CMR Techniques to Detect Cardiac and Vascular Injury after Treatment for Cancer

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Outline

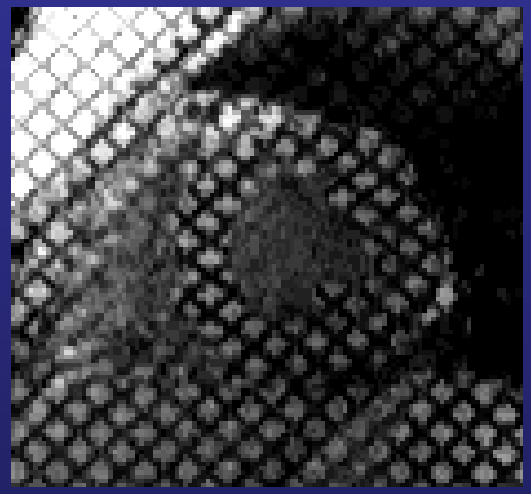
- In patients with cancer, review cardiovascular magnetic resonance (CMR) assessments of:
  - LV volumes, mass, ejection fraction, strain
  - Myocardial injury
  - Myocardial interstitial fibrosis
  - Vascular stiffness
- Feasibility of performing multi-center initiatives to develop predictive models of CV risk using CMR
- Ongoing NIH studies to investigate cardiotoxicity

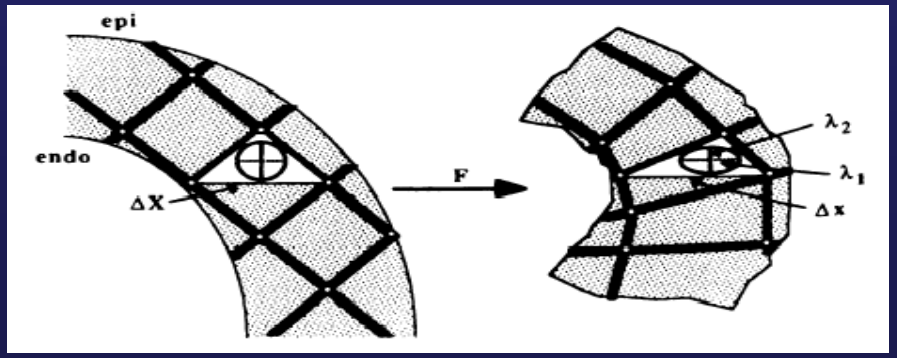
MRI methods (left ventricle)

WAKE FOREST UNIVERSITY
SCHOOL of MEDICINE
THE BOWMAN GRAY CAMPUS

A multi-phase, multi-slice cine white blood sequence was used to measure LV volumes and ejection fraction using a modified Simpson's Rule Method

Mean, mid-wall circumferential strain using tissue tagging



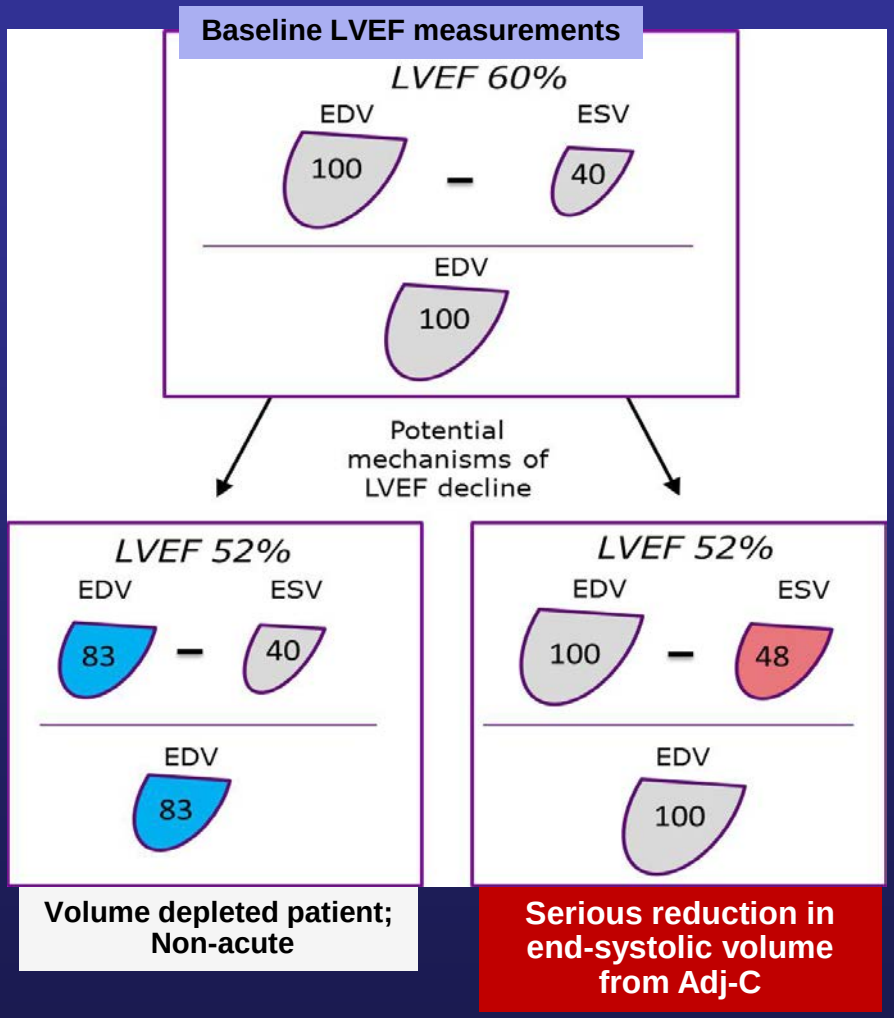


Comparison to 2D planar imaging incorporating area-length formulae

	Echo	*CMR*	*↓ sample size*
EDV, 10 ml	121	12	90%
ESV, 10 ml	53	10	81%
EF, 3%	102	15	85%
Mass, 10 g	273	9	97%

Bellenger NG et al, *J Cardiovasc Magn Reson* 2000;2:271

Two potential manifestations of LVEF decline: EDV decrease vs. ESV increase



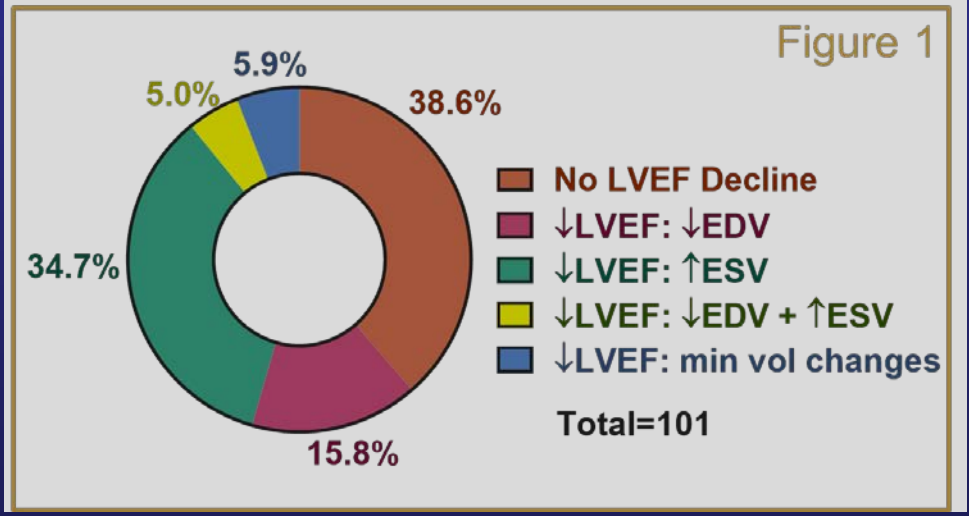
From 112 participants receiving potentially cardiotoxic chemotherapy, 26 participants experienced baseline to 3 months LVEF drops of >10% or a decline to an absolute value of <50%

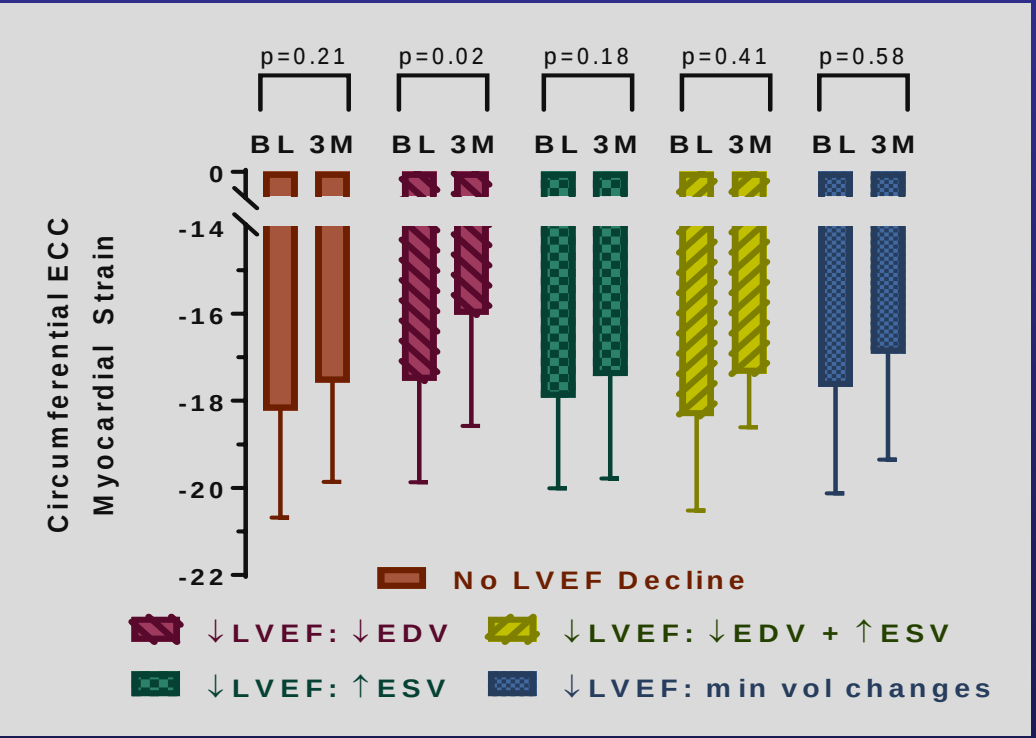
n=5 ↓ EDV – ESV	n=1 ↓ EDV ↑ ESV	n=15 – EDV ↑ ESV	n=5 – EDV – ESV
Suggested Intravascular Volume Depletion (19.23%)	Suggested Intravascular Volume Depletion + LV Systolic dysfunction (3.85%)	LV Systolic dysfunction (59.69 %)	Minor changes in either LV EDV or LV ESV (19.3%)

Melendez, et al., Global Cardio-Oncology Summit 2016

Reductions in LVEDV can impair LV strain 3 months after initiating cardiotoxic chemotherapy

101 participants aged 50 yrs, 70% women,
50% breast cancer 32% lymphoma, 12% leukemia:
74% with anthracycline chemotherapy.

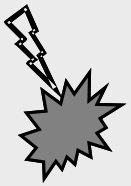




Jordan, et al., Global Cardio-Oncology Summit 2016

Patho-physiology

Exposure



→ Disrupted mitochondrial function & actin-myosin interaction / Intra- and extracellular edema, inflamation, cell injury → Impaired regional LV function → Myocellular death, collagen deposition, LV remodelling → Decreased LVEF, cardiac output → Neurohormonal activation, **CHF**

Surveillance

+ MRI contrast signal intensity

MRI T2 signal

+ serum cardiac Troponin I

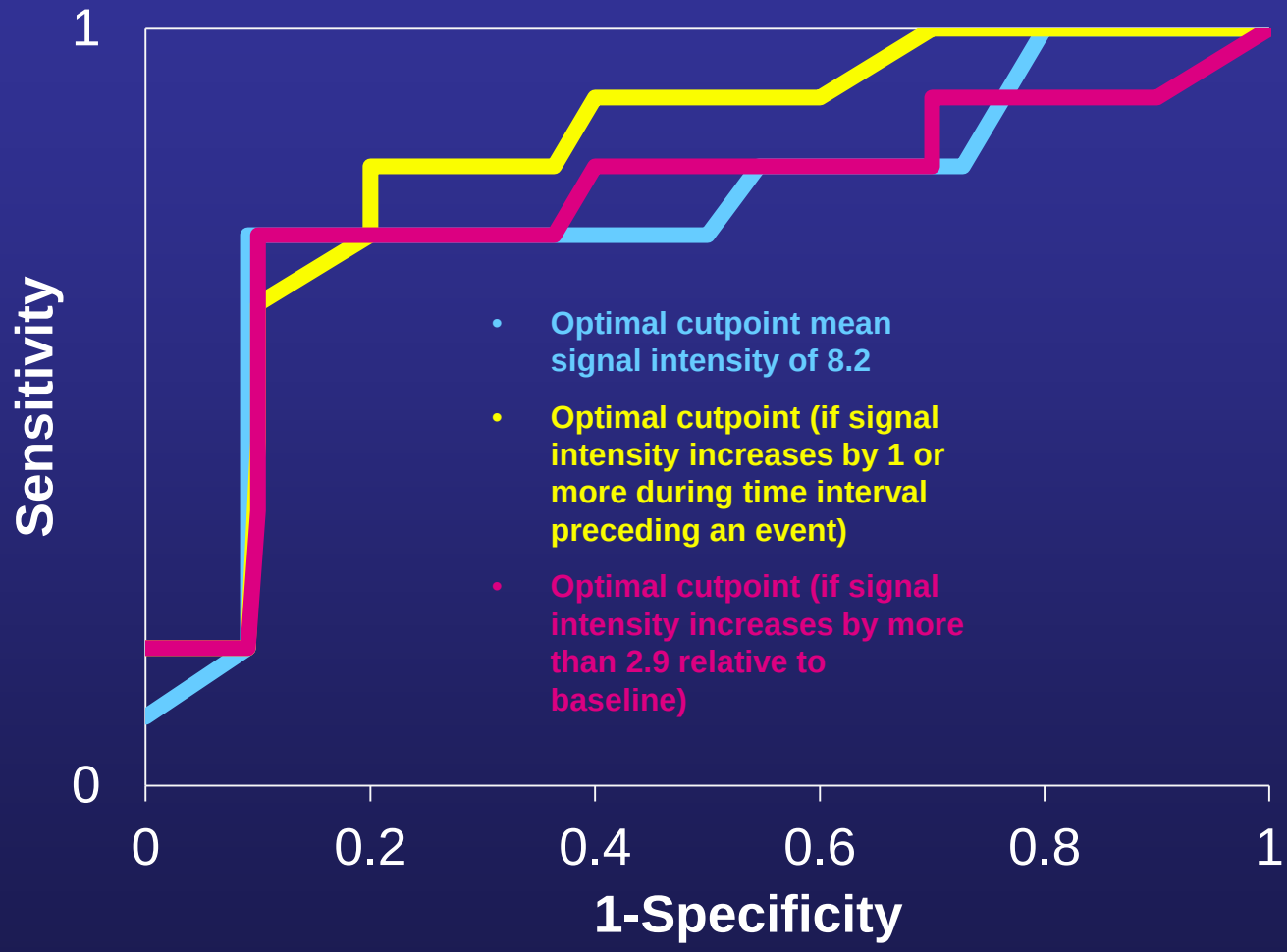
Decreased LVEF

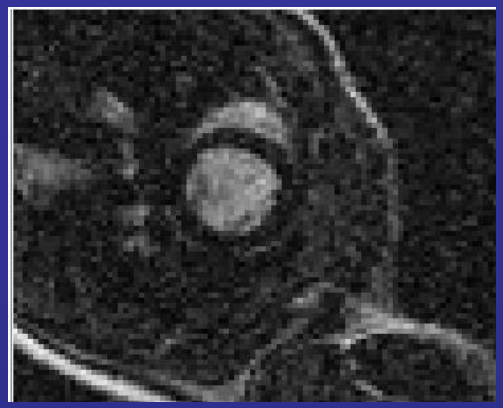
Exercise capacity

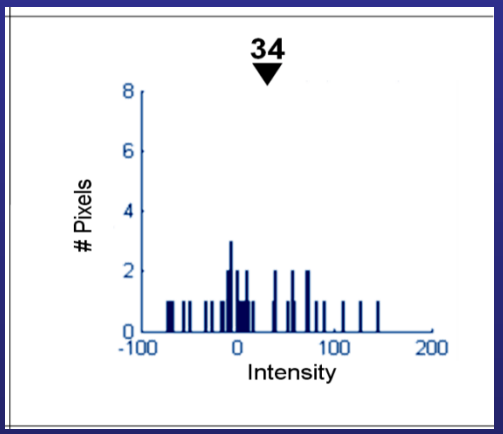
Abnormal regional function

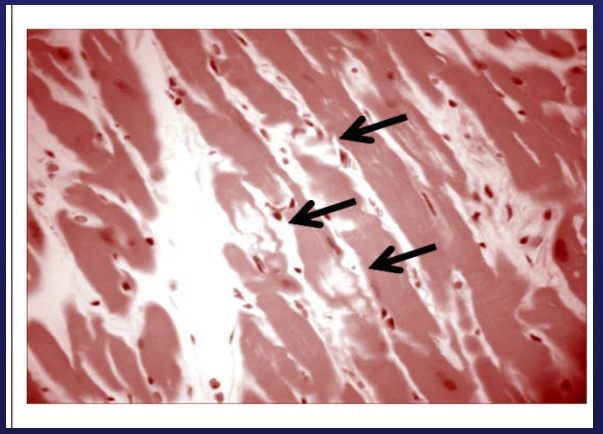
+ serum BNP measurement

ROC Curves Comparing Characteristics of Signal Intensity Change the Forecast Future Events









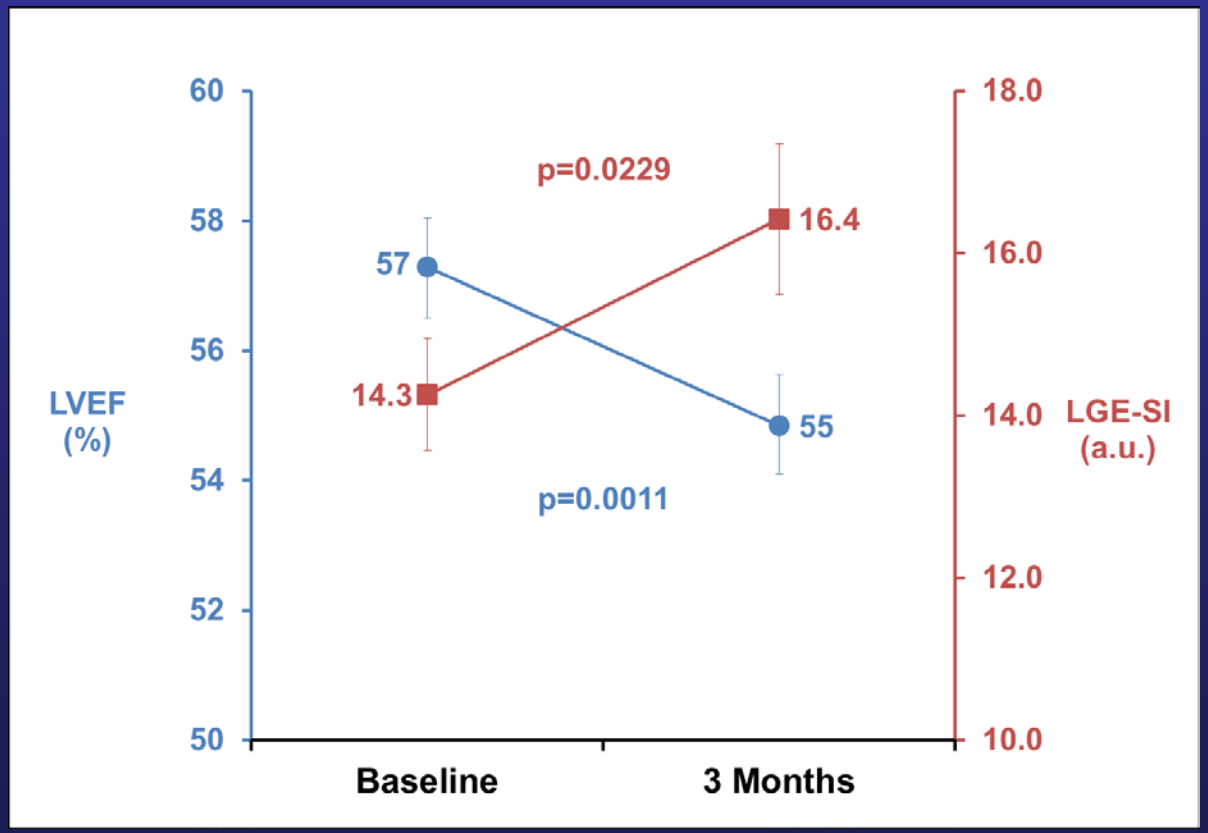
Lightfoot, et al., *Circ Cardiovasc Imag* 2010

Early changes in CMR tissue characterization with late gadolinium enhancement occur concurrently with subclinical declines in LVEF

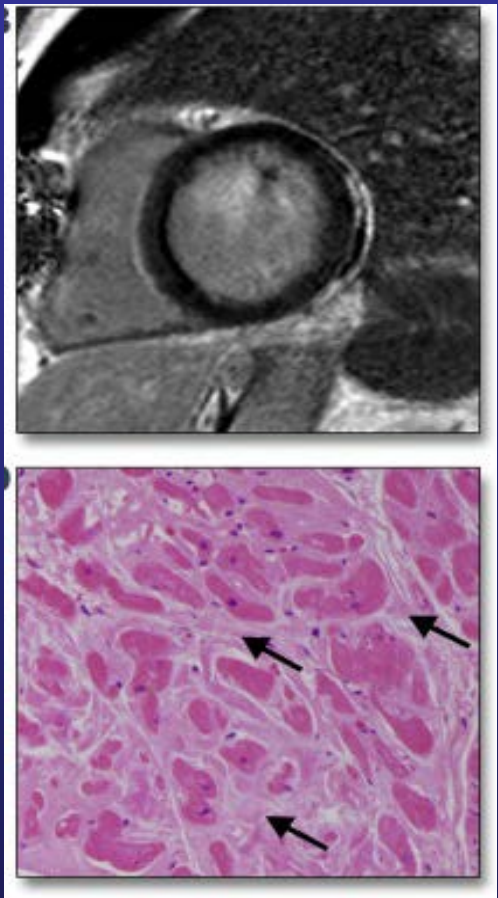
Study population:

n=67 participants receiving cardiotoxic chemotherapy

Aged 51±12 years
87% women
76% breast cancer
55% anthracyclines



Jordan JH et al. *Circ Cardiovasc Imaging* 2014; 7:872-879



Cardio-Oncology

Anthracycline-Associated T1 Mapping Characteristics Are Elevated Independent of the Presence of Cardiovascular Comorbidities in Cancer Survivors

Jennifer H. Jordan, PhD, MS; Sujethra Vasu, MD; Timothy M. Morgan, PhD; Ralph B. D'Agostino, Jr, PhD; Giselle C. Meléndez, MD; Craig A. Hamilton, PhD; Andrew E. Arai, MD; Songtao Liu, MD; Chia-Ying Liu, PhD; João A.C. Lima, MD; David A. Bluemke, MD, PhD; Gregory L. Burke, MD, MSc; W. Gregory Hundley, MD

n=310
Total study participants enrolled from rural communities of northwest NC, southwest VA, and east TN

n=236
Control Subjects

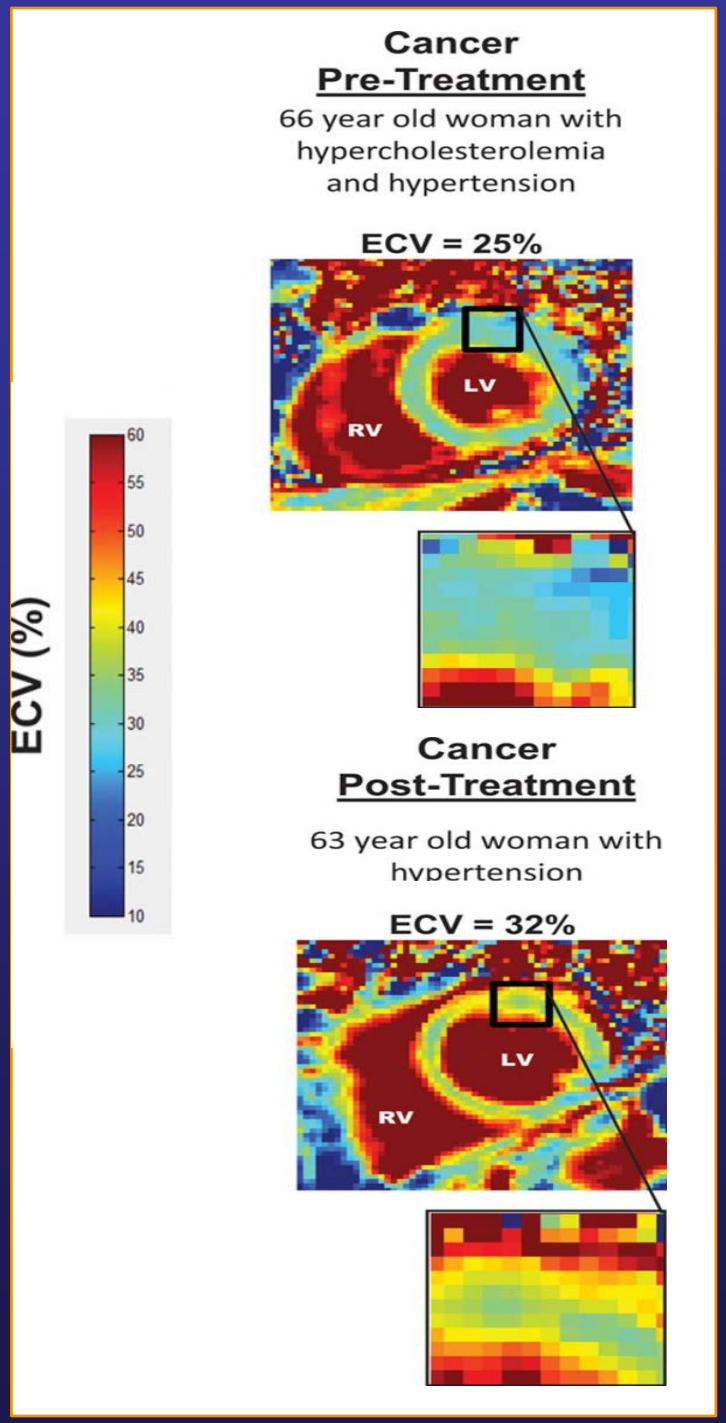
n=37
Cancer Patients Pre-Treatment

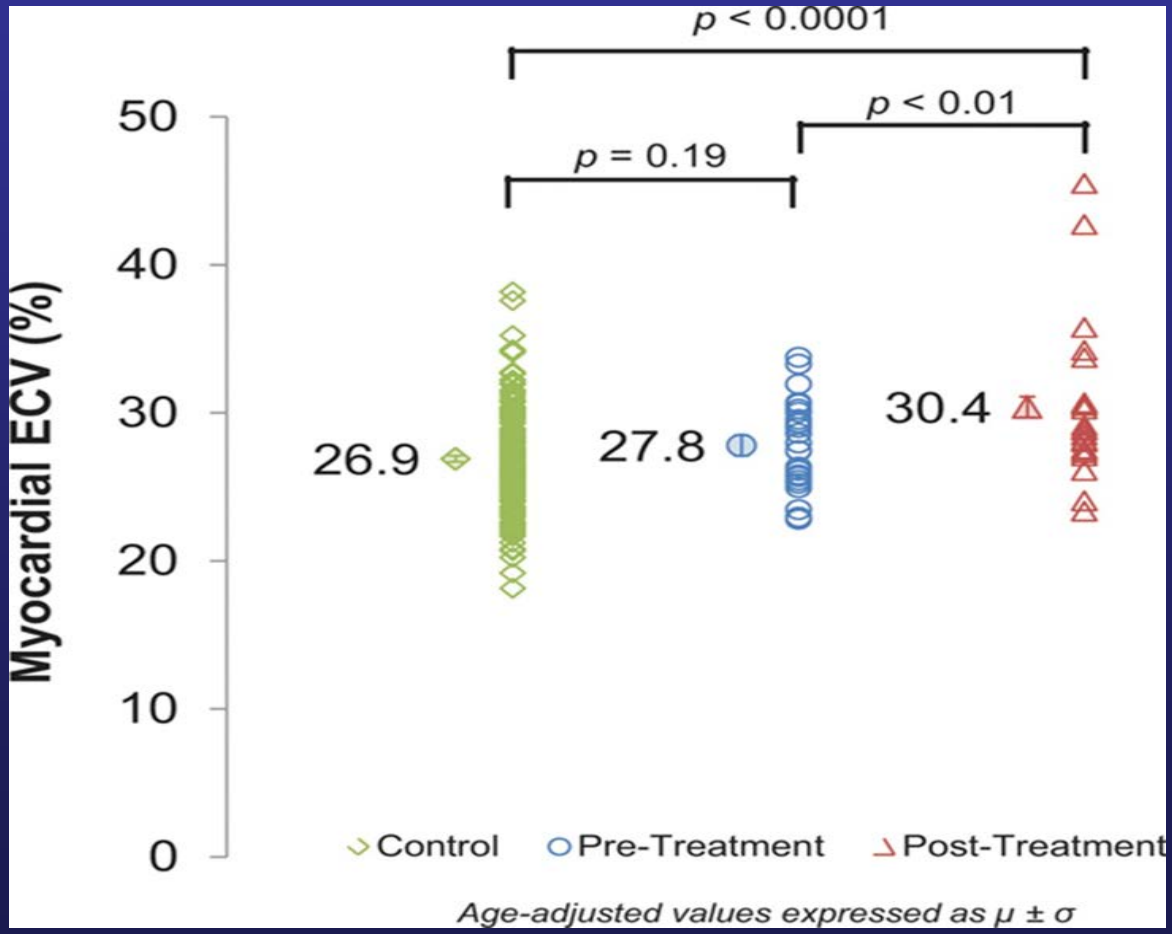
n=37
Cancer Survivors Post-Anthracycline Treatment

American Heart Association.

Jennifer H. Jordan et al. Circ Cardiovasc Imaging. 2016;9:e004325

Myocardial fibrosis is elevated in adult survivors 3 years after anthracycline treatment relative to comparators





Jennifer H. Jordan et al. Circ Cardiovasc Imaging. 2016;9:e004325

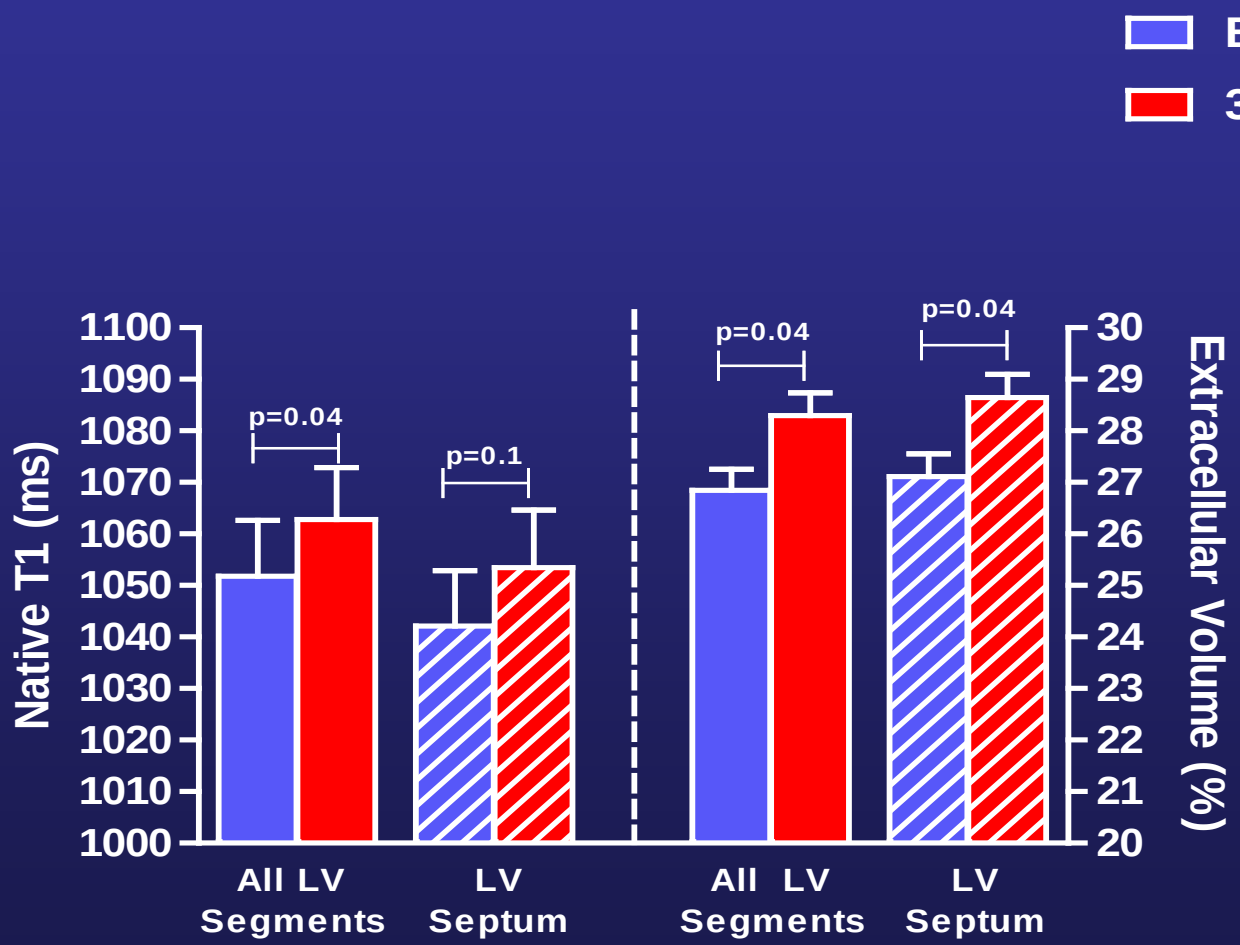
CMR findings of elevated fibrosis persist even after accounting for other risk factors such as age, the presence of cancer, or coexistent cardiovascular comorbidities

Model	Covariates	ECV
Model 1	Group	$p < 0.0001$
Model 2	Group + Age, Race, Gender, Age*Gender	$p < 0.0001$
Model 3	Model 2 + Weight, Heart Rate, Systolic BP, CAD, DM, DysL, HTN	$p < 0.0001$
Model 4	Model 3 + LVEF, LV Mass Index	$p < 0.0001$

Jennifer H. Jordan et al. Circ Cardiovasc Imaging. 2016;9:e004325

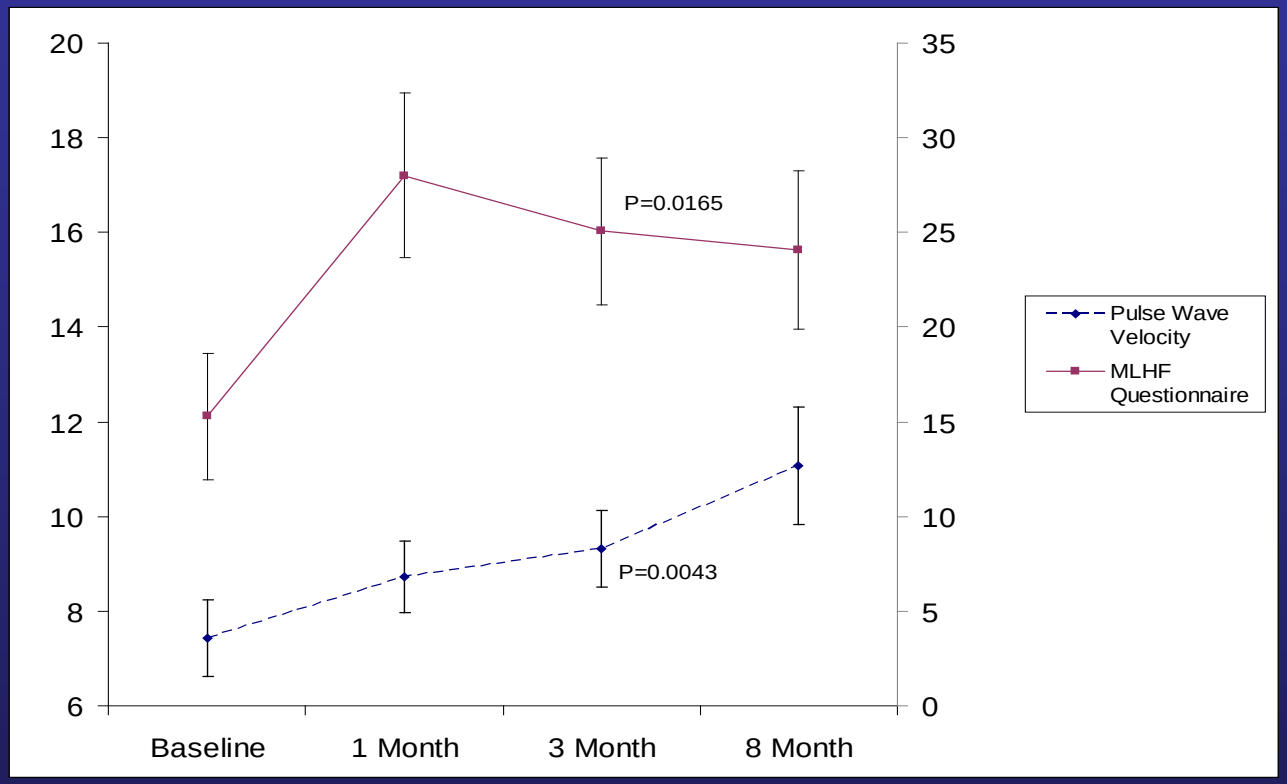
Progressive 3-Month Increase in Left Ventricular Myocardial Extracellular Volume Fraction After Receipt of Anthracycline-Based Chemotherapy

(n= 56; 66% women; 71% white and 29% black; aged 52 ± 13 years).



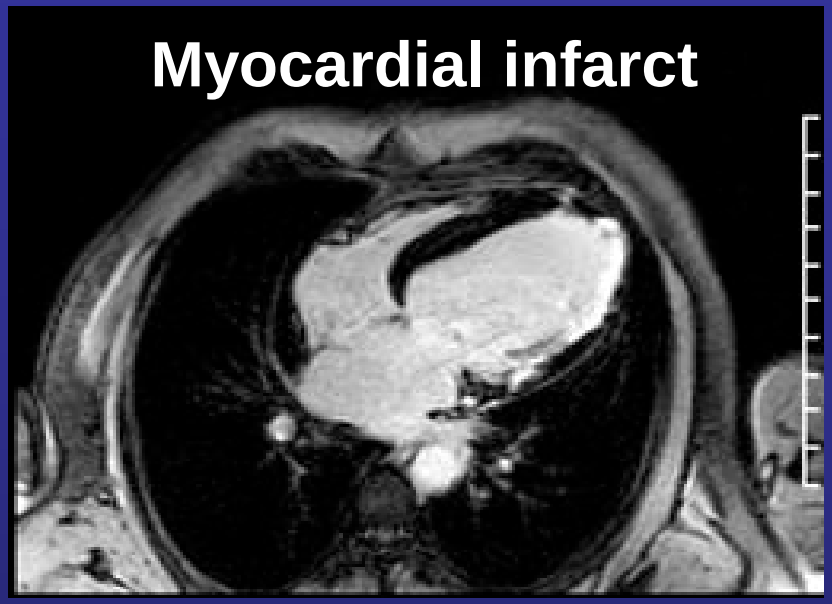
Meléndez GC, Jordan JH, D'Agostino,Jr RB, Vasu S, Hamilton CA, Hundley WG. Progressive three-month increase in left ventricular myocardial extracellular volume fraction after receipt of anthracycline based chemotherapy. *JACC: Cardiovascular Imaging*. (In Press. August 15, 2016)

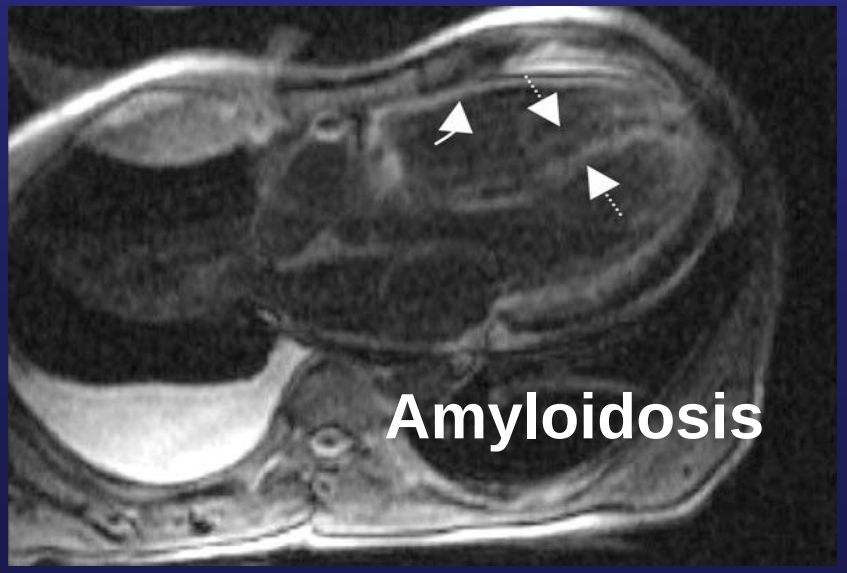
Moving beyond the heart: Relevance of abnormal pulse wave velocity for predicting CV events in population-based studies



Drafts BG, Twomley KM, D'Agostino R Jr., Lawrence J, Ellis LR, Thohan V, Jordan J, Melin SA, Torti FM, Little WC, Hamilton CA, Hundley WG. JACC-Imaging 2012.

Utility of CMR to define etiology of LV dysfunction: 63 yo woman with multiple myeloma with past history of CAD, HTN presents 5 weeks after treatment with new proteosome inhibitor with dyspnea and LVEF of 40%? What is her diagnosis?

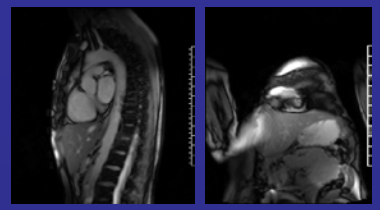


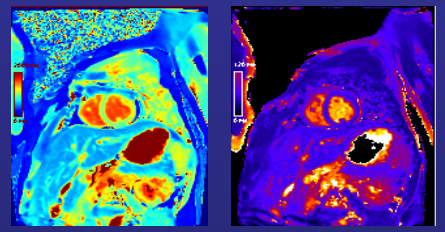
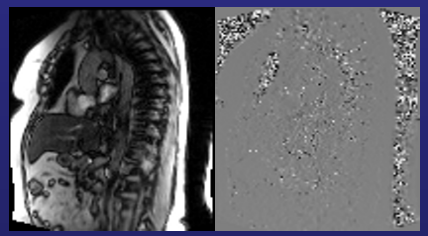
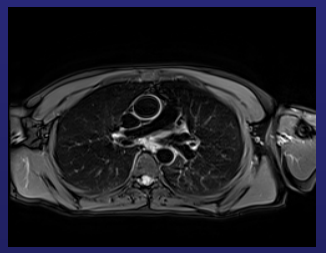
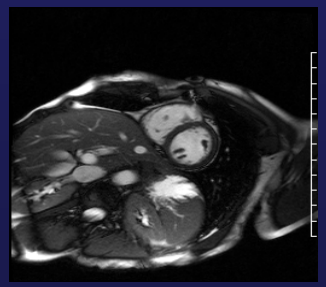
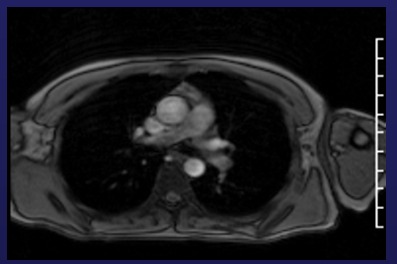


Comprehensive study in < 15 mins in community hospitals

Rapid Imaging Protocol

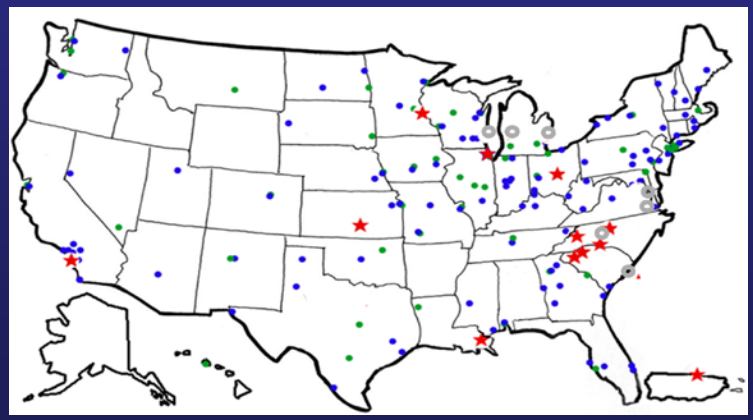
Localizers (x2)	0:30
Tagging	0:30
T1 and T2 Maps	1:00
Aorta Phase Contrast	2:00
Aorta Wall Thickness	0:30
Aorta Distensibility	0:30
LV Cine Stack	3:00
Total Time	**8-12 min**



Wake Forest NCORP Research Base

- One of two Cancer Center Prevention and control Research Bases in U.S.
- Initially funded in 1999, now operating on 4th competing renewal
- 41 individuals at Wake Forest funded by Research Base grant
  - Executive Steering Committee
  - Protocol Office
  - Data Management Center
  - Research Nursing
  - Cores: Biostatistics, Biospecimen



- Large Network of Community Hospital systems that perform clinical research. Cardiovascular MRI operative across 25 of these community hospitals.

Implementation of clinical CMR studies involving community hospitals

- **Our effort is focused on translational science approaches to diagnose, prevent and manage CV disease in patients treated for cancer.**

#	Title	Status
R21 CA 109224	MRI Detection of Doxorubicin Induced Cardiotoxicity	Completed
R33 CA121296-02	Optimized CMR Imaging of Chemotherapy Cardiotoxicity	Completed
Komen BCTR0707769	Early Detection of Chemotherapy Associated Cardiotoxicity in Women with Breast Cancer	Completed
R01 CA167821-01	Early Imaging Detection of CV Injury after Cancer (n=110)	Awarded through 2017
R43 CA174261	Advanced imaging detection of cardiac injury in high risk cancer patients	Awarded through 2016
R01 HL119980-01	CV injury, exercise intolerance, fatigue and risk prediction after chemotherapy for breast cancer (n=1000)	Awarded through 2020
R01 HL118740-01	Preventing anthracycline CV toxicity with statins (n=240)	Awarded through 2018
R43 HL120486-01	Community hospital ID of CV risk patients during cancer	Awarded through 2017

Summary

- In individuals treated for cancer, cardiovascular magnetic resonance measures of left ventricular structure and function are useful for identifying subclinical cardiovascular disease associated with adverse CV events.
- New initiatives are extending this technology into clinical healthcare delivery systems that facilitate patient care in community hospitals where a large proportion of the individuals with cancer are treated in the US.
- These new CMR techniques are commensurate with those used in other large NIH population based studies thus allowing for comparisons between individuals with cancer and others at risk for CV disease. Initiatives are underway to utilize risk prediction modeling to determine the utility of several of the new CMR metrics for forecasting CV events after treatment for cancer.