2018

VIENNA, AUSTRIA

SUPPORTIVE CARE MAKES EXCELLENT CANCER CARE POSSIBLE

28-30 JUNE 2018

MASCC/ISOO

ANNUAL MEETING ON SUPPORTIVE CARE IN CANCER

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VIENNA, AUSTRIA
SUPPORTIVE CARE MAKES EXCELLENT CANCER CARE POSSIBLE

Assessment of Cardiac Injury and Toxicity From Cancer Chemotherapy

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Head Non-invasive Imaging
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Connecticut Children's MEDICAL CENTER

UCONN
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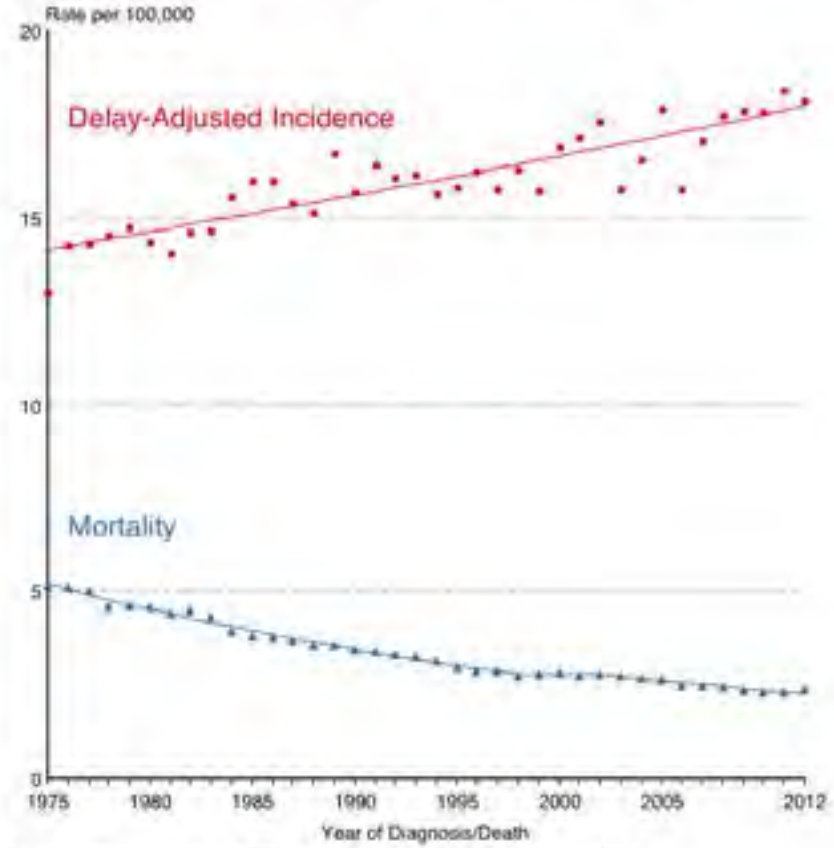
The Jackson Laboratory
Leading the search for tomorrow's cures

Objectives

- Discuss cardiotoxicity of most commonly used chemotherapeutic agents
- Risk stratification of patients exposed to cardiotoxic medications
- Early imaging and biomarkers for assessment of cardiac injury
- Take-home points
- Future directions

Figure 25.1

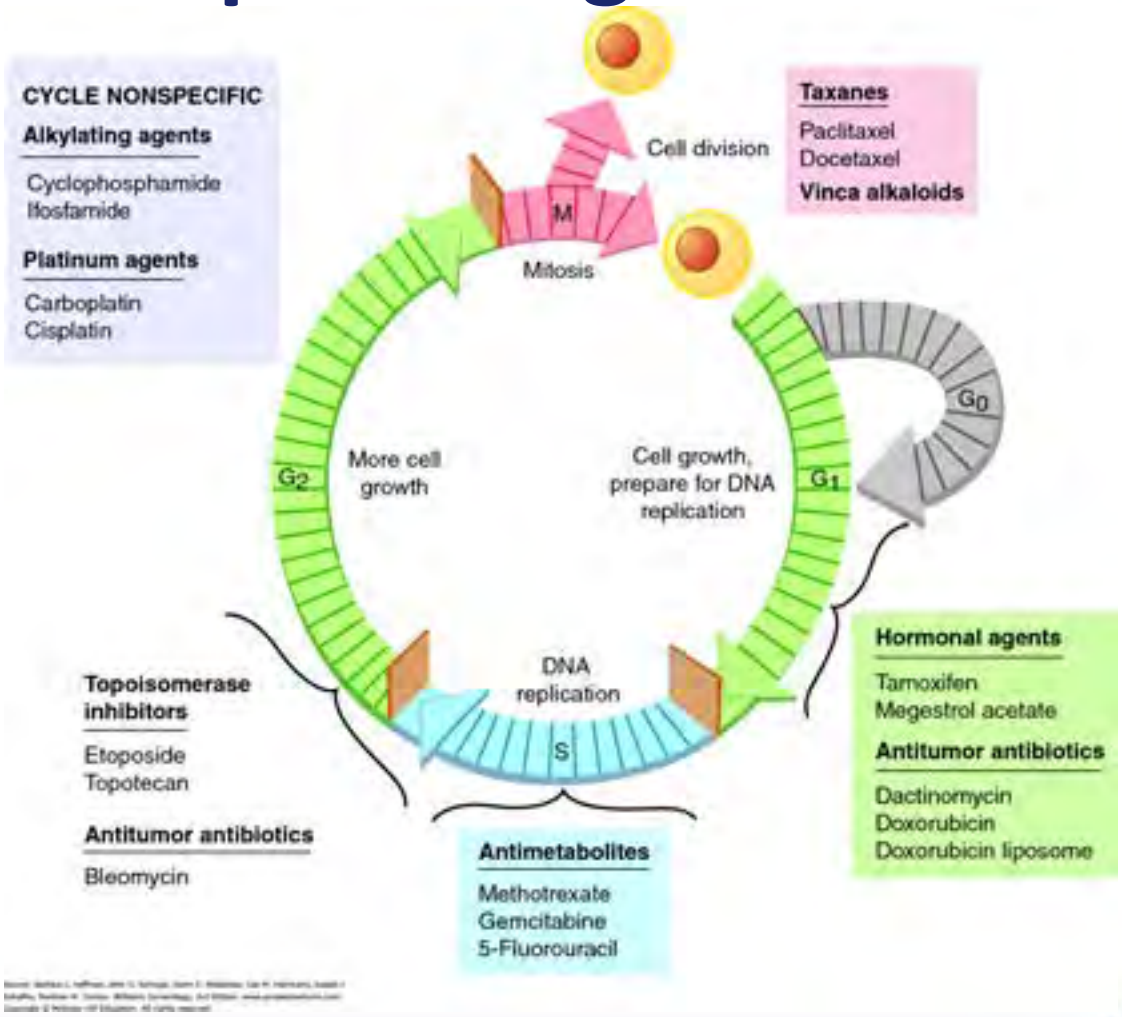
SEER Delay-Adjusted Incidence and US Mortality
All Childhood Cancers, Under 20 Years of Age
Both Sexes, All Races, 1975-2012



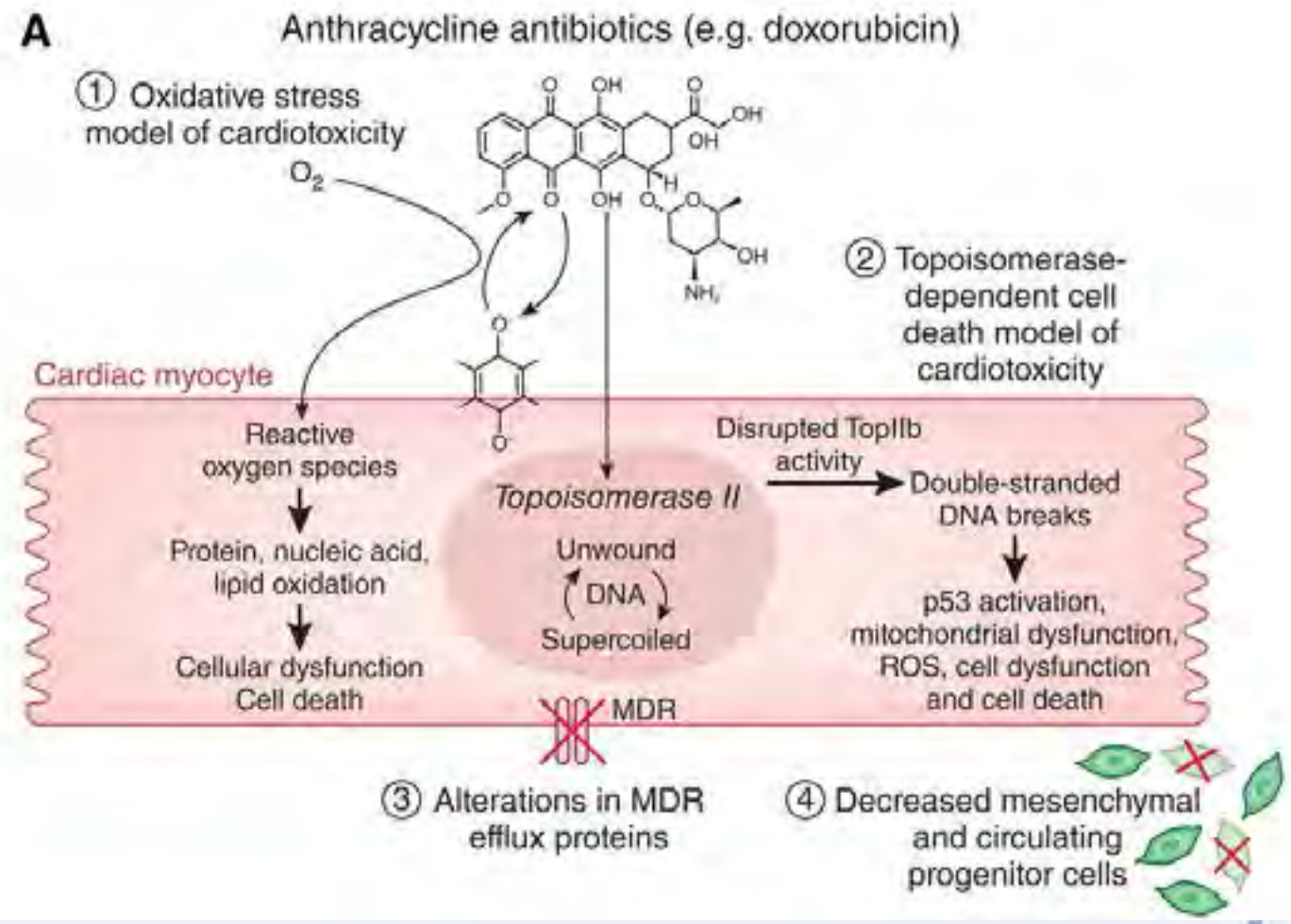
Source: SEER 9 areas and US Mortality Files (National Center for Health Statistics, CDC).
Rates are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1103).
Regression lines are calculated using the Joinpoint Regression Program Version 4.2.0, April 2015;
National Cancer Institute.

Surveillance, Epidemiology and End Results (SEER) Program

Chemotherapeutic Agents

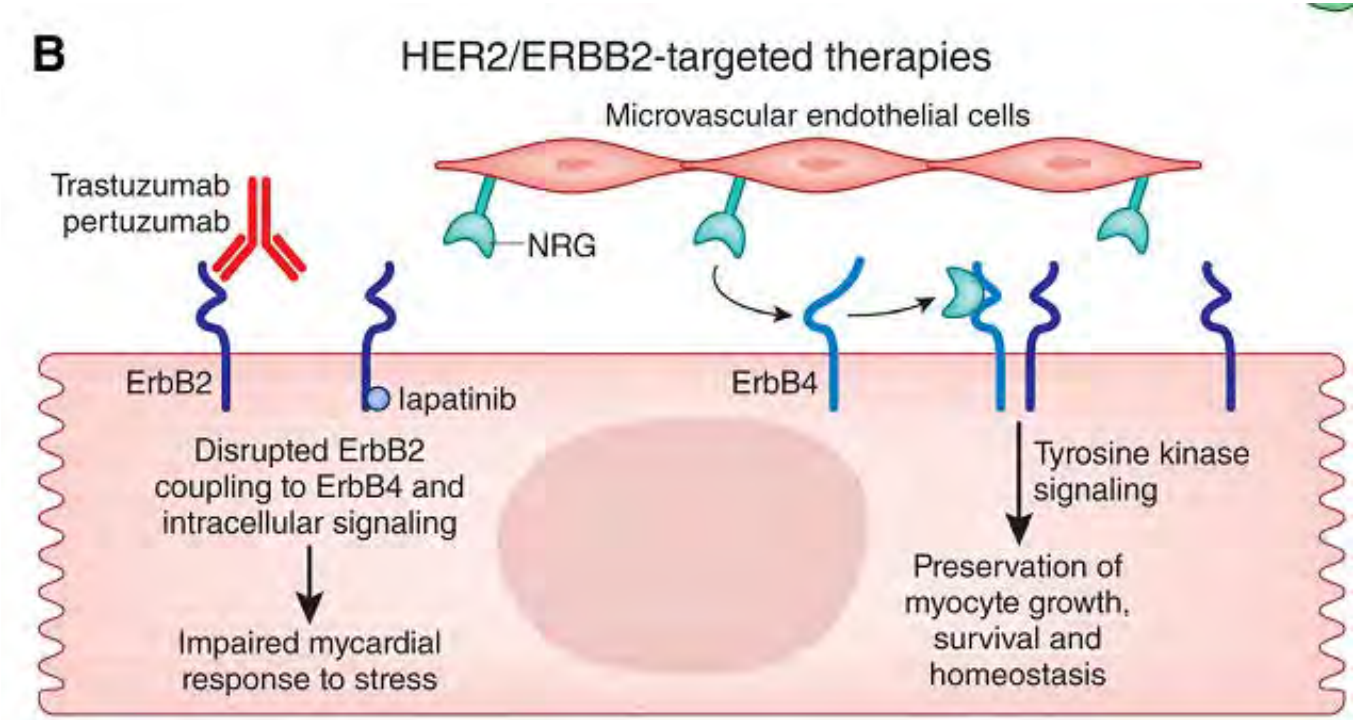


Anthracycline Induced Cardiotoxicity



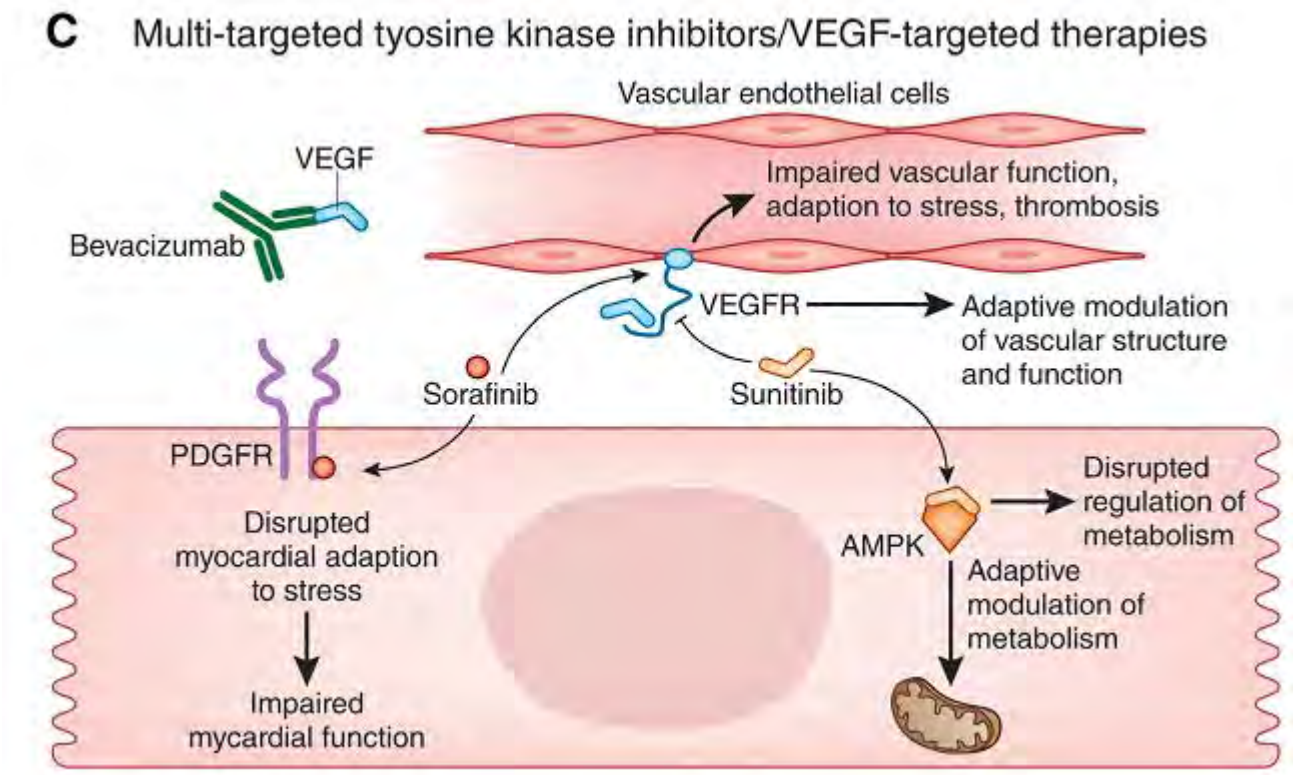
Carrie G. Lenneman, and Douglas B. Sawyer Circ Res. 2016;118:1008-1020

HER2/ERBB2- Targeted Therapies



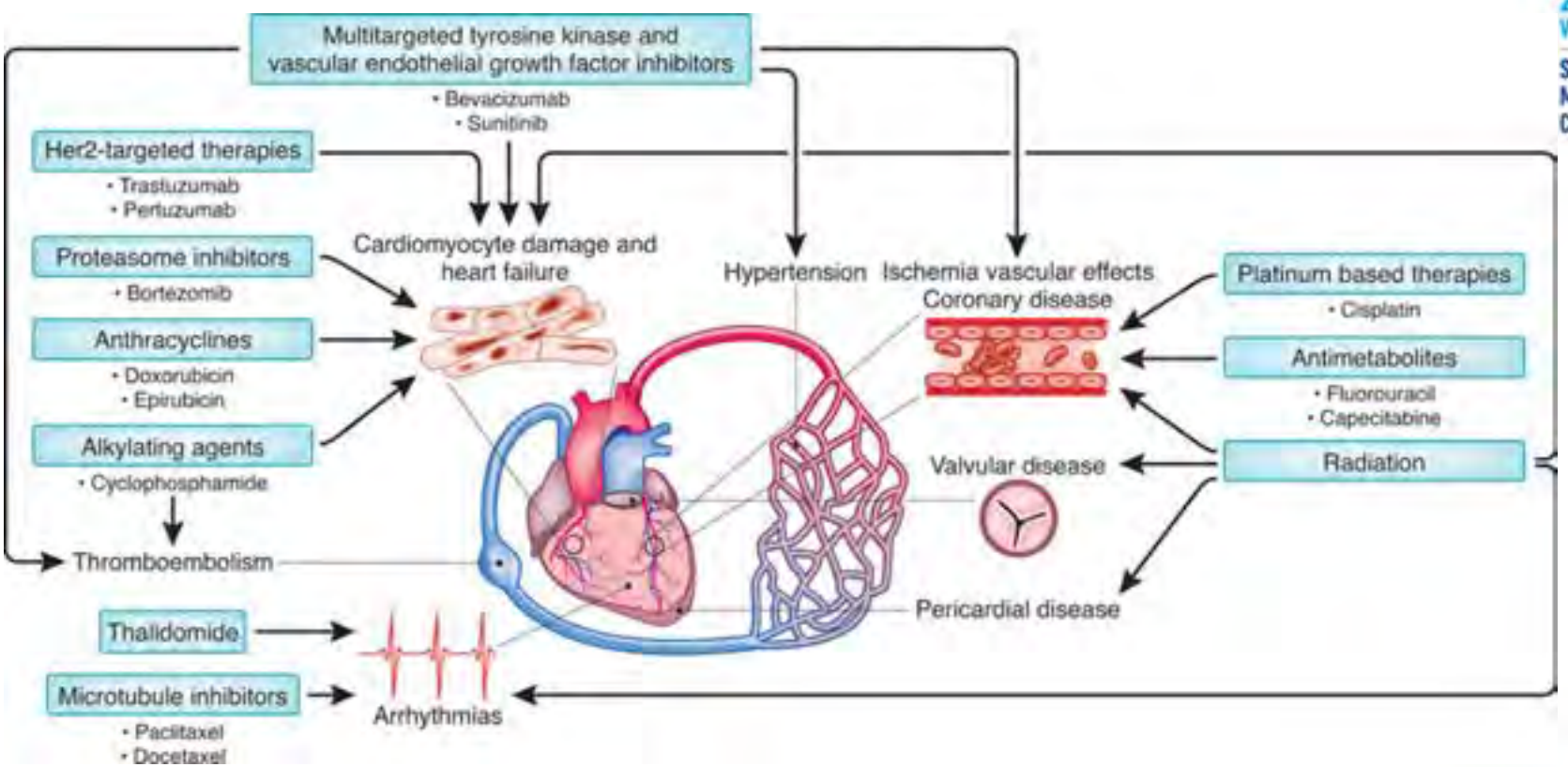
Carrie G. Lenneman, and Douglas B. Sawyer Circ Res. 2016;118:1008-1020

Small-molecule tyrosine kinase and VEGF inhibitors



Carrie G. Lenneman, and Douglas B. Sawyer Circ Res. 2016;118:1008-1020

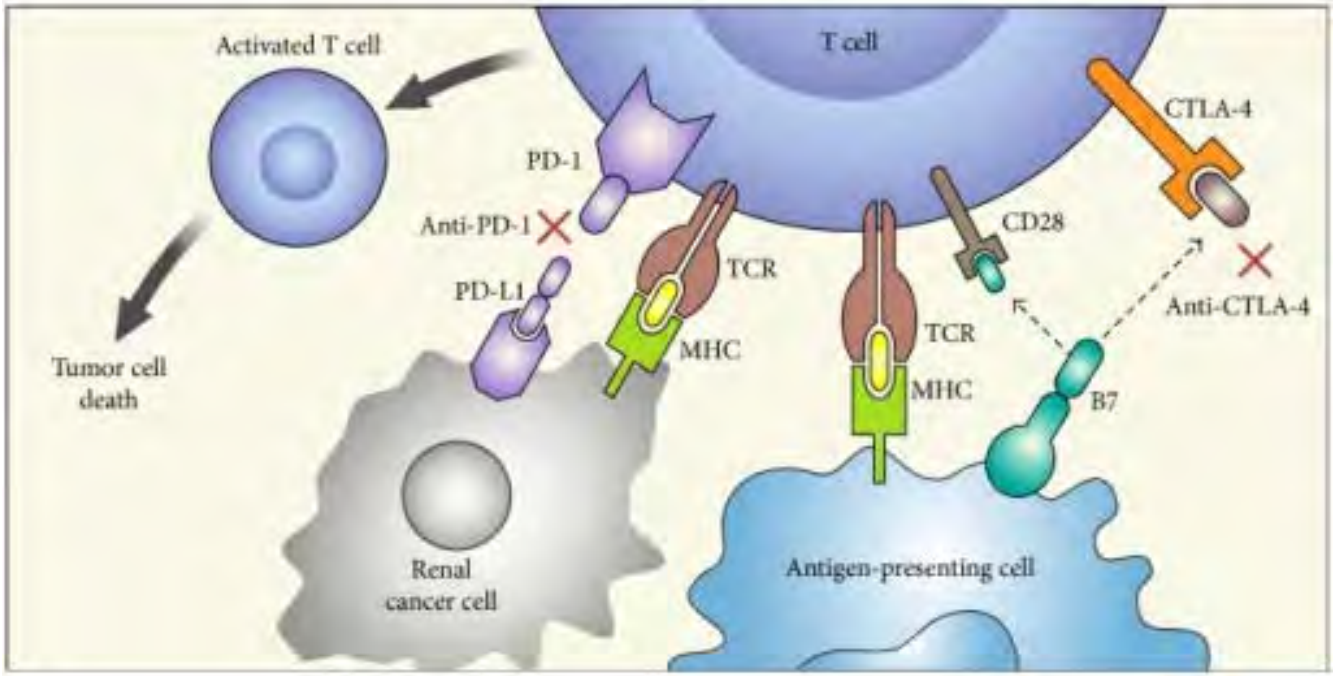
Cardiovascular Side Effects of Chemotherapy and Radiation



Carrie G. Lenneman, and Douglas B. Sawyer Circ Res. 2016;118:1008-1020

Fulminant Myocarditis with Combination Immune Checkpoint Blockade

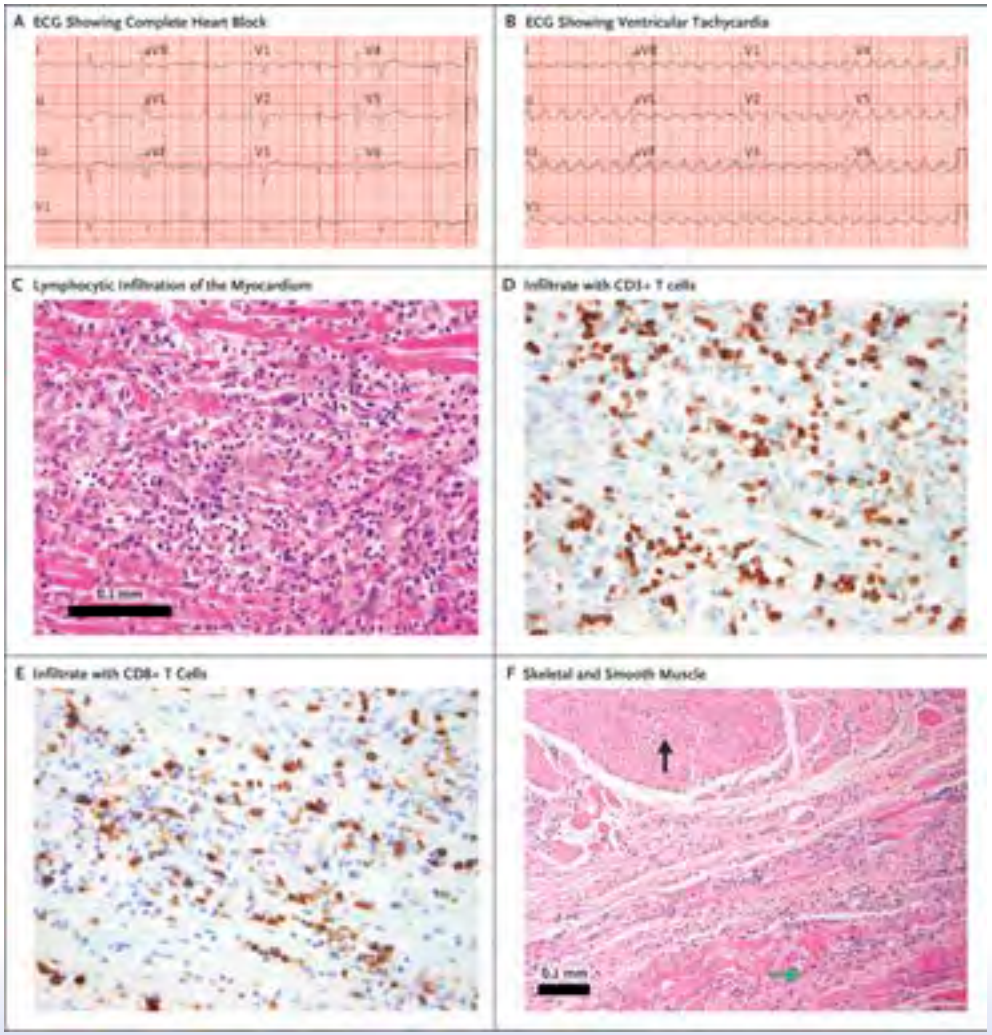
- Checkpoint inhibitors Cytotoxic T-lymphocyte antigen 4 (PD-1, CTLA-4)



Biomed Res Int. 2015; 2015: 367354.

N Engl J Med 2016; 375:1749-1755DOI: 10.1056/NEJMoa1609214

Fulminant Myocarditis with Combination Immune Checkpoint Blockade



N Engl J Med 2016; 375:1749-1755DOI: 10.1056/NEJMoa1609214

Types Anthracycline Cardiotoxicity

Acute: vasodilation, hypotension, arrhythmias

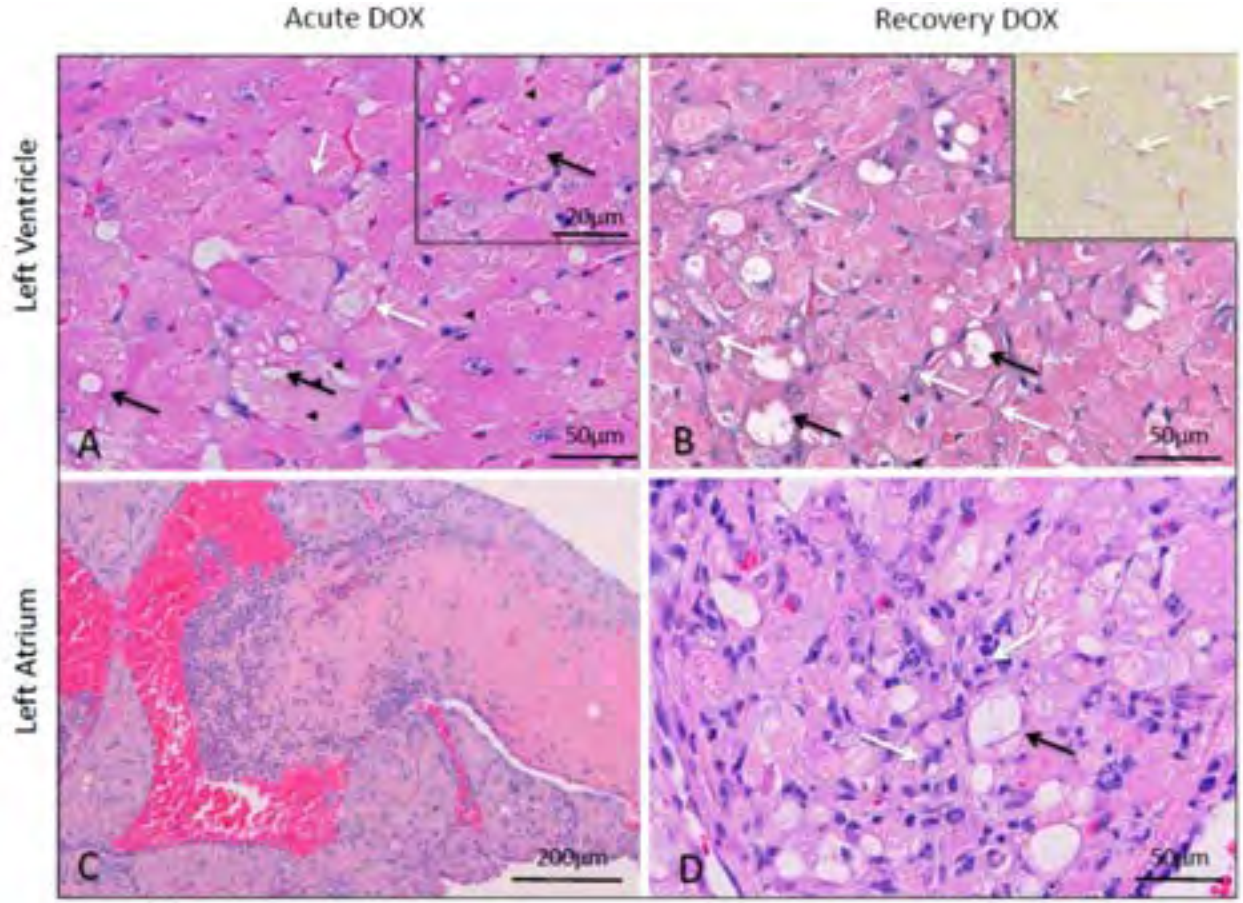
Early onset : acute myocyte damage with associated left ventricular dysfunction and less commonly pericarditis

Late Onset Cardiotoxicity

- **Occult:** Structural heart disease without signs and symptoms of heart failure, occurs at least a year after exposure to AC
- **Clinically Evident:** 10-20 years after the termination of therapy

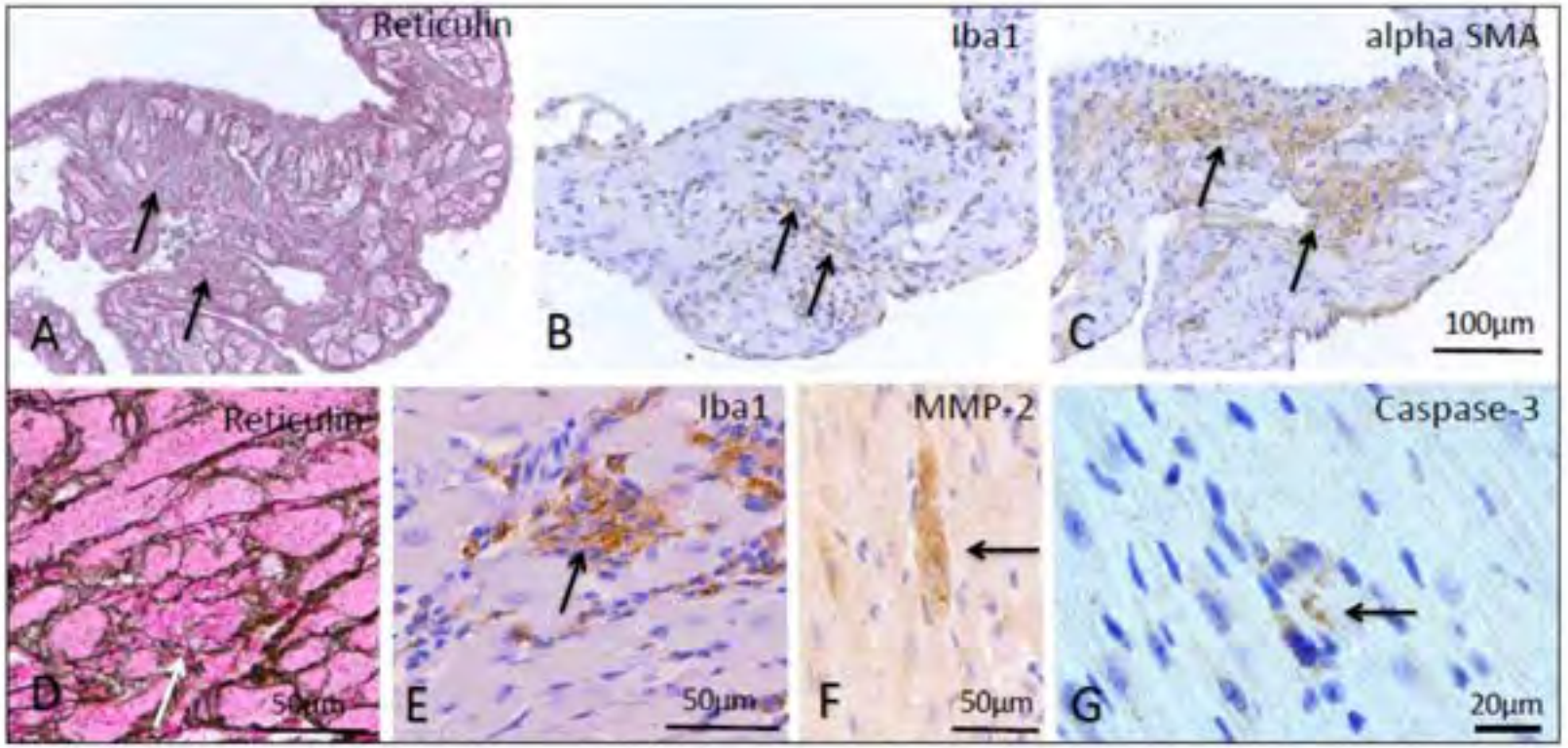
Ferrans VJ. Cancer Treat Rep 1978 Jun;62(6):955-61.
Pathology Section, National Heart, Lung and Blood Institute, NIH, Bethesda, MD 20892, USA

Anthracycline Induced Cardio-toxicity



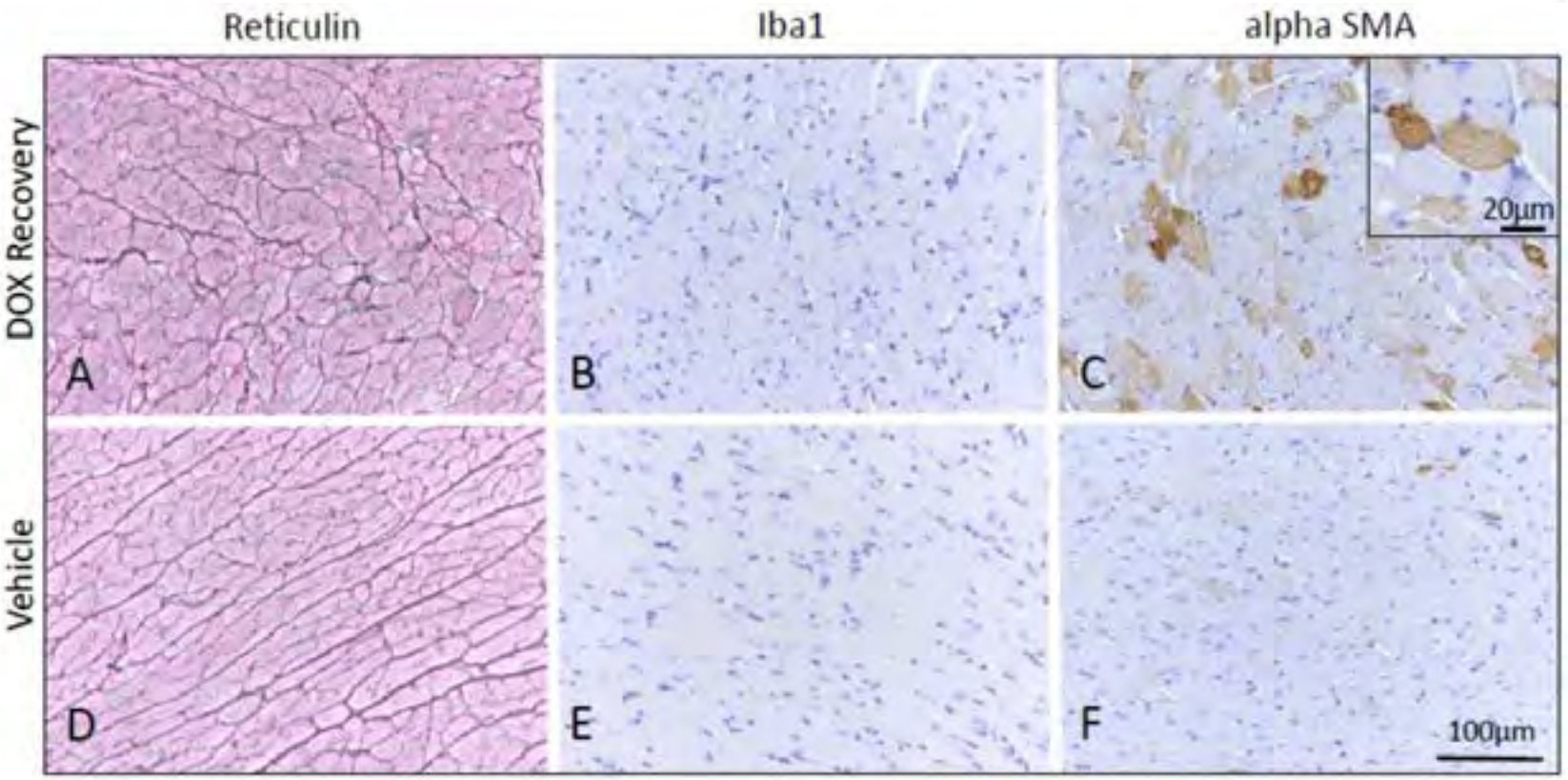
Zeiss C, Gatty D, Toro-Salazar et al, manuscript in progress

Chronic Cardiotoxicity



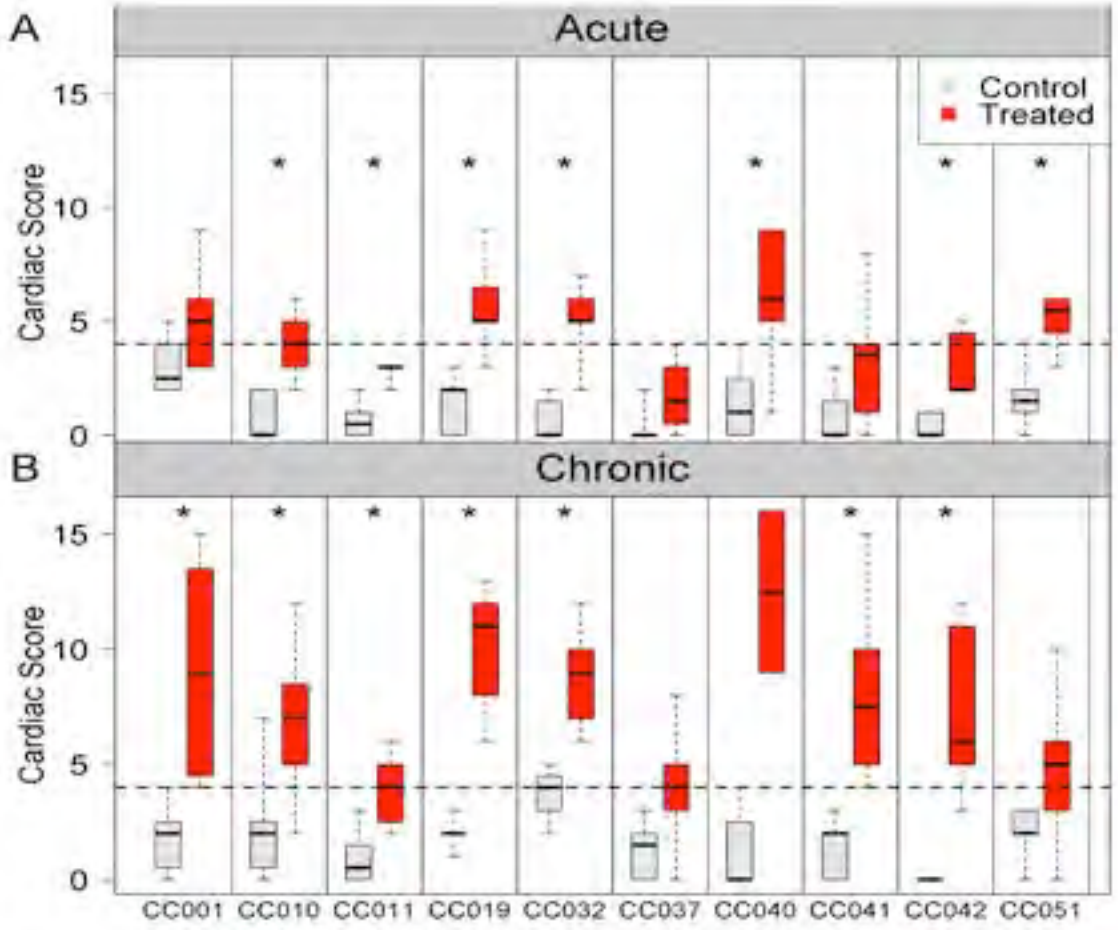
Zeiss C, Gatty D, Toro-Salazar et al, manuscript in progress

Diffuse Cardiac Fibrosis in AIC



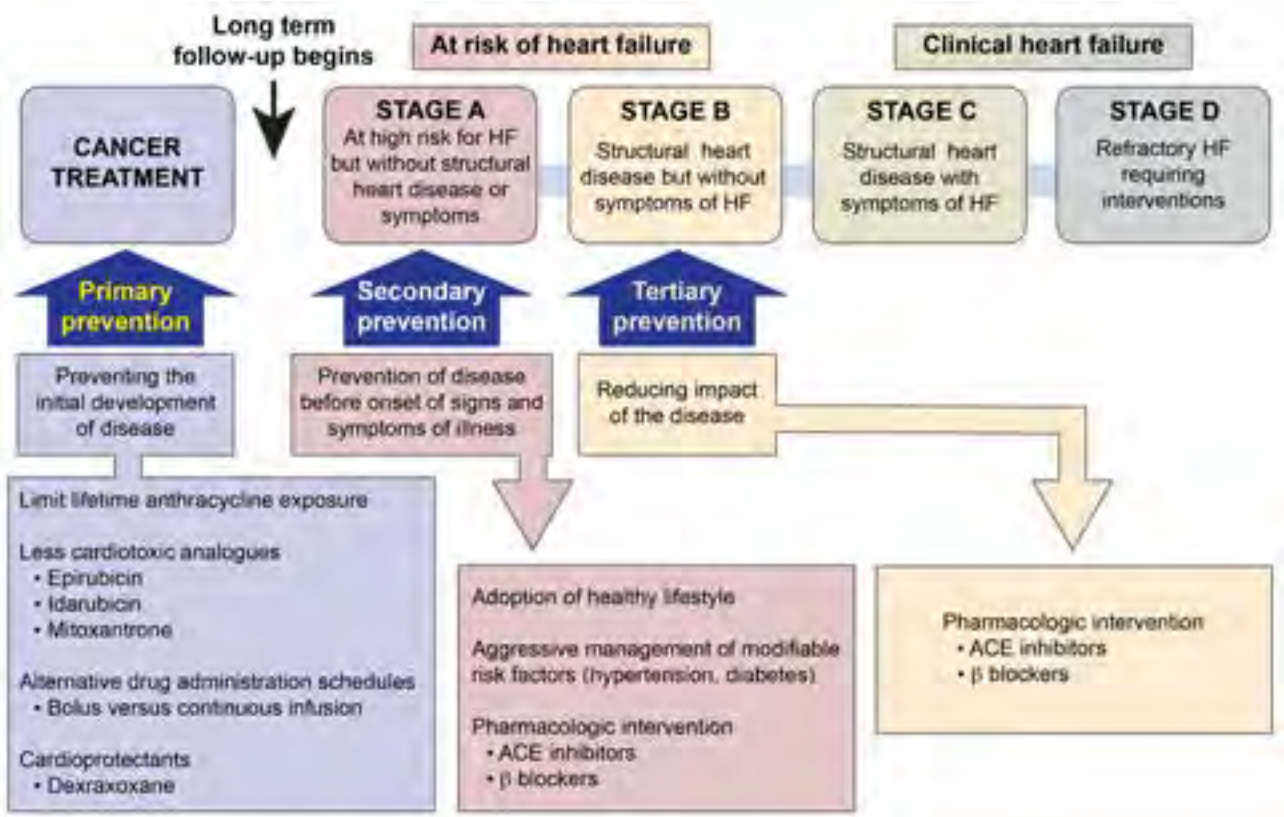
Zeiss C, Gatty D, Toro-Salazar et al, manuscript in progress

Genetic Diversity in AIC



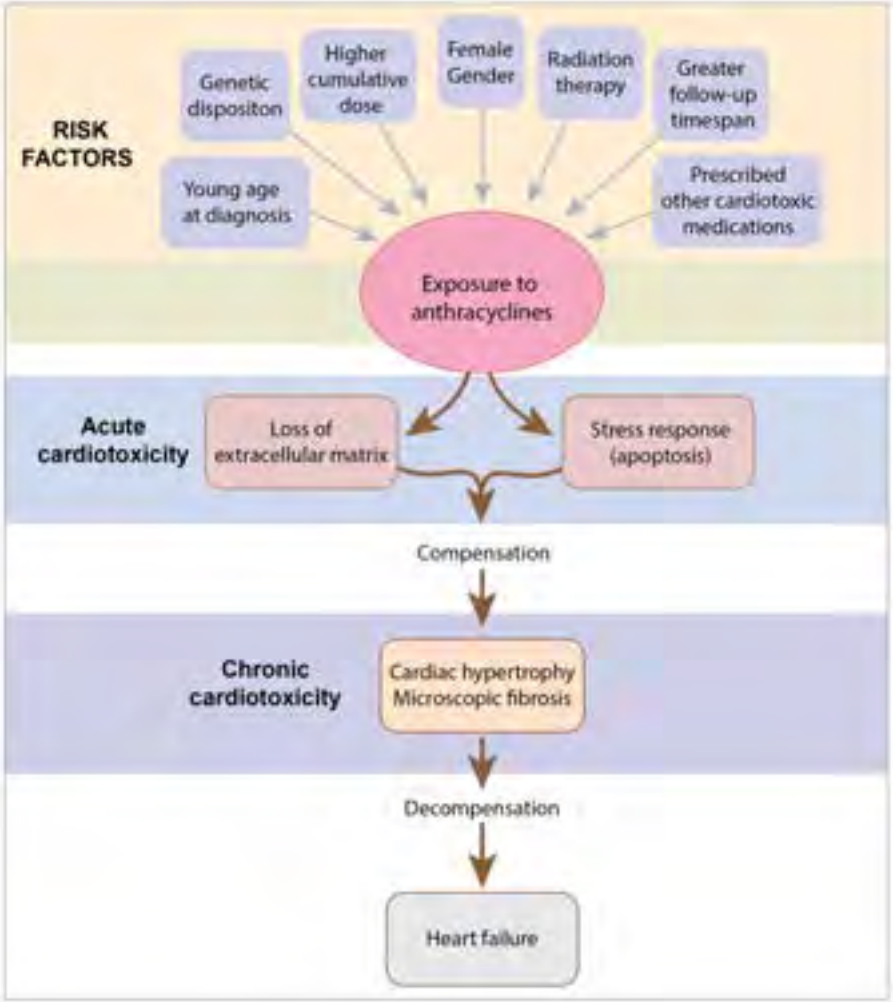
Zeiss C, Gatty D, Toro-Salazar et al, manuscript in progress

Stages in the development of HF and recommended therapy by stage based on published guidelines (ACC/ AHA)



Armenian SH et al. Cardiology research and practice. 2012;2012:713294.

Cardiotoxicity Model



The Effect of Risk Factors on Development of Persistent Cardiomyopathy

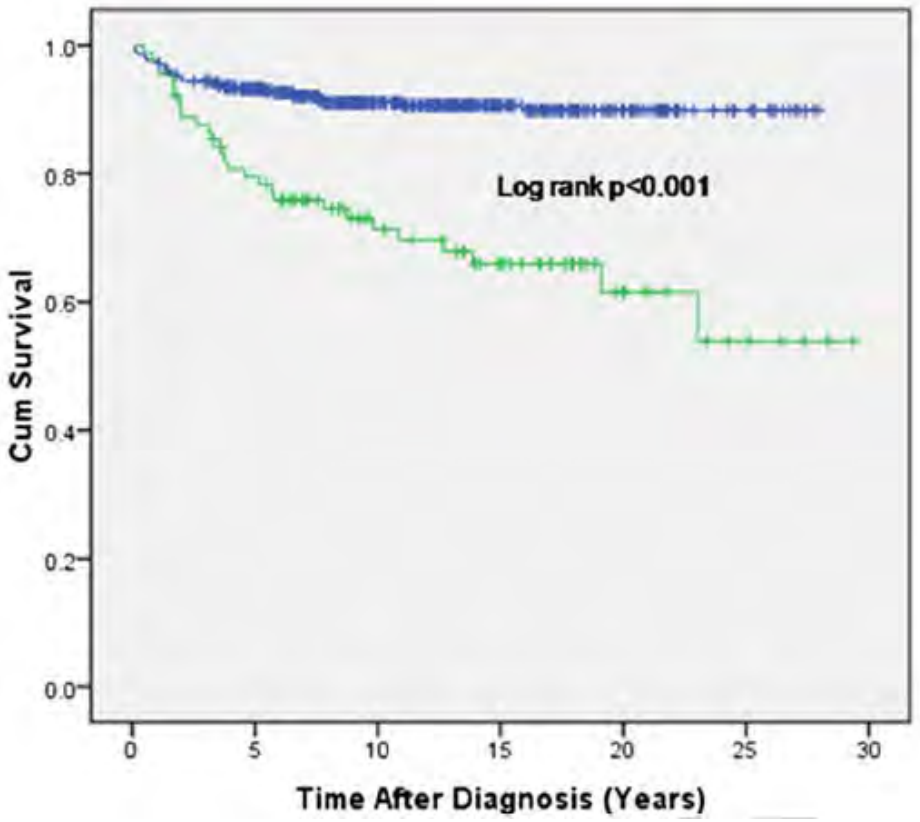
Risk Factors	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Years post-chemo	0.93	0.86, 1.01	0.09	---	---	---
Age at Diagnosis	1.06	0.99, 1.14	0.11	---	---	---
Gender	0.63	0.25, 1.60	0.33	---	---	---
Cumulative dose	1.00	1.00, 1.01	0.16	---	---	---
Radiation to chest	3.16	1.17, 8.54	0.02	2.33	0.77, 6.96	0.13
Vinca Alkaloids	1.01	0.33, 3.09	0.99	---	---	---
BMT	4.66	1.71, 12.76	0.003	4.17	1.37, 12.69	0.01
Previous heart disease†	5.05	1.84, 13.85	0.002	6.04	2.10, 17.34	0.001
Cardio-protective drugs	1.92	0.42, 8.67	0.40	---	---	---

*The 3 significant risk factors upon univariate analysis were selected as covariates for the multiple logistic regression model (radiation to the chest, BMT and previous heart disease)

†Previous heart disease defined as: presence of congenital heart disease, pericardial effusion/tamponade, SVC syndrome, myocardial dysfunction prior to chemotherapy.

Toro-Salazar et al. Cardio-Oncology. 2015;1(1).

Effect of Previous Myocardial Dysfunction on Survival



- SF>29%: Cumulative survival was 88% at 10 yrs from diagnosis, 85 % at 15 yrs, 84 % at 20 yrs, and 82 % at 25 yrs in subjects with SF >29%
- SF<29%:Cumulative survival of 71 % at 10 years, 66 % at 15 yrs 62 % at 20 yrs and 54 % at 25 yrs in subjects with SF < 29 %

Toro-Salazar et al. Cardio-Oncology. 2015;1(1).

The Effect of Risk Factors on All Cause Mortality

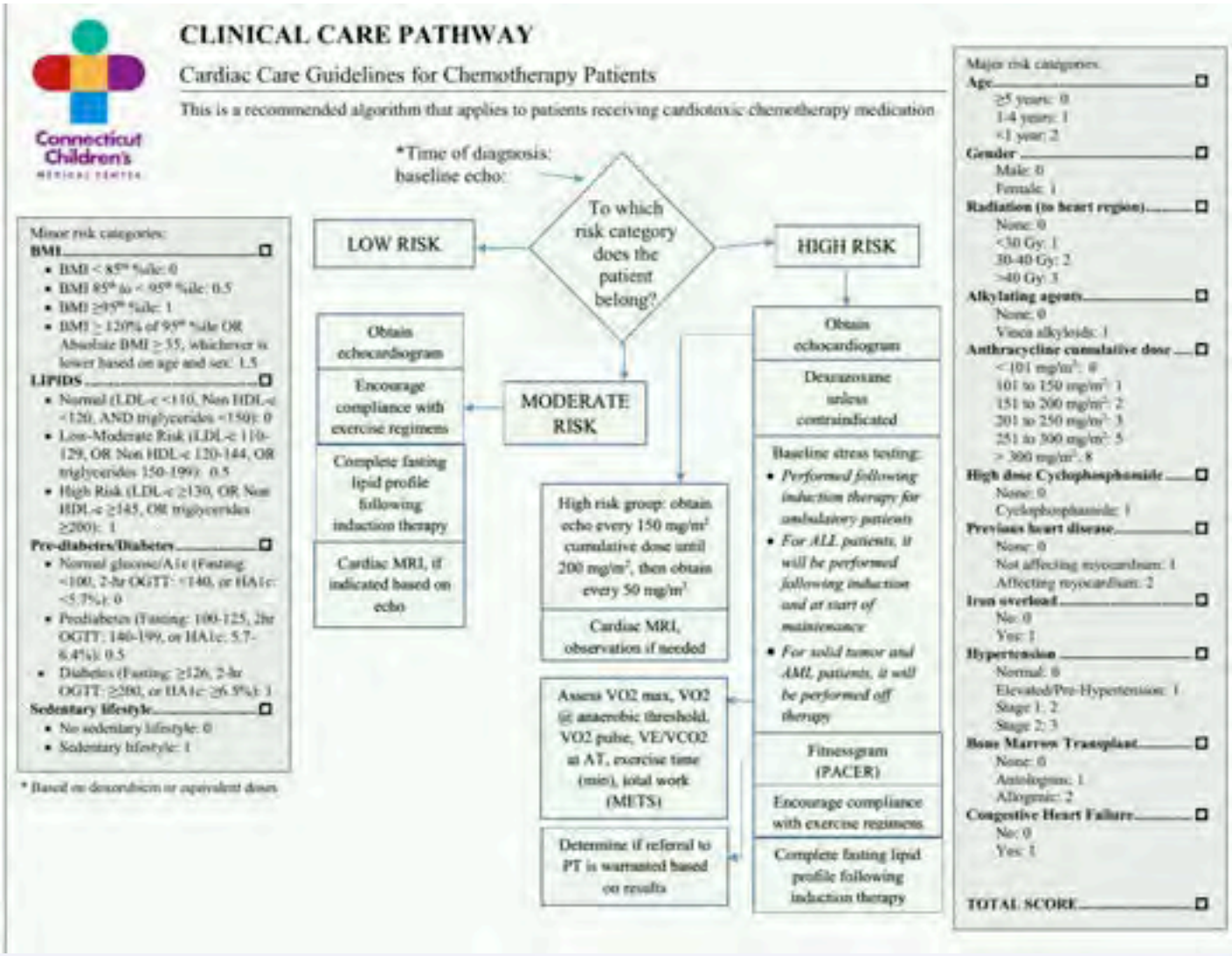
Risk Factors[1]*	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Years post-chemo	0.62	0.54, 0.70	<0.001	0.62	0.54, 0.71	<0.001
Age at Diagnosis (yrs)	1.05	1.01, 1.10	0.02	0.94	0.87, 1.02	0.12
Gender	0.69	0.42, 1.16	0.16	---	---	---
Cumulative dose	3.77	2.12, 6.71	<0.001	3.17	1.14, 8.85	0.03
Radiation to chest	1.32	0.66, 2.67	0.43	---	---	---
Vinca Alkaloids	0.32	0.19, 0.54	<0.001	0.37	0.13, 1.08	0.07
Previous SF < 29%	4.52	2.62, 7.79	<0.001	6.54	2.40, 17.81	<0.001
BMT	4.21	2.19, 8.09	<0.001	5.22	1.57, 17.37	0.007
Previous heart disease	1.66	0.76, 3.61	0.20	---	---	---
Cardio-protective drugs	0.71	0.21, 2.39	0.58	---	---	---
Solid Tumor Diagnosis	3.2	1.94, 5.42	<0.001	4.13	1.72, 9.87	0.001

[1] Risk factors for cardiotoxicity include increased length of post-chemotherapy interval (years), younger age at diagnosis, female gender, total cumulative dose ≥240 mg/m^2, radiation therapy to the chest, treatment with vinca alkaloids, previous shortening fraction < 29%, bone marrow transplant, previous heart disease, non-use of cardio-protective drugs, solid tumor diagnosis

*The 7 significant risk factors upon univariate analysis were selected as covariates for the multiple logistic regression model (increased length post-chemotherapy interval, younger age at diagnosis, total cumulative dose anthracyclines > 240 mg/m^2, use of vinca alkaloids, previous SF<29%, BMT, and solid tumor diagnosis)

Toro-Salazar et al. Cardio-Oncology. 2015;1(1).

Risk Stratification

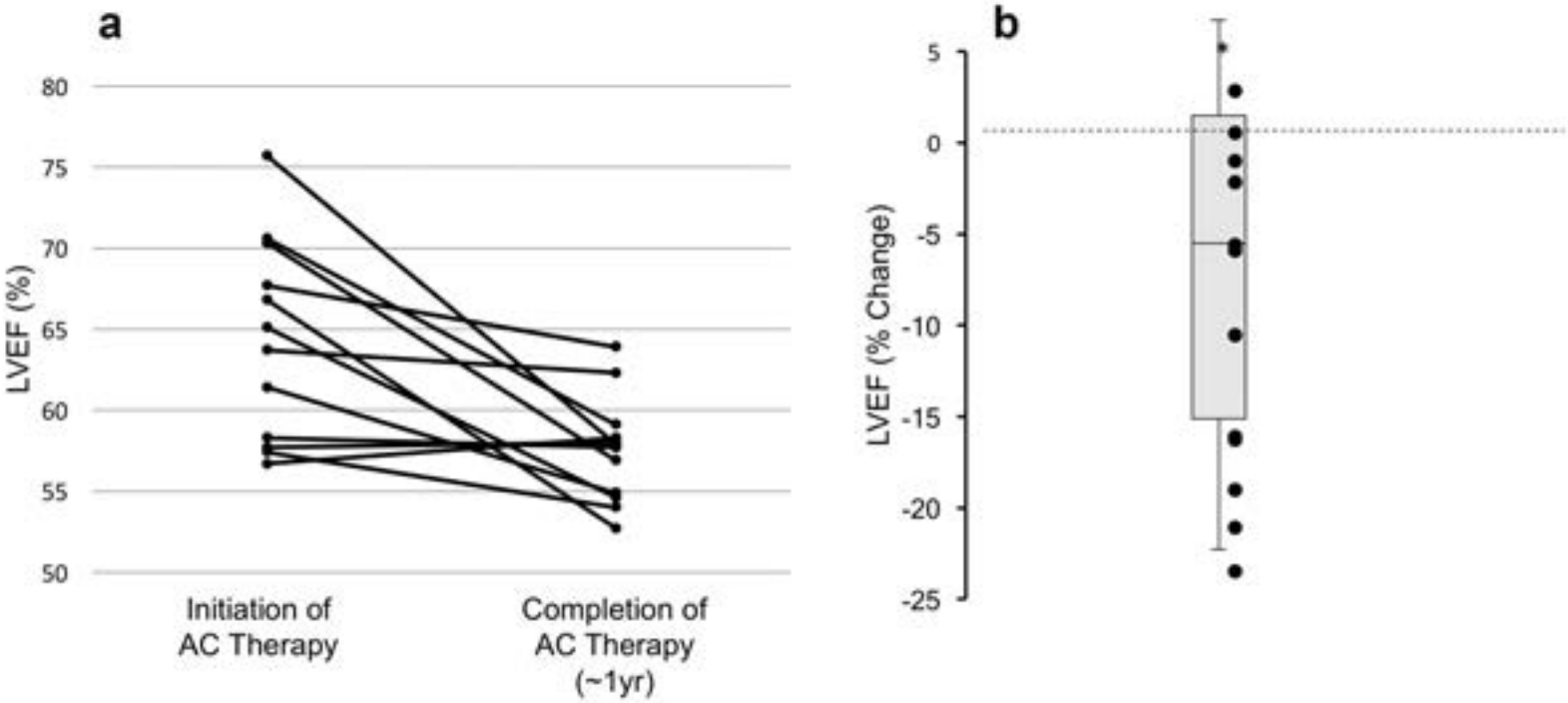


Cancer Therapeutics–Related Cardiac Dysfunction (CTRCD)

- CTRCD defined as a decrease in the LVEF of >10 percentage points, to a value <53% (normal reference value for two-dimensional (2D) echocardiography (2DE)in adults
- No pediatric guidelines available
- Need to go beyond quantification of EF to evaluation of myocardial deformation and adaptive microstructural and microvascular changes

Juan Carlos Plana, et al. Eur Heart J Cardiovasc Imaging. 2014 Oct;15(10):1063-1093

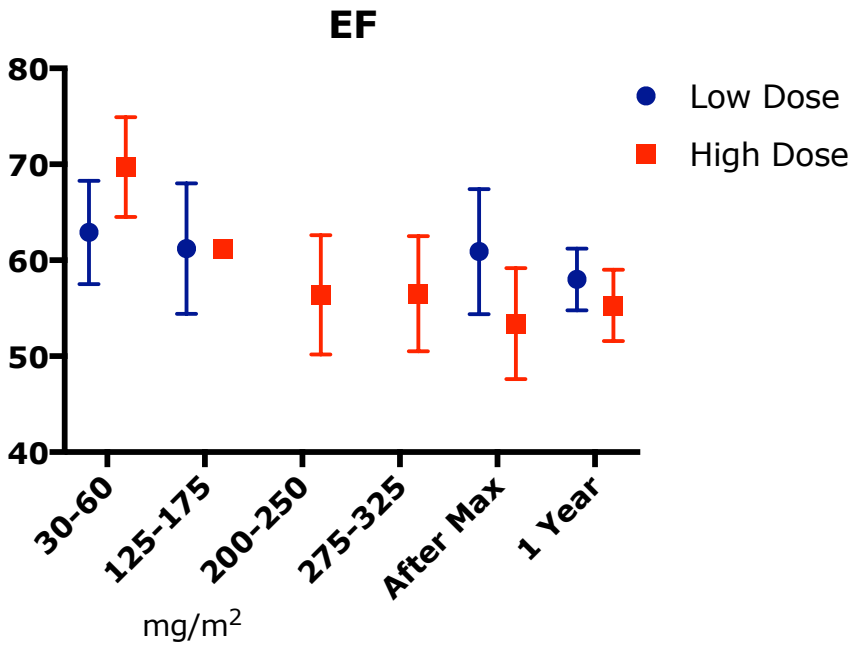
Measurements of Global Systolic Function

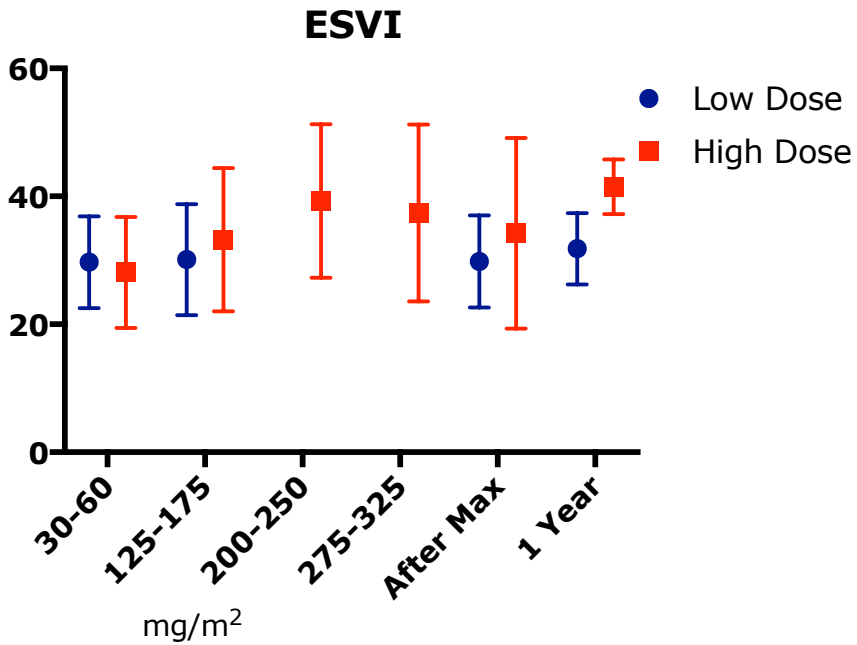


Comparison of LVEF following the initiation of AC vs. one year following completion of AC. Percent change in LVEF from initiation of AC to one year following completion of AC.

Toro-Salazar et al. Cardiooncology. 2018 ; 4: . doi:10.1186/s40959-018-0030-5.

Early Cardiotoxicity (EF, ESVI)

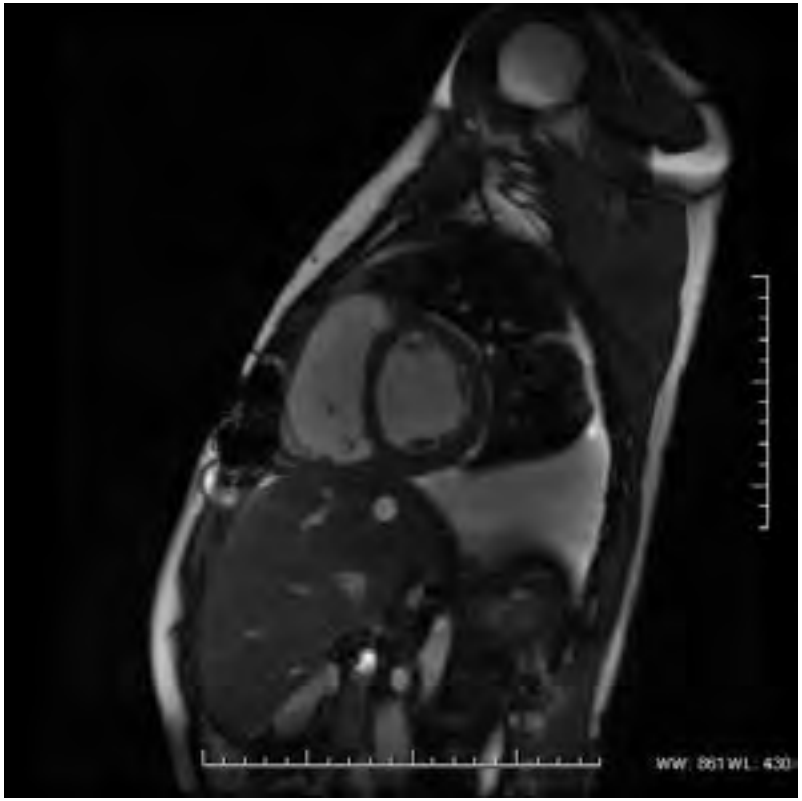


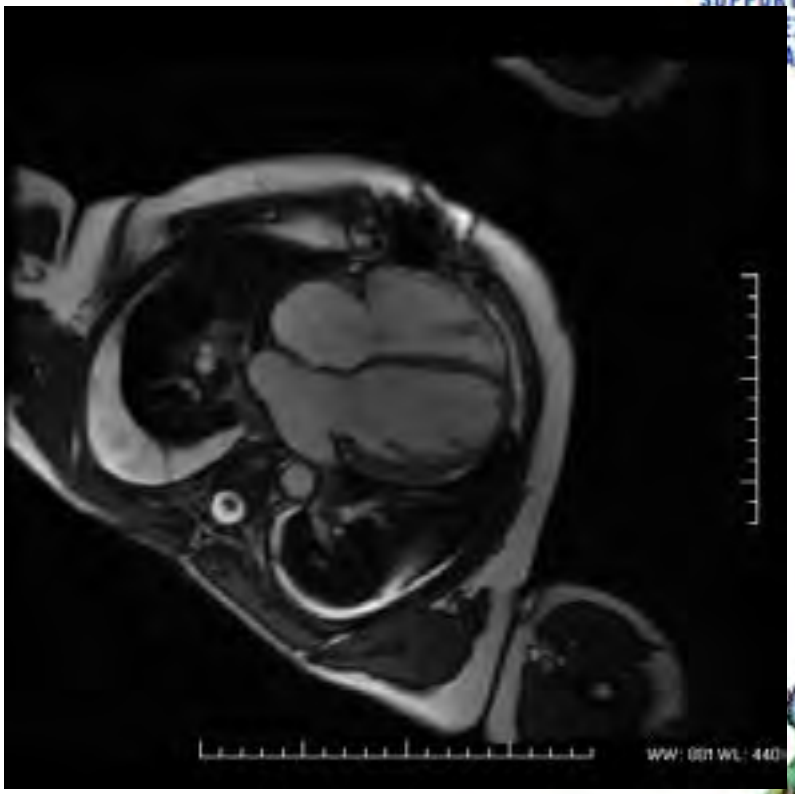


TCD Low Dose: 158-200 mg/m²
TCD High Dose: 442-450 mg/m²

Toro-Salazar et al. Cardiooncology. 2018 ; 4: . doi:10.1186/s40959-018-0030-5.

Late Cardiotoxicity



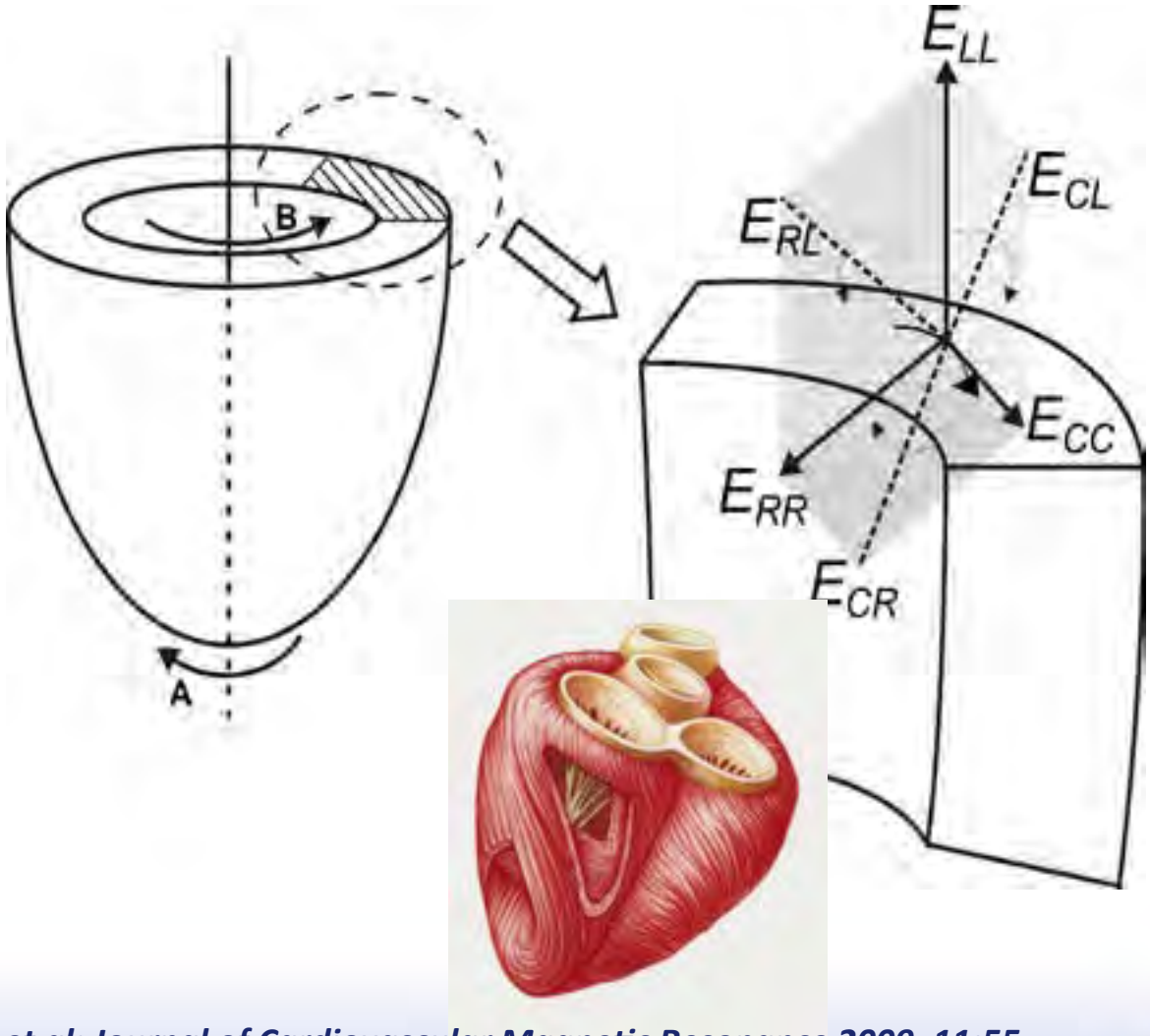


Olga H. Toro-Salazar et al. Circ Cardiovasc Imaging. 2013;6:873-880

Myocardial Mechanics: Moving beyond the basics (EF limitations)

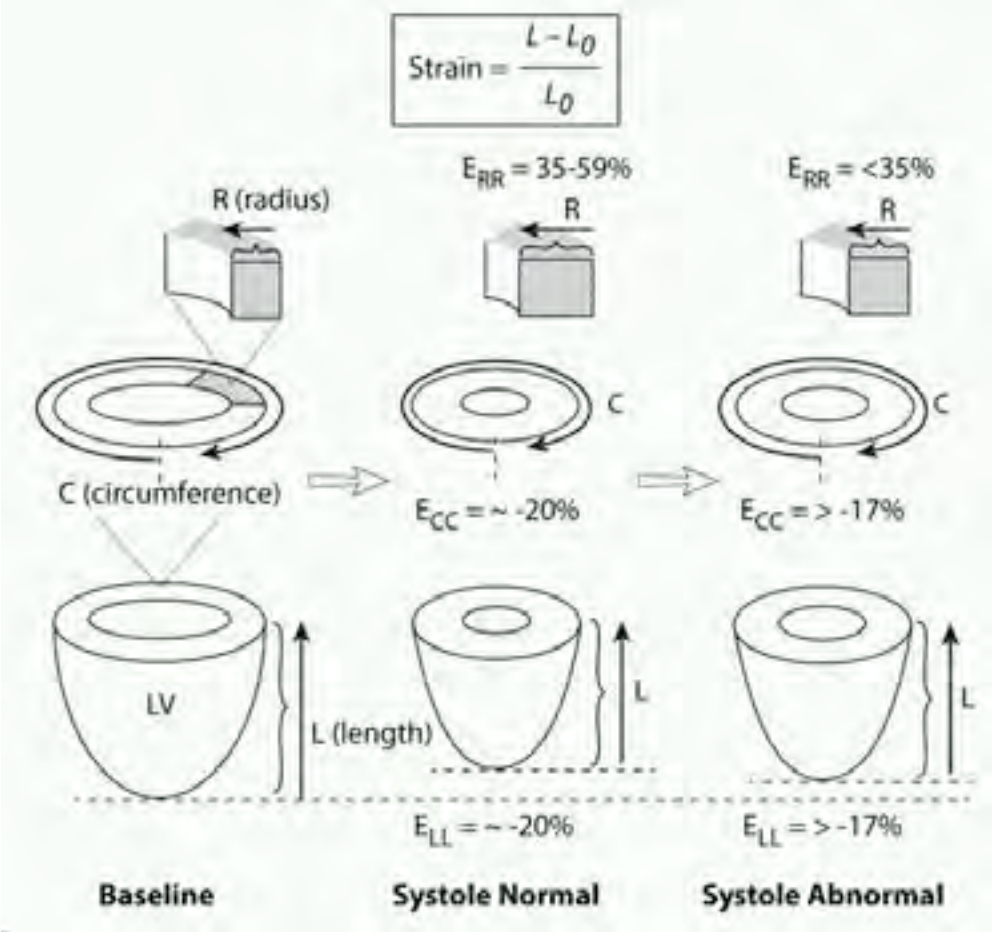
- EF is the gold standard for global functional assessment
- Does not consider regional contractile dysfunction
- EF insensitive to alterations in regional performance and may conceal underlying regional dysfunction

Myocardial Strain



Shehata *et al: Journal of Cardiovascular Magnetic Resonance 2009, 11:55*

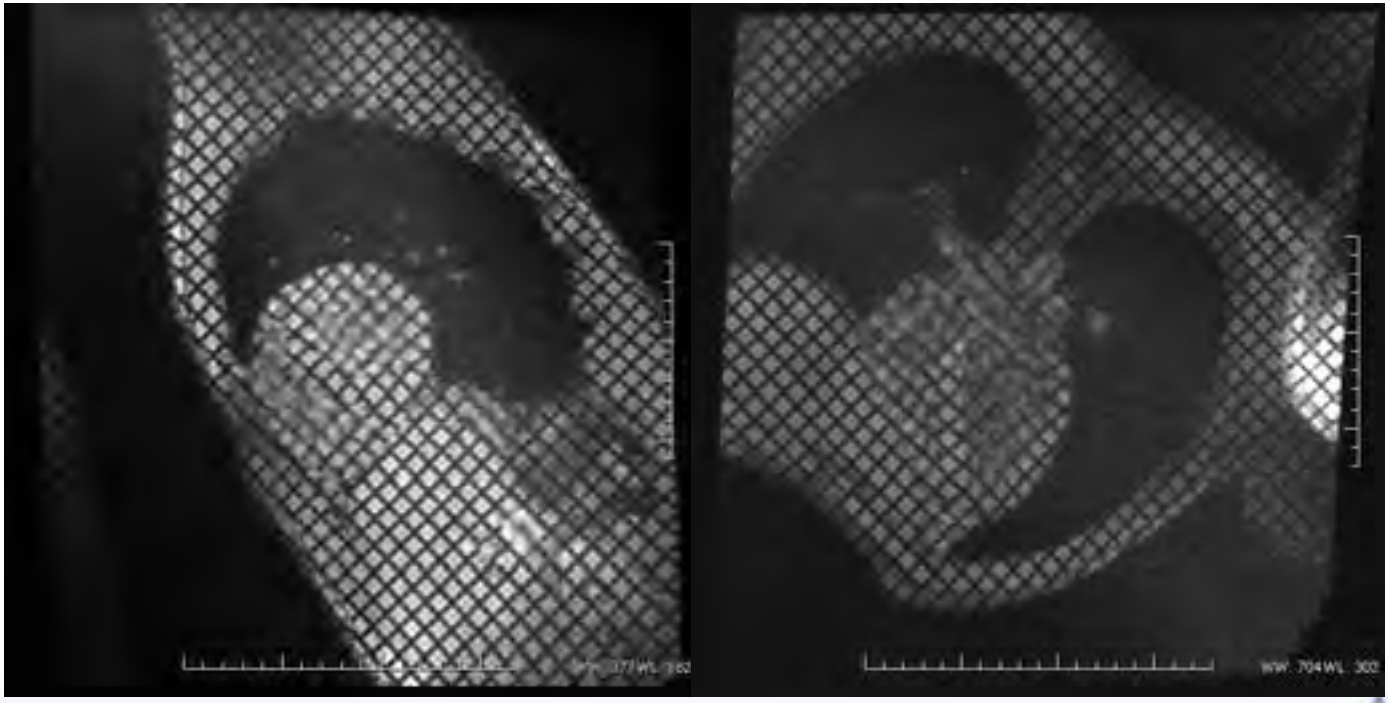
3D Circumferential-radial-longitudinal Coordinate System Used For Strain Calculation



Toro-Salazar et al. Cardiooncology. 2018 ; 4: . doi:10.1186/s40959-018-0030-5.

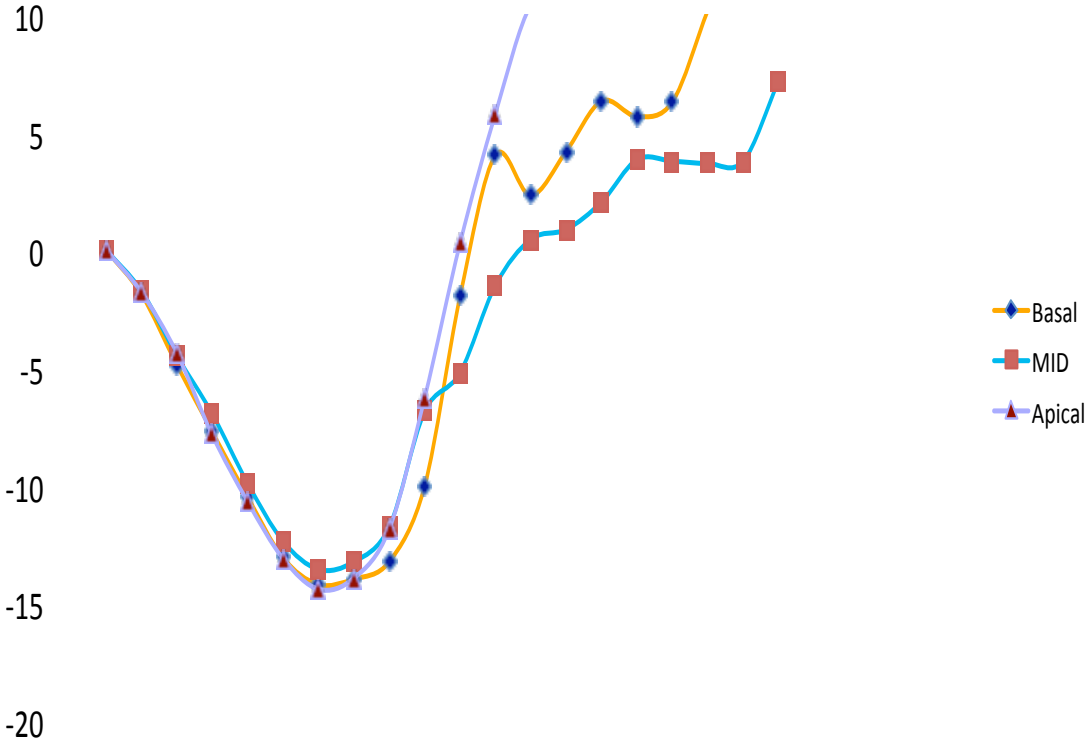
Myocardial Strain: The Gold Standard by Tagged Imaging

- Zerhouni et al (1988), Axel et al (1989)
- Visualization of myocardial deformation without implanting physical markers

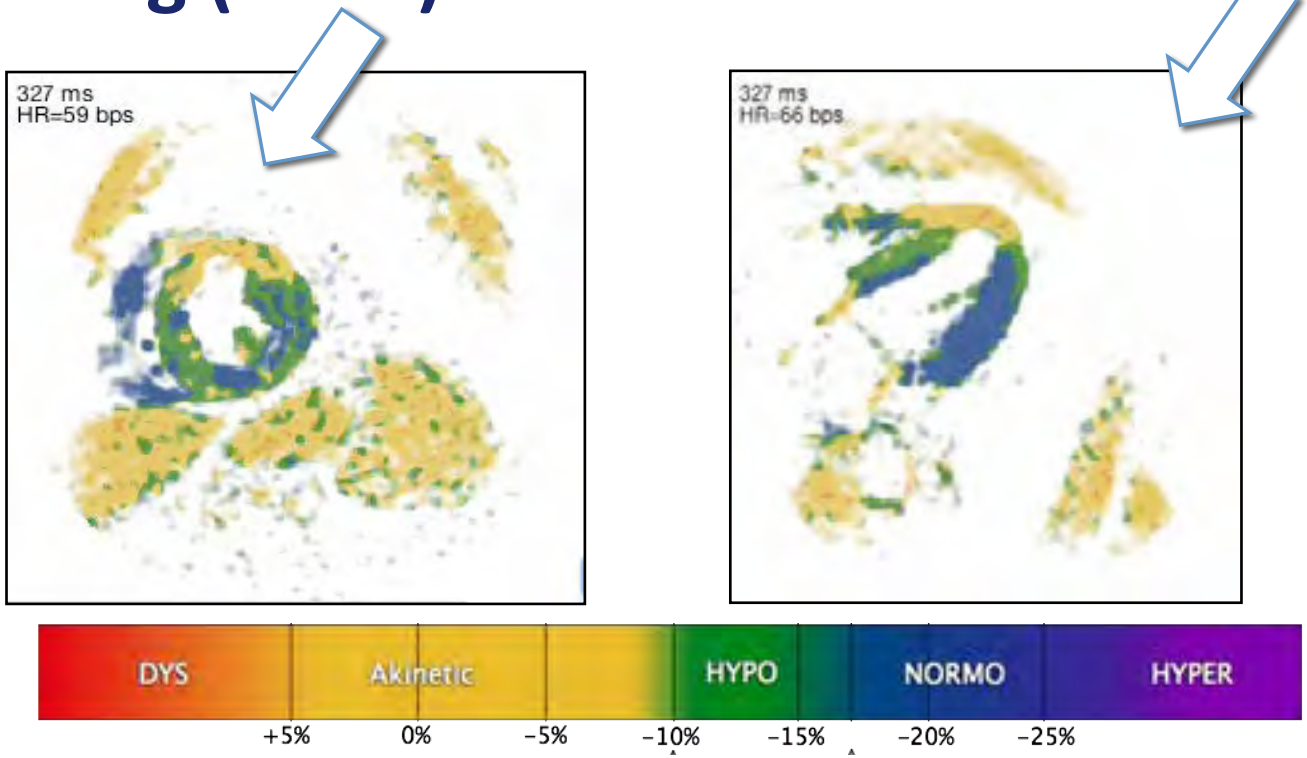


Zerhouni et al, Radiology, 1988; Axel et al, Radiology, 1989

HARP Analysis of SA Tagged-Images



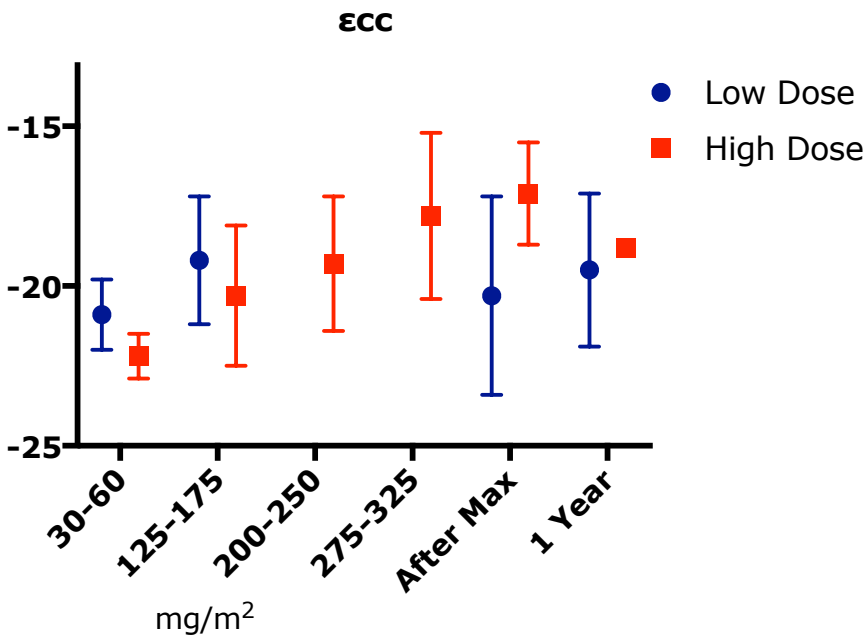
Ultra fast strain imaging with strain-encoding (SENC)

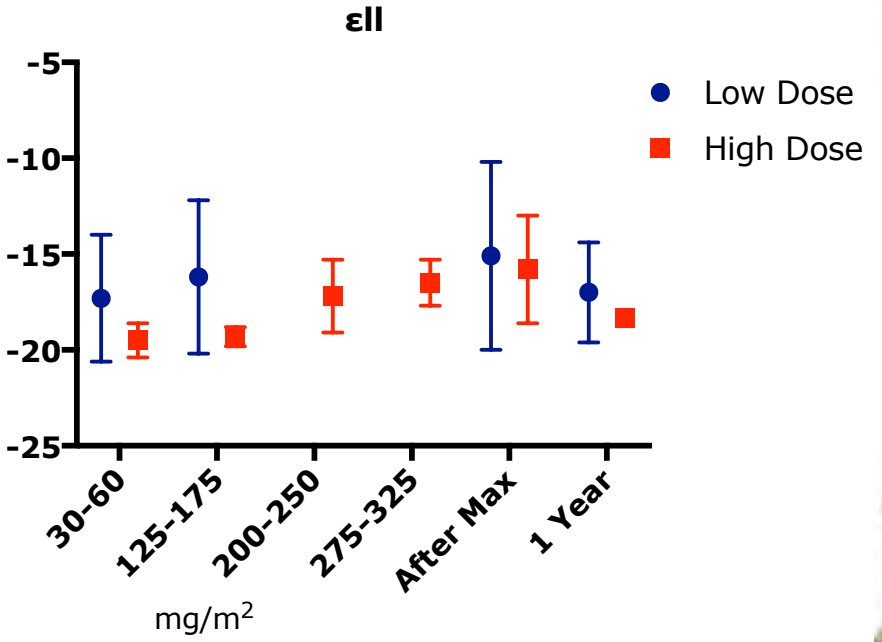


- Left Movie: Short-axis view shows longitudinal strain
- Right Movie: Long-axis view shows circumferential strain
- Each movie took less than a second to acquire and produce from the scanner
- The color scale shows peak strain values in the myocardium
- Arrows point to infarction

Courtesy from Nael Osman, Ph.D.CTO, Myocardial Solutions, Inc.

Tagged Imaging Strain/Early Cardiotoxicity





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TCD High Dose: 442-450 mg/m^2

Toro-Salazar et al. Cardiooncology. 2018 ; 4: . doi:10.1186/s40959-018-0030-5.

Circulation
Cardiovascular Imaging

2018

American Heart Association®

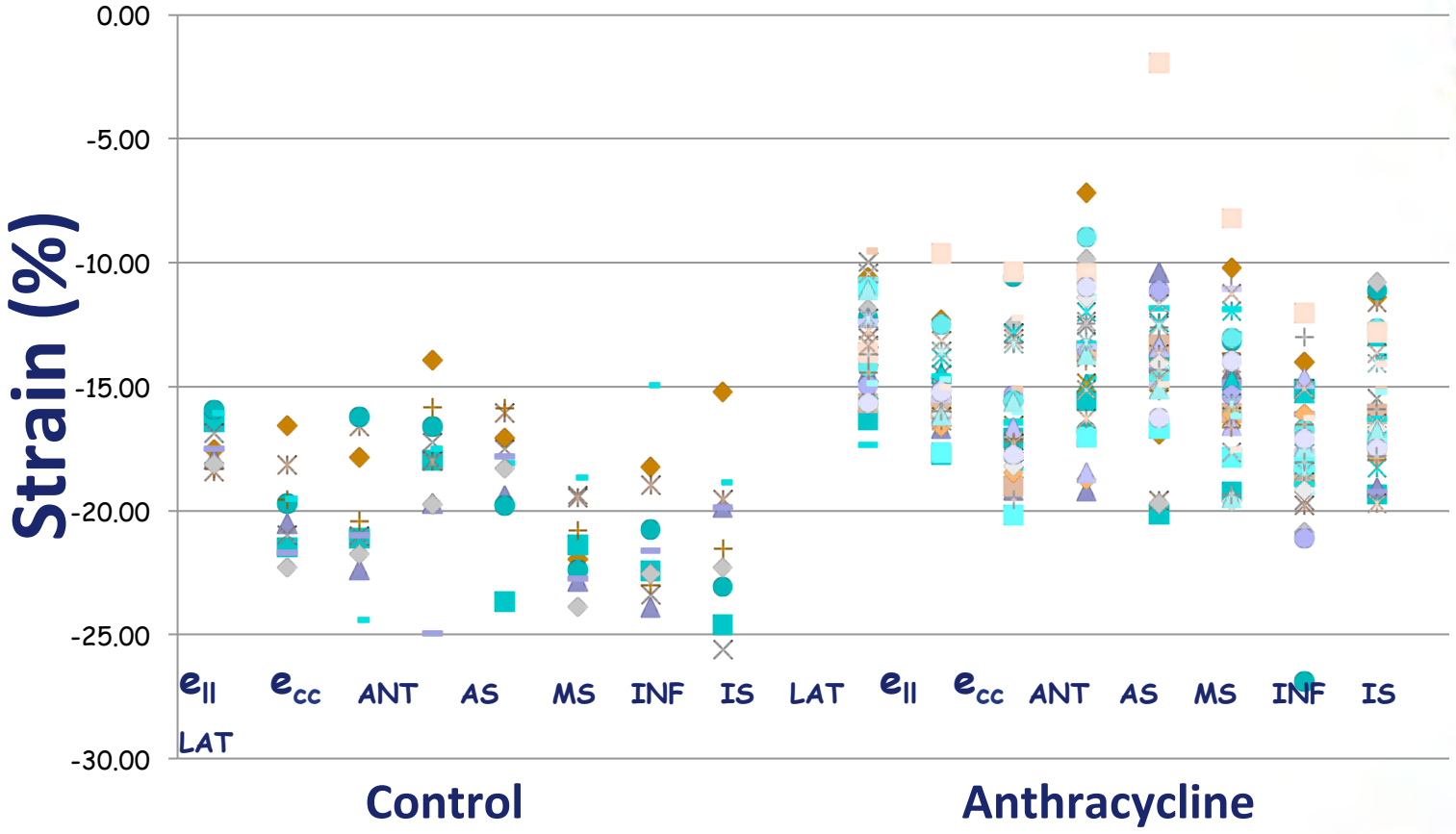
Occult Cardiotoxicity in Childhood Cancer Survivors Exposed to Anthracycline Therapy

Olga H. Toro-Salazar, Eileen Gillan, Michael T. O'Loughlin, Georgine S. Burke, Joanna Ferranti, Jeffrey Stainsby, Bruce Liang, Wojciech Mazur, Subha V. Raman and Kan N. Hor

Circ Cardiovasc Imaging. 2013;6:873-880; originally published online October 4, 2013;
doi: 10.1161/CIRCIMAGING.113.000798
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-9651. Online ISSN: 1942-0080

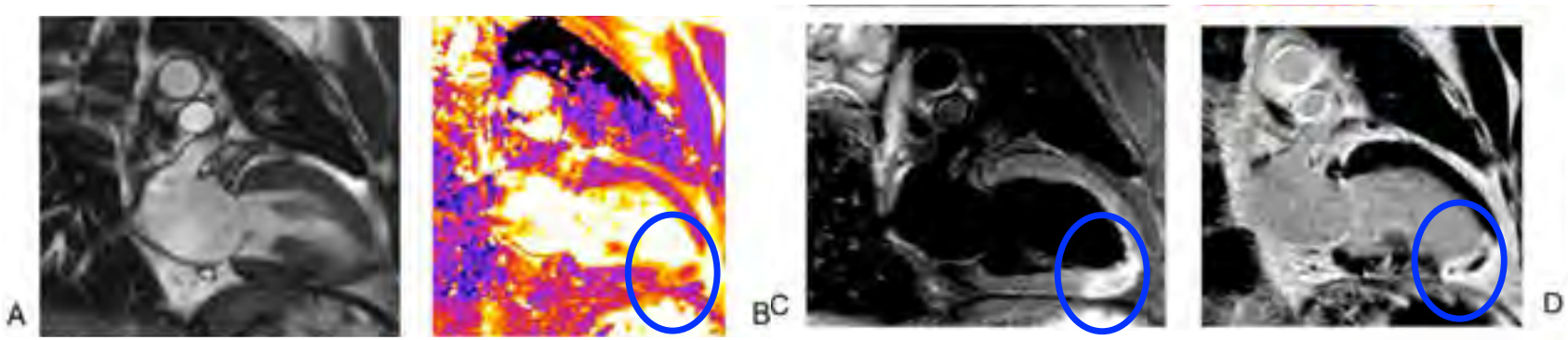
Myocardial Strain Magnitude
Late Cardiotoxicity



Olga H. Toro-Salazar et al. Circ Cardiovasc Imaging. 2013;6:873-880

T2 mapping – identifies myocardial edema

- Basis: increase myocardial water content changes magnetic relaxation properties influencing the CMR signal (normal value < 60 ms, range 46-80 ms)
- Example: acute myocardial infarction with bright areas on T2 mapping, T2-weight STIR and LGE images



Abdel-Aty et al, JACC, 2005, Aletras et al, Circ, 2006, Friedrich et al, JACC Cardiovasc Imaging 2011, Lurz et al, JACC Cardiovasc Imaging 2012, Scholz et al, Magn Reson Med 1992, Boxt et al, Magn Reson Imaging 1993

T1 Mapping – Detects Diffuse Fibrosis

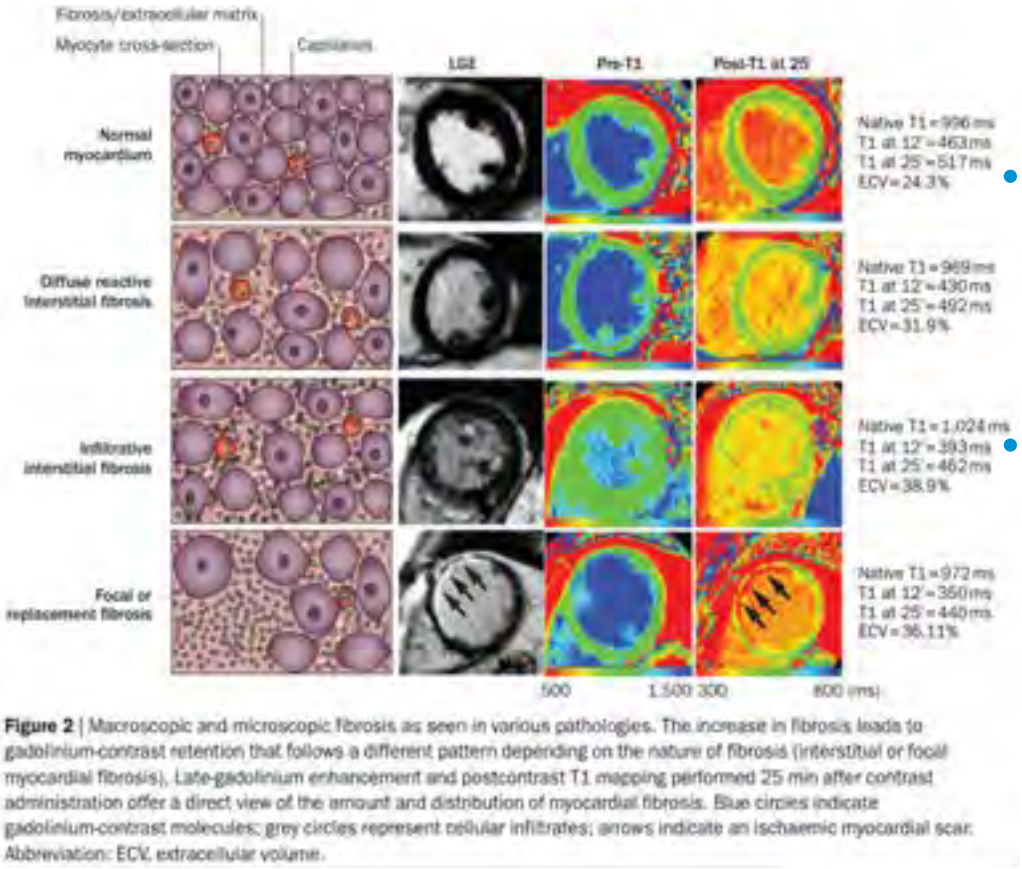
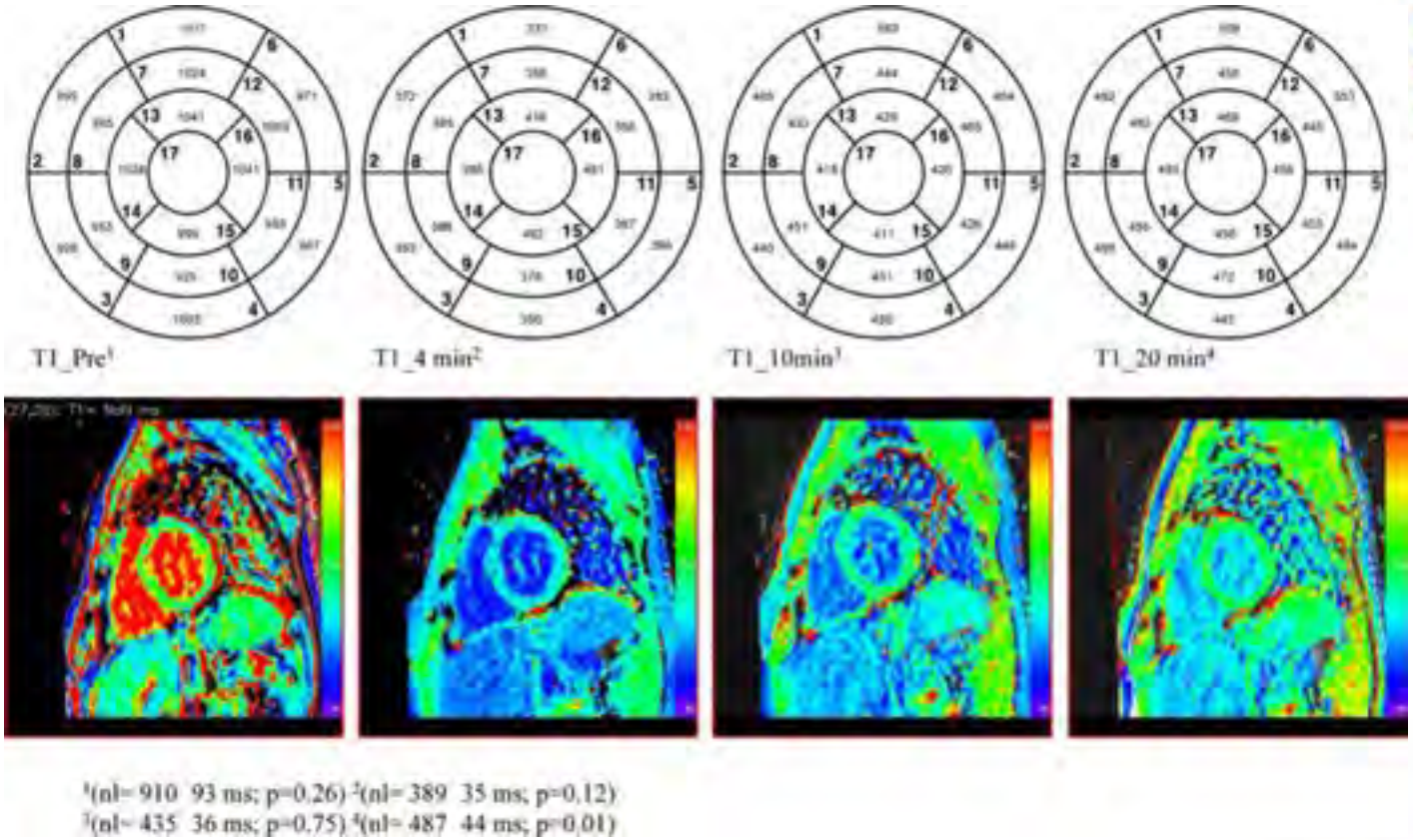


Figure 2 | Macroscopic and microscopic fibrosis as seen in various pathologies. The increase in fibrosis leads to gadolinium-contrast retention that follows a different pattern depending on the nature of fibrosis (interstitial or focal myocardial fibrosis). Late-gadolinium enhancement and postcontrast T1 mapping performed 25 min after contrast administration offer a direct view of the amount and distribution of myocardial fibrosis. Blue circles indicate gadolinium-contrast molecules; grey circles represent cellular infiltrates; arrows indicate an ischaemic myocardial scar. Abbreviation: ECV, extracellular volume.

- Basis: signal intensity of pixels is based on the relaxation of hydrogen nuclei protons – varies between different tissue
- Myocardium with diffuse fibrosis has greater retention of contrast material (ie shorter T1 times)

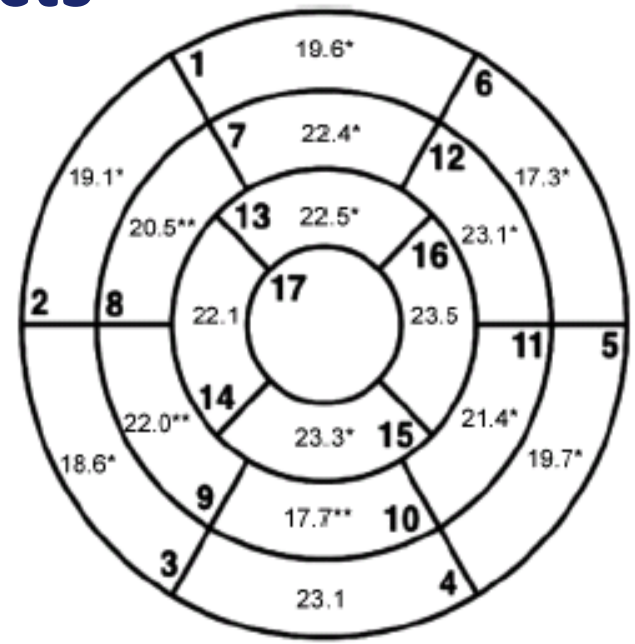
Burt et al, Radiographics 2014, Jellis et al, Cardiovascular Diagnosis and Therapy. 2014, Hwang et al, Korean Circulation J 2013, Messroghli et al, Radiology 2006, Chow et al, Magn Reson Med 2013, Messroghli et al, Circ Cardiovasc Imaging 2011, Lee et al, Cardiovasc Magn Reson 2011, Bull et al, Heart 2013 , Ambale-Venkatesh and Lima, Nature Review Cardiology, 2015

Chronic Cardiotoxicity

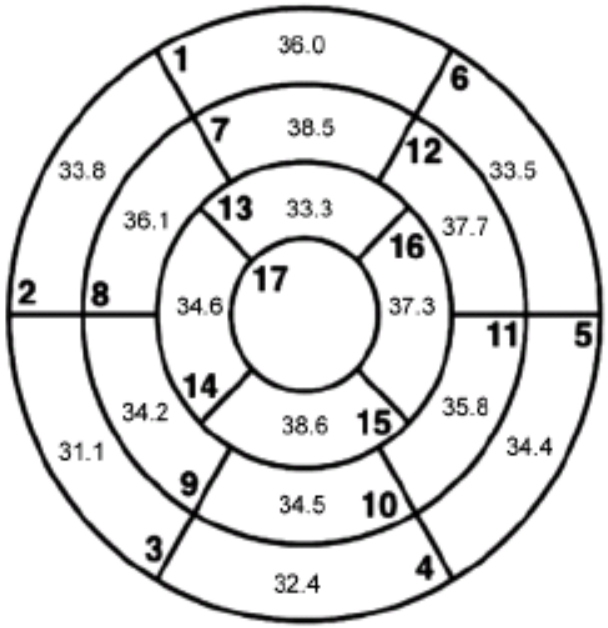


Toro-Salazar et al. Circ Cardiovasc Imaging. 2013;6:873-880

Higher Mean ECV Observed in Female Subjects



Male



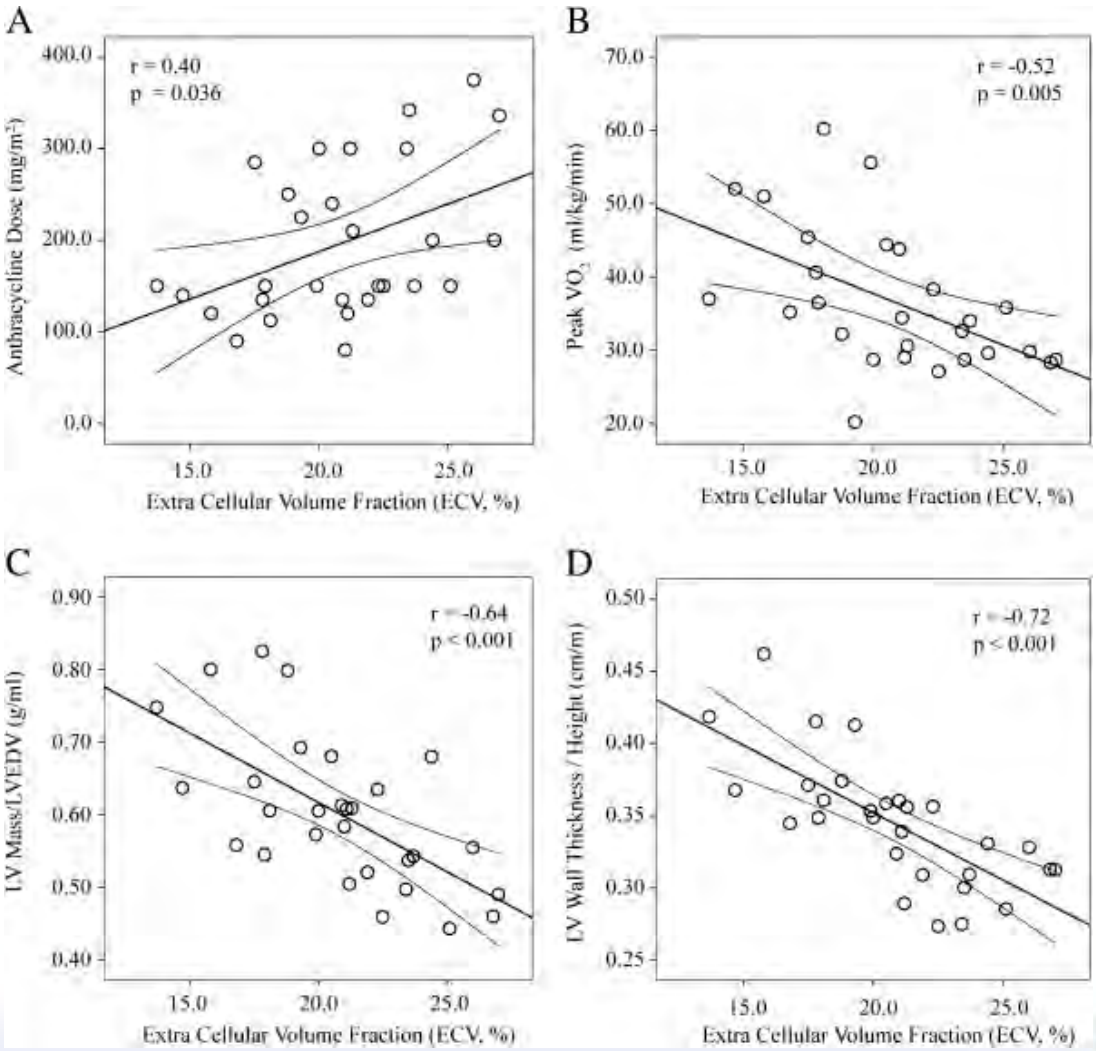
Female

- * P< 0.05
- **P< 0.001

- Higher mean ECV was observed in patients with cumulative dose ≥400mg/m^2 (0.27 vs. 0.21, p<0.05)

Olga H. Toro-Salazar et al. Circ Cardiovasc Imaging. 2013;6:873-880

Correlation of ECV with A) anthracycline dose, B) peak VO_2, C) LVmass/LVEDV and D) LV wall thickness/height.



Tham et al: J Cardiovasc Magn Reson. 2013; 15(1): 48. Published online 2013 Jun 10.

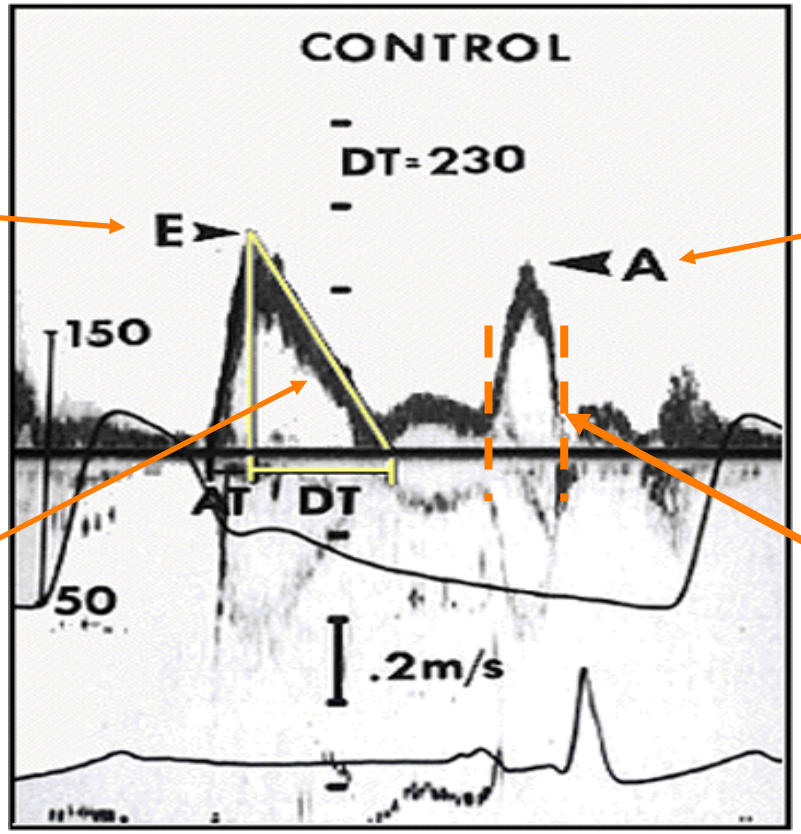
Feasibility of Echocardiographic Techniques to Detect Subclinical CTRCD among High-Dose Patients When Compared with CMR

- ESV values > 29 mL/m2
- 3DE GLS magnitude > −17%
- Decrease in early atrial myocardial velocity of <10 cm/sec at the IVS
- **3DE EF correlated best with EF obtained by CMR**

Toro-Salazar et al. Journal of the American Society of Echocardiography , Volume 29 , Issue 2 , 119 - 131

Doppler LV Inflow

Variables Measured



Peak E

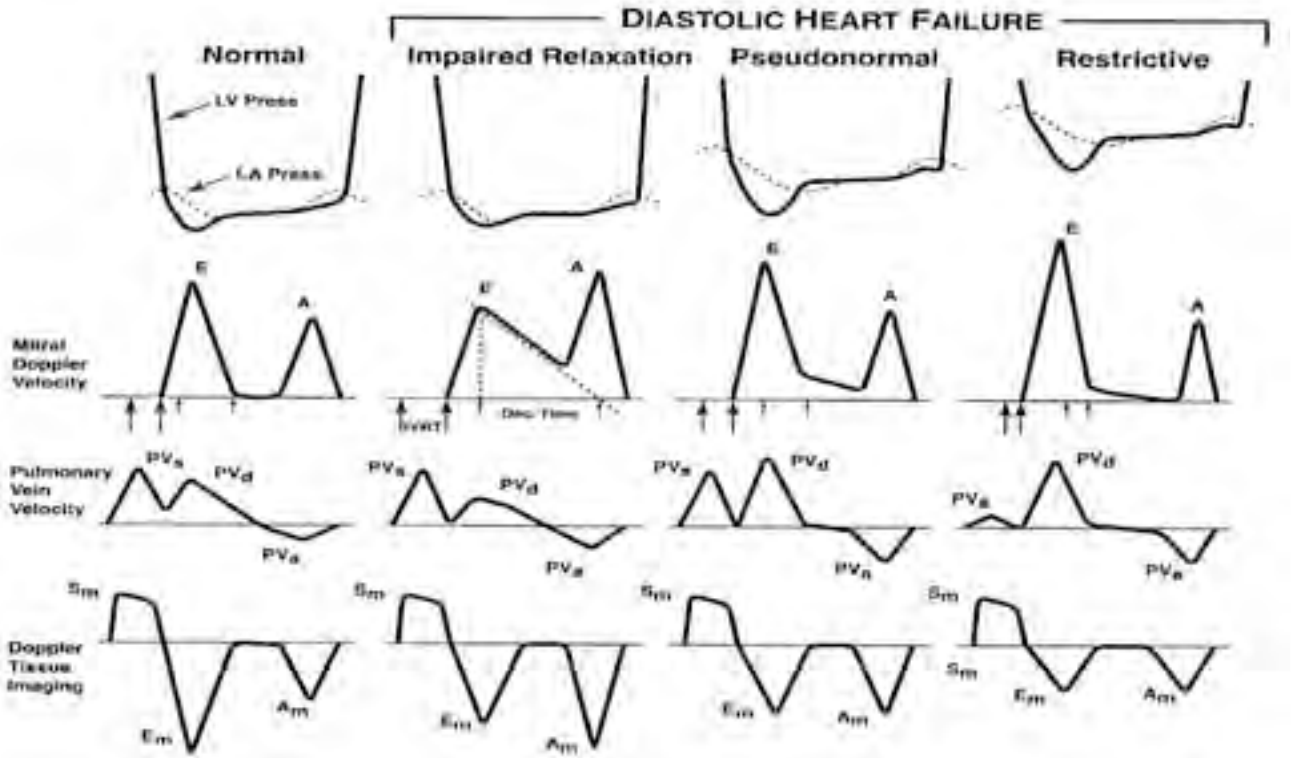
Peak A

Deceleration Time

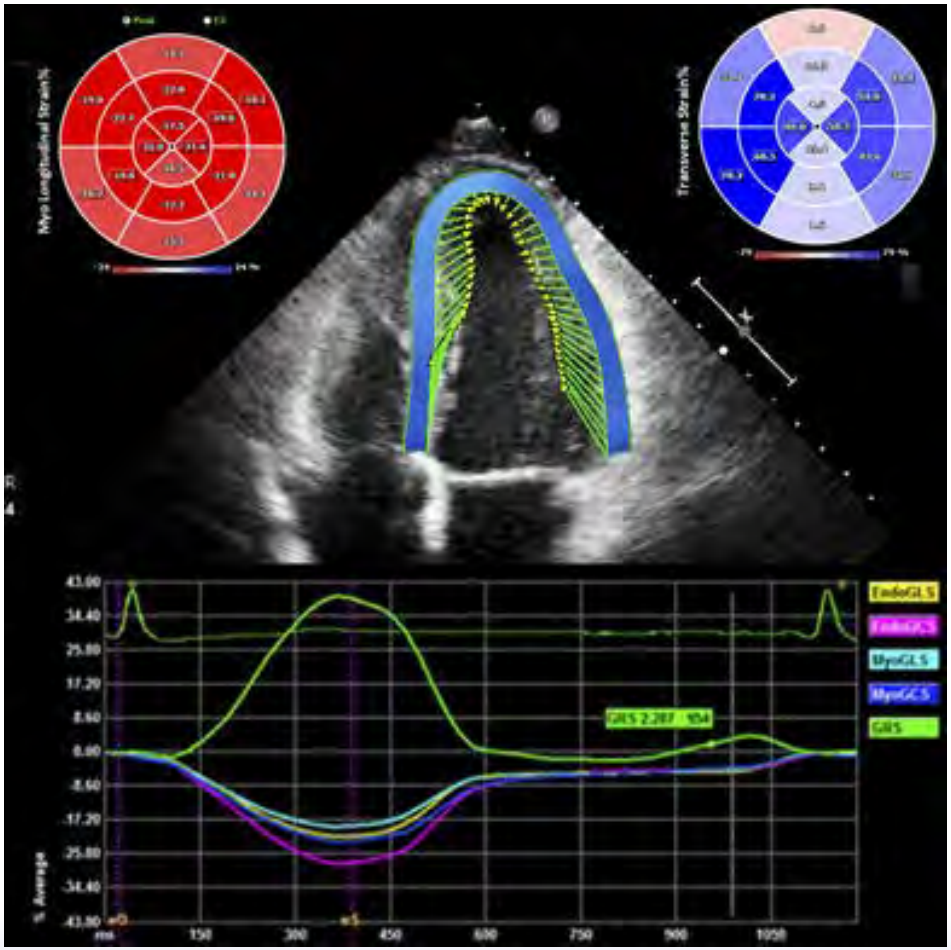
A Duration

Doppler Diastolic Waveforms

Transmitral, Pulm. Vein, Mitral annulus



3DE Strain



Echocardiographic Myocardial Deformation Parameters

	Controls		Anthracycline	p-value
Global (GCS) [1] (%)	-29.6±3.2		-25.9±3.5	0.002
Global (GCS) [2] (%)	-30.0±2.5		-25.5±3.4	<0.0001
Longitudinal (GLS) [3] (%)	-20.1±3.4		-19.3±3.6	0.49
Longitudinal (GLS) [4] (%)	-21.5±2.0	-	17.6 ±2.4	<0.0001
Longitudinal (GLS) [5] (%)	-22.5±1.9	-	19.7±2.9	0.005

[1] Global (GCS): 2D (Anthracycline n=53; control n=12)
[2] **Global (GCS): 3D (Anthracycline n= 51)**
[3] Longitudinal (GLS) 4ch (anthracycline n=53; control n=12)
[4] **Longitudinal (GLS) 3D (anthracycline n=51; control n=12)**
[5] Longitudinal (GLS) 2D 4ch_2ch average (n=48; control n=12)

Toro-Salazar et al. Journal of the American Society of Echocardiography , Volume 29 , Issue 2 , 119 - 131

Effect of Dexrazoxane on Myocardial Injury in Doxorubicin-Treated Children with ALL

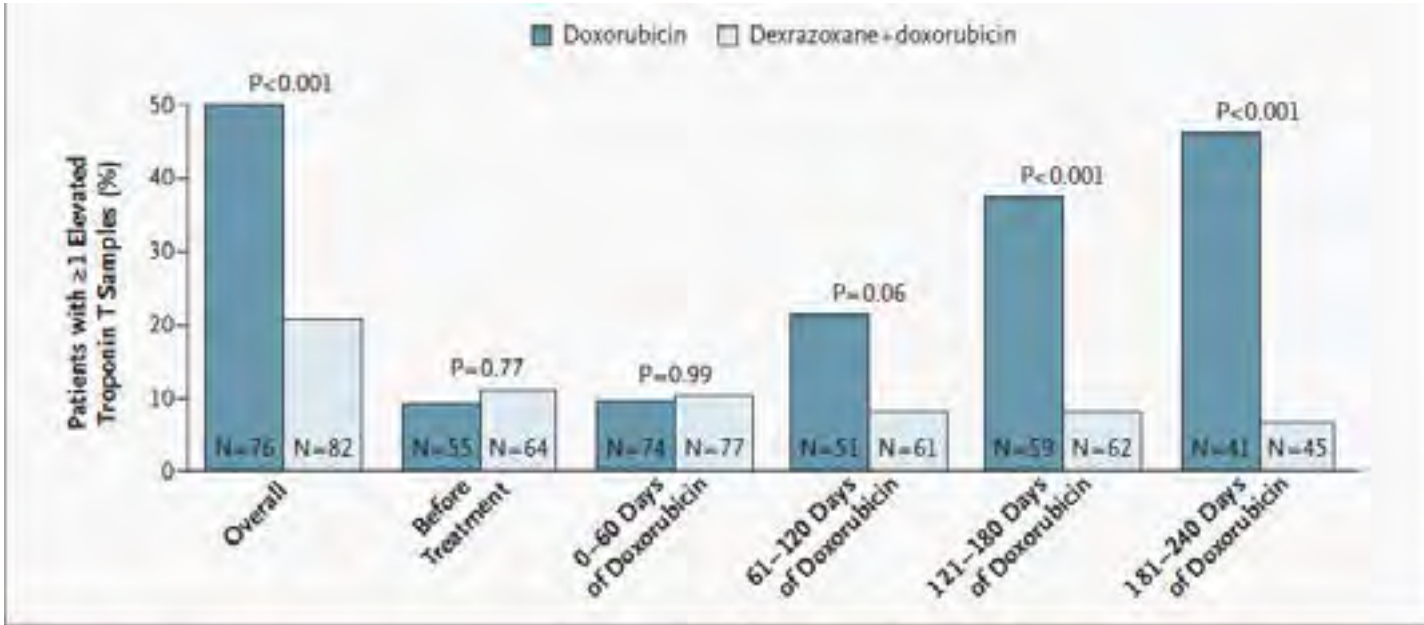


Figure 2. Percentage of Patients with at Least One Elevated Cardiac Troponin T Level Overall, before Treatment with Doxorubicin, and during Treatment.

An elevated level of troponin T was defined as one that exceeded 0.01 ng per milliliter. The number of patients in whom troponin T was measured at least once during the specified intervals is shown in each bar.

Lipshultz, et al: N Engl J Med 2004; 351:145-153July 8, 2004

NT-proBNP

- Few studies have shown that higher baseline concentrations of NT-proBNP can predict the development of overt heart failure after cardiotoxic chemotherapy
- Cut-offs of natriuretic peptides that could play a predictive role are still elusive
- A level of NT-proBNP between 300 ng/l and 500 ng/l may indicate patients with a higher propensity for further heart failure
- Further studies needed to validate this findings

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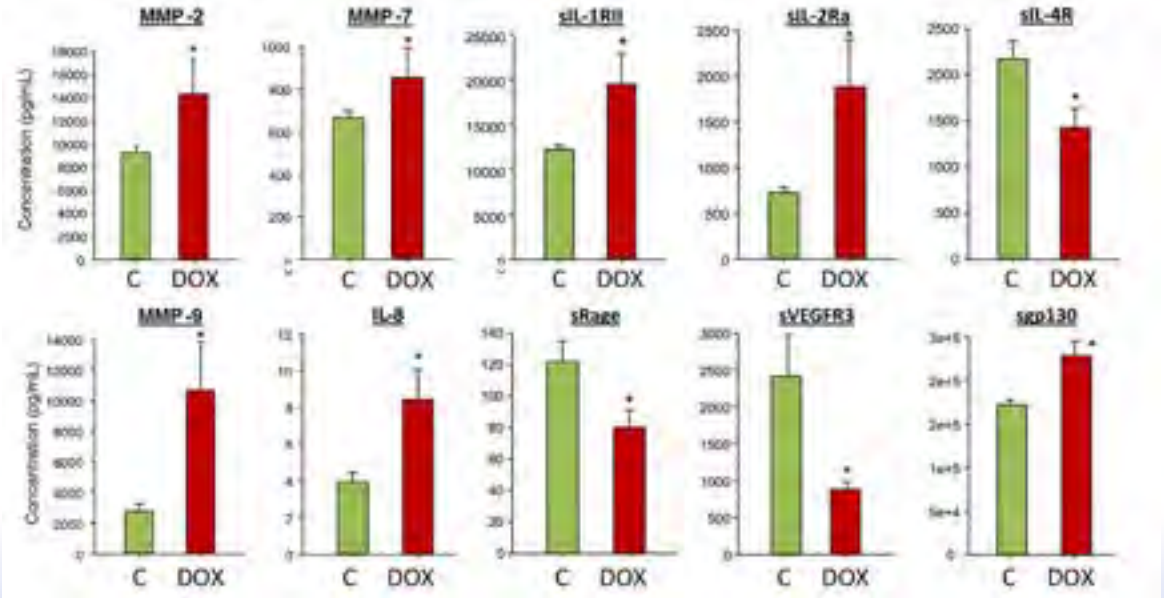
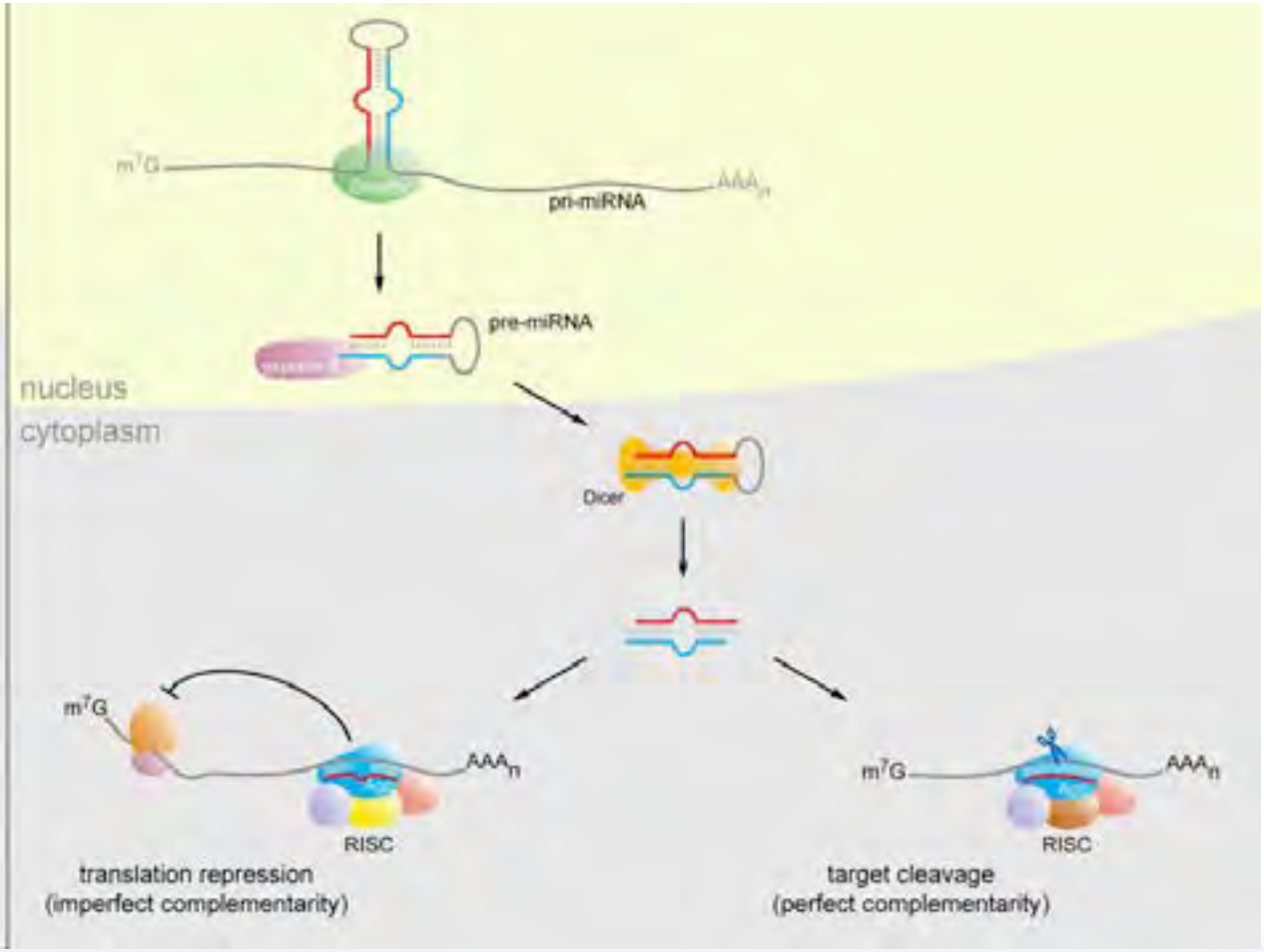
Use of integrated imaging and serum biomarker profiles to identify subclinical dysfunction in pediatric cancer patients treated with anthracyclines

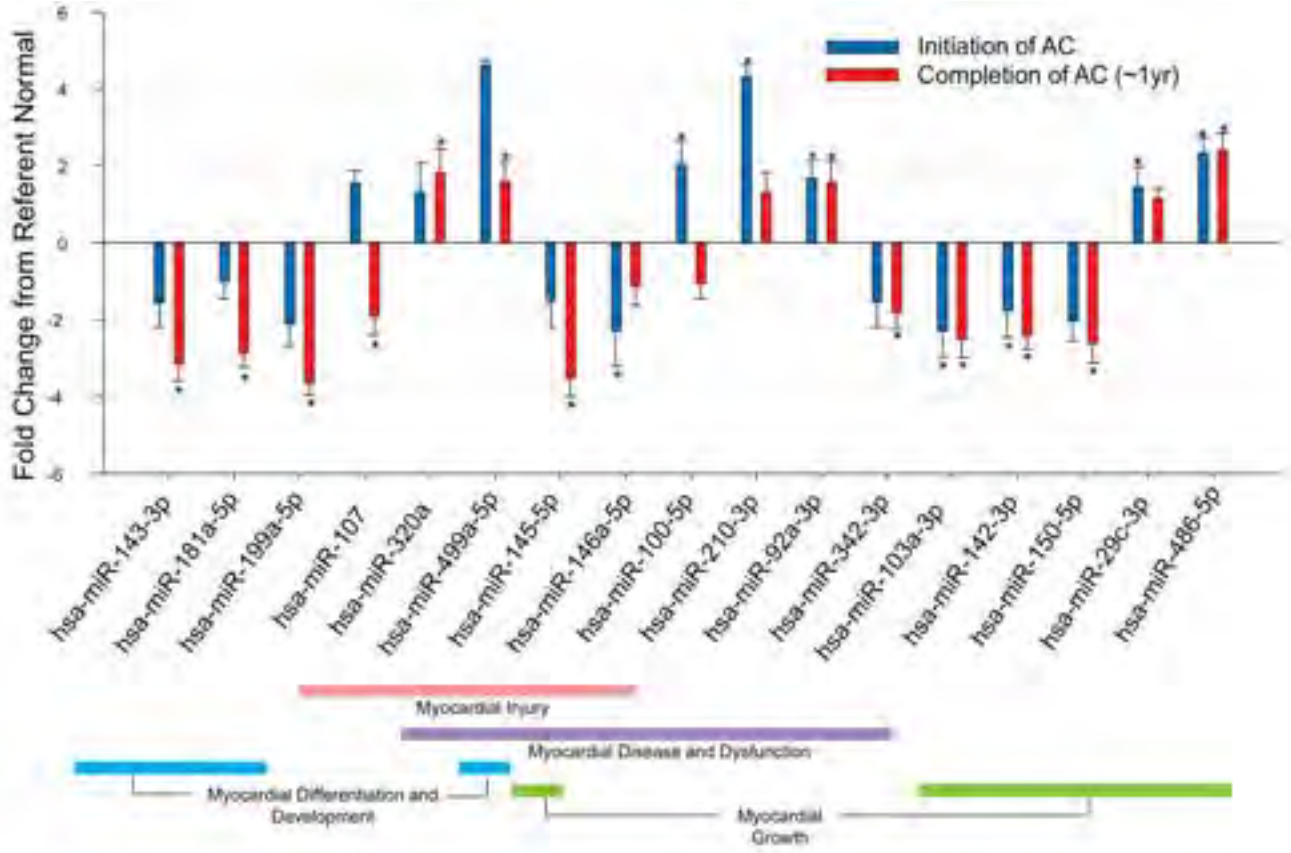
Olga H. Toro-Salazar[1,7,*], Ji Hyun Lee[1], Kia N. Zellars[2], Paige E. Perreault[2], Kathryn C. Mason[2], Zhu Wang[1], Kan N. Hor[3], Eileen Gillan[1], Caroline J. Zeiss[4], Daniel M. Gatti[5], Brooke T. Davey[1], Shelby Kutty[6], Bruce T. Liang[7], and Francis G. Spinale[2]



Micro RNAS

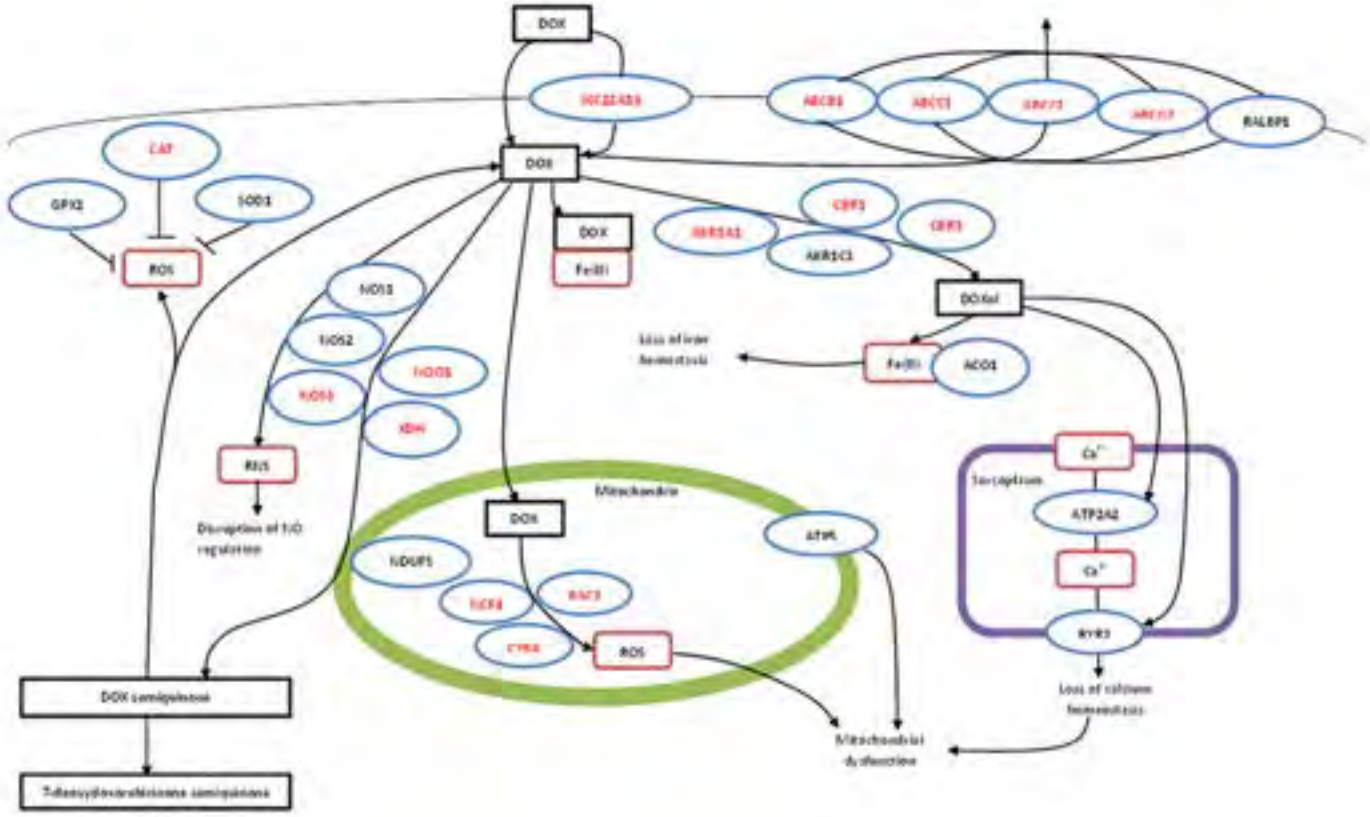


MicroRNAs



Oatmen, Toro-Salazar OH, et al, AJPHeart, in review.

Genetic Susceptibility



Leong, et.al. Scientific RepoRts | 7: 39 | DOI:10.1038/s41598-017-00075-1

Take Home Points

- Need for validated biomarkers that are surrogate end points for clinically important cardiovascular disease and treatments that prevent or control CTRCD
- A cross-disciplinary approach has the best chance to identify and treat cancer patients at risk for cardiotoxicity

Future Directions

- Comprehensive, evidence-based personalized prevention, detection, and treatment strategies for CTRCD are needed
- New knowledge on molecular mechanisms that dictate susceptibility or resistance to CTRCD will inform new therapeutic approaches
- Insights into the regulatory pathways responsible for CTRCD and developing a biomarker signature of early myocardial dysfunction will allow us to identify patients most at risk for severe toxicity, as well as to evaluate new preventive therapies for CHF

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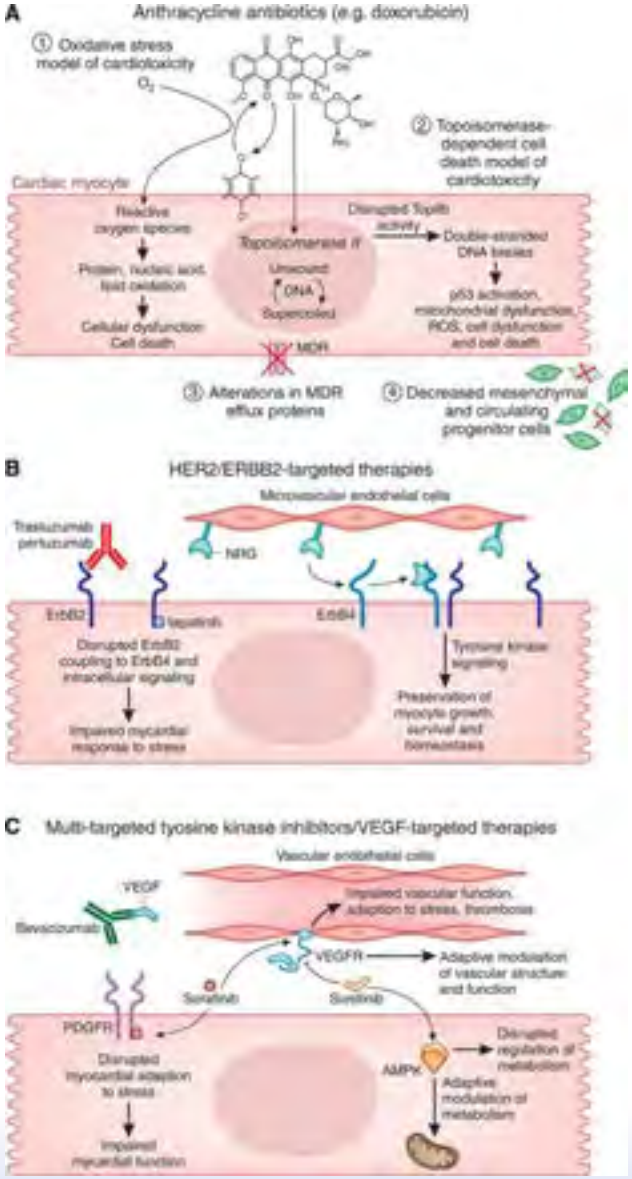
Molecular Pathways Involved In Cardiotoxicity



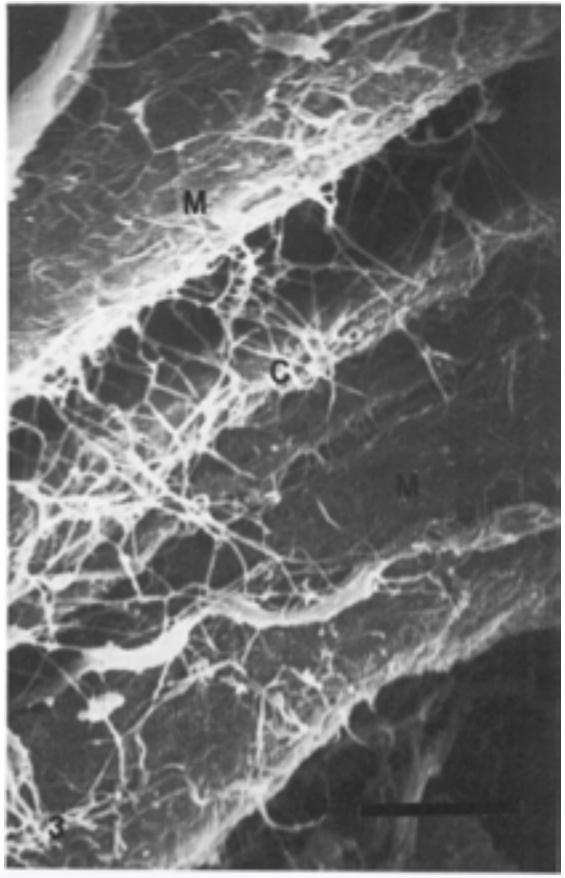
Carrie G. Lenneman, and Douglas B. Sawyer Circ Res. 2016;118:1008-1020

Anthracycline Cardio-toxicity

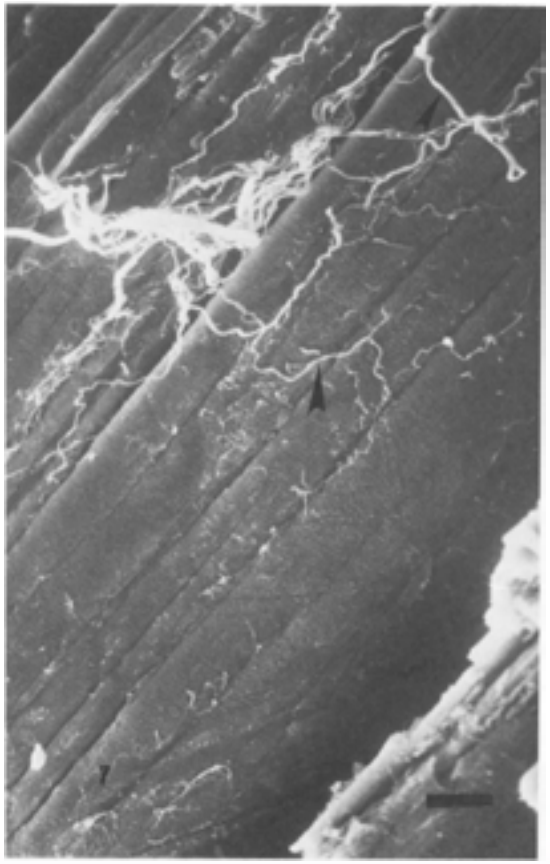
- Anthracycline toxicity is highly prevalent
- Traditional assessment by ejection fraction is inadequate to detect subclinical anthracycline toxicity
- Early cardiac injury is characterized by a progressive decline in global average circumferential (εcc) and longitudinal strain magnitude (εll)
- Tissue characterization (T1 mapping, T2 mapping) identify myocardial edema (early) and microscopic fibrosis (late).
- Biomarkers

Cardiac Matrix Alterations Caused by Adriamycin

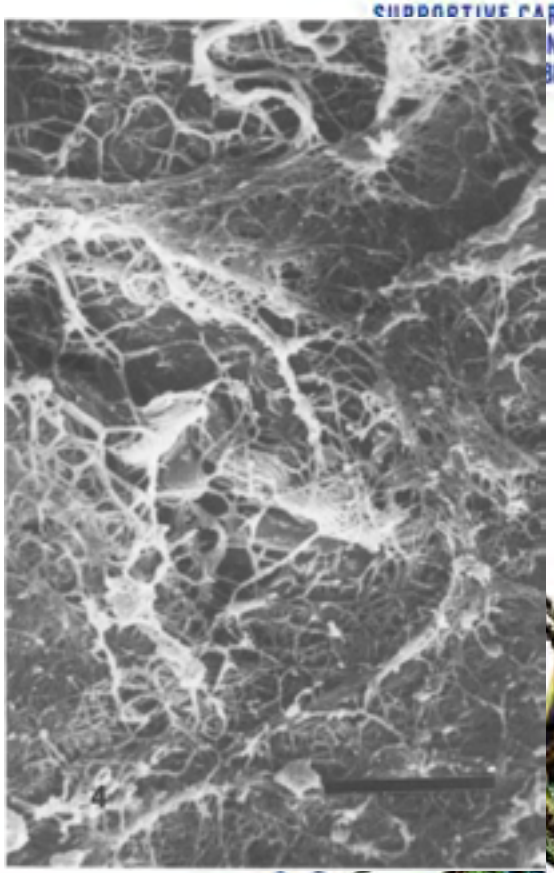
Normal



Denuded

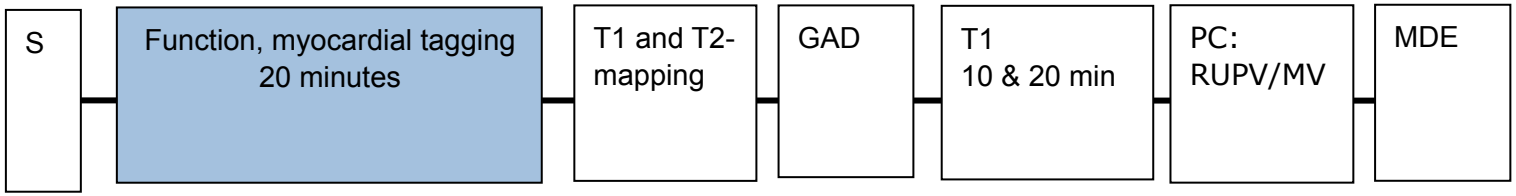


Diffuse fibrosis



Caulfield and Bittner (Am J Pathol 1988,133:298-305)

Anthracycline Protocol



Diagnosis

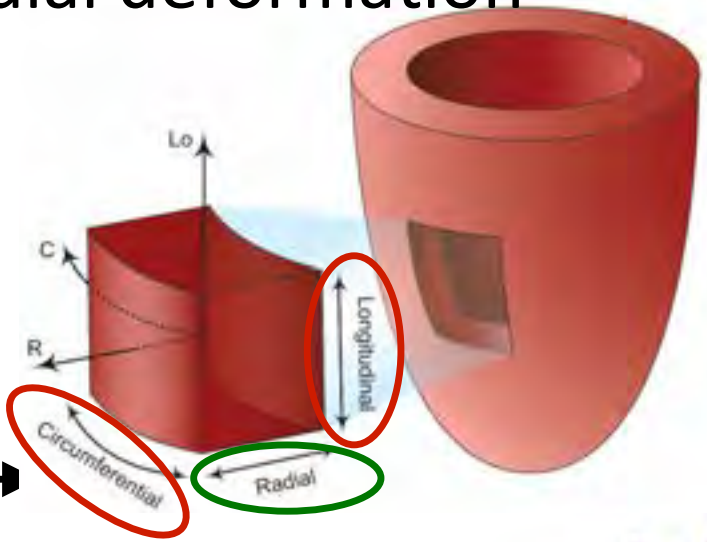
- Measurement of global and regional myocardial function:
  - Global systolic function: SF, EF
  - Regional Myocardial function (global longitudinal and circumferential strain magnitude
  - Indices of diastolic function
- CMR tissue characterization (T1 and T2 mapping), MDE
- Biomarkers
  - Biomarkers of inflammation and oxidative stress (CRP and TNF-α)
  - Myocyte injury (Troponin, Caspase-3)and
  - Heart failure: BNP or NT-proBNP)
  - Extracellular matrix (PICP, CITP, MMPs and TIMPs)
  - Growth cell and viability: sRAGE and VEGEF
  - MmicroRNAs

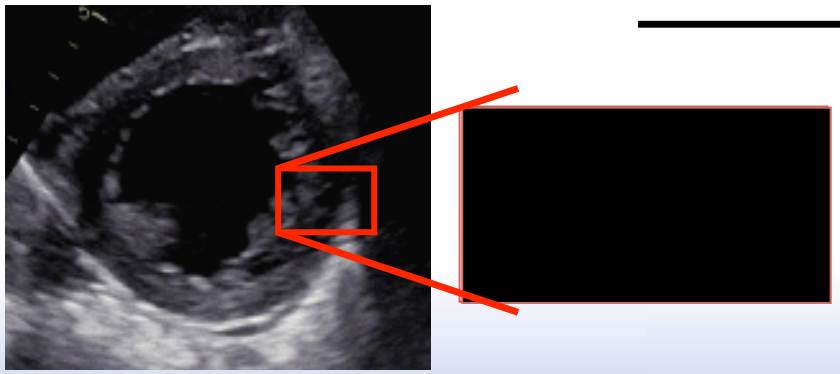
Pediatric Chemotherapy Agents with Cardiotoxic Potential

Anthracyclines	Danorubicin, Doxorubicin (including pegylated liposomal form), Epirubicin,Idarubicin, Mitoxantrone (anthraquinone)
Ankylating agents	Busulfan, Carboplantin, Cisplantin, Cyclophosphamide
	Ifosfamide, Mitomycin, Trabectedin
Antimetabolites	Clofarabine, Cytarabine, 5-fluorouracil, Methotrexate
Antimicrotubule agents	Docetaxel, Paclitaxel, Vinblastine, Vincristine, Vinorelbine
Interleukins	Aldesleukinh
Monoclonal antibodies	Alemtuzumab, Bevacizumab, Rituximab, Trastuzumab
Small-molecule tyrosine kinase and VEGF inhibitors	Dasatinib, Imatinib, Pazopanib, Sorafenib, Sunitinib
Topoisomerase inhibitor	Etoposide
Miscellaneous agents	All-trans-retinoic acid, Arsenic, Asparaginase, Bleomycin, Lenalidomide, 6-mercaptopurine, Thalidomide

Concept of Myocardial Strain

- Strain = Myocardial Deformation
- Strain analysis – detects myocardial deformation
- Positive strain = stretching
- Negative strain = shortening





displacement

Circumferential Strain

Radial Strain

Courtesy Kan Hor