Risonanza magnetica cardiaca: è possibile un ruolo nella identificazione di cardiotossicità da chemioterapici ?

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Milan, October 16th 2012

BACKGROUND

The use of multimodality treatment, including surgery, chemotherapy, radiotherapy, and 'targeted therapies', has significantly decreased the mortality related to cancer.

Because more and more oncological patients have a long life expectancy, however, treatment-related comorbidity and its prevention become more and more an issue for cancer survivors.

Cardiac toxicity results in myocardial dysfunction which can become apparent immediately or long after the end of therapy and often is irreversible.

Awareness of the need to balance the goals of the oncologist (to maximally kill cancer cells or inhibit tumor cell division, vascularization, and spread) with those of the cardiologist (to protect the heart from damage related to the tumor or its treatment) was an entity by the mid-1980s.

The recognition of cardiac dysfunction as a consequence of cancer treatment became crucial in the management of these patients

Cardiovascular Toxicity: risk factors

PATIENT-RELATED FACTORS

- age
- presence of cardiovascular risk factors or coexisting cardiac disease
- previous mediastinal irradiation

TREATMENT-RELATED FACTORS

- type of drug
- cumulative dose and schedule of administration
- combination of potentially cardiotoxic drugs
- association with radiotherapy

	Incidence	Reversible
Anthracycline* 400 mg/m2 550 mg/m2 700 mg/m2	 3% 7% 18%	No
Trastuzmab*	5% - 15%#	Yes

*irradiation: injuring capillary endothelial cells
#: previous Anthracycline

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Cardiovascular Toxicity

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JOURNAL OF CLINICAL ON

Late Card

Daniel J. Lenihan

Table 1. Causes of Selected Common Late Cardiovascular Conditions in Cancer Survivors

Condition and Causes
Vascular
Atherosclerosis
Hypertension
Arterial thrombosis
Deep venous thrombosis/pulmonary embolus
Structural
Valvular heart disease
Pericardial effusion
Pericardial constriction
Conduction system disease
Myocardial dysfunction and heart failure
Anthracyclines
Trastuzumab
Antiangiogenic therapy
Radiation therapy
Restrictive cardiomyopathy

Cardiovascular Toxicity

Table 2. Practical Screening Tools for Cardiovascular Disease in Cancer Survivors

Test	Timing Interval
Fasting lipid profile	Yearly, if abnormal
TSH (especially with neck irradiation)	Every several years, unless symptoms occur
Self-measurement of blood pressure	Several times per week in high-risk patients
Careful history and physical examination	At least yearly
Echocardiography (especially with any mediastinal irradiation or previous cardiotoxic chemotherapy)	Every 1-2 years in high-risk patients
Carotid ultrasound (particularly with mantle or neck irradiation)	Every 2 years in high-risk patients
Cardiac biomarkers (troponin, BNP)	Every 1-2 years in high-risk patients, unless symptoms occur
ECG	At least once every 2-3 years

Abbreviations: BNP, B-type natriuretic peptide level; TSH, thyroid-stimulating hormone.

New potential biomarkers of cardiotoxicity: cythocrome C, microRNA

Novel Imaging technique: tissue Doppler, strain

OVERCOME (preventiOn of left Ventricular dysfunction with Enalapril and ca
tr
ar

MANTICOR (Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research) trial,92 evaluating a different ACE-I, perindopril, and bisoprolol (BB) in the prevention of trastuzumab-mediated cardiotoxicity.

CARDIAC MAGNETIC RESONANCE

Circulation
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ACCF/ACR/AHA/NASCI/SCMR 2010 Expert Consensus Document on Cardiovascular Magnetic Resonance. A Report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents

W. Gregory Hundley, David A. Bluemke, J. Paul Finn, Scott D. Flamm, Mark A. Fogel, Matthias G. Friedrich, Vincent B. Ho, Michael Jerosch-Herold, Christopher M. Kramer, Warren J. Manning, Manesh Patel, Gerald M. Pohost, Arthur E. Stillman, Richard D. White and Pamela K. Woodard

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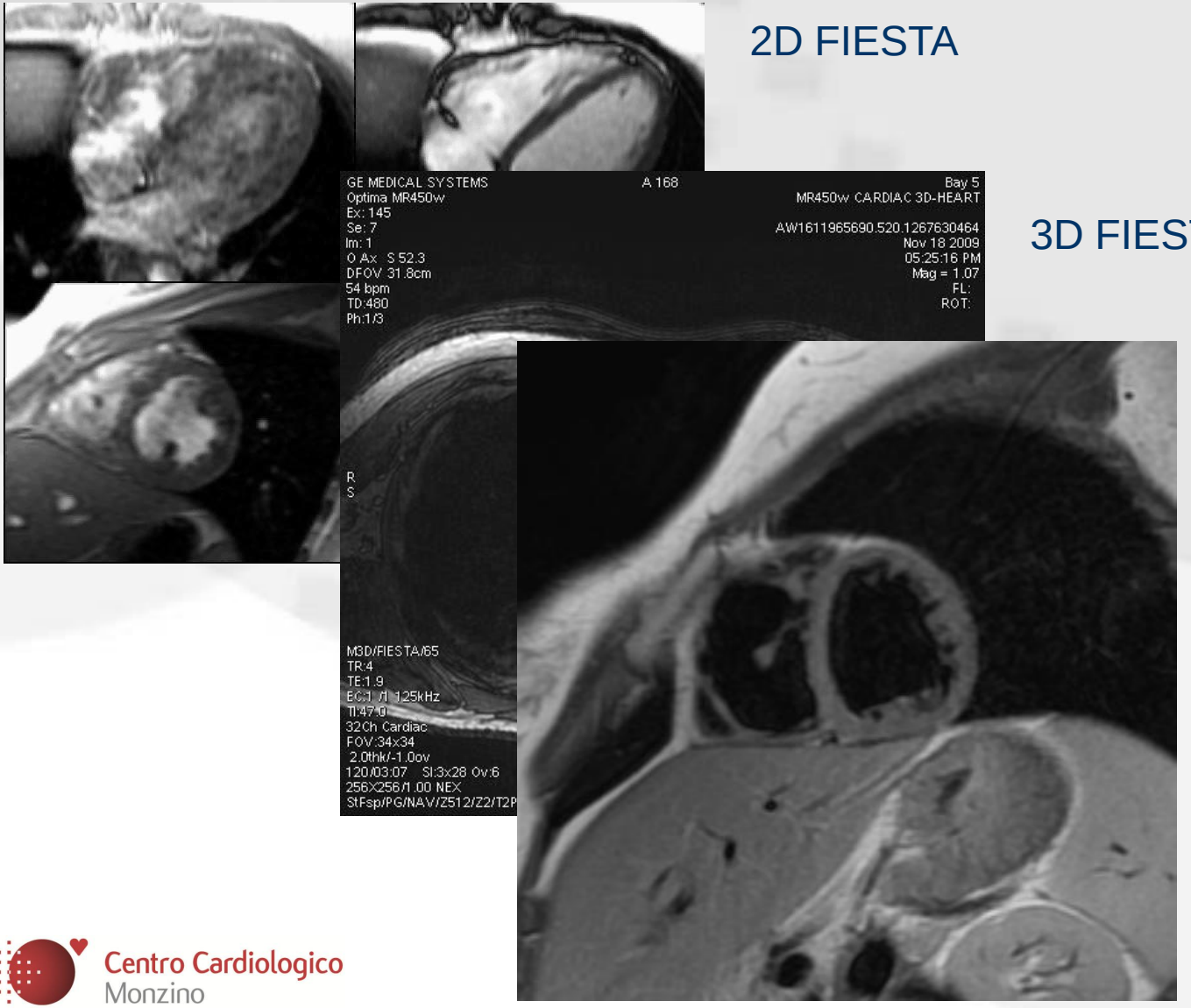
- ANATOMY and TISSUE CHARACTERIZATION
- FUNCTION and BLOOD FLOW
- PERFUSION
- LATE GADOLINIUM ENHANCEMENT

Cardiac Magnetic Resonane

Anatomy and Tissue Characterization



2D FIESTA

3D FIESTA

INVERSION RECOVERY
T1➔ mdc
T2➔edema

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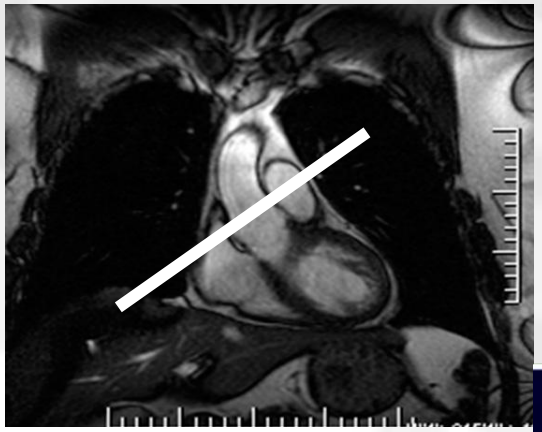
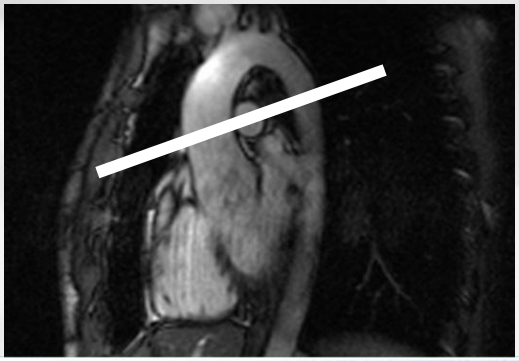
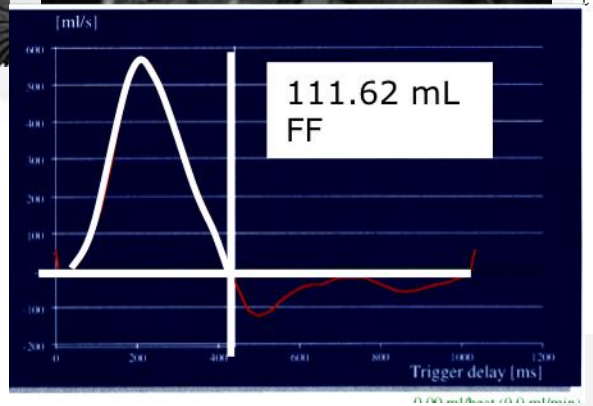
Cardiac Magnetic Resonane

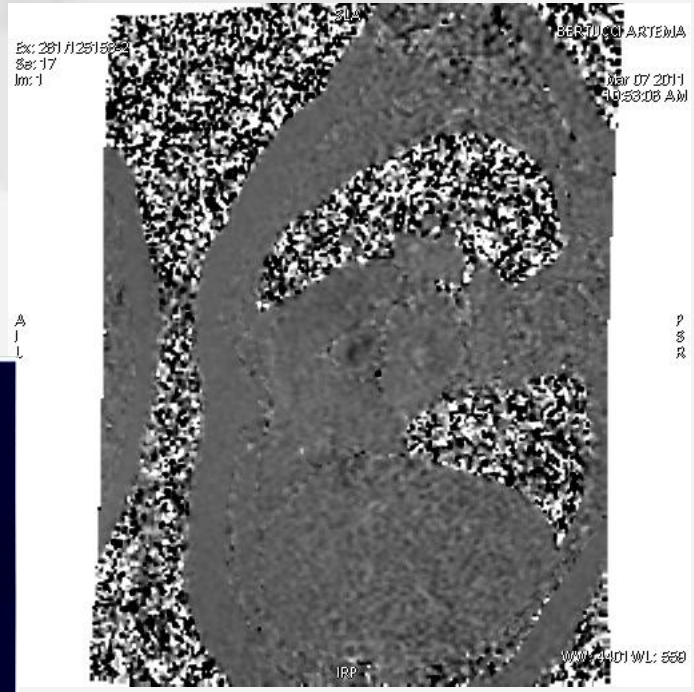
Flow

- In addition to the magnitude data used to generate cine CMR images of cardiac function, the phase data collected from the image acquisition can be used to measure velocity (Firmin DM Magn Reson Med 1990)



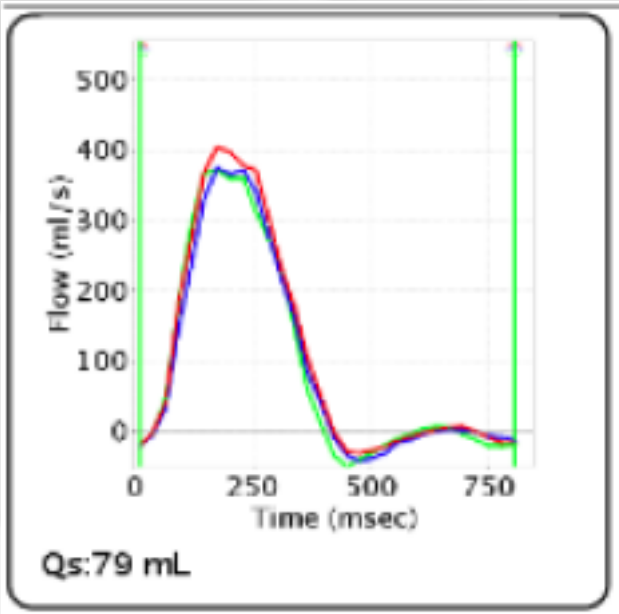




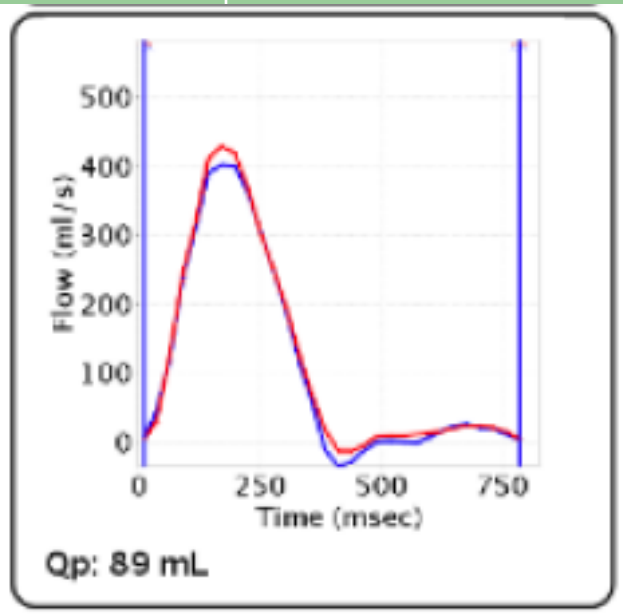


Cardiac Magnetic Resonane

Overall accuracy



	Echo	MRI (SI	Reduction
	1 cm		
	0.9 cm		
	6.3 cm		
	5.9 cm		
	301.1 ml	7.4	
	218.1 ml		
	28 %	6.5	
	154.4 ml/m²		
LV End-Systolic Vol Index	111.8 ml/m²	2.5	
Fractional Shortening	7 %		
Stroke Volume	83 ml		
Stroke Volume Index	42.6 ml/m²	6.4/9	97
Heart Rate		RV End-Diastolic Volume	135.8 ml
Cardiac Output		RV End-Systolic Volume	47.3 ml
Cardiac Index		RV Ejection Fraction	65 %
		RV Stroke Volume	88.5 ml
		RV End-Diastolic Vol Index	69.6 ml/m²
		RV End-Systolic Vol Index	24.3 ml/m²



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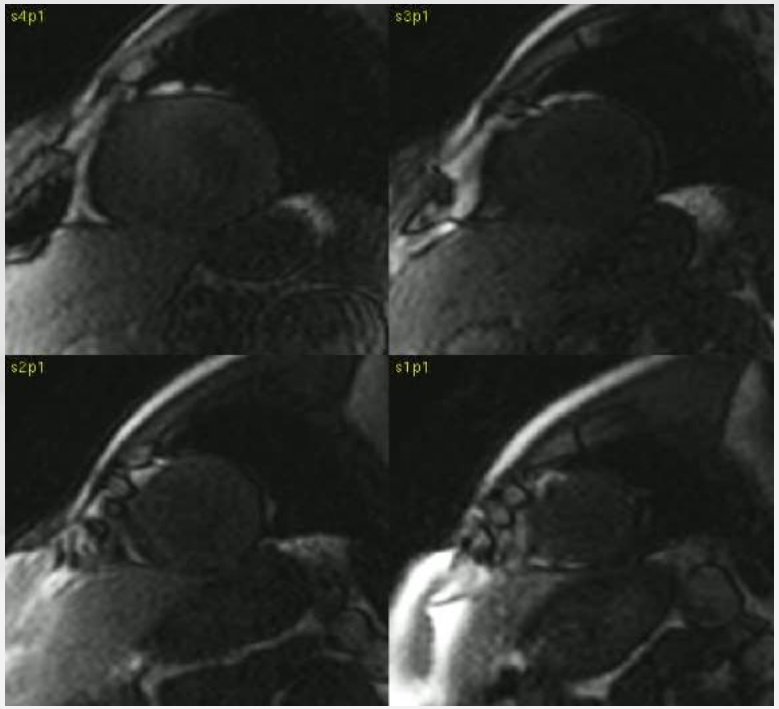
Cardiac Magnetic Resonane

Perfusion

FIESTA Time Course

Asset
Te 1.2ms TR 2.8ms flip°36
TI 119ms 0.5Nex 125kHz
FOV 40 128x128 thk 8mm
4 slices/1 R-R 60 phases
Rest phase : 20ml DTPA at 5ml



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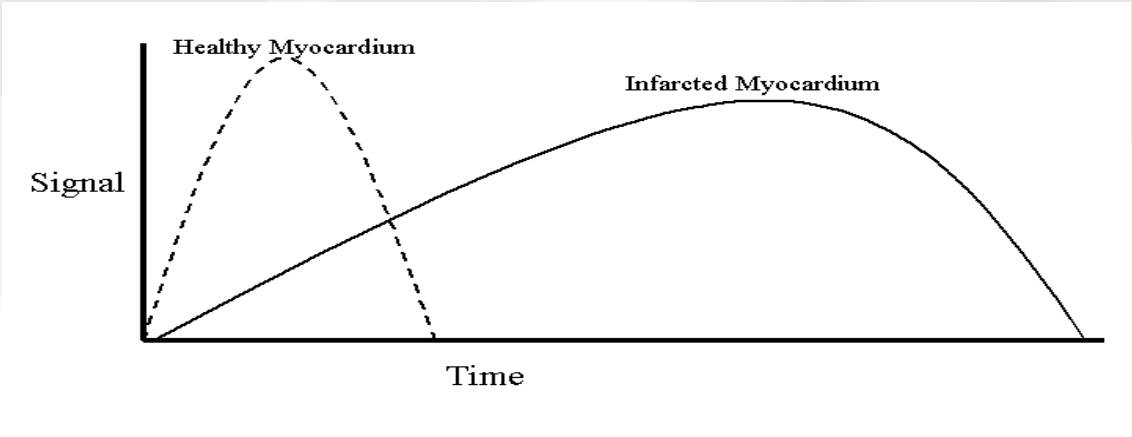
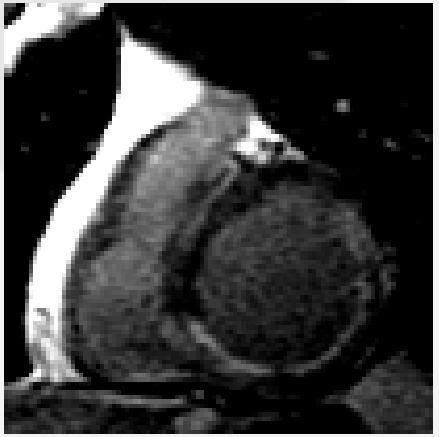
Cardiac Magnetic Resonane

Late Gadolimium Enhancement

Early after the first pass of Gd, a significant fraction of the injected Gd enters the interstitial space. Several minutes after intravenous administration of Gd, the larger volume of distribution available in necrotic or fibrotic myocardium results in a higher concentration of contrast agent than what is present in viable myocardium. This is typically referred to as "delayed (hyper)enhancement" or "late gadolinium enhancement" (LGE).





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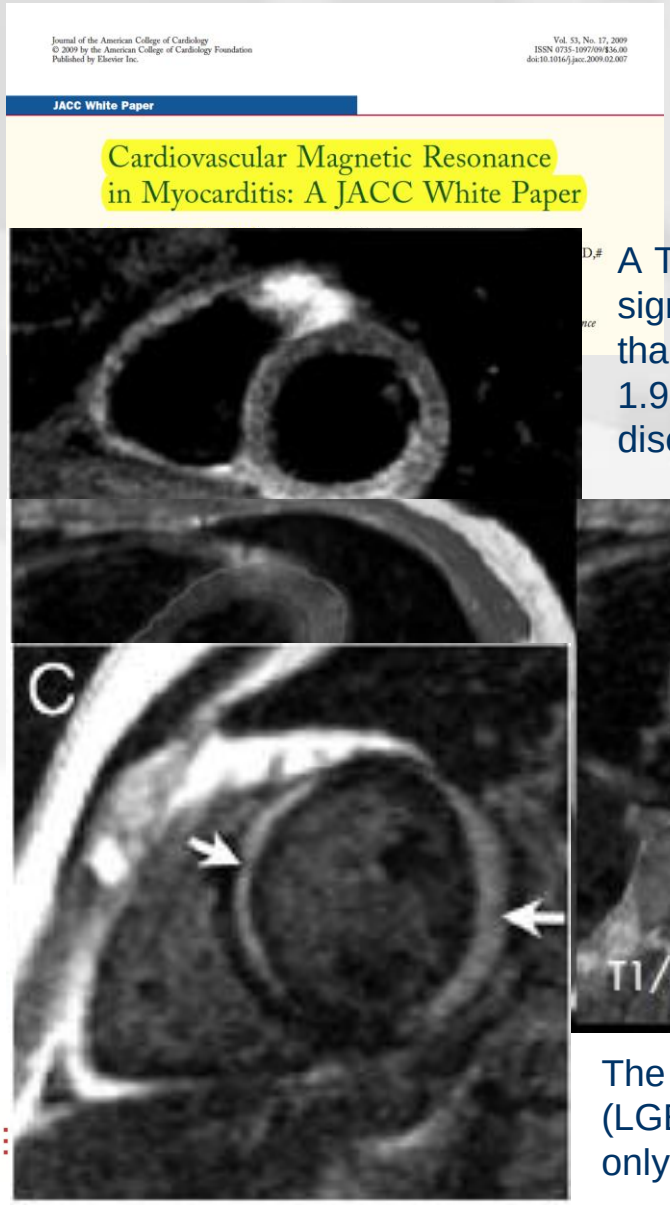
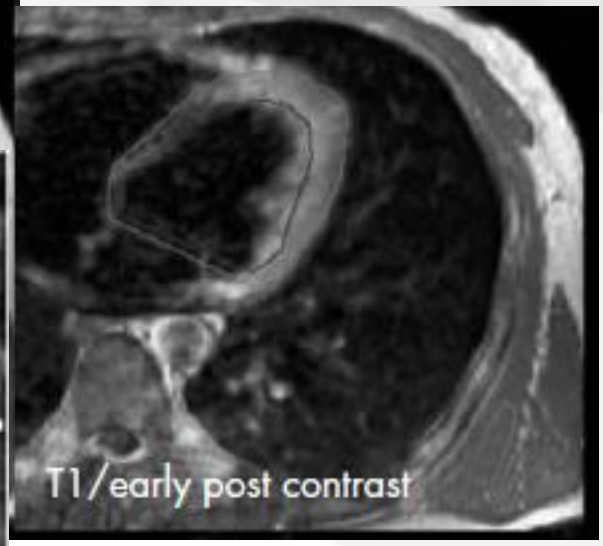
Cardiac Magnetic Resonane

Myocarditis



A T2-weighted triple inversion recovery pulse sequence showed a significantly higher global myocardial signal intensity in patients than in volunteers, although there was overlap. A cut-off value of 1.9 had a sensitivity of 84% and a specificity of 74% to identify the disease.



A T1-weighted spin echo before and shortly after contrast injection yielded a significantly higher global myocardial relative enhancement in patients than in volunteers. A cut-off value of 4.0 had a sensitivity of 80% and a specificity of 73% to identify myocarditis.

The sensitivity of a inversion recovery gradient echo pulse sequence (LGE sequence) started 10 minutes after contrast injection was lower at only 44% but the specificity was high (100%).

Cardiovascular Toxicity

1. Cardiac Magnetic Resonance: volume and EF

VOLUME 30 · NUMBER 23 · AUGUST 10 2012
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Screening Adult Survivors of Childhood Cancer for Cardiomyopathy: Comparison of Echocardiography and Cardiac Magnetic Resonance Imaging

Gregory T. Armstrong, Juan Carlos Plana, Nan Zhang, Deokumar Srivastava, Daniel M. Green, Kirsten K. Ness, F. Daniel Donovan, Monika L. Metzger, Alejandro Arevalo, Jean-Bernard Durand, Vijaya Joshi, Melissa M. Hudson, Leslie L. Robison, and Scott D. Flamm

Purpose

To compare two-dimensional (2D) echocardiography, the current method of screening for treatment-related cardiomyopathy recommended by the Children's Oncology Group Guidelines, to cardiac magnetic resonance (CMR) imaging, the reference standard for left ventricular (LV) function.

Patients and Methods

Cross-sectional, contemporaneous evaluation of LV structure and function by 2D and three-dimensional (3D) echocardiography and CMR imaging in 114 adult survivors of childhood cancer currently median age 39 years (range, 22 to 53 years) exposed to anthracycline chemotherapy and/or chest-directed radiation therapy.

Results

In this survivor population, 14% (n = 16) had an ejection fraction (EF) less than 50% by CMR. Survivors previously undiagnosed with cardiotoxicity (n = 108) had a high prevalence of EF (32%) and cardiac mass (48%) that were more than two standard deviations below the mean of normative CMR data. 2D echocardiography overestimated the mean EF of this population by 5%. Compared with CMR, 2D echocardiography (biplane method) had a sensitivity of 25% and a false-negative rate of 75% for detection of EF less than 50%, although 3D echocardiography had 53% and 47%, respectively. Twelve survivors (11%) had an EF less than 50% by CMR but were misclassified as ≥ 50% (range, 50% to 68%) by 2D echocardiography (biplane method). Detection of cardiomyopathy was improved (sensitivity, 75%) by using a higher 2D echocardiography cutoff (EF < 60%) to detect an EF less than 50% by the reference standard CMR.

Conclusion

CMR identified a high prevalence of cardiomyopathy among adult survivors previously undiagnosed with cardiac disease. 2D echocardiography demonstrated limited screening performance. In this high-risk population, survivors with an EF 50% to 59% by 2D echocardiography should be considered for comprehensive cardiac assessment, which may include CMR.

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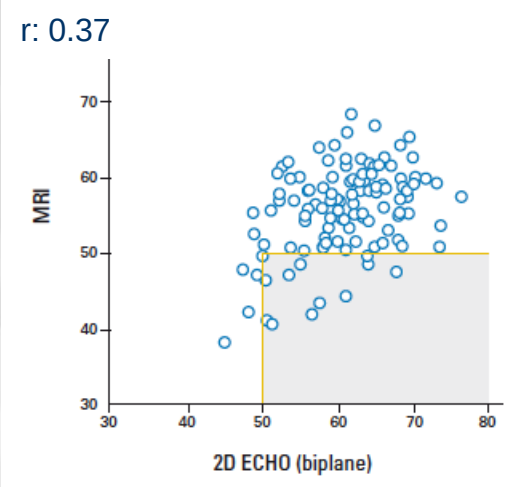
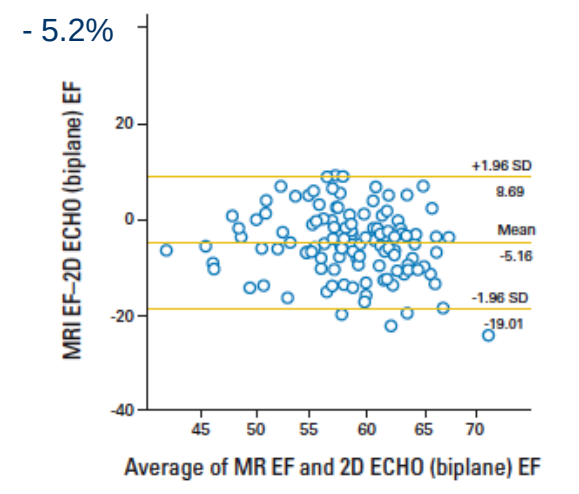
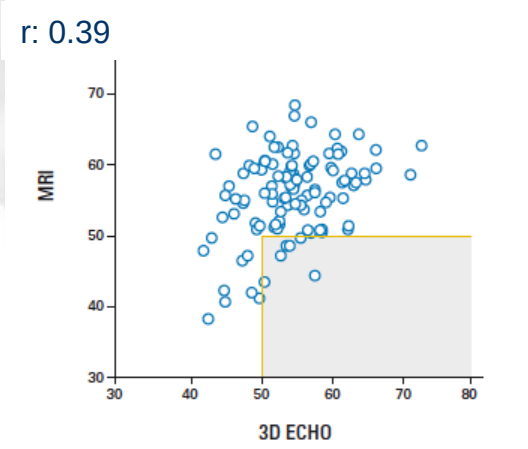
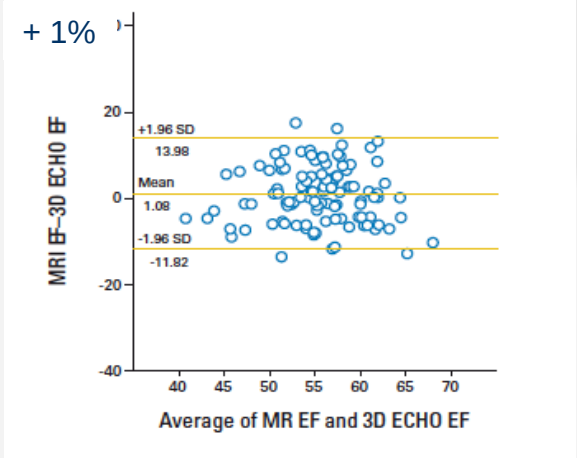
Cardiovascular Toxicity

1. Cardiac Magnetic Resonance: volume and EF









Pearson's Correlation and Bland-Altman plots for agreement of cardiac magnetic resonance imaging (MRI) with 2D and 3D Echo for assessment of ejection fraction (EF). SD, standard deviation.

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Cardiovascular Toxicity

1. Cardiac Magnetic Resonance: volume and EF

Table 3. Screening Performance of Echocardiogram Compared With CMR for Detection of an EF < 50%

Variable	3D Echocardiography		2D Echocardiography			
			Biplane		Apical 4-Chamber	Teichholz
	No.	%	No.	%	No.	No.	%
Patients with EF < 50%*							
Sensitivity							29
Specificity							79
False-negative rate							71
False-positive rate							21
Positive predictive value							17
Negative predictive value							88

Abbreviations: 2D, two-dimensi
*Frequency of patients for a gi

screening evaluation. On the basis of our data, survivors with 2D echocardiography (biplane method) EF values greater than 60% can be reasonably certain to have normal cardiac function. In addition, use of a 2D echocardiography cutoff for referral to less than 60% EF (as opposed to < 50% with the biplane method) improved sensitivity (75% sensitive) for detection of a CMR EF of less than 50%. Thus, for this high-risk population, previously exposed to cardiotoxic therapy, consideration should be given to referring survivors with an EF of 50% to 59% by 2D echocardiography for comprehensive cardiology assessment that includes cardiac history, symptom index and examination, biomarker assessment, consideration of CMR, functional assessment by treadmill testing, and possibly medical therapy to prevent progression of disease. Future studies should consider the use of intravenous

Cardiovascular Toxicity

2. Cardiac Magnetic Resonance: LV mass

Left Ventricular Mass in Patients With Cardiomyopathy After Treatment With Anthracyclines

Tomas G. Neilan, MD[a,b,*], Otavio R. Coelho-Filho, MD, MPH[a], Diego Pena-Herrera[a], Ravi V. Shah, MD[a,b], Michael Jerosch-Herold, PhD[c], Sanjeev A. Francis, MD[b], Javid Moslehi, MD[a,d], and Raymond Y. Kwong, MD, MPH[a]

We aimed to describe the cardiac magnetic resonance (CMR) findings and determine the prognostic variables in patients with a cardiomyopathy after treatment with anthracyclines. CMR imaging was performed in 91 patients (58% men, mean age 43 ± 18 years, and mean anthracycline dose of 276 ± 82 mg/m^2) with a reduced ejection fraction after anthracycline-based chemotherapy. Major adverse cardiovascular events were defined as cardiovascular death, appropriate implantable cardioverter-defibrillator therapy, and admission for decompensated heart failure. Patients presented a median of 88 months (interquartile range 37 to 138) after chemotherapy and were followed for 27 months (interquartile range 22 to 38). Late gadolinium enhancement was an uncommon finding (5 patients, 6%) despite a reduced ejection fraction (36 ± 8%). An inverse association was found between the anthracycline dose and the indexed left ventricular (LV) mass by CMR ($r = -0.67$, $p < 0.001$). A total of 52 adverse cardiac events occurred (event rate of 22%/year). When the patients were grouped according to the presence or absence of a major adverse cardiovascular event, the indexed LV mass and glomerular filtration rate were lower and the anthracycline dose was greater among the patients who experienced an adverse event. In a multivariate model, the indexed LV mass demonstrated the strongest association with major adverse cardiovascular events (hazard ratio 0.89, chi-square 26, $p < 0.001$). In conclusion, myocardial scar by late gadolinium enhancement-CMR is infrequent in patients with anthracycline-cardiomyopathy despite a reduced ejection fraction, the event rate in patients with established anthracycline-cardiotoxicity is high, and indexed LV mass by CMR imaging is a predictor of adverse cardiovascular events. © 2012 Elsevier Inc. All rights reserved. (Am J Cardiol 2012;xx:xxx)

Cardiovascular Toxicity

2. Cardiac Magnetic Resonance: LV mass

Table 2
Imaging findings stratified by major adverse cardiac events (MACE)

Variable	Cohort (n = 91)	MACE		p Value
		Yes (n = 52)	No (n = 39)	
Echocardiography				
Left ventricular ejection fraction (%)	35 ± 8	36 ± 9	35 ± 7	0.61
Left ventricular internal dimensions in diastole (mm)	49 ± 6	49 ± 5	49 ± 7	0.95
Estimated pulmonary artery systolic pressure (mm Hg)	33 ± 10	33 ± 10	33 ± 9	0.98
Left ventricular mass index (g/m^2)	78 ± 18	78 ± 18	78 ± 17	0.97
Cardiac magnetic resonance				
Left ventricular end-diastolic volume (cm^3)	181 ± 48	186 ± 44	173 ± 52	0.23
Indexed left ventricular end-diastolic volume (ml/m^2)	92 ± 22	100 ± 23	89 ± 18	0.31
Left ventricular end-systolic volume (cm^3)	116 ± 34	118 ± 35	112 ± 32	0.42
Indexed left ventricular end-systolic volume (ml/m^2)	59 ± 17	61 ± 22	53 ± 14	0.16
Left ventricular ejection fraction (%)	36 ± 8	37 ± 7	35 ± 7	0.23
Left ventricular mass index (g/m^2)	60 ± 16	51 ± 5	71 ± 12	<0.0001
Right ventricular end-diastolic volume (cm^3)	154 ± 41	155 ± 41	154 ± 42	0.73
Indexed right ventricular end-diastolic (ml/m^2)	78 ± 18	80 ± 20	77 ± 16	0.41
Right ventricular end-systolic volume (cm^3)	84 ± 33	77 ± 32	82 ± 29	0.18
Indexed right ventricular end-systolic volume (ml/m^2)	43 ± 15	45 ± 15	41 ± 14	0.21
Right ventricular ejection fraction (%)	46 ± 12	44 ± 11	47 ± 11	0.25
Relative T_2-weighted signal intensity	1.6 ± 0.2	1.6 ± 0.2	1.5 ± 0.2	0.46
Late gadolinium enhancement	5 ± 6	3 ± 6	2 ± 5	0.88
Volume of late gadolinium enhancement* (% of mass)	7 ± 4	9 ± 5	4 ± 1	0.27

All data are presented as mean ± SD.
* Volume of LGE as percentage of total LV volume using 2 standard deviation (SD) method in patients identified with LGE.

Cardiovascular Toxicity

2. Cardiac Magnetic Resonance: LV mass

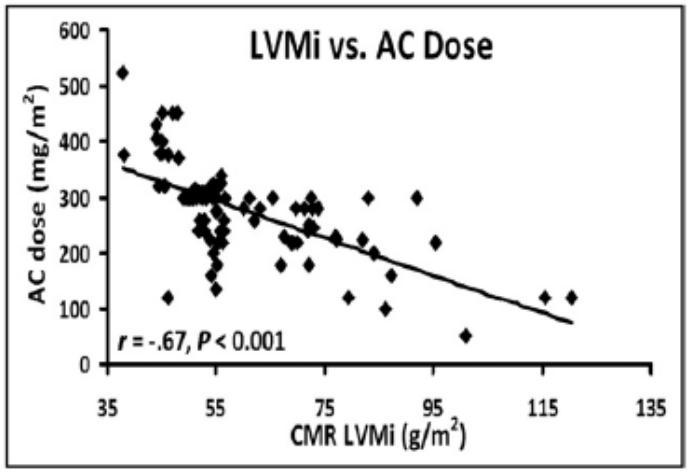
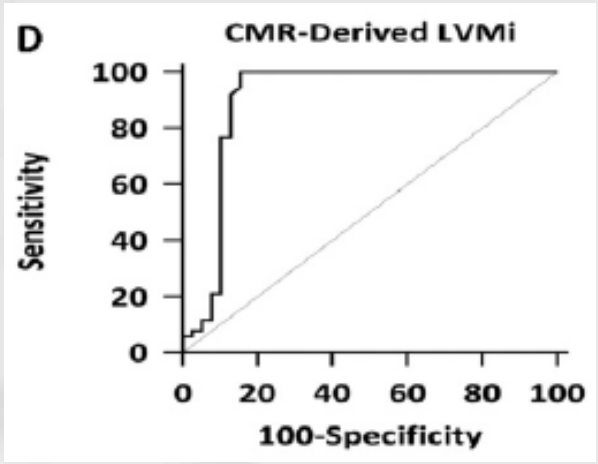
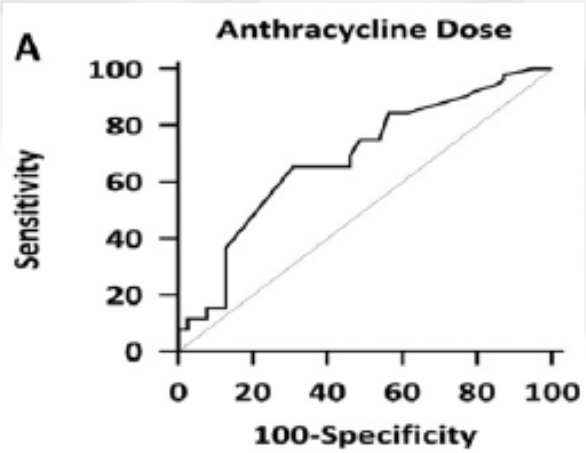


Figure 1. Association of LV mass derived by CMR with anthracycline dose ($r = -0.67$, $p < 0.001$).





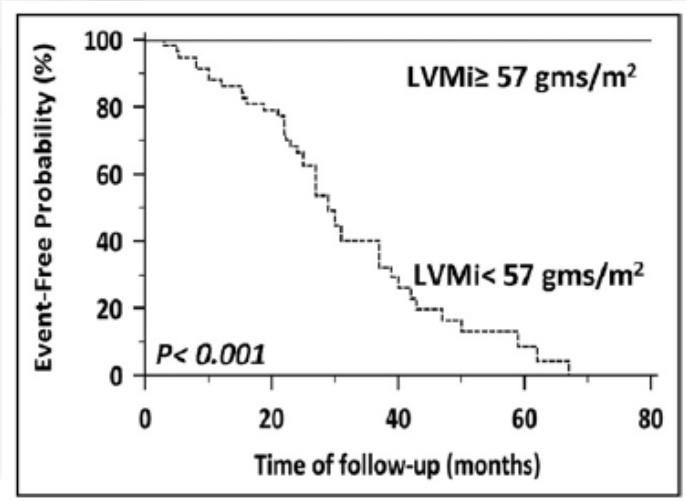


Figure 4. Receiver operating characteristic curve analysis revealed CMR-derived LV mass index (LVMi) of <57 g/m^2 provided sensitivity of 100% and specificity of 85% for prediction of adverse cardiac events. Kaplan-Meier curves displaying event-free probability according to LV mass index of ≥ 57 or <57 g/m^2.

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Cardiovascular Toxicity

3. Cardiac Magnetic Resonance: relative enhancement

Subclinical cardiotoxic effects of anthracyclines as assessed by magnetic resonance imaging—A pilot study

Ralf Wassmuth, MD,[a] Suzanne Lentzsch, MD,[b] Uta Erdbruegger, MD,[a] Jeanette Schulz-Menger, MD,[a] Bernd Doerken, MD,[b] Rainer Dietz, MD,[a] and Matthias G. Friedrich, MD[a] *Berlin, Germany*

Background Anthracyclines are potent chemotherapeutics burdened by their cardiotoxicity. So far no marker to detect early cardiac damage exists. We tested the ability of magnetic resonance imaging (MRI) to show early changes in myocardial signal and cardiac function after anthracycline therapy.

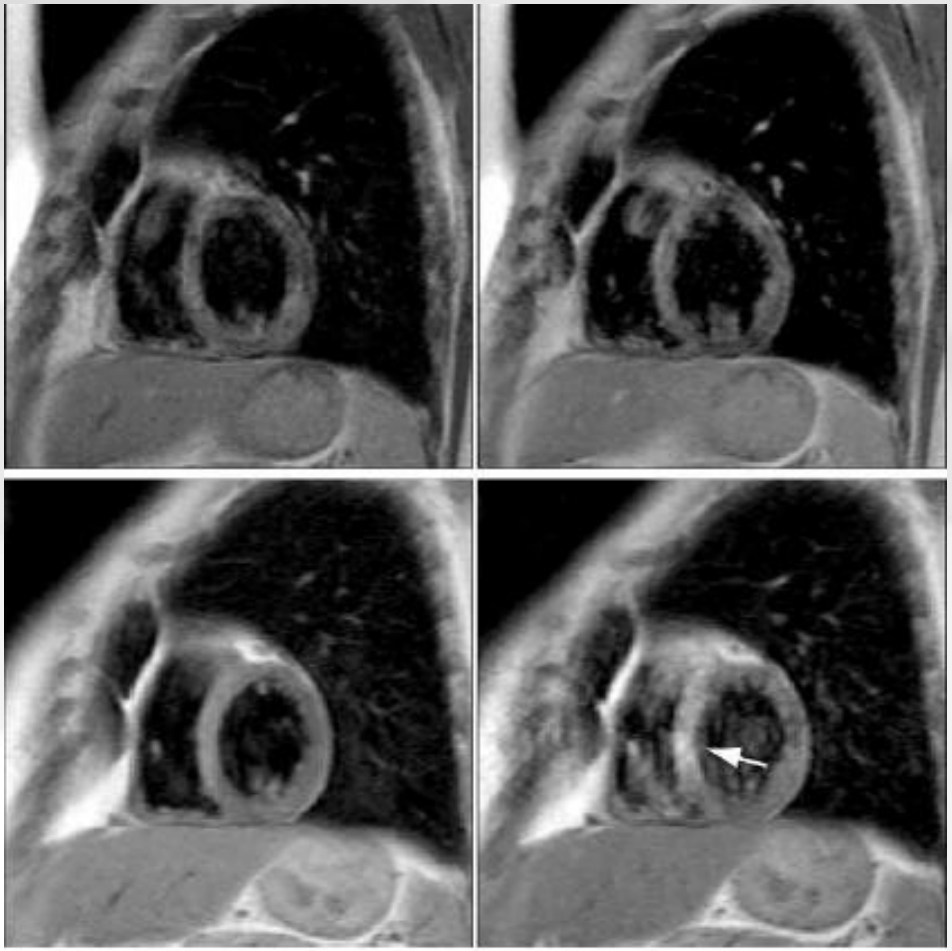
Methods Twenty-two patients with normal cardiac function were investigated by MRI before and 3 and 28 days after anthracycline chemotherapy. Contrast enhanced fast spin echo images were obtained to characterize myocardial enhancement. Left ventricular ejection fraction was measured by MRI in contiguous short-axis planes.

Results All patients remained clinically stable. Ejection fraction decreased from 67.8% ± 1.4% to 58.9% ± 1.9% after 28 days ($P < .05$). The relative myocardial contrast enhancement increased from 3.8 ± 0.4 to 6.9 ± 1.1 ($P < .01$). An increase of the enhancement of >5 on day 3 compared with baseline predicted a significant loss of ejection fraction at 28 days (67.5% ± 2.8% to 51.4% ± 5.6%, mean difference 16.1% ± 6.6%; $P < .05$), whereas an increase of +5 was not associated with a significant loss of ejection fraction (67.6% ± 1.7% to 62.5% ± 1.4%, mean difference 4.1% ± 2.6%; P not significant).

Conclusions MRI detects early changes in myocardial contrast and slightly deteriorating cardiac function in patients receiving anthracyclines. Larger patient cohorts and longer follow-up are needed to evaluate MRI as a predictor for anthracycline cardiotoxicity. (Am Heart J 2001;141:1007-13.)

Cardiovascular Toxicity

3. Cardiac Magnetic Resonance: relative enhancement



$$RE = \frac{\dfrac{(SI\ myocardium_{contrast} - SI\ myocardium_{plain})}{SI\ myocardium_{plain}}}{\dfrac{(SI\ skeletal\ muscle_{contrast} - SI\ skeletal\ muscle_{plain})}{SI\ skeletal\ muscle_{plain}}}$$

T1-weighted spin echo images before *(left) and after (right) administration of contrast media. Contrast enhanced* fast spin echo reveals increased myocardial enhancement 3 days after the onset of anthracycline therapy *(lower panel) in comparison to the baseline study (upper panel). Note prominent contrast enhancement in the septum (arrow).*

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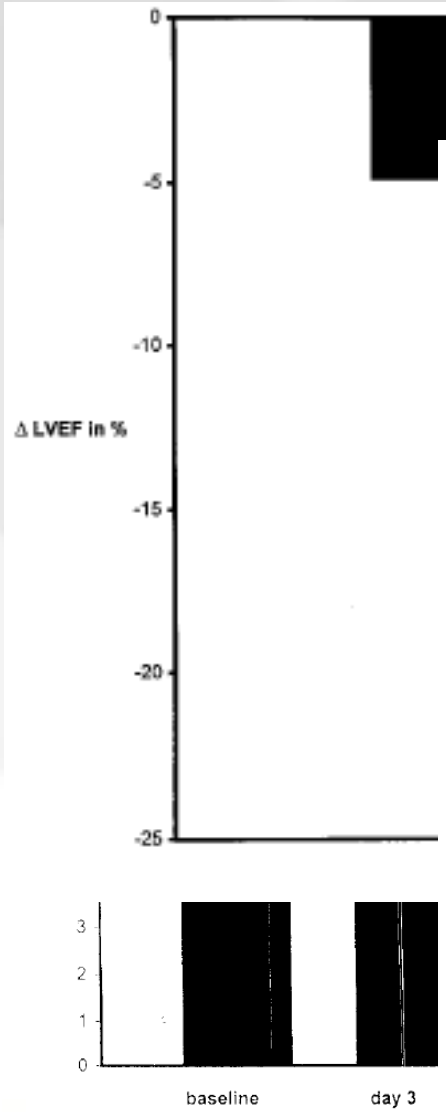
Cardiovascular Toxicity

3. Cardiac Magnetic Resonance: relative enhancement



In summary, MRI is able to detect functional and tissue changes in clinically stable patients undergoing potentially cardiotoxic drug therapy. An increase of contrast accumulation was observed early after onset of therapy in this longitudinal study, whereas ejection fraction decreased in our patients. Marked changes of contrast enhancement by the first course of chemotherapy were predictive for a significant loss of LVEF during the first month of treatment. Different from all other diagnostic modalities, our combined approach to both hyperemic response and loss of contractile function provides information on different aspects of cardiotoxicity within one session. Thus MRI may serve as a simple and noninvasive tool in the follow-up of these patients. Additional studies are necessary to confirm these findings in more patients and to further test the prognostic value of contrast-enhanced MRI.

After 28 days the patients with an the to or 5 arger n F – .6%) hose less F – %); *t*

Cardiovascular Toxicity

4. Cardiac Magnetic Resonance: late enhancement

Journal of Cardiovascular Magnetic Resonance

BioMed Central

Case report

Open Access

Delayed contrast enhancement cardiac magnetic resonance imaging in trastuzumab induced cardiomyopathy

Nazanin Fallah-Rad[1], Matthew Lytwyn[1], Tielan Fang[1], Iain Kirkpatrick[3] and Davinder S Jassal*[1,2,3]

Abstract

Background: Trastuzumab (Herceptin), an antagonist to the human epidermal growth factor 2 (HER2) receptor significantly decreases the rates of breast cancer recurrence and mortality by 50%. Despite therapeutic benefits, the risk of cardiotoxicity with trastuzumab ranges from 10–15% when administered sequentially following anthraycline chemotherapy. Little is known about the utility of cardiac magnetic resonance (CMR) in the assessment of trastuzumab mediated cardiomyopathy.

Methods and results: Between 2005–2006 inclusive, 160 breast cancer patients were identified at a single tertiary care oncology centre. Of the total population, 10 patients (mean age 40 ± 8 years) were identified with trastuzumab induced cardiomyopathy, based on a LVEF less than 40% on serial MUGA or echocardiography. CMR was performed in all patients to determine LV volumes, systolic function and evidence of late gadolinium enhancement (LGE). At the time of diagnosis of trastuzumab induced cardiomyopathy, the mean LVEF was 29 ± 4%. Subepicardial linear LGE was present in the lateral portion of the left ventricles in all 10 patients.

Conclusion: LGE-CMR is a novel way of detecting early changes in the myocardium due to trastuzumab induced cardiotoxicity.

Cardiovascular Toxicity

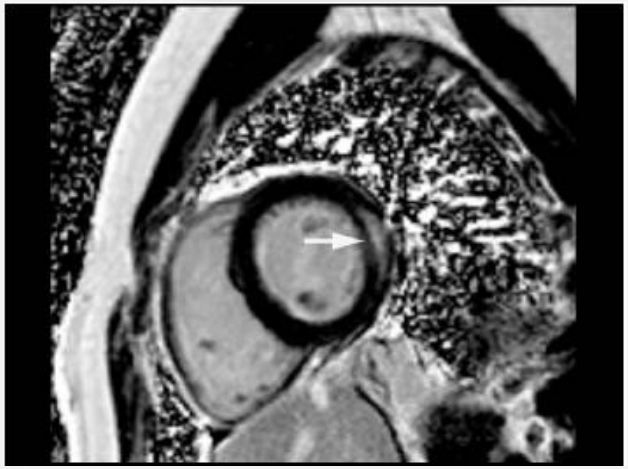
4. Cardiac Magnetic Resonance: late enhancement

Case No.	Age	CV risk	Radiotherapy	Baseline LVEF (%)	Trastuzumab Duration
1	33	None	Yes	55	4 months
2	41	HTN	Yes	60	5 months
3	27	None	Yes	54	4 months
4	39	None	Yes	65	3 months
5	44	Lipids	Yes	58	4 months
6	38	None	Yes	56	5 months
7	56	HTN	Yes	60	3 months
8	45	HTN	Yes	54	4 months
9	32	None	Yes	55	5 months
10	40	HTN	Yes	60	4 months

CV, cardiovascular; LVEF, left ventricular ejection fraction; chemothx, chemotherapy; HTN, hypertension.

Table 2: CMR findings of patient population (n = 10)

Case No.	Age	LVEF (%)	Delayed enhancement
1	33	32	Lateral, septal
2	41	28	Lateral
3	27	30	Lateral
4	39	25	Lateral
5	44	35	Lateral, septal
6	38	30	Lateral
7	56	25	Lateral
8	45	24	Lateral
9	32	30	Lateral
10	40	34	Lateral



Cardiovascular Toxicity

4. Cardiac Magnetic Resonance: late enhancement

Novel Approach to Early Detection of Doxorubicin Cardiotoxicity by Gadolinium-Enhanced Cardiovascular Magnetic Resonance Imaging in an Experimental Model

James C. Lightfoot, MD; Ralph B. D'Agostino, Jr, PhD; Craig A. Hamilton, PhD; Jennifer Jordan, BS; Frank M. Torti, MD; Nancy D. Kock, DVM, PhD; James Jordan, PhD; Susan Workman; W. Gregory Hundley, MD

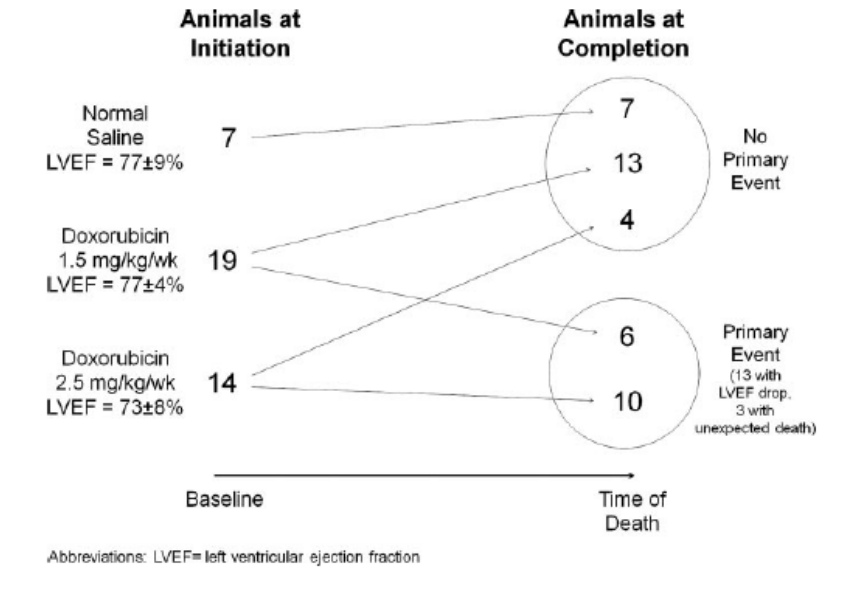
Background—We sought to determine whether cardiovascular magnetic resonance measures of gadolinium (Gd) signal intensity (SI) within the left ventricular myocardium are associated with future changes in left ventricular ejection fraction (LVEF) after receipt of doxorubicin (DOX).

Methods and Results—Forty Sprague-Dawley rats were divided into 3 groups scheduled to receive weekly intravenous doses of normal saline (n=7), 1.5 mg/kg DOX (n=19), or 2.5 mg/kg DOX (n=14). Magnetic resonance determinations of LVEF and myocardial Gd-SI were performed before and at 2, 4, 7, and 10 weeks after DOX initiation. During treatment, animals were euthanized at different time points so that histopathologic assessments of the left ventricular myocardium could be obtained. Within-group analyses were performed to examine time-dependent relations between Gd-SI and primary events (deterioration in LVEF or an unanticipated death). Six of 19 animals receiving 1.5 mg/kg DOX and 10 of 14 animals receiving 2.5 mg/kg DOX experienced a primary event; no normal saline animals experienced a primary event. In animals with a primary event, histopathologic evidence of myocellular vacuolization occurred ($P=0.04$), and the Gd-SI was elevated relative to baseline at the time of the event ($P<0.0001$) and during the measurement period before the event ($P=0.0001$). In all animals (including normal saline) without an event, measures of Gd-SI did not differ from baseline.

Conclusions—After DOX, low serial measures of Gd-SI predict an absence of an LVEF drop or unanticipated death. An increase in Gd-SI after DOX forecasts a subsequent drop in LVEF as well as histopathologic evidence of intracellular vacuolization consistent with DOX cardiotoxicity. (***Circ Cardiovasc Imaging*. 2010;3:550-558.**)

Cardiovascular Toxicity

4. Cardiac Magnetic Resonance: late enhancement

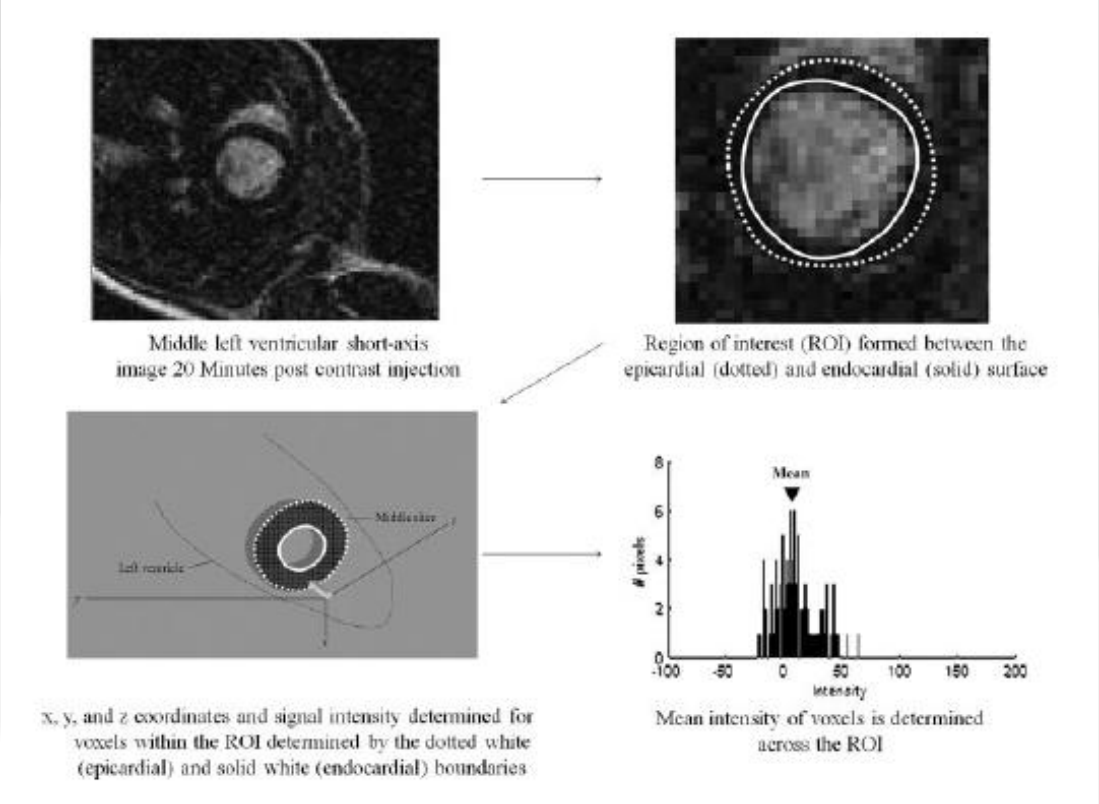


The primary outcome in this study was predefined as 1 of 3 conditions: (1) a drop in LVEF of >10% from the resting baseline value at a subsequent measurement; (2) when the absolute level of LVEF dropped <65% at any time; or (3) when an animal died unexpectedly. These metrics were selected to be similar to clinical

Study design. As shown, 7, 19, and 14 animals were initiated into this study in groups receiving NS, 1.5 mg/kg per week of DOX, and 2.5 mg/kg per week of DOX, respectively. At the end of the experiment, 24 animals had not experienced a primary event and 16 animals experienced a primary event (13 with a drop in LVEF; 3 with sudden death).

Cardiovascular Toxicity

4. Cardiac Magnetic Resonance: late enhancement



LV myocardial SI. At top left is a middle LV short-axis image obtained 20 minutes after Gd contrast. As shown, the LV myocardial cavity is white and the LV myocardium is dark. On this shortaxis image, a region of interest was identified (top right) bounded by the LV endocardial surface (solid line) and the LV epicardial surface (dotted line). Within this region of interest, the *x, y, and z* coordinates, along with SI for all of the boxes, were recorded (bottom left). The number of voxels along with their intensity was plotted, and the mean voxel intensity was determined (bottom right). This value was then subtracted from the background noise to obtain mean voxel intensity

The method of analysis of the Gd-enhanced images used in this study differs from those used previously to identify myocellular injury after a myocardial infarction, in which myocellular injury is defined in voxels with an SI 2 SDs above background intensity within nonenhanced LV myocardium. Methods that visualize well-circumscribed myocardial infarcts are not well suited for a process that causes diffuse cardiac injury throughout the heart.

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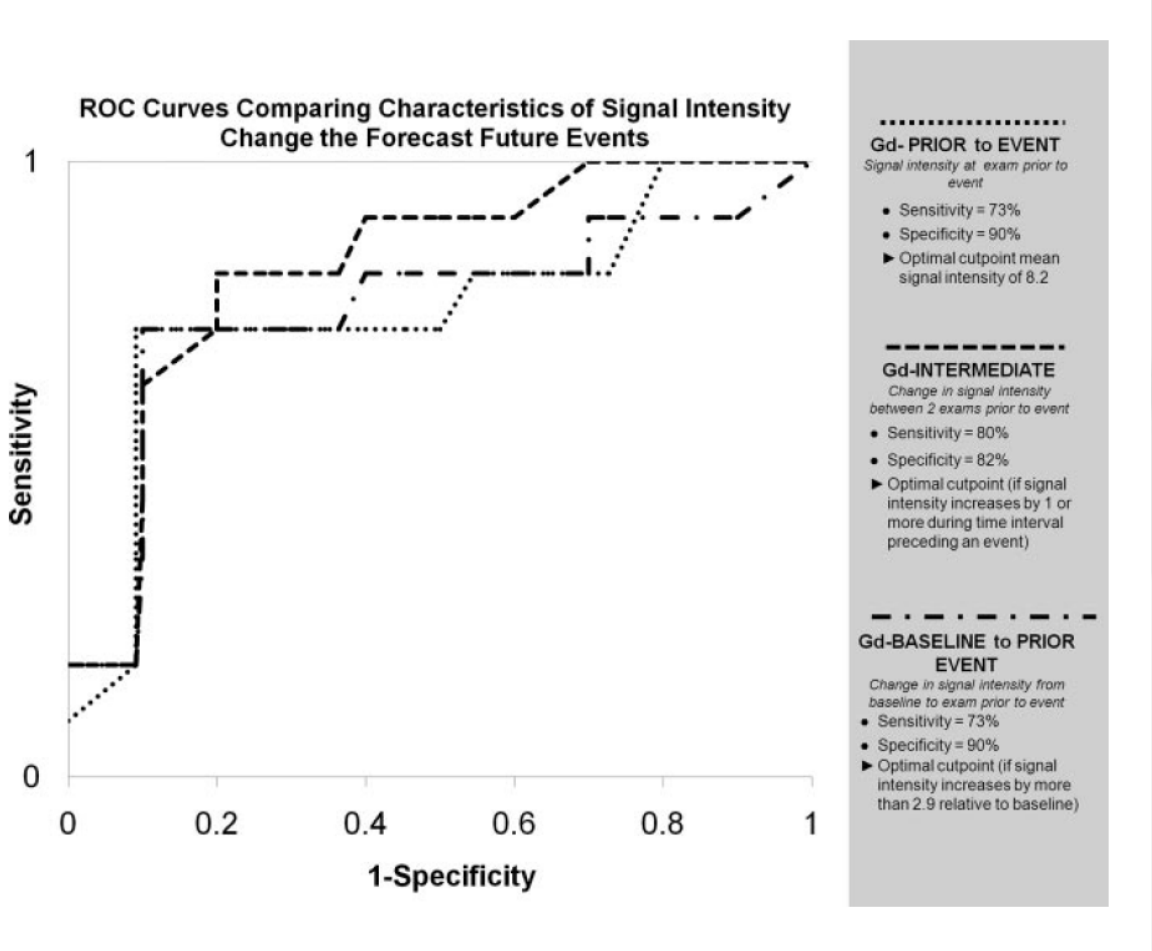
Cardiovascular Toxicity

4. Cardiac Magnetic Resonance: late enhancement



Prediction of future primary events. Receiving operator characteristic (ROC) curves to determine the cutoff point for (1) the SI of the point before a primary event (Gd-Before Event; dotted line); (2) the change in SI from the 2 examinations before the primary event (Gd-intermediate; dashed line); and (3) the change in SI from baseline to the point before the primary event (Gdbaseline to prior event; dash/dot line). As shown, changes in SI early in the study predicted future events.

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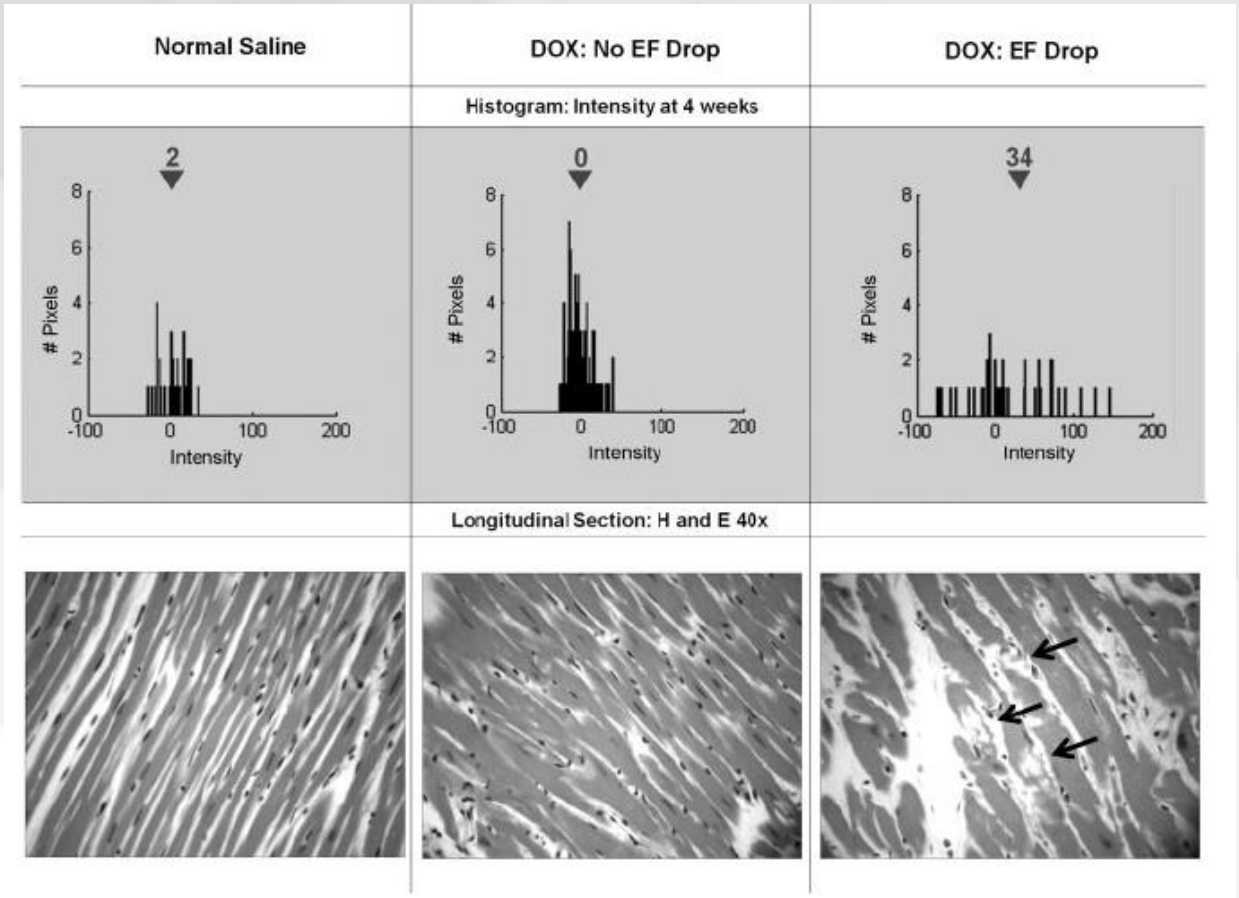
Cardiovascular Toxicity

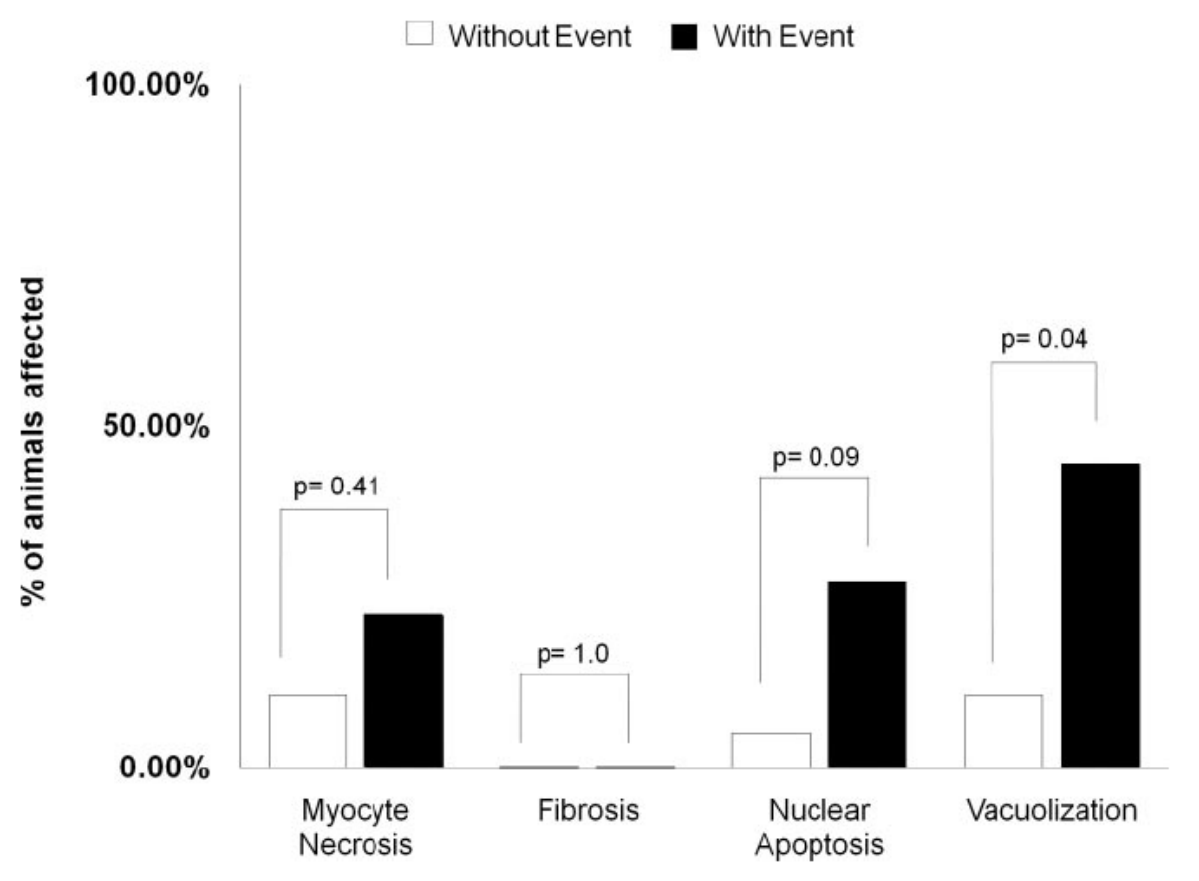
4. Cardiac Magnetic Resonance: late enhancement



Serial histograms and histopathology. On the top portion of the figure are shown 4-week histograms of the number of pixels (*y axes) and intensities* (*x axes) in individual animals after receipt* of NS (top left), DOX without an EF drop (top middle), and DOX with an EF drop (top right). Below the histograms are 40 hematoxylin and eosin histopathologic images from the same animals. As shown, mean intensity increased in the animals that had a drop in EF corresponding to vacuolization (arrows, bottom right).

Cardiovascular Toxicity

4. Cardiac Magnetic Resonance: late enhancement



Myocardial morphology. Bar graph displays the percentage of animals that developed myocellular necrosis, fibrosis, apoptosis, and vacuolar degeneration. Animals experiencing the primary end point of death (n 3) or drop in LVEF (n 13) exhibited more vacuolization relative to animals that did not experience these primary endpoints.

Cardiovascular Toxicity

Cardiac Magnetic Resonance vs other imaging modality

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Imaging and Biomarkers

The Utility of Cardiac Biomarkers, Tissue Velocity and Strain Imaging, and Cardiac Magnetic Resonance

Objectives The aim of this study was to evaluate whether cardiac biomarkers, tissue velocity (TVI) and strain imaging, and cardiac magnetic resonance imaging can predict early left ventricular (LV) dysfunction in human epidermal growth factor receptor II–positive breast cancer patients treated with trastuzumab in the adjuvant setting.

Background Early indexes of LV systolic dysfunction with noninvasive cardiac imaging would be useful for addressing the cardiac safety profile of trastuzumab, potentially avoiding the detrimental effects of heart failure.

Methods We used cardiac biomarkers, TVI and strain imaging, and cardiac magnetic resonance imaging to detect pre-clinical changes in LV systolic function, before conventional changes in left ventricular ejection fraction (LVEF) in human epi-

Results of 6 mg/kg every 3 weeks for 1 year. Trastuzumab-mediated cardiomyopathy (CM) was defined as a decline in LVEF of at least 10% below 55%, with accompanying signs or symptoms of CHF, necessitating discontinuation of the drug (6–8) The study protocol was approved by the local follow-up in all 10 patients, necessitating discontinuation of the drug. All 10 patients demonstrated delayed enhancement of the lateral wall of the LV within the mid-myocardial portion, consistent with trastuzumab-induced CM.

Conclusions Both TVI and strain imaging were able to detect pre-clinical changes in LV systolic function, before conventional changes in LVEF, in patients receiving trastuzumab in the adjuvant setting. (J Am Coll Cardiol 2011;57: 2263–70) © 2011 by the American College of Cardiology Foundation

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Cardiovascular Toxicity

Cardiac Magnetic Resonance vs other imaging modality

Table 1 Baseline Characteristics of Total Population

Characteristics	Normal (n = 32)	CM (n = 10)	Total Population (n = 42)	p Value
Age (yrs)	46 ± 8	47 ± 10	47 ± 9	0.48
BMI (kg/m^2)	26 ± 5	25 ± 6	25 ± 7	0.90
CV risk factors				
Hypertension	4 (13)	1 (10)	5 (12)	1.00
Diabetes	4 (13)	2 (20)	6 (14)	0.62
Hyperlipidemia	12 (38)	3 (30)	15 (36)	1.00
Smoking history	2 (6)	2 (20)	7 (17)	0.24
Family history of CAD	4 (13)	3 (30)	12 (29)	0.33
Location of Ca				
Right	19 (59)	6 (60)	25 (60)	1.00
Left	11 (34)	4 (40)	15 (39.5)	1.00
Bilateral	2 (2.6)	0 (0)	2 (2.0)	1.00
Size of Ca (cm)	3.0 ± 2.0	3.2 ± 1.4	3.1 ± 1.7	0.83
Radiation	31 (97)	10 (100)	41 (98)	1.00
Lymph node +	19 (58)	5 (50)	24 (57)	0.72
Chemotherapy				
FEC	29 (91)	8 (80)	37 (88)	0.58
AC	3 (7)	2 (20)	5 (12)	0.58

n = 42. Values are mean ± SD or n (%). p values were calculated by Student *t* test for difference in means between normal and cardiomyopathy (CM) groups and the Fisher exact test for differences in proportions.

AC = adriamycin, cyclophosphamide; BMI = body mass index; Ca = cancer; CAD = coronary artery disease; CV = cardiovascular; FEC = fluorouracil, epirubicin, cyclophosphamide.

Table 2 Summary of Serial Cardiac Biomarkers of Patients With and Without Trastuzumab-Mediated CM in Entire Population

Cardiac Biomarkers	Normal (n = 32)	CM (n = 10)	p Value
Troponin T (μg/l)			
Baseline	<0.01	<0.01	1.00
3 months	<0.01	<0.01	1.00
6 months	<0.01	<0.01	1.00
9 months	<0.01	<0.01	1.00
12 months	<0.01	<0.01	1.00
CRP (mg/l)			
Baseline	5.5 ± 1.2	5.8 ± 1.7	0.76
3 months	5.4 ± 1.8	5.6 ± 1.9	0.81
6 months	6.1 ± 1.1	6.0 ± 1.4	0.88
9 months	5.8 ± 1.4	6.3 ± 2.1	0.72
12 months	6.0 ± 1.6	6.2 ± 1.7	0.84
NT-proBNP (pmol/l)			
Baseline	27.5 ± 2.4	28.4 ± 2.5	0.81
3 months	28.3 ± 2.2	29.1 ± 1.9	0.80
6 months	28.2 ± 2.1	28.7 ± 1.3	0.89
9 months	29.1 ± 3.1	30.1 ± 3.1	0.88
12 months	30.5 ± 1.9	31.4 ± 2.8	0.84

n = 42. Values are mean ± SD unless otherwise indicated.

CRP = C-reactive protein (normal reference: <8 mg/l); NT-proBNP = N-terminal pro-brain natriuretic peptide (normal reference: <35 pmol/l); TnT = cardiac troponin T (normal reference: <0.01 μg/l); other abbreviations as in Table 1.

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Cardiovascular Toxicity

Cardiac Magnetic Resonance vs other imaging modality

Table 3 Echocardiographic Parameters of Patients With and Without Trastuzumab-Mediated CM in Entire Population

Echocardiographic Variables	Normal (n = 32)	CM (n = 10)	p Value
TDI parameters			
Mean S′ (cm/s)			
2D speckle tracking			
Peak global longitudinal strain			
Peak global radial strain			

Table 4 ROC Curve Analysis for TVI and Strain Imaging

Echocardiographic Variables	Cutoff Value	Sensitivity (95% CI)	Specificity	PPV	NPV
S′ (cm/s)	0.60	0.93 (0.59–0.99)	0.99	0.96	0.98
Longitudinal strain	2.00	0.79 (0.51–0.96)	0.82	0.60	0.92
Radial strain	0.80	0.86 (0.57–0.98)	0.81	0.60	0.95

The cutoff values with the difference of baseline and 3-month measurements for the systolic annular velocity of the lateral left ventricular wall (S′), longitudinal strain, and radial strain. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are shown for each respective echocardiographic parameter.

CI = confidence interval; ROC = receiver-operator characteristic; TVI = tissue velocity imaging.

In our study, TVI and strain parameters did allow for the early detection of subclinical cardiac dysfunction before conventional echocardiographic parameters in breast cancer patients receiving trastuzumab in the adjuvant setting. Although there was no difference in conventional LVEF 3 months after initiation of adjuvant trastuzumab therapy, TVI (S wave) and strain decreased in all 10 patients who developed cardiotoxicity. As compared with both global longitudinal and radial strain, only S= was able to identify all 10 patients who developed trastuzumab-mediated CM, with no false positives in the normal cohort at 3 months. The LVEF subsequently decreased at 6 months of follow-up in all 10 patients, necessitating discontinuation of the drug.

Cardiovascular Toxicity

Cardiac Magnetic Resonance vs other imaging modality

Table 5 Cardiac MRI Parameters of Patients With and Without Trastuzumab-Mediated CM in Entire Population

CMR Variables, LV Dimensions	Normal (n = 32)	CM (n = 10)	p Value
LVEDV (ml)			
Baseline	155 ± 22	161 ± 19	0.78
12 months	161 ± 21	190 ± 23*†	<0.05
LVESV (ml)			
Baseline	55 ± 10	58 ± 12	0.71
12 months	58 ± 14	98 ± 18*†	<0.05
LVEF			
Baseline	65 ± 3	66 ± 5	0.89
12 months	63 ± 5	47 ± 4*†	<0.05

n = 42. Values are mean ± SD. *p < 0.05 was considered significant comparing normal population versus CM at same time point with the Mann-Whitney *U* test. †p < 0.05 was considered significant versus baseline within each group with a repeated measures analysis of variance and Dunnett's test.

CMR = cardiac magnetic resonance imaging; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; other abbreviations as in Tables 1 and 3.

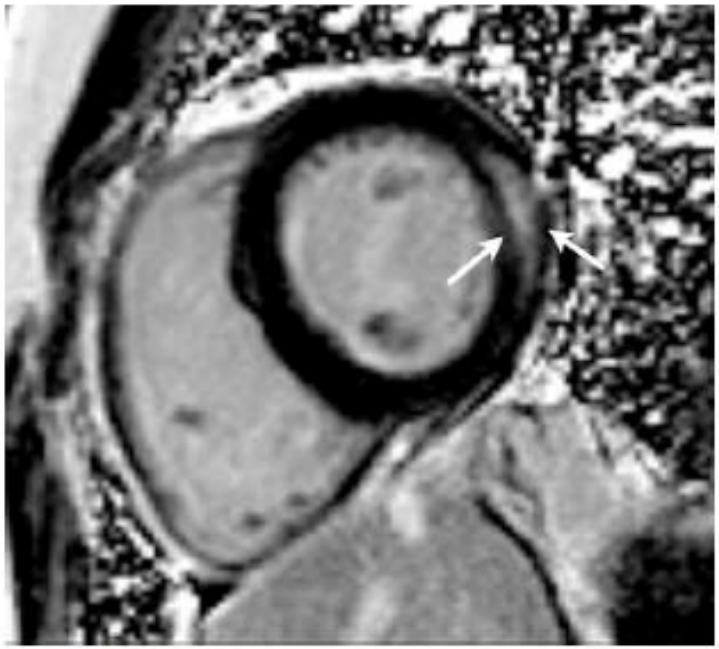

Figure 1 Delayed Enhancement Cardiac Magnetic Resonance Imaging in Trastuzumab-Mediated Cardiotoxicity

Short-axis phase sensitive reconstructed inversion recovery–true fast imaging with steady-state precession image through the mid-ventricle at the level of the papillary muscles, demonstrating midmyocardial delayed enhancement **(arrows)** in the lateral wall of a patient who developed trastuzumab-mediated cardiotoxicity.

There was evidence of subepicardial linear delayed enhancement in the lateral wall of the LV **in all 10 patients** who developed trastuzumabinduced cardiac dysfunction. The average size of LGE was 18 4% of LV mass in these patients.

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Cardiovascular Toxicity

5. Cardiac Magnetic Resonance: Spectroscopy

Acute Administration of Epi
Depression in Isolated Rat
Radical Species Evalua
Resonance S

Stéphanie Delemasure, PharmD, Pierre Sicard, M
Catherine Vergely, PharmD, PhD,

(*J Cardiovasc Pharm*

Abstract: The aim of our study was to evaluate the acute effect of epirubicin (EPI), an anthracycline anticancer drug, on the evolution of cardiac functional parameters and production of reactive oxygen/nitrogen species (RONS). Isolated perfused rat hearts were subjected to 70 minutes of EPI (10.3 μM) infusion and to 5 minutes of isoproterenol (ISO, 0.1 μM) at the end of the protocol. Coronary flow (CF), left ventricular developed pressure (LVDP), and lactate dehydrogenase (LDH) release in the coronary effluents were evaluated throughout the protocol. RONS were detected in the coronary effluents by electron spin resonance spectroscopy with a spin probe, 1-hydroxy-3-carboxy-pyrrolidine (CP-H, 0.1 mM). EPI induced a reduction in CF and in LVDP ($P < 0.001$). ISO infusion enhanced CF and RPP in the control group; in the EPI group, these increases were significantly impaired. Release of LDH was significantly increased during EPI infusion ($P < 0.001$). RONS was 2.5 times greater in the EPI group than in the control group ($P < 0.05$). In conclusion, a significant deterioration in cardiac function was observed after EPI perfusion and was associated with cellular injury and the generation of myocardial RONS. Further investigations are now needed to determine whether new cardioprotective agents targeting oxidative stress may reduce the incidence of anthracycline-induced cardiotoxicity.

Cardiovascular Toxicity

5. Cardiac Magnetic Resonance

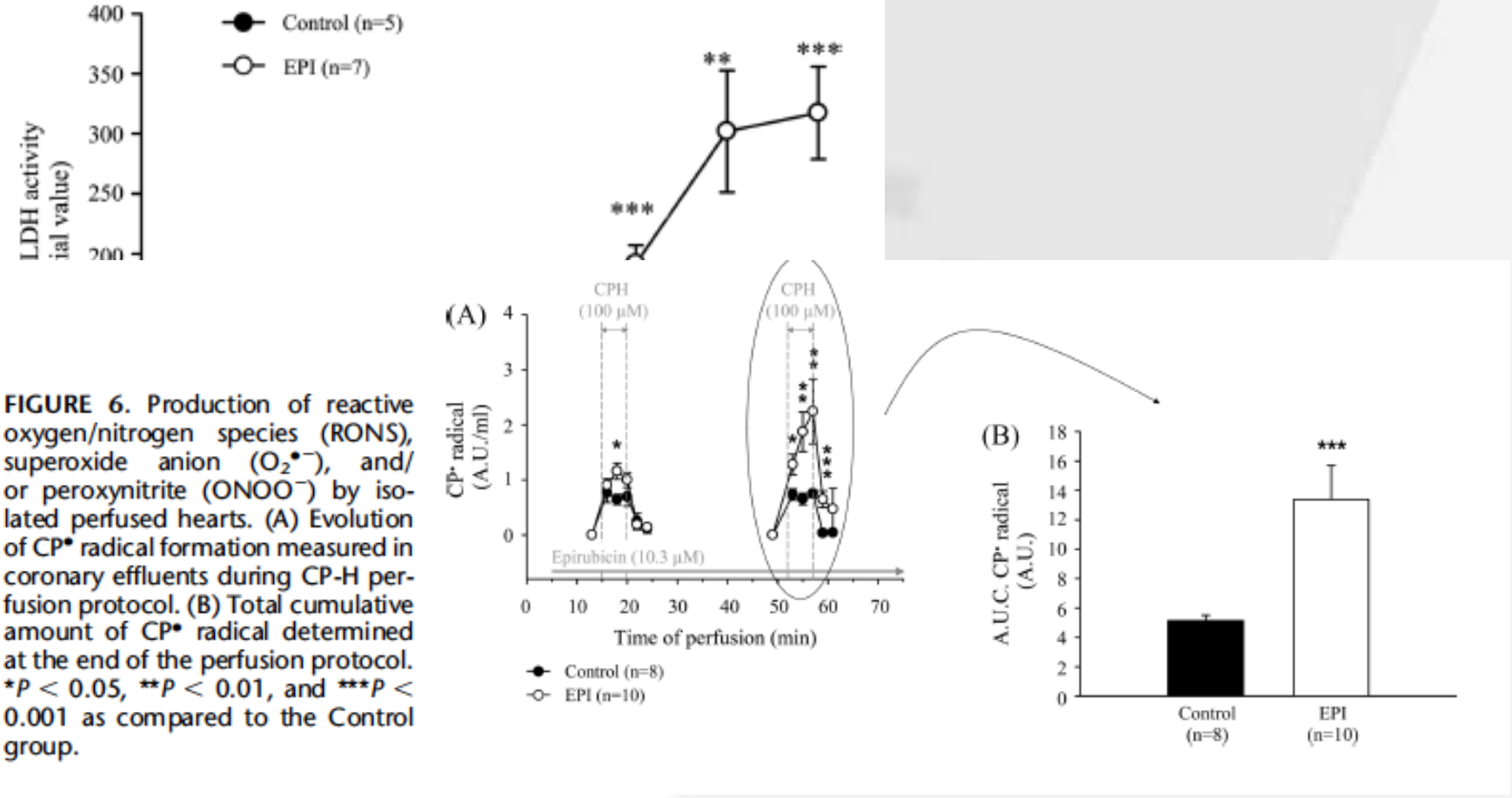
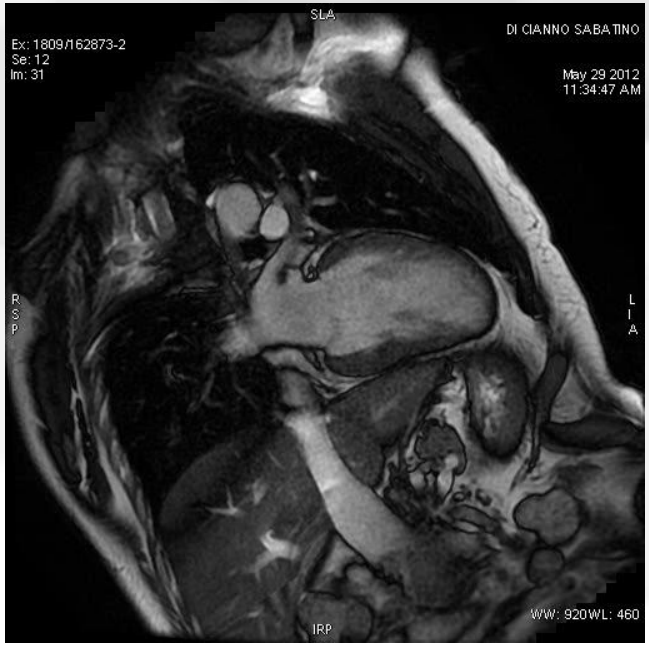
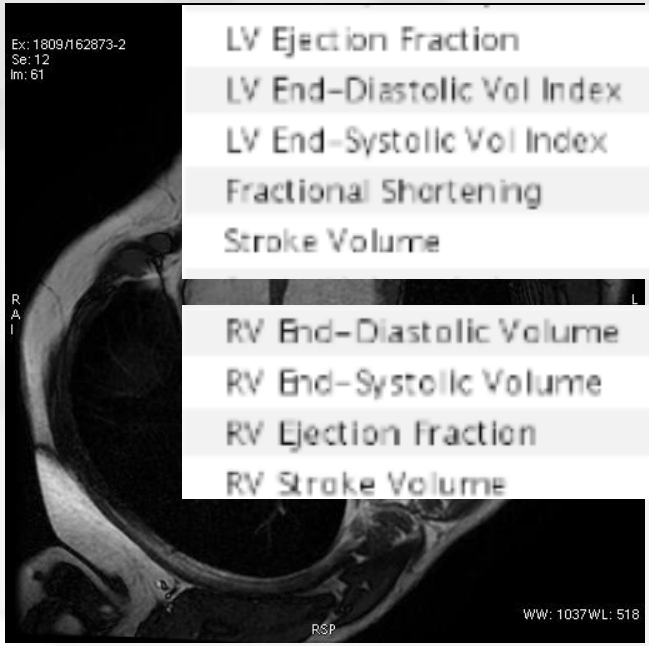


FIGURE 6. Production of reactive oxygen/nitrogen species (RONS), superoxide anion ($O_2^{\bullet -}$), and/or peroxynitrite ($ONOO^-$) by isolated perfused hearts. (A) Evolution of CP• radical formation measured in coronary effluents during CP-H perfusion protocol. (B) Total cumulative amount of CP• radical determined at the end of the perfusion protocol. $^*P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ as compared to the Control group.

Clinical Case 1

Male 34 yo, previous kidney transplantation, symptomatic for dyspnea





LV Ejection Fraction	56 %
LV End-Diastolic Vol Index	102.7 ml/m²
LV End-Systolic Vol Index	44.9 ml/m²
Fractional Shortening	27 %
Stroke Volume	116.5 ml
RV End-Diastolic Volume	199.1 ml
RV End-Systolic Volume	85.3 ml
RV Ejection Fraction	57 %
RV Stroke Volume	113.8 ml

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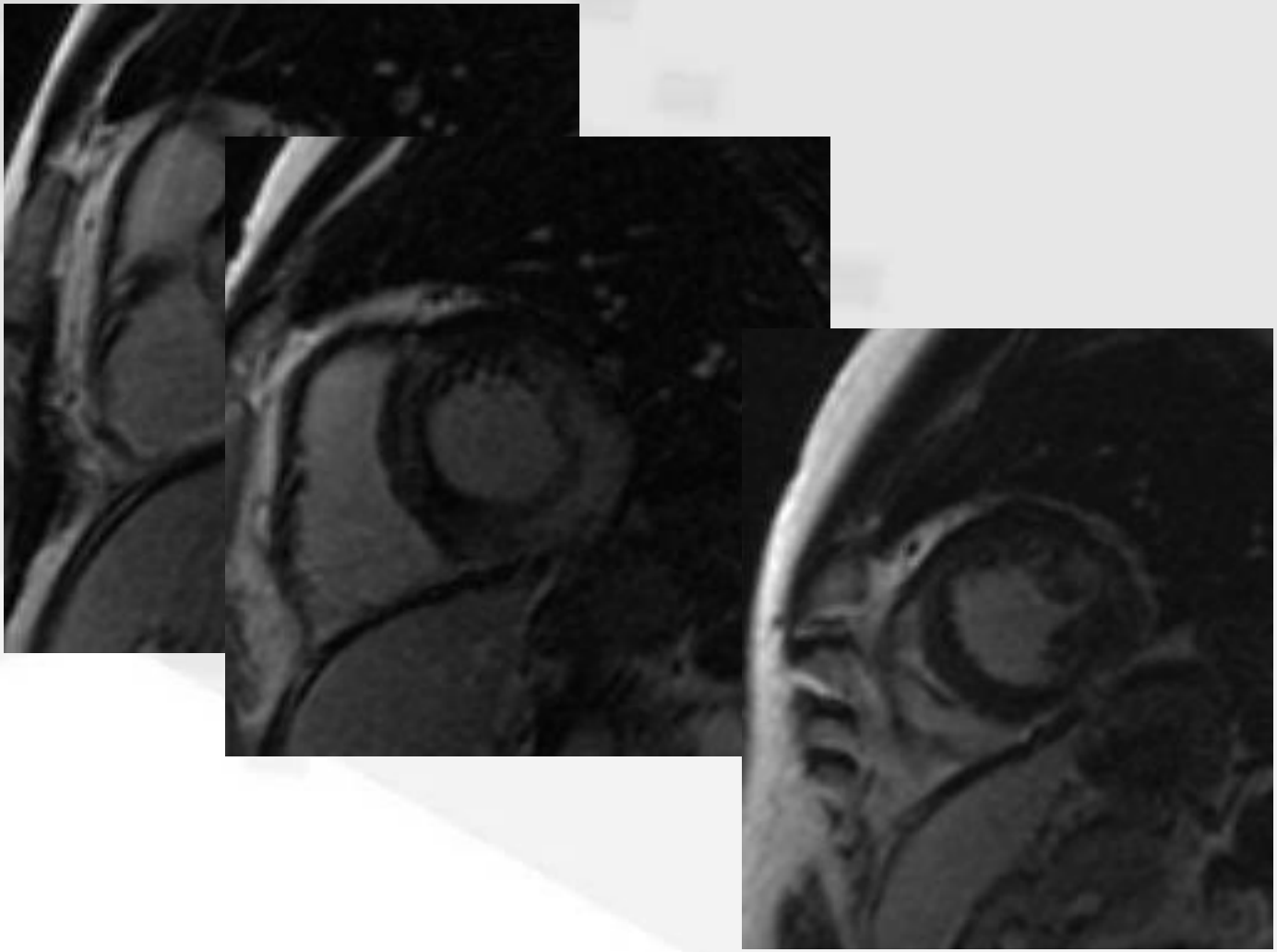
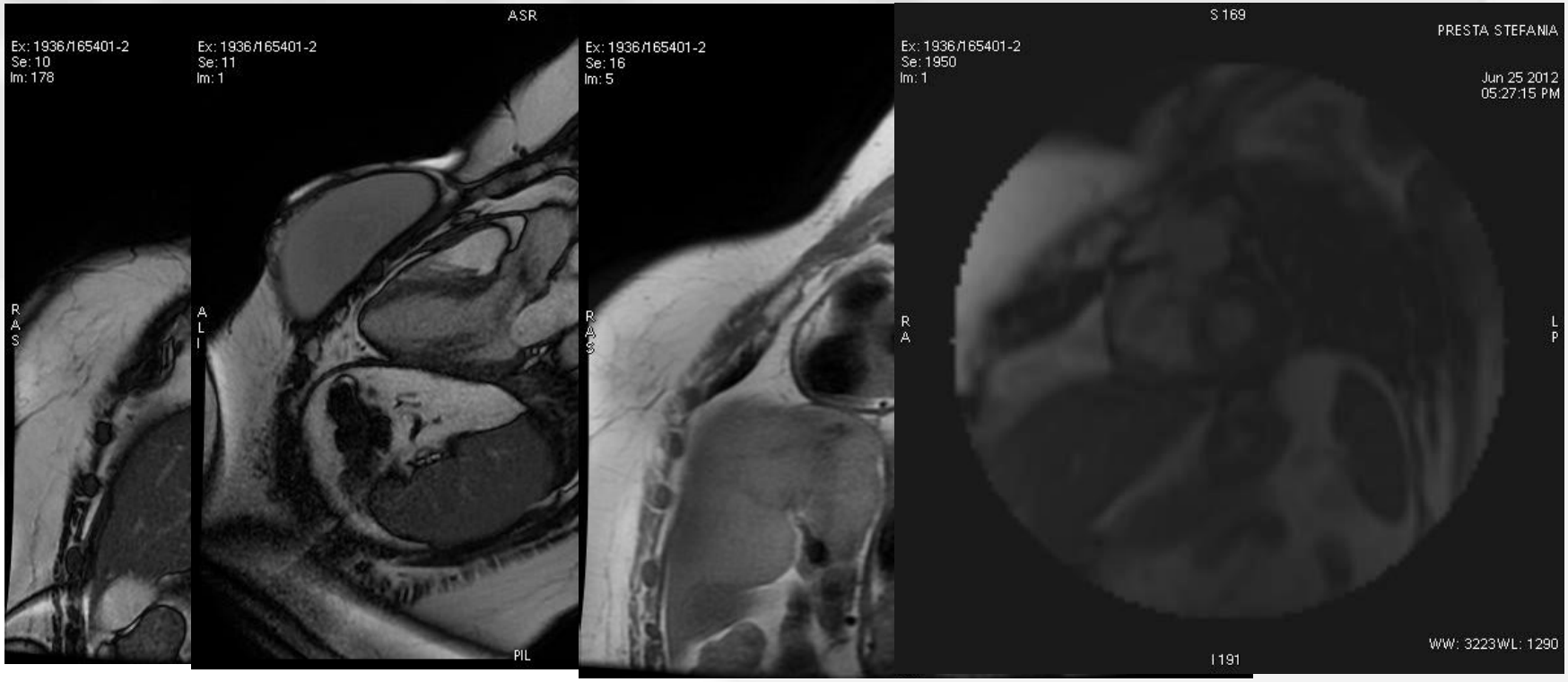
Clinical Case 1



Clinical Case 2

Female 36 yo, previous LH and breast cancer treated with RT and CT symptomatic for congestve heart failure.



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OPEN ISSUES

Prospective Studies

Large Sample Size

CMR at baseline
post CT
3 – 6 -12 monts

LV and RV evaluation
Mass
Relative Edema $T2^W$
Relative enhancement $T1^W$
Global Late enhancement IR sequences $T1^W$

Outcome

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CONCLUSIONS

Conclusions

CMR now plays a key role in the ini
ment of patients presenting with
onset of chest pain and unobstruc
safely allowed the non-invasive i
ogy without irradiation in appro
The role of CMR needs to be empl
registry organized with a view to
this common clinical presentatio

CONCLUSION

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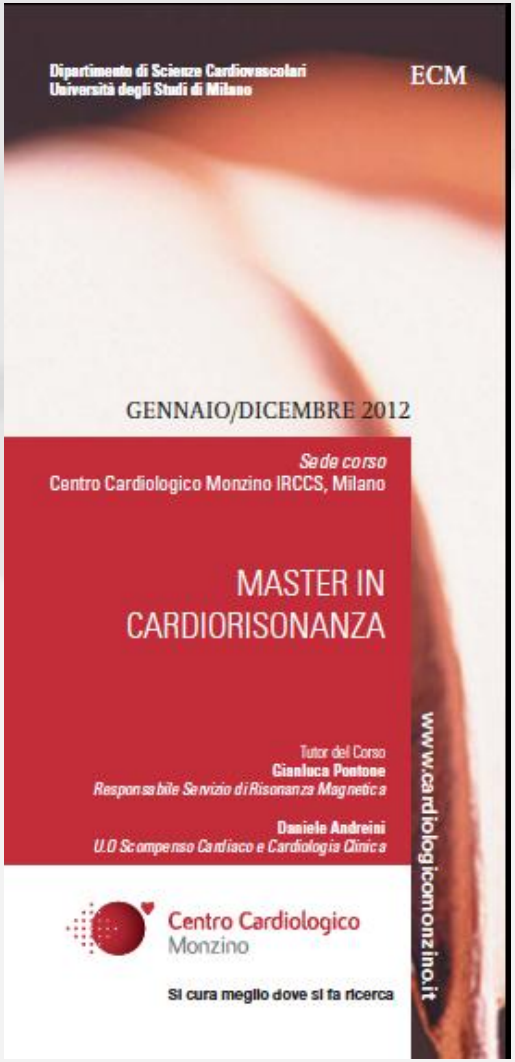

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