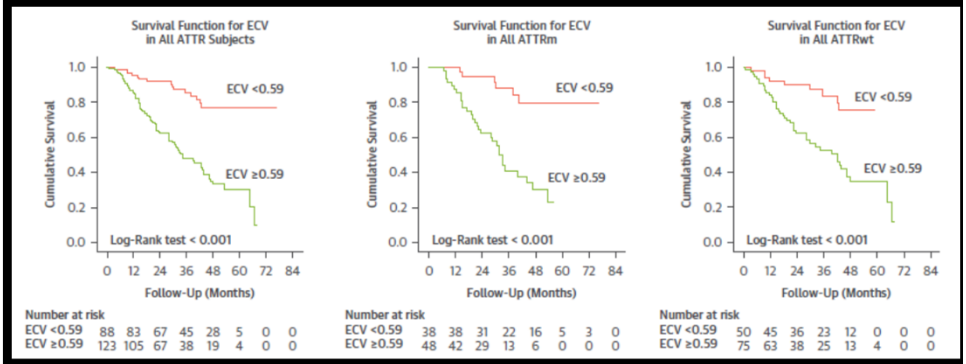
Cardiac MR with ECV for diagnosis as well as ATTR risk stratification



AUC
0.91 for ECV



Martinez-Naharro M, et al. J Am Coll Cardiol Img 2019;12:810–9 https://doi.org/10.1016/j.jcmg.2018.02.006

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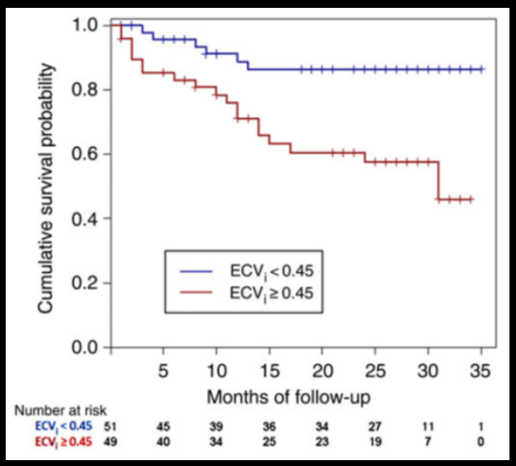
ECV risk stratification for AL cardiac amyloidosis



Banypersad SM, et al. Eur Heart J (2015) 36, 244–251 doi:10.1093/eurheartj/ehu444

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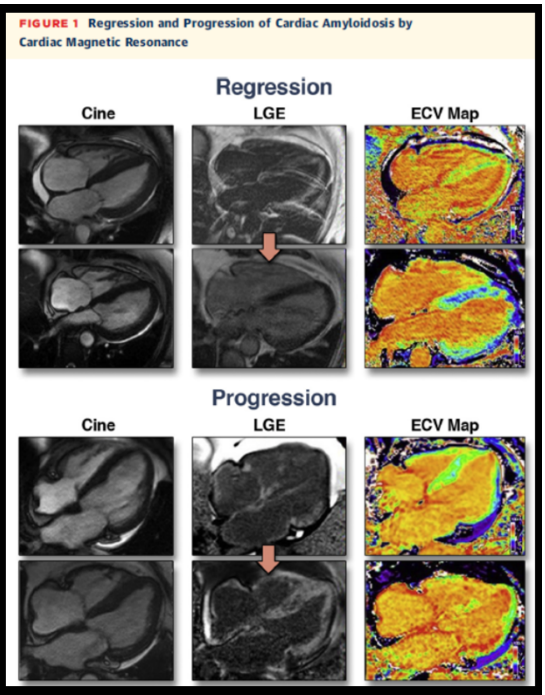
ECV can track response to therapy!

Or lack thereof…



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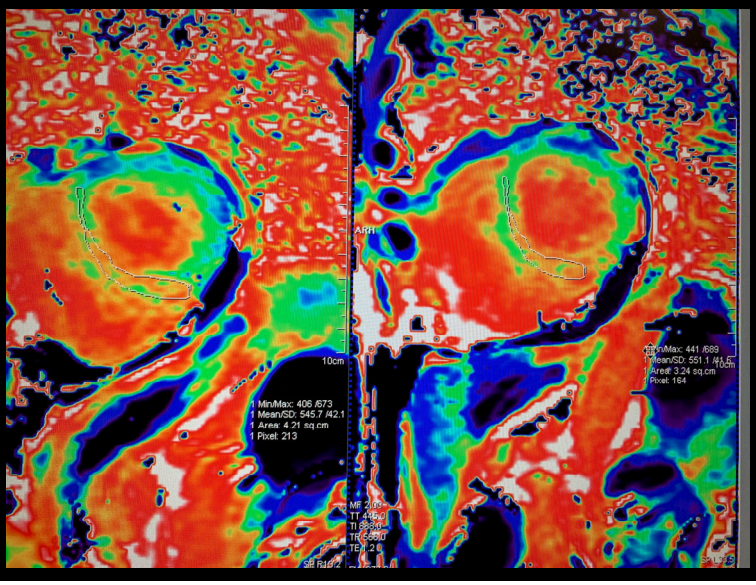
No change in ECV 1 yr after patisiran Rx for ATTR

Despite other testing suggesting regression



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Cavalcante et al. Journal of Cardiovascular Magnetic Resonance (2017) 19:98
DOI 10.1186/s12968-017-0415-x

Journal of Cardiovascular Magnetic Resonance

RESEARCH Open Access

Cardiac amyloidosis is prevalent in older patients with aortic stenosis and carries worse prognosis

João L. Cavalcante[1,2*], Shasank Rijal[1], Islam Abdelkarim[1], Andrew D. Althouse[1], Michael S. Sharbaugh[1], Yaron Fridman[1,2], Prem Soman[1], Daniel E. Forman[1], John T. Schindler[1], Thomas G. Gleason[1], Joon S. Lee[1] and Erik B. Schelbert[1,2]

Abstract

Background: Non-invasive cardiac imaging allows detection of cardiac amyloidosis (CA) in patients with aortic stenosis (AS). Our objective was to estimate the prevalence of clinically suspected CA in patients with moderate and severe AS referred for cardiovascular magnetic resonance (CMR) in age and gender categories, and assess associations between AS-CA and all-cause mortality.

Methods: We retrospectively identified consecutive AS patients defined by echocardiography referred for further CMR assessment of valvular, myocardial, and aortic disease. CMR identified CA based on typical late-gadolinium enhancement (LGE) patterns, and ancillary clinical evaluation identified suspected CA. Survival analysis with the Log rank test and Cox regression compared associations between CA and mortality.

Results: There were 113 patients (median age 74 years, Q1-Q3: 62–82 years), 96 (85%) with severe AS. Suspected CA was present in 9 patients (8%) all > 80 years. Among those over the median age of 74 years, the prevalence of CA was 9/57 (16%), and excluding women, the prevalence was 8/25 (32%). Low-flow, low-gradient physiology was very common in CA (7/9 patients or 78%). Over a median follow-up of 18 months, 40 deaths (35%) occurred. Mortality in AS + CA patients was higher than AS alone (56% vs. 20% at 1-year, log rank 15.0, $P < 0.0001$). Adjusting for aortic valve replacement modeled as a time-dependent covariate, Society of Thoracic Surgery predicted risk of mortality, left ventricular ejection fraction, CA remained associated with all-cause mortality (HR = 2.92, 95% CI = 1.09–7.86, $P = 0.03$).

Conclusions: Suspected CA appears prevalent among older male patients with AS, especially with low flow, low gradient AS, and associates with all-cause mortality. The importance of screening for CA in older AS patients and optimal treatment strategies in those with CA warrant further investigation, especially in the era of transcatheter aortic valve implantation.

Keywords: Aortic Stenosis, Cardiac Amyloidosis, Outcomes, Cardiovascular magnetic resonance

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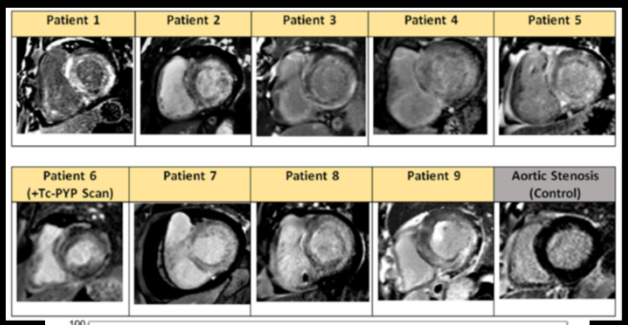
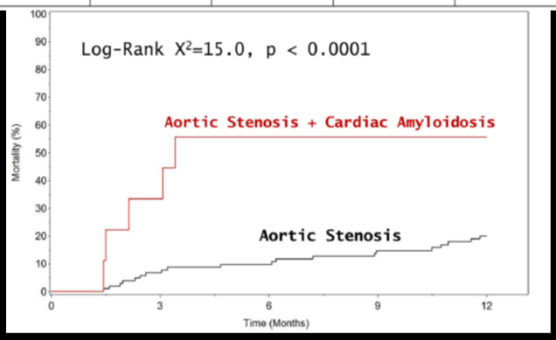
Pittsburgh experience with amyloidosis in aortic stenosis





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