The Cancer Connection: Cardiovascular Disease & Breast Cancer

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November 15, 2019

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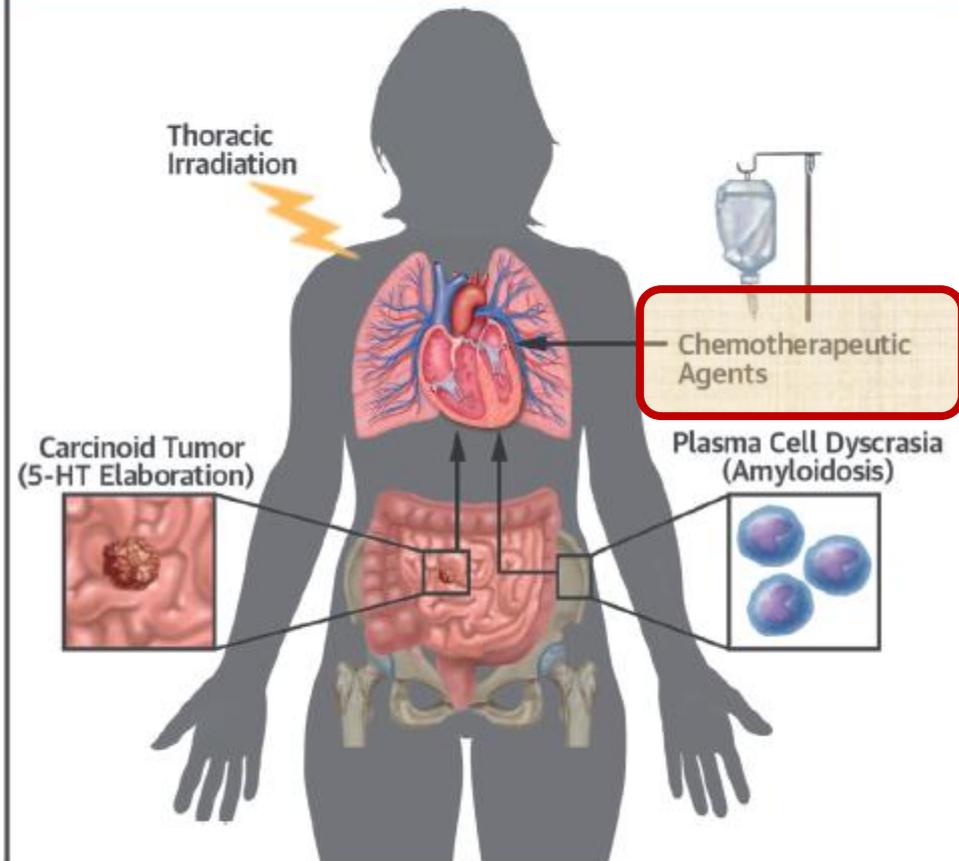
Presenter	Disclosure
Gautam Kedia, MD	None

CENTRAL ILLUSTRATION Mechanisms of Cardiac Involvement in Neoplastic Disease
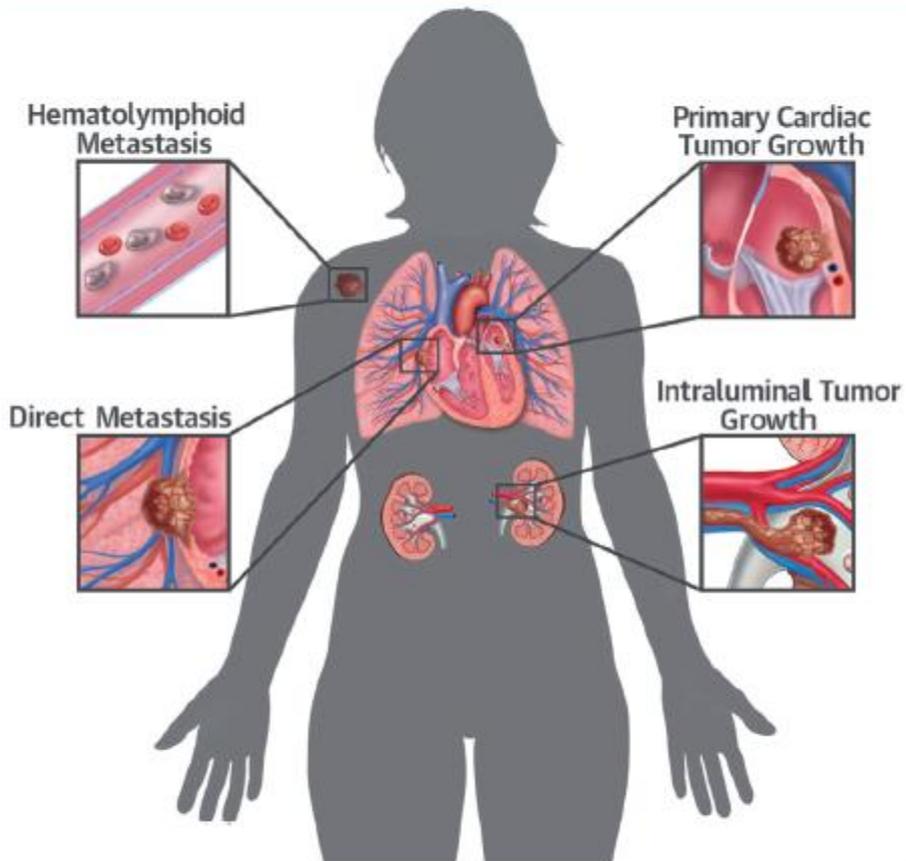
Maleszewski, J.J. et al. J Am Coll Cardiol. 2018;72(2):202-27.

(A) Direct and (B) indirect mechanisms. 5-HT = 5-hydroxytryptamine (serotonin).

Chemotherapy

Table 1. Cancer Therapies and Associated Cardiovascular Toxic Effects

Radiation	Myocardial ischemia, pericarditis, myocarditis, valvular disease, arrhythmia
Anthracyclines	Cardiomyopathy, arrhythmia, acute myocarditis, pericarditis
Platinum	Hypertension, myocardial ischemia
Antimetabolites	Myocardial ischemia, arrhythmia
Alkylating agents	Congestive heart failure, myocarditis, pericarditis
Antimicrotubule agents	Arrhythmia, myocardial ischemia, coronary spasm, thrombosis
HER2 inhibitors*	Congestive heart failure
VEGF signaling pathway inhibitors*	Hypertension, thrombosis, cardiomyopathy
Tyrosine kinase inhibitors	Pulmonary hypertension, ECG QT prolongation, vascular events, cardiomyopathy, arrhythmia
Immunomodulatory drugs	Arterial and venous thromboembolic events
Proteosome inhibitors	Cardiomyopathy, hypertension, thrombosis, arrhythmia
Immune checkpoint inhibitors	Myocarditis

*HER2.
ECG indicates electrocardiographic; HER2, human epidermal growth factor receptor2; VEGF, vascular endothelial growth factor.

Anthracyclines
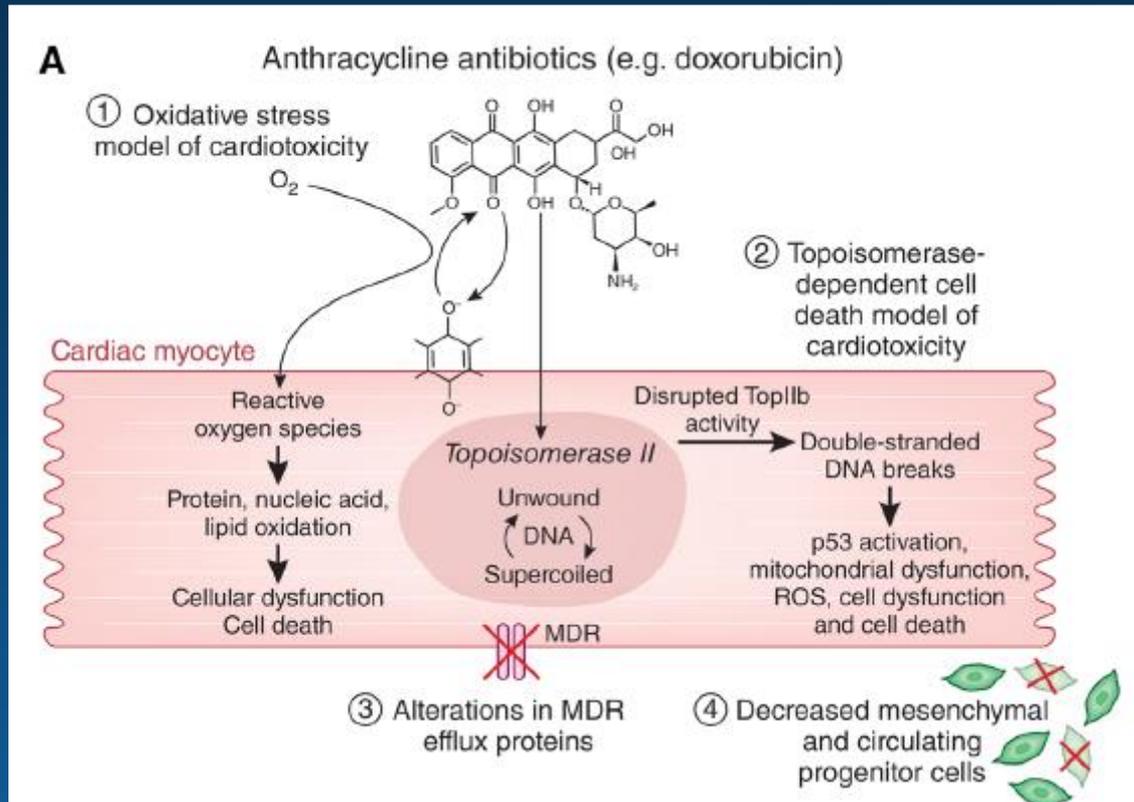
- Acute cardiac toxicity
  - ~3%
  - SVT, VT
  - AV block
  - Pericarditis/myocarditis
  - Self-limited

Anthracyclines: Late Toxicity

- Typically 2-3 years after exposure
- Related to systolic CHF
- Often irreversible

Anthracyclines: Mechanism

Topoisomerases: responsible for DNA transcription, replication

Lenneman CG & Sawyer DB.
Circ Res. 2016;118:1008-1020

Anthracyclines: dose dependent

TABLE 4
Estimated Cumulative Percentage of Patients with On Study or Off Study, Doxorubicin-Related Congestive Heart Failure, by Cumulative Dose

| | Cumulative percentage and SE | | | | | | | |
| | Study 088001 (n = 348 patients, 21 events) | | Study 088002 (n = 111 patients, 6 events) | | Study 088006 (n = 171 patients, 5 events) | | All studies (n = 630 patients, 32 events) | |
Dose (mg/m^2)	%	SE	%	SE	%	SE	%	SE
150	0.3	0.3	0.0	—	0.0	—	0.2	0.2
300	2.1	0.9	3.2	2.2	0.0	—	1.7	0.6
400	5.7	2.2	7.6	4.8	0.0	—	4.7	1.6
450	5.7	2.2	19.2	8.7	5.0	4.9	7.9	2.4
500	16.4	4.9	19.2	8.7	10.6	7.1	15.7	3.7
550	31.0	7.8	19.2	8.7	18.0	9.7	26.0	5.4
600	37.9	9.6	19.2	8.7	29.8	13.6	32.4	6.6
650	55.6	12.6	19.2	8.7	43.8	16.6	48.0	9.4
700	55.6	12.6	19.2	8.7	43.8	16.6	48.0	9.4
750	55.6	12.6	19.2	8.7	43.8	16.6	48.0	9.4
800	55.6	12.6	19.2	8.7	43.8	16.6	48.0	9.4
850	100.0	—	100.0	—	—	—	100.0	—

CHF defined as meeting at least 3/5: total dox dose, initial LVEF, change in LVEF, ECG changes, additional info (CXR, labs)

Swain SW et al. Cancer 2003;97:2869-79

Anthracyclines: dose dependent

TABLE 6
Estimated Cumulative Percentage of Patients with On Study Cardiac Events, by Cumulative Dose

	Cumulative percentage and SE							
	Study 088001 (n = 348 patients, 87 events)		Study 088002 (n = 111 patients, 32 events)		Study 088006 (n = 171 patients, 30 events)		All studies (n = 630 patients, 149 events)	
Dose (mg/m^2)	%	SE	%	SE	%	SE	%	SE
50	0.6	0.4	0.0	—	0.0	—	0.4	0.3
100	0.6	0.4	1.1	1.1	0.0	—	0.5	0.3
150	4.2	1.1	14.0	3.6	6.7	2.0	6.5	1.0
200	5.0	1.3	17.8	4.1	7.5	2.2	7.8	1.2
250	5.8	1.4	19.2	4.2	8.3	2.3	8.8	1.2
300	14.4	2.2	24.7	4.8	14.6	3.1	16.2	1.7
350	16.4	2.6	27.3	5.2	14.6	3.1	17.9	1.9
400	32.9	4.2	41.2	7.5	23.7	5.7	32.4	3.2
450	40.7	4.8	45.7	8.2	23.7	5.7	37.9	3.5
500	58.5	5.4	62.0	9.7	33.2	8.1	53.9	4.2
550	73.0	5.7	62.0	9.7	45.4	10.2	65.4	4.6
600	76.0	5.8	69.6	11.3	61.0	11.8	72.0	4.8
650	86.3	5.6	69.6	11.3	68.8	11.8	80.6	4.9
700	90.9	5.3	69.6	11.3	79.2	11.6	86.2	4.8
750	90.9	5.3	69.6	11.3	79.2	11.6	86.2	4.8
800	95.4	4.2	69.6	11.3	—	—	90.8	4.9
850	100.0	—	100.0	—	—	—	100.0	—

Cardiac Event: defined CHF or significant reduction in EF.

Swain SW et al. Cancer 2003;97:2869-79

Anthracyclines: Risk Factors

- Hypertension
- Coronary artery disease
- Diabetes Type 2
- Age >65
- Preexisting cardiac disease
- Concomitant radiation

Anthracycline Toxicity: Prevention

- Limiting the dose of chemotherapy
- Developing anthracycline analogs
- Continuous infusion vs bolus – mixed results
  - 24 hr infusion is better
    - Sarcomas & leukemias
    - Not well studied/FDA-approved for breast cancer
- Drug free intervals between doses
- Liposomal encapsulation

Witteles RM & Bosch X. Circulation 2015;132:1835-1845

Prevention: Dexrazoxane
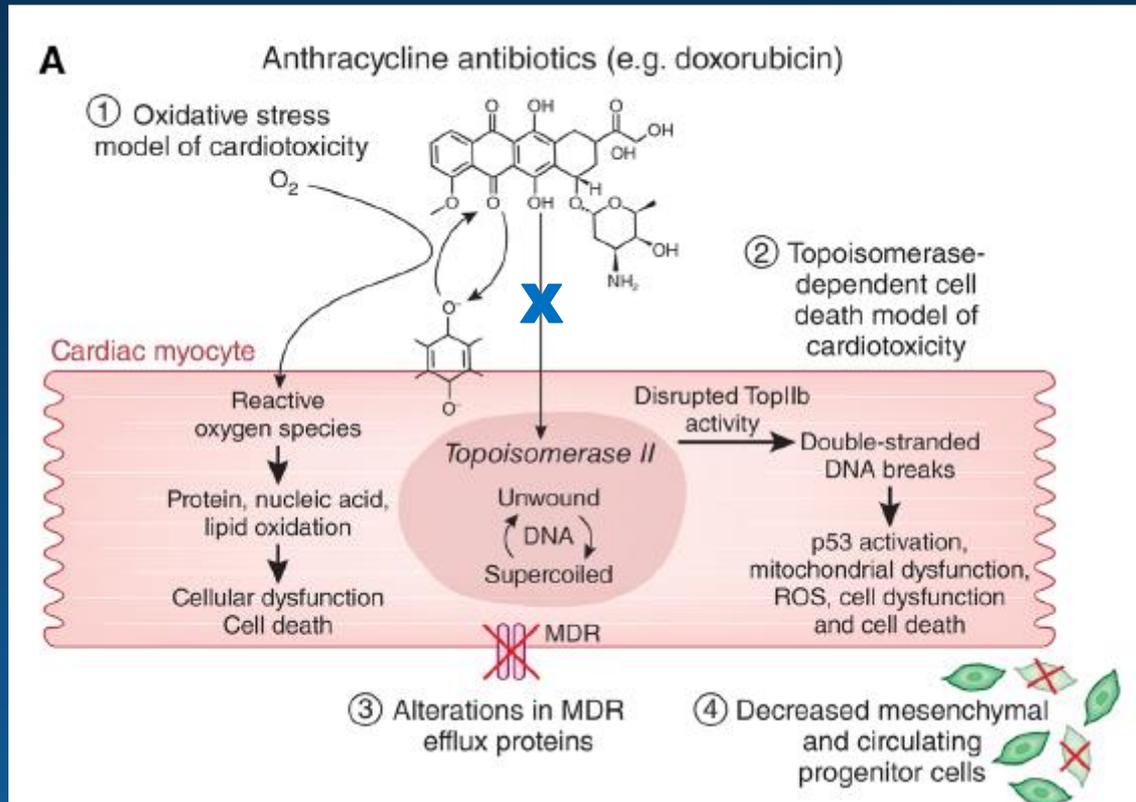
Prevents doxorubicin from binding to the Topo2B-DNA complex.

Lenneman CG & Sawyer DB.
Circ Res. 2016;118:1008-1020

Prevention: Dexrazoxane

- Dexrazoxane
  - Reduces incidence of CHF and LV dysfunction
  - However, reports of AML and MDS in children
  - No longer routinely used

-----------------------**INDICATIONS AND USAGE**----------------------
ZINECARD is a cytoprotective agent indicated for reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m^2 and who will continue to receive doxorubicin therapy to maintain tumor control. Do not use ZINECARD with doxorubicin initiation. (1)

FDA LABEL

Prevention: Cardiac Meds

- Studied:
  - Ace-inhibitors
  - Angiotensin receptor blockers
  - Beta blockers

Prevention: Cardiac Meds

- Limitations:

> submitted to pharmacological cardioprevention. Large, randomized, multicenter studies performed in patients treated with and without novel therapies are clearly needed to confirm these results.

  chemotherapy regimens used
  - Short follow-up times
  - Reductions in LVEF decline > no change in mortality

Prevention: Cardiac Meds

Table 2 Primary and secondary endpoints, estimated values from linear mixed models (intention-to-treat analysis)

	n	Baseline	EOS	Change from baseline to EOS	Between-group difference in change from baseline to EOS	P-value
LVEF						
No candesartan	60	63.2 (62.0, 64.4)	60.6 (59.4, 61.8)	−2.6 (−3.8, −1.5)	1.9 (0.2, 3.5)[a]	0.026
Candesartan	60	62.1 (61.0, 63.3)	61.4 (60.2, 62.6)	−0.8 (−1.9, 0.4)		
No metoprolol	62	62.8 (61.6, 64.0)	61.0 (59.8, 62.2)	−1.8 (−3.0, −0.7)	0.2 (−1.4, 1.9)	0.772
Metoprolol	58	62.5 (61.3, 63.7)	61.0 (59.8, 62.2)	−1.6 (−2.8, −0.4)		

9/2011-2014, 120 pts with breast cancer and receiving epirubicin, in 2x2 randomization

Gulat G et al. Eur Heart J. 37(21); 2016:1671-80.

Anthracycline Toxicity: Management

- Lacking definitive data
- In presence of LV dysfunction:
  - Referral to cardiologist
  - Treat as early as possible
  - ACEis/BBs

Trastuzumab ("Herceptin")

- Monoclonal antibody against HER2, which is overexpressed in 20-25% of all breast cancers
- Given as IV injection q3 weeks upto 1 year
- Decreased systolic function
  - Reversible
  - Not related to cumulative dosing
  - Risk factors: age>65, anthracycline use

Table 1 Characteristics of type I and II CTRCD

	Type I	Type II
Characteristic agent	Doxorubicin	Trastuzumab
Clinical course and typical response to antiremodeling therapy (β-blockers, ACE inhibitors)	May stabilize, but underlying damage appears to be permanent and irreversible; recurrence in months or years may be related to sequential cardiac stress	High likelihood of recovery (to or near baseline cardiac status) in 2–4 months after interruption (reversible)
Dose effects	Cumulative, dose related	Not dose related
Effect of rechallenge	High probability of recurrent dysfunction that is progressive; may result in intractable heart failure or death	Increasing evidence for the relative safety of rechallenge (additional data needed)
Ultrastructure	Vacuoles; myofibrillar disarray and dropout; necrosis (changes resolve over time)	No apparent ultra structural abnormalities (though not thoroughly studied)

Others

- Tyrosine Kinase Inhibitors
  - Pulmonary HTN, QT prolongation
- VEGF Inhibitors
  - Hypertension, LV dysfunction, thromboembolism

Cardiac Imaging in Chemotherapy

- Left ventricular ejection fraction

- Strain imaging

Cardiac Imaging in Chemotherapy

- LV EF
  - MUGA: less inter-observer variability, high reproducibility
  - Echo is routine, easily available
    - Exact cut-offs for normal or abnormal not well defined
    - Different measurement techniques
    - Important to visually compare studies over time

LV Ejection Fraction

- Can miss small changes in EF
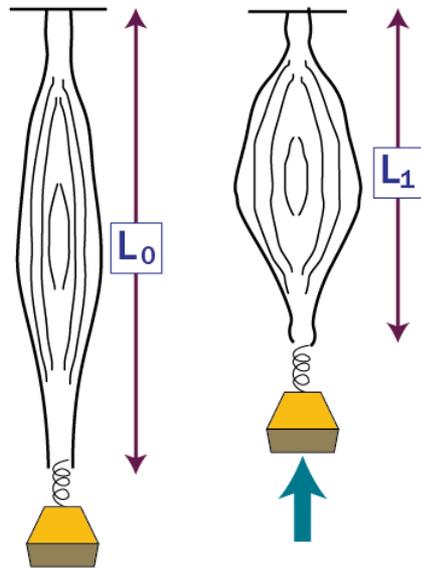- 2D-Echo appears to be reliable in detecting differences close to 10% in EF
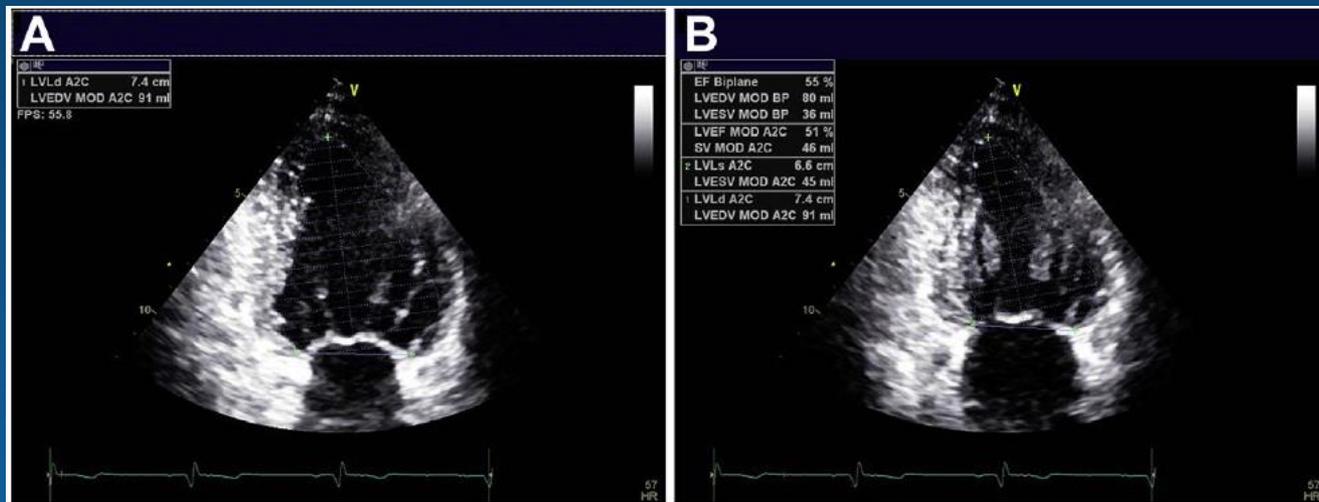
Strain Imaging

- To identify earlier parameters of myocardial dysfunction, to prevent irreversible cardiotoxicity
- I.e. to detect subclinical LV dysfunction

Myocardial Strain

Strain is change in shape of the myocardium resulting from contraction or relaxation:

$$\varepsilon = \frac{L_1 - L_0}{L_0}$$

$L_0 = 10$ mm
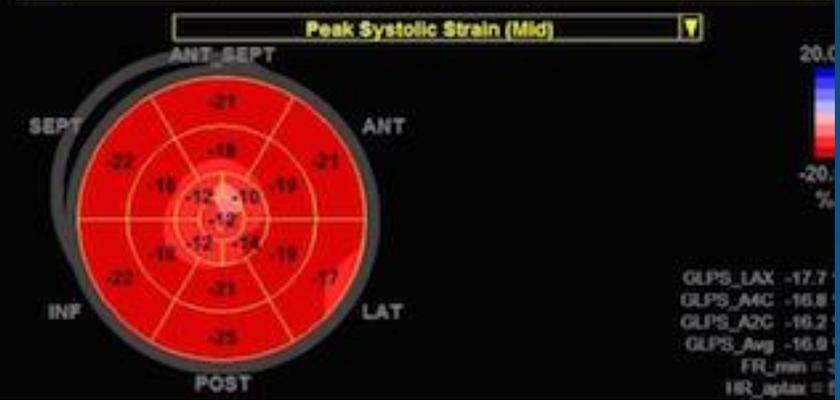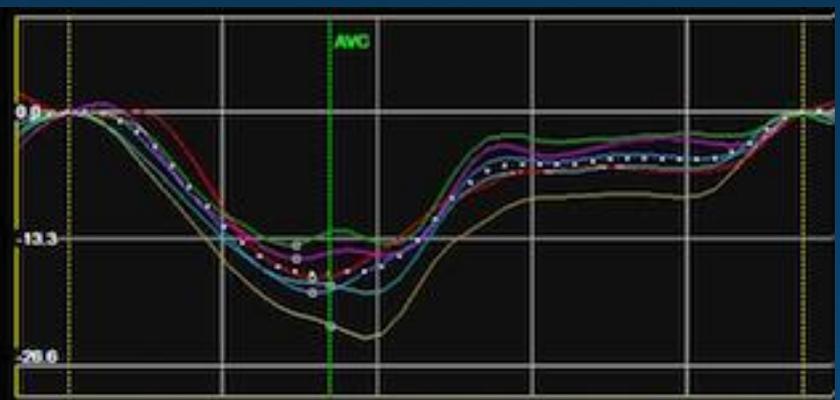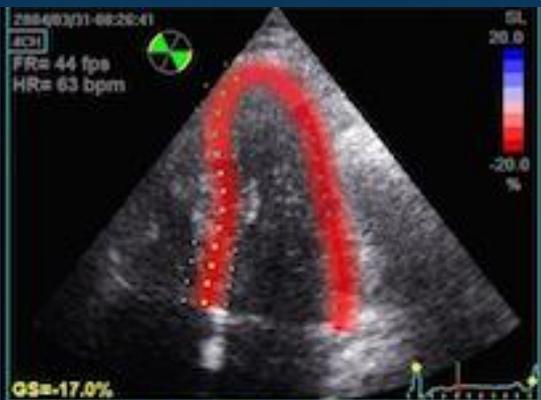$L_1 = 8$ mm

$$\varepsilon = \frac{8 - 10}{10} = -20\%$$

ACC Echo SAP

Strain Imaging

- Defined simply as the change in shape (i.e. deformation) of the myocardium resulting from contraction or relaxation
- Based on 'speckle tracking' – a pattern of speckles throughout the myocardium
- Not angle dependent
    - Such as in TDI
- Considered a natural tool to track myocardial motion over time

Strain Imaging: Data

Table 4. Sensitivity, Specificity, PPV, and NPV of the Predictors of Cardiotoxicity

Predictors (Measured At the Completion of Anthracyclines)	Sensitivity	Specificity	PPV	NPV
Long strain <19%	17/23 (74%) (0.51–0.90)	40/55 (73%) (0.59–0.84)	17/32 (53%)	40/46 (87%)
usTnI >30 pg/mL	11/23 (48%) (0.27–0.69)	40/55 (73%) (0.59–0.84)	11/26 (44%)	40/52 (77%)
Long strain <19% and usTnI>30 pg/mL	8/23 (35%) (0.16–0.57)	51/55 (93%) (0.82–0.98)	8/12 (67%)	51/66 (77%)
Long strain <19% or usTnI>30 pg/mL	20/23 (87%) (0.66–0.97)	29/55 (53%) (0.39–0.66)	20/46 (43%)	29/32 (91%)

82 females with HER2+ breast cancer, treated with anthracyclines, then paclitaxel, then trastuzumab. Echo+Labs at: beginning of study, after anthracyclines, and q3months.

- Significant decrease in LVEF (≥8%, at completion of anthracycline treatment) was detected only in 15% of patients developing cardiotoxicity at 15-month follow-up
- Changes in troponin or strain were present in 78% of patients developing subsequent cardiotoxicity
- Longitudinal strain <19% was present in all patients who later developed symptomatic CHF
- NT-proBNP did not predict cardiotoxicity

Sawaya H et al. Circ Cardiovasc Imaging. 2012;5:596-603

Strain Imaging: Pitfalls

Table 5 Effect of vendor age and gender on GLS

Vendor	Age group (y)						P
	0–19	20–29	30–39	40–49	50–59	≥60	
V1							
Overall	−22.1 ± 2.4	−21.2 ± 1.9	−21.1 ± 2.1	−21.4 ± 2.0	−21.0 ± 2.2	−20.3 ± 1.9	.0218
Male	−21.7 ± 3.1	−20.9 ± 1.9	−20.6 ± 1.9	−20.9 ± 1.8	−21.0 ± 1.9	−19.7 ± 1.4	.1982
Female	−22.4 ± 1.6	−22.3 ± 1.6	−22.8 ± 1.8	−22.6 ± 2.1	−23.3 ± 1.9	−20.9 ± 2.1	.0348
P (male vs female)	.4292	.0316	<.0001	.0178	.0029	.1381	
V2							
Overall	−19.9 ± 2.5	−19.0 ± 2.1	−19.5 ± 2.2	−18.2 ± 2.5	−17.6 ± 2.5	−16.7 ± 2.1	<.0001
Male	−19.4 ± 2.7	−18.8 ± 2.0	−19.1 ± 2.3	−17.9 ± 2.8	−16.9 ± 2.3	−15.8 ± 1.4	.0019
Female	−20.5 ± 2.2	−20.6 ± 2.3	−20.2 ± 2.0	−19.3 ± 0.9	−20.4 ± 1.5	−17.3 ± 2.3	.0002
P (male vs female)	.1349	.0248	.1083	.4316	.0294	.0928	
V3							
Overall	−21.4 ± 1.7	−20.2 ± 2.1	−20.4 ± 2.3	−19.4 ± 2.2	−18.5 ± 2.6	−17.8 ± 2.8	<.0001
Male	−21.6 ± 2.0	−20.2 ± 2.0	−20.4 ± 2.2	−19.8 ± 2.3	−18.7 ± 2.6	−16.3 ± 3.1	<.0001
Female	−21.2 ± 1.5	−20.2 ± 2.4	−20.4 ± 2.8	−18.7 ± 1.8	−18.3 ± 2.8	−18.6 ± 2.3	.0141
P (male vs female)	.6076	.9787	.9201	.1415	.7374	.0668	

V1, Vivid 7 or Vivid E9 (GE Healthcare); V2, iE33 (Philips Medical Systems); V3, Artida or Aplio (Toshiba Medical Systems).
Reproduced with permisssion from Circulation Journal.[166]

Plano JC et al. Expert Consensus Document. JASE 2014;27:911-39

Strain Imaging: Pitfalls

- However, there have been no studies to demonstrate that early intervention based on change in strain alone can result in reduction of clinically significant (eg, symptomatic cardiac dysfunction) risk in patients with cancer. There are important studies under way that will provide insight into this question (eg, Strain Surveillance During Chemotherapy for Improving Cardiovascular Outcomes [SUCCOUR]).

Sawaya H et al. Circ Cardiovasc Imaging. 2012;5:596-603

Biomarkers

Prognostic Value of Troponin I in Cardiac Risk Stratification of Cancer Patients Undergoing High-Dose Chemotherapy

- 703 cancer patients
  - TnI measured soon after chemo, and 1 month later
  - Troponin "positive" for values ≥0.08 ng/mL

Cardinale D, Sandri MT, Colombo A, et al: Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation 109:2749-2754, 2004

Biomarkers

TABLE 3.   Cardiac Events in the Study Groups

	Total (n=703)	TnI$^{-/-}$ (n=495)	TnI$^{+/-}$ (n=145)	TnI$^{+/+}$ (n=63)
Sudden death	3 (0.4)	0 (0)	0 (0)	3 (5)
Cardiac death	2 (0.3)	0 (0)	0 (0)	2 (3)
Acute pulmonary edema	3 (0.4)	0 (0)	1 (0.7)	2 (3)
Heart failure	47 (7)	1 (0.2)	18 (12)	28 (44)
Asymptomatic left ventricular dysfunction	37 (5)	2 (0.4)	24 (17)	11 (17)
Life-threatening arrhythmias	17 (2)	2 (0.4)	10 (7)	5 (8)
Conduction disturbances requiring pacemaker implantation	2 (0.3)	0 (0)	0 (0)	2 (3)
Cumulative events	111 (16)	5 (1)	53 (37)*	53(84)*†

Values are given as n (%).
*$P<0.001$ vs TnI$^{-/-}$ group; †$P<0.001$ vs TnI$^{+/-}$ group.

Cardinale D, Sandri MT, Colombo A, et al: Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation 109:2749-2754, 2004

Journal of Clinical Oncology, 2017

Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Saro H. Armenian, Christina Lacchetti, Ana Barac, Joseph Carver, Louis S. Constine, Neelima Denduluri, Susan Dent, Pamela S. Douglas, Jean-Bernard Durand, Michael Ewer, Carol Fabian, Melissa Hudson, Mariell Jessup, Lee W. Jones, Bonnie Ky, Erica L. Mayer, Javid Moslehi, Kevin Oeffinger, Katharine Ray, Kathryn Ruddy, and Daniel Lenihan

Surveillance & Monitoring:
During Treatment

- Routine monitoring may be offered during treatment in asymptomatic patients at increased risk

- Echo is the modality of choice

- Frequency… should be determined by healthcare providers… based on clinical judgment

Surveillance & Monitoring:
After Treatment

- In asymptomatic patients considered to be at increased risk:
  - Echo may be performed 6-12 months after chemotherapy
  - If no cardiac dysfunction at this point:
    - No recommendation can be made regarding frequency and duration
- If cardiac dysfunction is noted:
  - Referral to a cardiologist

Anthracycline Toxicity:
Team-Based Approach

Witteles RM & Bosch X. Circulation 2015;132:1835-1845
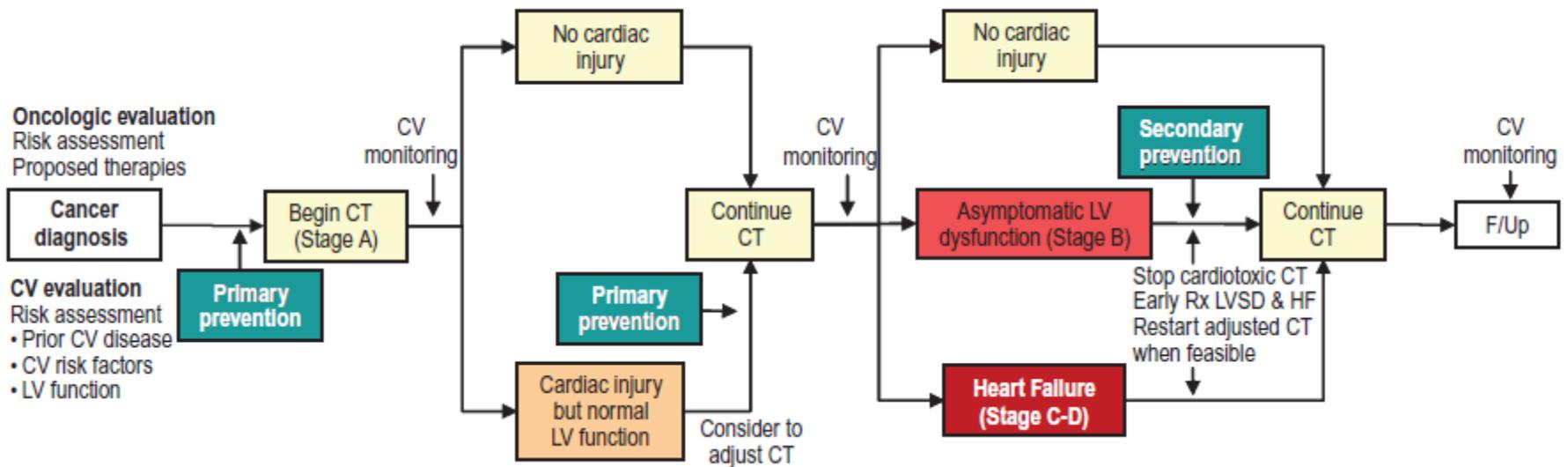
Potential Surveillance Algorithm

- Anthracyclines, no Herceptin:
  - Strain Echo + troponin prior to chemo, after anthracyclines finished, and:
    - Minimal risk factors: Echo annually for 3 years
    - Multiple risk factors: Echo every 6 months x2, then annually, upto 3 years
- Anthracyclines, with Herceptin:
  - Strain Echo + troponin prior to chemo, after anthracyclines finished, and q3months during Herceptin

Practical Aspects, Future Directions

- Cardiology + Oncology
  - Work hand in hand
  - Factor in patient risk factors
- Need joint guidelines
  - *Many unanswered questions*
- Consider alternative options
  - Alternative treatments
  - Genomic assays to determine who will respond to which treatment

THANK YOU!

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November 15, 2019