

Early Diagnosis of Anthracycline-Induced Cardiotoxicity

Borja Ibanez, MD PhD FESC

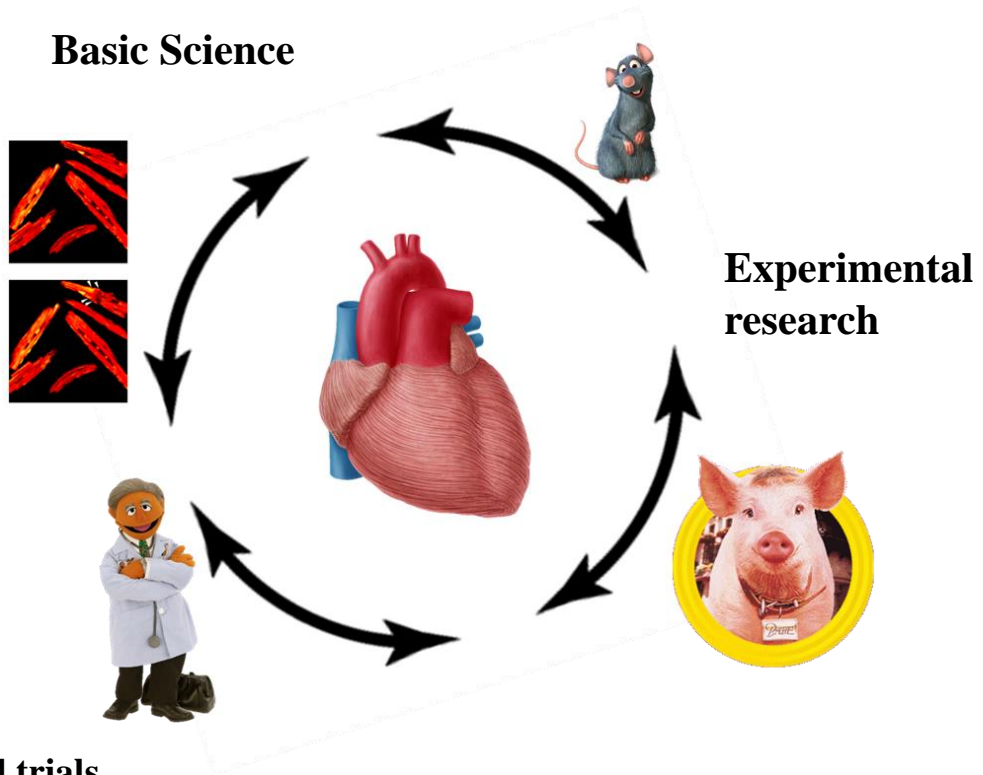


National Center for Cardiovascular Research, Spain

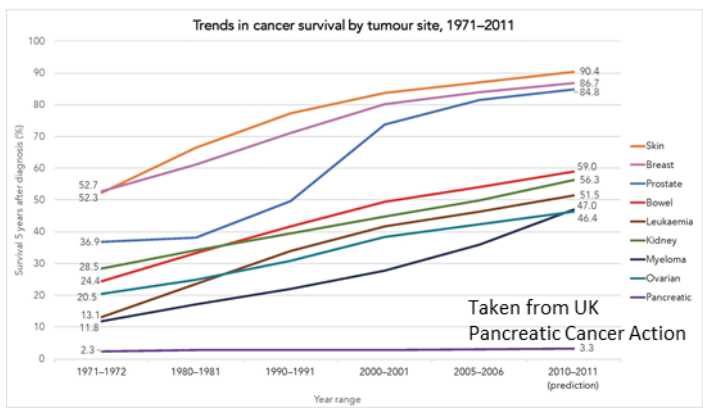
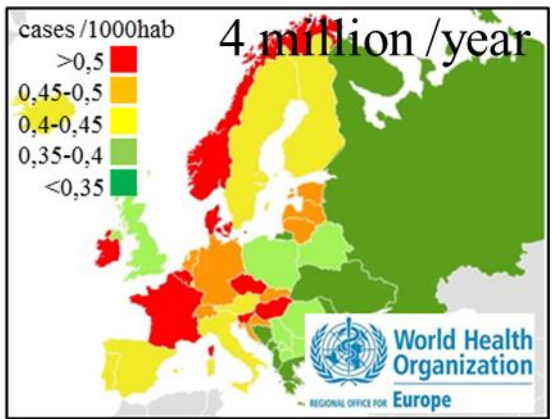


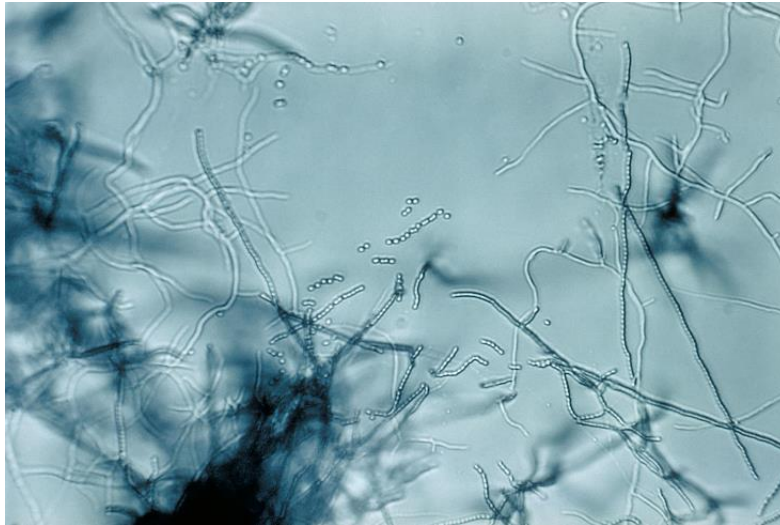
Fundación Jiménez Díaz University Hospital, Spain





Clinical trials
Clinical Practice Guidelines





1950s

Streptomyces peucetius

Daunorubicin

Daunorubicin → Adryamycin (doxorubicin)

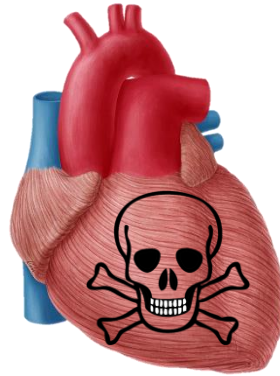
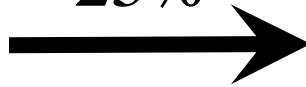
Leukemias, Lymphomas, Sarcoma, Gastric Ca, Breast Ca,



Anthracyclines



25%





Anthracycline Cardiotoxicity: Prevalence, Pathogenesis and Treatment

Maria Volkova¹ and Raymond Russell*, III^{1,2}

¹Section of Cardiovascular Medicine, Yale University School of Medicine; ²Smilow Cancer Hospital

Table 1. Dose Related Risk of Doxorubicin-Induced Congestive Heart Failure (Based on Data from (9))

Cumulative Dose (mg/m ²)	Patients with CHF (%)
150	0.2
300	1.6
450	3.3
600	8.7

Very long after chemotherapy finish



ESC

European Society
of Cardiology

ESC CPG POSITION PAPER

**2016 ESC Position Paper on cancer treatments
and cardiovascular toxicity developed under the
auspices of the ESC Committee for Practice
Guidelines**

**The Task Force for cancer treatments and cardiovascular toxicity of
the European Society of Cardiology (ESC)**

Table I Incidence of left ventricular dysfunction
associated with chemotherapy drugs¹⁰⁻²¹

Chemotherapy agents	Incidence (%)
Anthracyclines (dose dependent)	
Doxorubicin (Adriamycin)	
400 mg/m ²	3-5
550 mg/m ²	7-26
700 mg/m ²	18-48

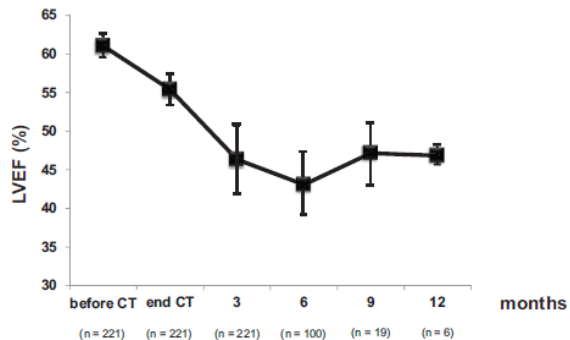
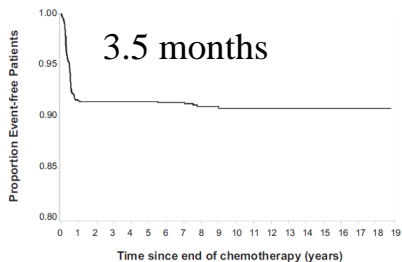


Heart Failure

Early Detection of Anthracycline Cardiotoxicity and Improvement With Heart Failure Therapy

Daniela Cardinale, MD, PhD, FESC; Alessandro Colombo, MD; Giulia Bacchiani, MD;
Ines Tedeschi, MSc; Carlo A. Meroni, MD; Fabrizio Veglia, PhD; Maurizio Civelli, MD;
Giuseppina Lamantia, MD; Nicola Colombo, MD; Giuseppe Curigliano, MD, PhD;
Cesare Fiorentini, MD; Carlo M. Cipolla, MD

Circulation. 2015;131:1981-1988.





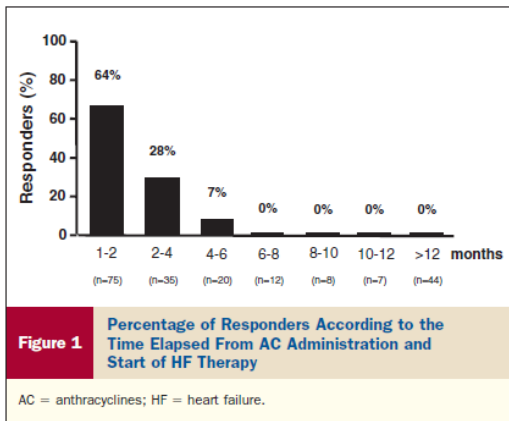
Anthracycline-Induced Cardiomyopathy

CME

Clinical Relevance and Response to Pharmacologic Therapy

Daniela Cardinale, MD, PhD,* Alessandro Colombo, MD,* Giuseppina Lamantia, MD,*
Nicola Colombo, MD,* Maurizio Civelli, MD,* Gaia De Giacomi, MD,* Mara Rubino, MD,†
Fabrizio Veglia, PhD,† Cesare Fiorentini, MD,† Carlo M. Cipolla, MD*

Milan, Italy







ESC
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of Cardiology

ESC CPG POSITION PAPER

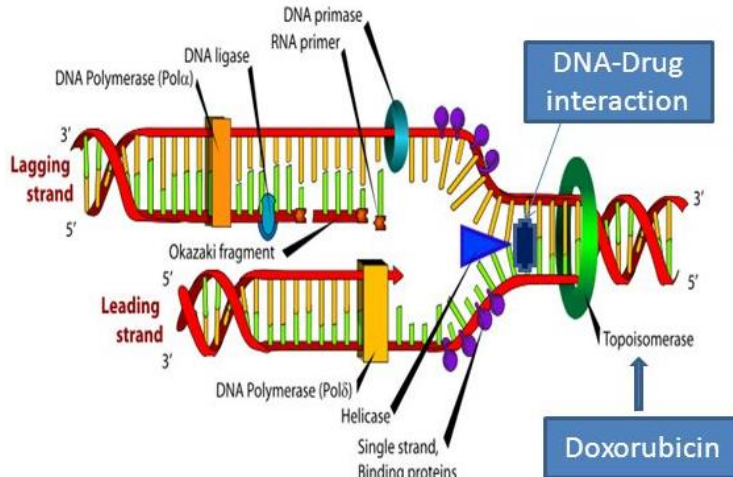
2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

Table 6 Proposed diagnostic tools for the detection of cardiotoxicity

Technique	Currently available diagnostic criteria	Advantages	Major limitations
Echocardiography: - 3D-based LVEF - 2D Simpson's LVEF - GLS	<ul style="list-style-type: none"> LVEF: >10 percentage points decrease to a value below the LLN suggests cardiotoxicity. GLS: >15% relative percentage reduction from baseline may suggest risk of cardiotoxicity. 	<ul style="list-style-type: none"> Wide availability. Lack of radiation. Assessment of haemodynamics and other cardiac structures. 	<ul style="list-style-type: none"> Inter-observer variability. Image quality. GLS: inter-vendor variability, technical requirements.
Nuclear cardiac imaging (MUGA)	<ul style="list-style-type: none"> >10 percentage points decrease in LVEF with a value <50% identifies patients with cardiotoxicity. 	<ul style="list-style-type: none"> Reproducibility. 	<ul style="list-style-type: none"> Cumulative radiation exposure. Limited structural and functional information on other cardiac structures.
Cardiac magnetic resonance	<ul style="list-style-type: none"> Typically used if other techniques are non-diagnostic or to confirm the presence of LV dysfunction if LVEF is borderlines. 	<ul style="list-style-type: none"> Accuracy, reproducibility. Detection of diffuse myocardial fibrosis using T1/T2 mapping and ECVF evaluation. 	<ul style="list-style-type: none"> Limited availability. Patient's adaptation (claustrophobia, breath hold, long acquisition times).
Cardiac biomarkers: - Troponin I - High-sensitivity Troponin I - BNP - NT-proBNP	<ul style="list-style-type: none"> A rise identifies patients receiving anthracyclines who may benefit from ACE-Is. Routine role of BNP and NT-proBNP in surveillance of high-risk patient needs further investigation. 	<ul style="list-style-type: none"> Accuracy, reproducibility. Wide availability. High-sensitivity. 	<ul style="list-style-type: none"> Insufficient evidence to establish the significance of subtle rises. Variations with different assays. Role for routine surveillance not clearly established.

MECHANISM?



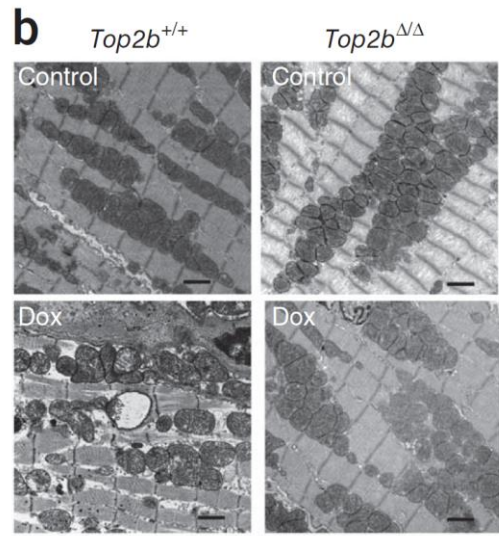
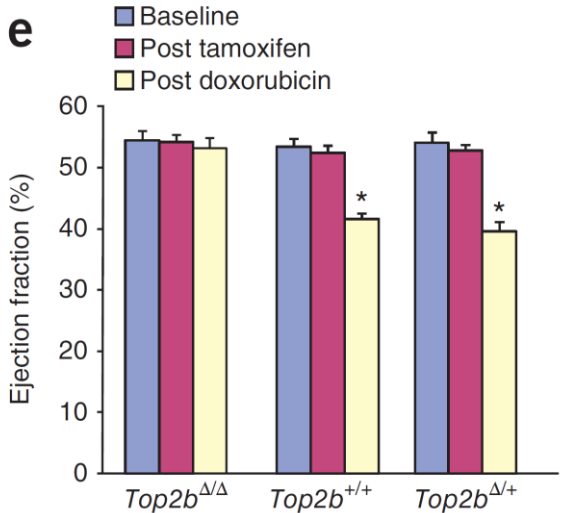
Topoisomerase 2 α highly expressed in tumour cells
Cardiomyocytes barely replicates

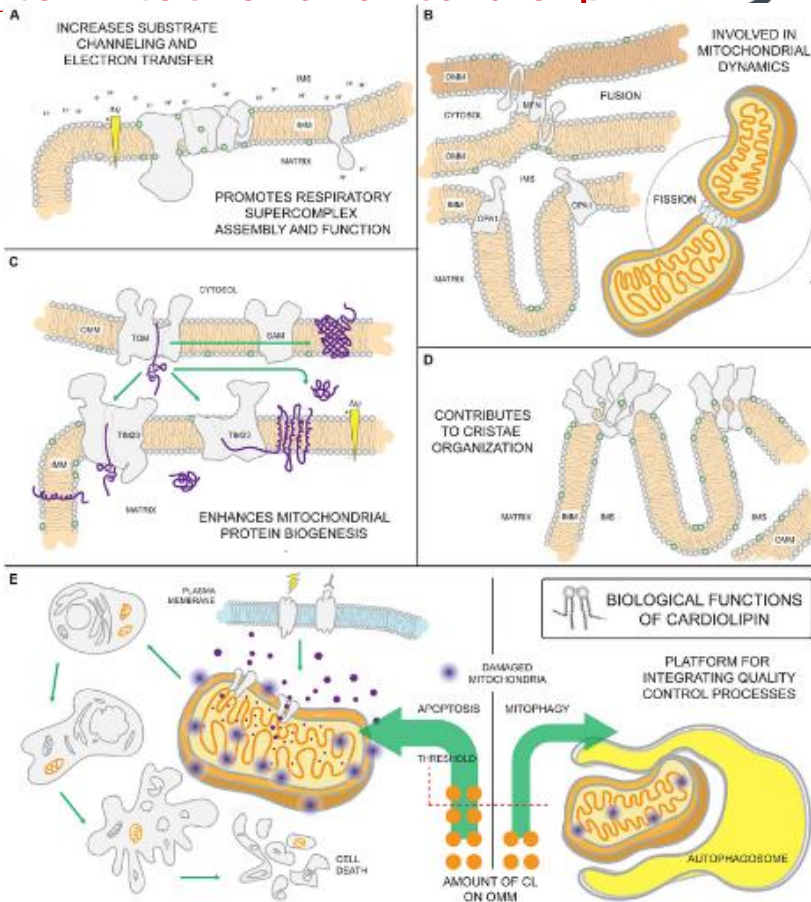
NATURE MEDICINE VOLUME 18 | NUMBER 11 | NOVEMBER 2012

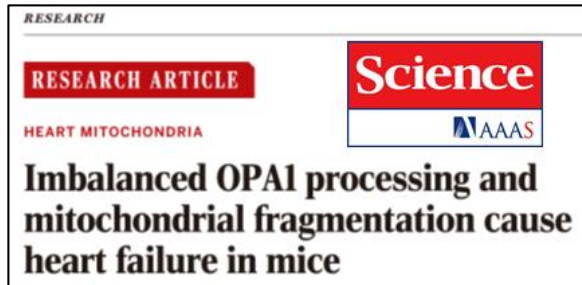
Identification of the molecular basis of doxorubicin-induced cardiotoxicity

nature
medicine

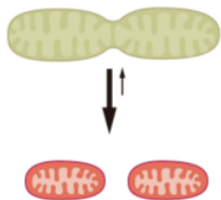
Sui Zhang¹, Xiaobing Liu^{2,3}, Tasneem Bawa-Khalfe¹, Long-Sheng Lu²,
Yi Lisa Lyu⁴, Leroy F Liu⁴ & Edward TH Yeh^{1,2}



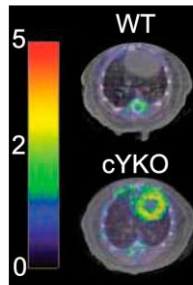




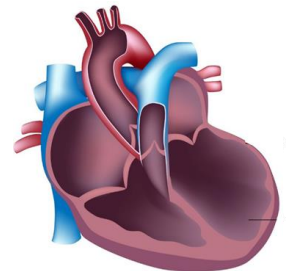
Wai et al *Science* 2015



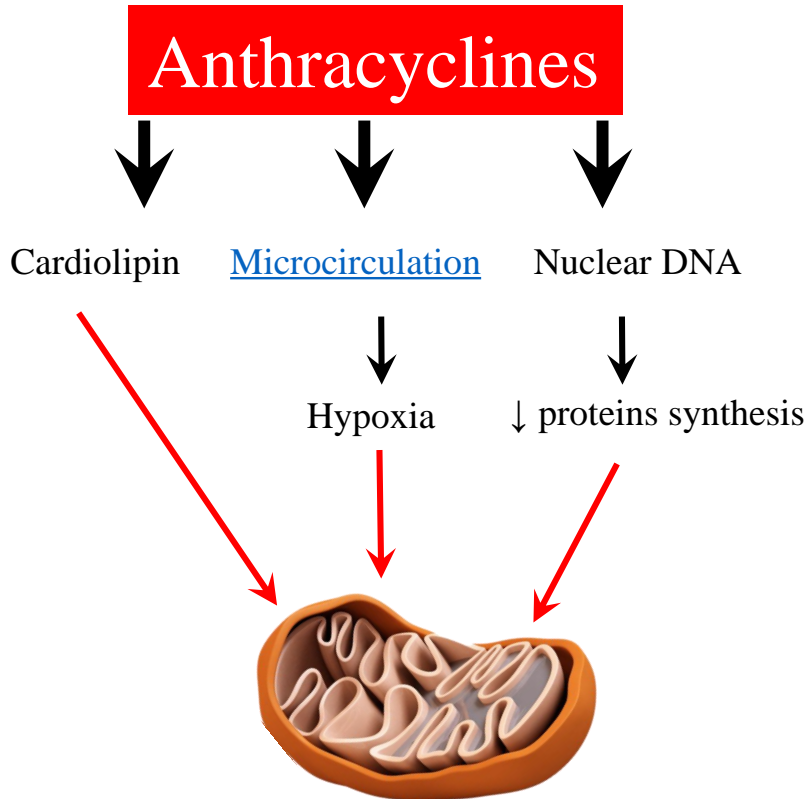
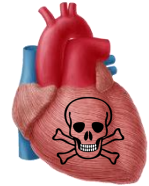
Altered mitochondrial dynamics



Metabolic Reprogramming



DCM; Heart failure



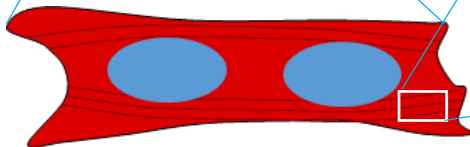
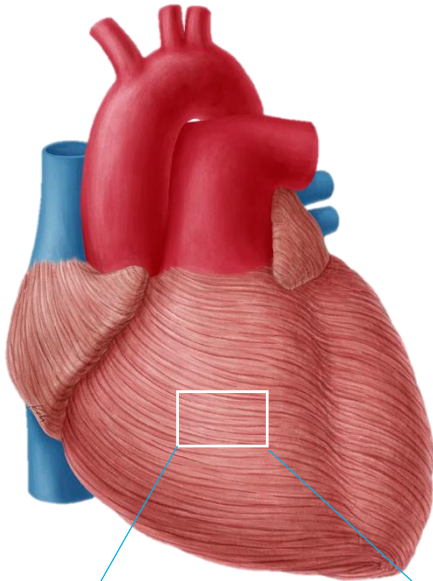


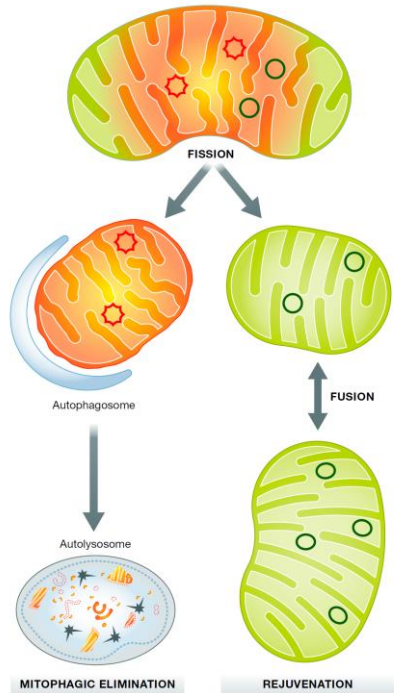
Pump 7000 L /day.

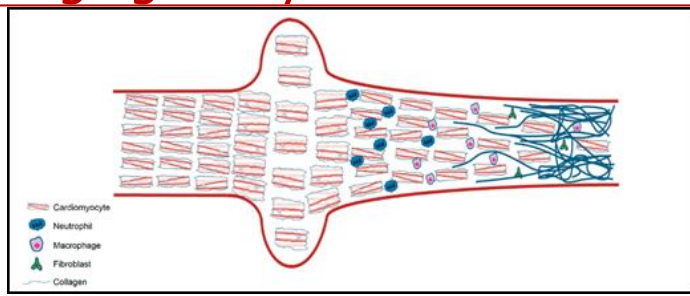
6 kg of ATP per day

3×10^9 beats in a life

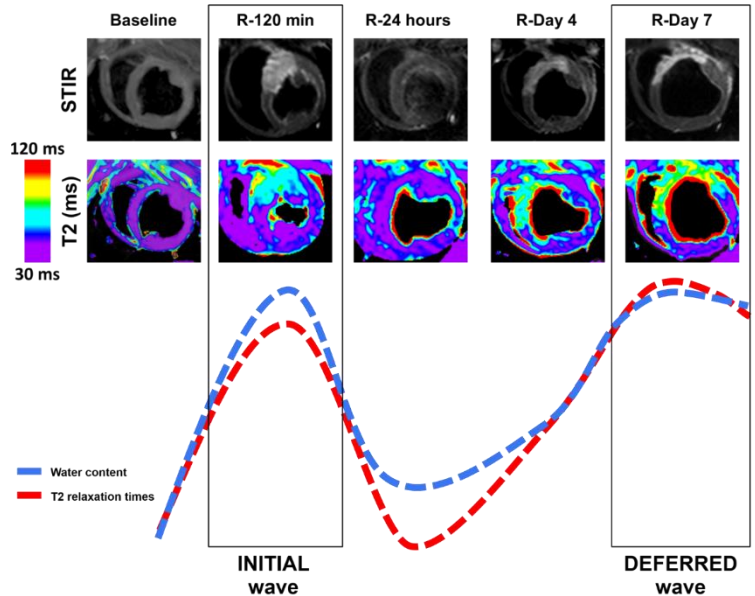
Cardiomyocytes barely replicate

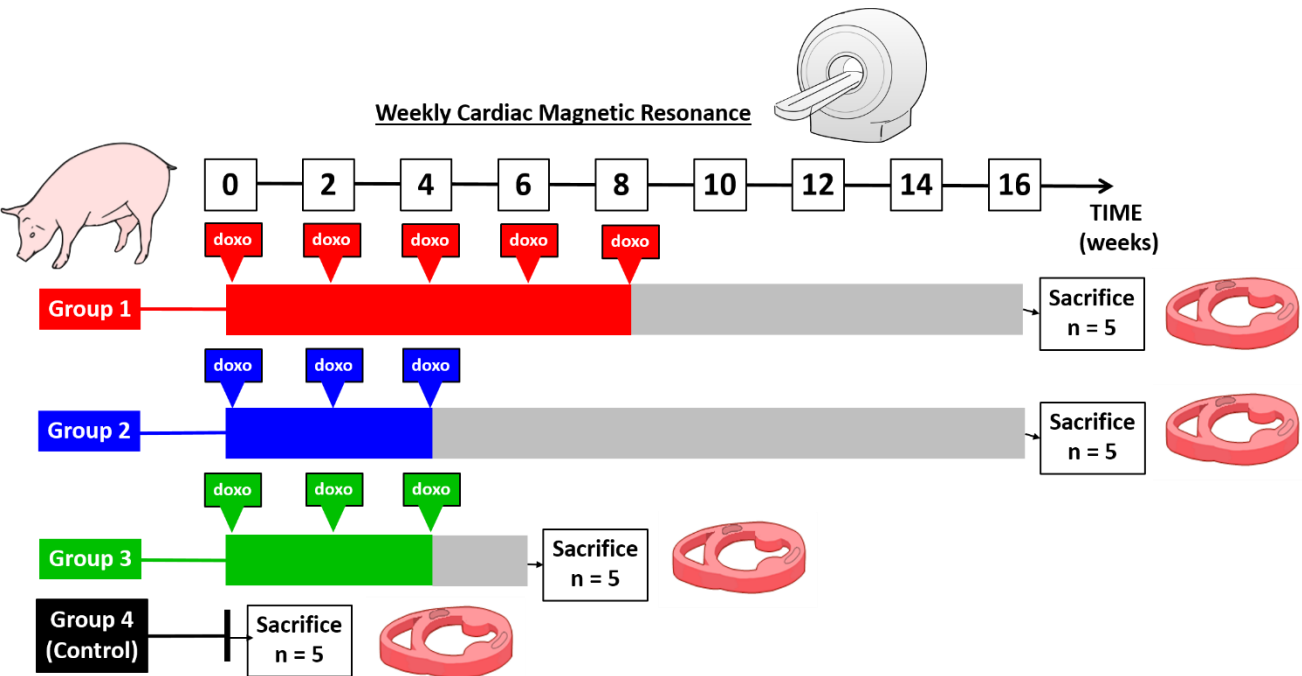


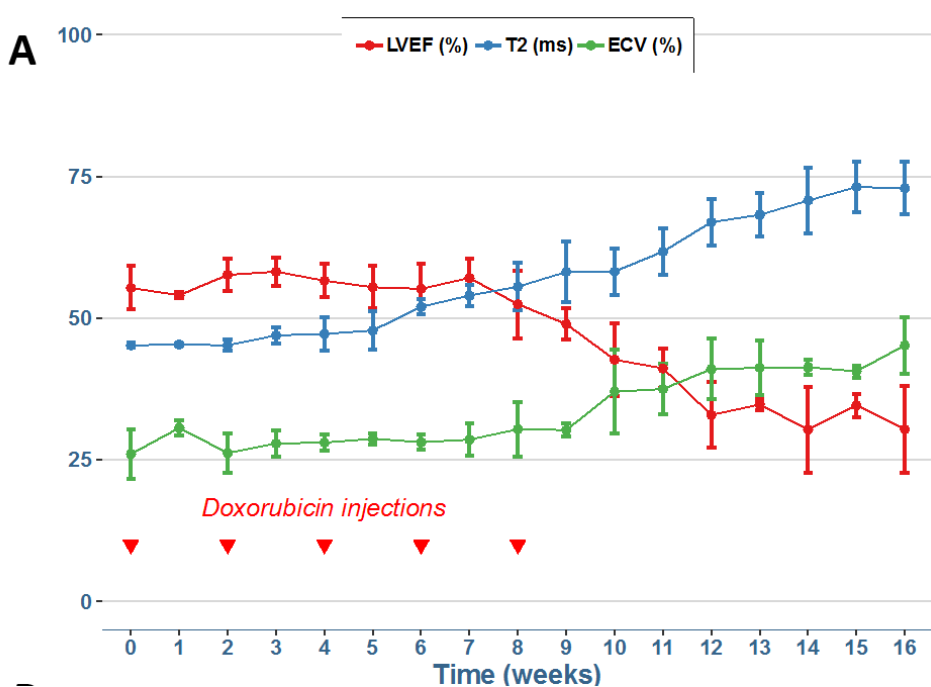
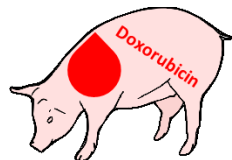


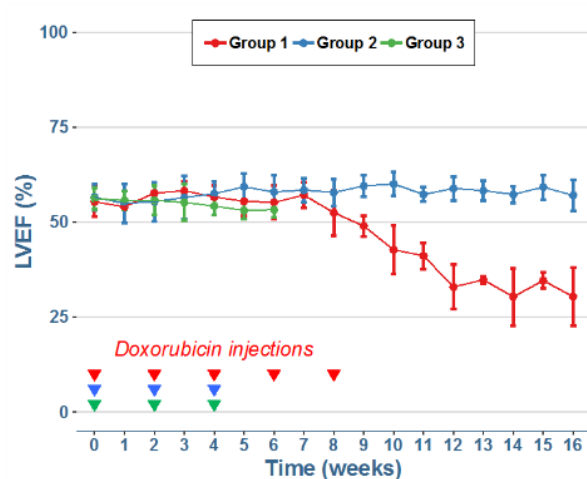
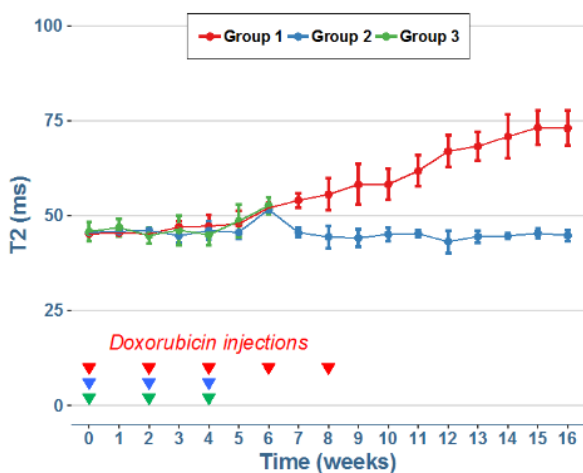


J Am Coll Cardiol 2015;65:315-23
J Am Coll Cardiol 2015; 66:816-28
Circulation. 2017; 136:1288-1300
Circ Res. 2017 121:439-450

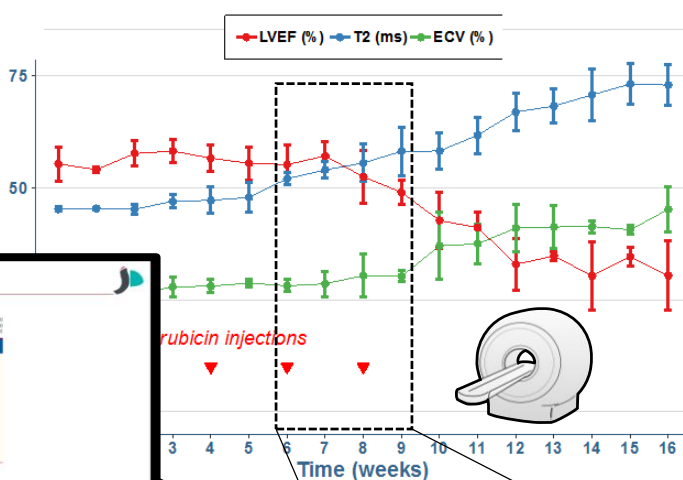
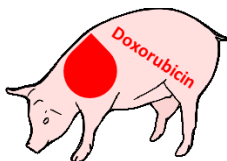








Galán-Arriola et al *J Am Coll Cardiol* 2019



Early diagnosis is critical

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Heart Failure

Anthracycline-Induced Cardiomyopathy

Clinical Relevance and Response to Pharmacologic Therapy

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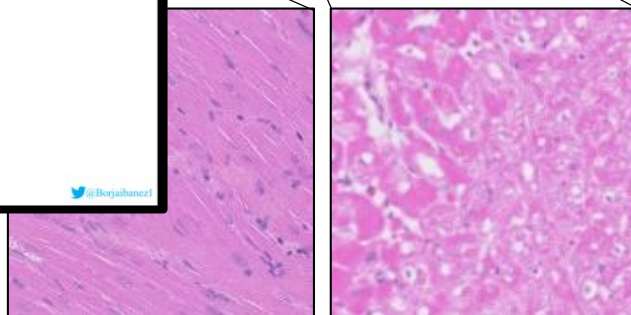
Time Elapsed (months)	Percentage of Responders (%)
1-2	64%
2-4	28%
4-6	7%
6-8	0%
8-10	0%
10-12	0%
>12	0%

3.5 months

Figure 1. Percentage of Responders According to the Time Elapsed From AC Administration and Start of HF Therapy.

AC = anthracycline; HF = heart failure.

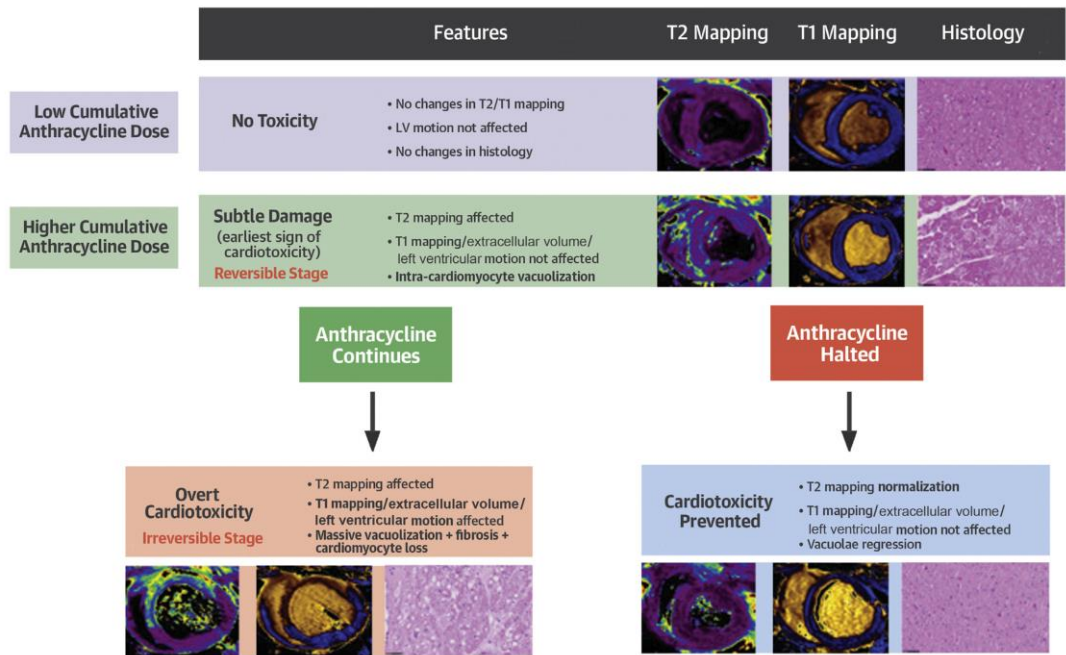
@Dojinbanczi





CENTRAL ILLUSTRATION Serial CMR Evaluations During On-(Anthracycline) Treatment Allows Very Early Detection of Subtle Myocardial Damage

Serial Cardiac Magnetic Resonance During On-Anthracycline Treatment





- ✓ Anthracyclines are very effective anti cancer drugs.
Dose limited by cardiotoxicity (frequent)
- ✓ Current Rx are unspecific and more effective if initiated early
- ✓ Current diagnostic algorithms are poor (unspecific)
- ✓ Mechanisms of anthracycline cardiotox involve mitochondria
- ✓ Intra-cardiomyocyte edema is the earliest cardiotox marker,
(mapping CMR can visualize this → much earlier)
- ✓ Diagnosis and therapy based on pathophysiology

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FUNDACIÓN
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Atrévete a descubrir.
Atrévete a equivocarte

