Imaging in Cardio-Oncology: The Role of Cardiac MRI

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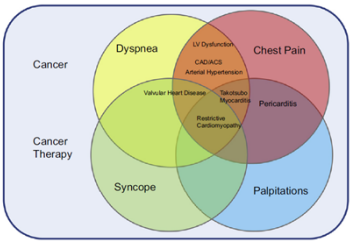
NOVEMBER 17, 2021

Cardiovascular Symptoms and Cancer Treatment



J Am Coll Cardiol CardioOnc 2020;2:270–92

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Cardiac MRI (CMR) for the Cancer Patient

- Imaging is critical for the surveillance and diagnosis of cancer treatment-related cardiotoxicities
- CMR is a robust imaging modality which enhances our clinical acumen in the diagnosis and management of various cardiomyopathies
- Echo remains a first line imaging modality for the diagnosis of a cardiomyopathy, while cardiac MRI provides more accurate functional assessment and critical information about tissue characterization
- Cancer treatment-related cardiotoxicities wide and varied:
  - Cardiomyopathy
  - CHF
  - Myocarditis
  - Pericarditis
  - Infarcts
- CMR has become a critical imaging modality to evaluate etiology of cardiomyopathy
- Newer parametric mapping techniques provide a non-invasive biopsy of the myocardium

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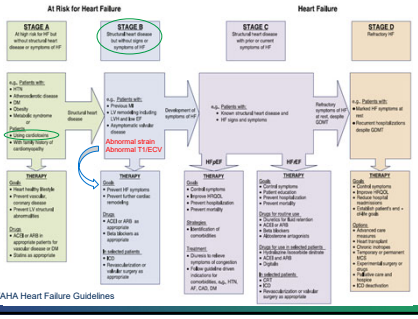
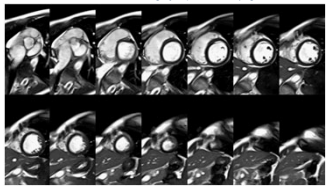
Stages of Heart Failure

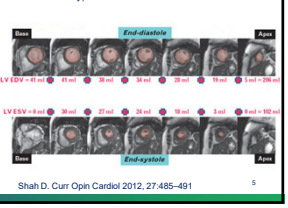


Yancy et al. 2013 ACCF/AHA Heart Failure Guidelines

CMR for Cardiac Function

- Standard CMR imaging allows the acquisition of high resolution cine images
- CMR is the gold standard for LVEF, volumetric assessment, and myocardial mass measurements
- CMR measurements are highly reproducible (high inter- and intra-observer reliability)





Shah D. Curr Opin Cardiol 2012, 27:485–491

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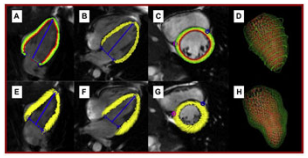
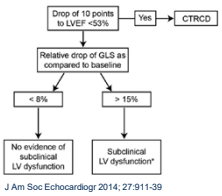
CMR for Myocardial Strain

- Myocardial deformation and strain changes serve to identify early signs of cardiotoxicity
- Echo strain literature validated and included in imaging guidelines
- Strain by CMR is feasible; limited literature for its use thus far





J Am Soc Echocardiogr 2014; 27:911-39

J Am Coll Cardiol CardioOnc 2020;2:270–92

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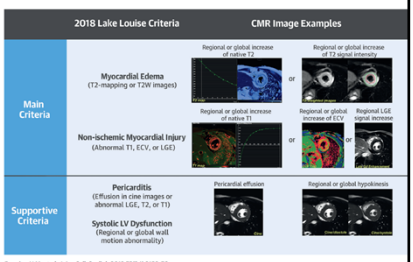
CMR for Myocardial Inflammation and Edema

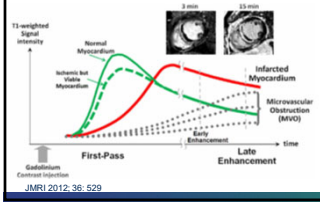
- CMR is the imaging modality of choice for myocardial edema assessment
- T2 weighted imaging as well as newer T2 mapping techniques allow for highly accurate assessment of inflammation/edema that is evident qualitatively and quantitatively



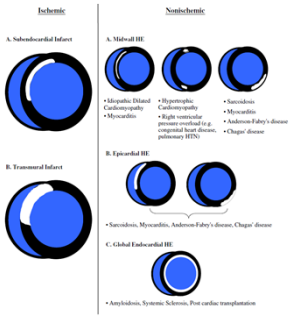
Ferreira, V.M. et al. J Am Coll Cardiol. 2018;72(24):3158–76.

CMR for Myocardial Fibrosis – Late Gadolinium Enhancement

- Late gadolinium enhancement (LGE) imaging of the myocardium allows direct visualization of focal areas of extracellular expansion due to fibrosis and scarring



JMRI 2012; 36: 529



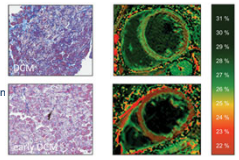
Cardiol Clin 2007; 25:35

CMR for Diffuse Interstitial Changes - Parametric Mapping Techniques

- Diffuse changes to the interstitial space can be accurately assessed with T1 mapping and extracellular volume (ECV) measurements
- LGE imaging allows for discrimination of focal areas of fibrosis when compared to normal myocardium
- Parametric mapping techniques (T1, T2, T2*) allow for a "non-invasive biopsy" of the myocardium
- ECV is derived from post-contrast T1 and pre-contrast T1 values

$$ECV = \left(\frac{\left(\frac{1}{T1_{myocardial}} - \frac{1}{T1_{myocardial}}\right)}{\left(\frac{1}{T1_{blood}} - \frac{1}{T1_{blood}}\right)}\right) \times (100 - hematocrit)$$

- ECV correlates well with pathology
- ECV can be a means to monitor response to therapy and risk stratification



European Heart Journal – Cardiovascular Imaging (2015) 16, 210–216

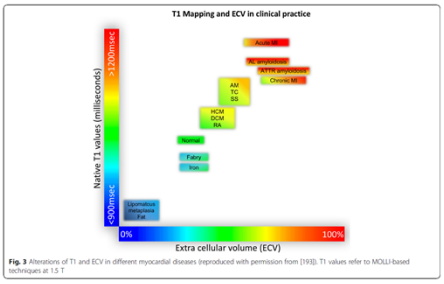
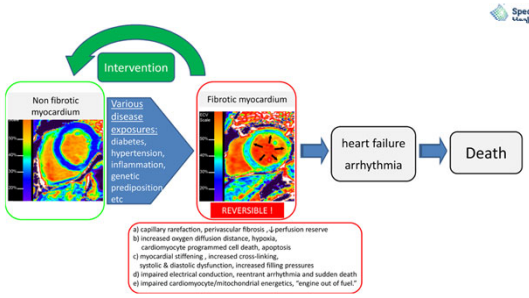


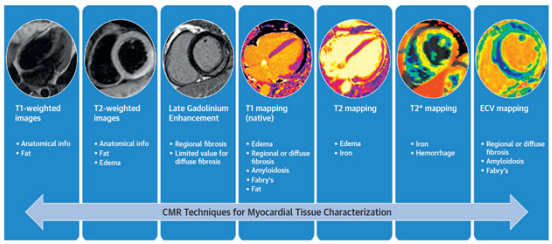
Fig. 3 Alterations of T1 and ECV in different myocardial diseases (reproduced with permission from [193]). T1 values refer to MOLLI-based techniques at 1.5 T

Journal of Cardiovascular Magnetic Resonance (2017) 19:75



Schelbert et a. Circ Cardiovasc Imaging. 2017;10:e005619

CMR Techniques for Myocardial Tissue Characterization



Karamitsos, T.D. et al. J Am Coll Cardiol Img. 2020;13(5):1221-34.

Ongoing Trials – Imaging as Outcomes

TABLE 4. Ongoing Pharmacologic Cardioprotection Trials

Trial Name (Identifier; Principle Investigator)	Trial Intervention	Population	Outcomes
PREVENT (NCT01988571; Hundley, Wake Forest)	Statins (atorvastatin) vs. placebo	Breast cancer, lymphoma, chemotherapy with anthracyclines	MRI, biomarkers, symptoms at 2 years
STOP-CA (NCT02943590; Neilan, Scherrer Crosbie, MGH)	Statins vs. placebo	Non-Hodgkin lymphoma, chemotherapy with anthracyclines	MRI, echocardiography at 12 months
SWOG S1501 (NCT02562716; Floyd, Leja, Fabian, SWOG)	Carvedilol vs. no intervention	Metastatic HER2^{+} breast cancer	Echocardiography and many secondary endpoints
ICOS-ONE (NCT01968200; Cipolla, European Institute of Oncology)	Enalapril preventatively vs. after indication of cardiotoxicity	Cancer, chemotherapy with anthracyclines	Cardiac troponin levels
PROACT (NCT03265574; Change, Newcastle University)	Enalapril vs. no intervention	Postsurgical breast cancer to be treated with epirubicin	Cardiac troponin T release during epirubicin treatment
CARDIAC CARE (ISRCTN24439460; Maclean, The Queen's Medical Research Institute)	Angiotensin receptor blockers and β-blocker or no intervention	Breast cancer, chemotherapy with anthracyclines, increased cardiac troponin levels	MRI at 6 months
PRADA II (NCT03760588; Omland, Gulati)	Entresto vs. placebo	Breast cancer, chemotherapy with anthracyclines	Left ventricular ejection fraction by cardiovascular magnetic resonance at 18 months

American Society of Clinical Oncology Educational Book 40 (March 26, 2020) 501-515.

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Cancer-induced Changes to the Myocardium Detected by CMR

- Common pathways have been proposed in the pathogenesis of cancer and heart disease
- No clear understanding of the baseline cardiovascular characteristics of newly diagnosed cancer patients
- Prospective cohort study of recently diagnosed breast cancer and lymphoma patients **before** chemotherapy underwent baseline CMR
  - 381 cancer patients
  - 102 healthy volunteers

Journal of the American Heart Association

ORIGINAL RESEARCH

Effect of Active Cancer on the Cardiac Phenotype: A Cardiac Magnetic Resonance Imaging-Based Study of Myocardial Tissue Health and Deformation in Patients With Chemotherapy-Naïve Cancer

Dina Labib, MD; Alessandro Sattano, PhD; Steven Dykstra, MSc; Reis Hansen, BSc; Yoko Mikami, MD, PhD; David G. Guzzardi, PhD; Zdenka Slavikova, BSc; Patricia Feuchter, MSc; Jacqueline Rewitt, MSc; Sandra Rivest, RN; Rosa Sandonato, BScN, RN; Carmen P. Lydell, MD; Andrew G. Howarth, MD, PhD; Louis Kolman, MD; Brian Clarke, MD; D. Ian Paterson, MD; Gavin Y. Oudit, MD, PhD; Edith Pituskin, RN, PhD; Winson Y. Cheung, MD, MPH; Joon Lee, PhD; James A. White, MD

BACKGROUND: The overlap between cancer and cardiovascular care continues to expand, with intersections emerging before, during, and following cancer therapies. To date, emphasis has been placed on how cancer therapeutics influence downstream cardiac health. However, whether active malignancy itself influences chamber volumes, function, or overall myocardial tissue health remains uncertain. We sought to perform a comprehensive cardiovascular magnetic resonance–based evaluation of cardiac health in patients with chemotherapy-naïve cancer with comparison with a healthy volunteer population.

J Am Heart Assoc. 2021;10:e019811

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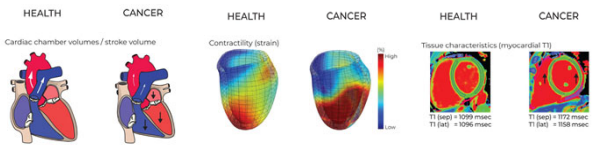
Cancer-induced Changes to the Myocardium Detected by CMR



- Newly diagnosed cancer patients have reduced chamber volumes, reduced stroke volumes, elevated strain, and elevated native T1 compared to healthy volunteers (independent of gender, age, hypertension, and diabetes)
- Changes to the cardiovascular system likely a consequence of the activation of inflammatory pathways in cancer
- Such data – and future investigations of the baseline CV characteristics of cancer patients – may help predict which patients are more susceptible to cardiotoxicity

J Am Heart Assoc. 2021;10:e019811

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Myocardial Strain by CMR – Predicting Toxicity and Outcomes

- Prospective single-center nonrandomized study
- 61 patients (breast cancer and lymphoma)
- CMRs obtained prior to chemo treatment and q 3 – 6 months
- Cardiotoxicity defined as reduction of at least 10% points of LVEF to < 53% in patients who develop HF symptoms
- Subclinical cardiotoxicity defined as reduction in average GLS value of at least 15% compared with baseline who are asymptomatic
- Follow-up time of 2 years

Circulation: Cardiovascular Imaging

ORIGINAL ARTICLE

Multiparametric Early Detection and Prediction of Cardiotoxicity Using Myocardial Strain, T1 and T2 Mapping, and Biochemical Markers

A Longitudinal Cardiac Resonance Imaging Study During 2 Years of Follow-Up

Sorin Giusca, MD*
Grigorios Korosoglou, MD*
Moritz Montenbruck, MD
Blaž Gorišak, MD
Arne Kristian Schwarz, MD
Sebastian Esch, MD
Sebastian Kelle, MD
Pia Wülfing, MD
Susan Dent, MD
Daniel Lenihan, MD
Henning Steen, MD

BACKGROUND: Our goal was to evaluate the ability of cardiovascular magnetic resonance for detecting and predicting cardiac dysfunction in patients receiving cancer therapy. Left ventricular ejection fraction, global and regional strain utilizing fast-strain-encoded, T1 and T2 mapping, and cardiac biomarkers (troponin and BNP [brain natriuretic peptide]) were analyzed.

METHODS: Sixty-one patients (47 with breast cancer, 11 with non-Hodgkin lymphoma, and 3 with Hodgkin lymphoma) underwent cardiovascular magnetic resonance scans at baseline and at regular intervals during 2 years of follow-up. The percentage of all left ventricular myocardial segments with strain >−17% (normal myocardium [%]) was analyzed. Clinical cardiotoxicity (CTX) and sub-CTX were defined according to standard measures.

Circ Cardiovasc Imaging. 2021;14:e012459

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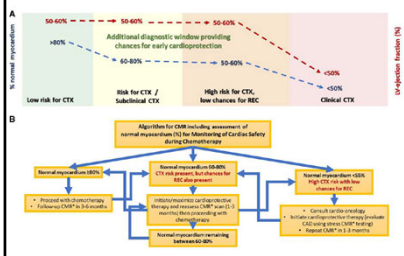
Myocardial Strain by CMR – Predicting Toxicity and Outcomes



- CMR-derived strain:
  - Detects cardiotoxicity early
  - Predicts cardiotoxicity before chemo by using % normal baseline myocardial strain
  - Predicts functional recovery from cardiotoxicity based on % normal baseline myocardial strain

Circ Cardiovasc Imaging. 2021;14:e012459

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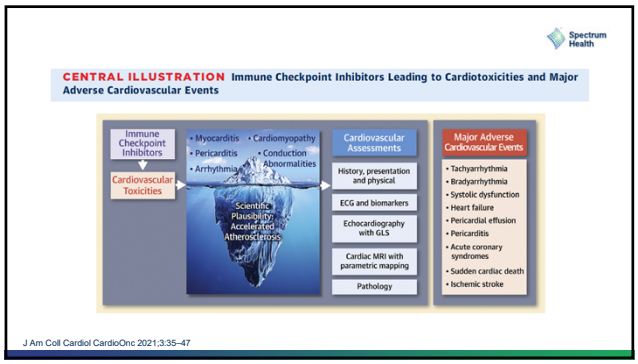
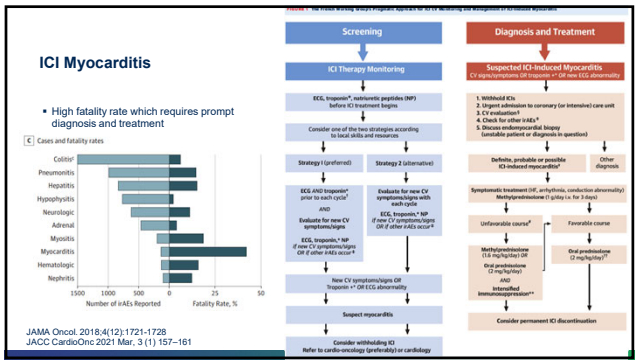
Immune-checkpoint Inhibitor (ICI) Cardiotoxicity

- Approx 36% of US population is estimated to be eligible for ICI treatment (JAMA Netw Open 2020;3:e200423)
- Clinically detectable immune-related AE in 70% to 90% of patients
- Incidence of myocarditis: single agent ICI: 0.6 – 1.3%; double agent ICI: 2.4%
- ICI-related myocarditis typically presents early after starting treatment (median 65 days or approx. after 3 cycles)
- No clear evidence that patients with underlying autoimmune disease, pre-existing CV, obesity, and diabetes mellitus are at increased risk
- Diagnosis:
  - ECG and troponin (abnormal in > 90% of cases)
  - ECHO (normal in > 60% of cases)
  - CMR (normal in ~ 50% of cases; but applying parametric mapping, abnormal in 95% of cases)
  - Endomyocardial biopsy

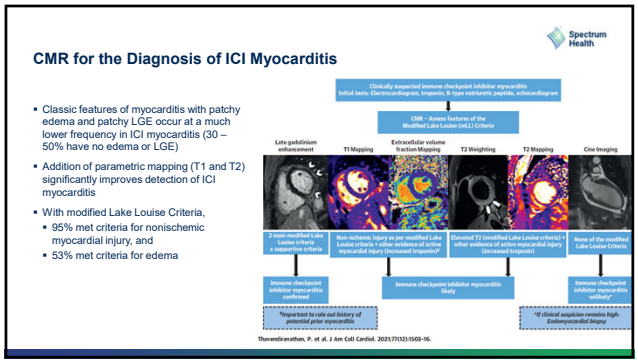
AACR Cancer Disparities Progress Report 2020



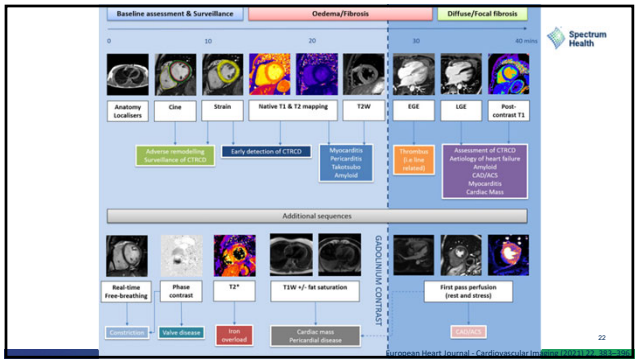
J Am Coll Cardiol CardioOnc 2021;3:35–47

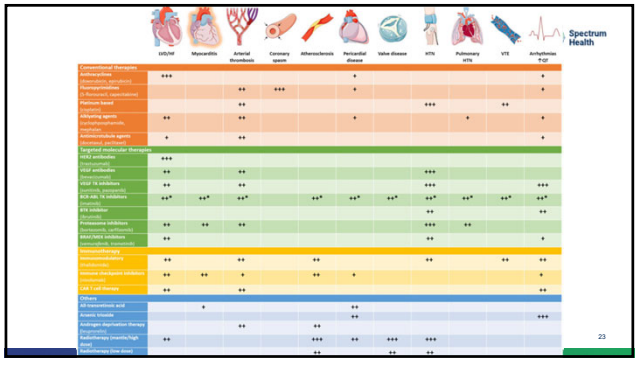


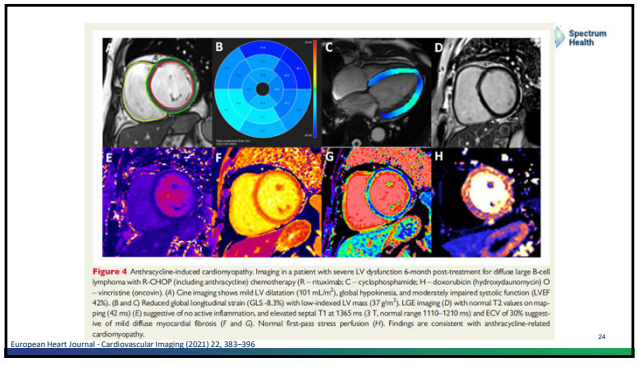
JAMA Oncol. 2018;4(12):1721-1728
JACC CardioOnc 2021 Mar, 3 (1) 157–161



Thavendiranathan, P. et al. J Am Coll Cardiol. 2021;77(12):1503-16.







European Heart Journal - Cardiovascular Imaging (2021) 22, 383–396

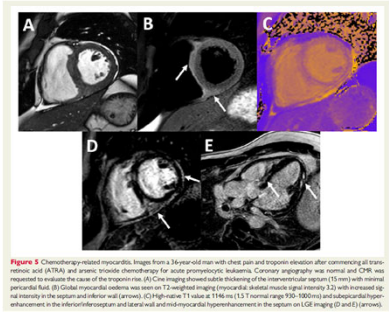


Figure 5 Chemotherapy-related myocarditis. Images from a 36-year-old man with chest pain and troponin elevation after commencing all trans-retinoic acid (ATRA) and arsenic trioxide chemotherapy for acute promyelocytic leukaemia. Coronary angiography was normal and CMR was requested to evaluate the cause of the troponin rise. (A) Cine imaging showed subtle thickening of the interventricular septum (15 mm) with minimal pericardial fluid. (B) Global myocardial oedema was seen on T2-weighted imaging (myocardial: skeletal muscle signal intensity 3.2) with increased signal intensity in the septum and inferior wall (arrows). (C) High-native T1 value at 1146 ms (1.5 T normal range 930–1000 ms) and subepicardial hyperenhancement in the inferior/inferoseptum and lateral wall and mid-myocardial hyperenhancement in the septum on LGE imaging (D and E) (arrows).

European Heart Journal - Cardiovascular Imaging (2021) 22, 383–396

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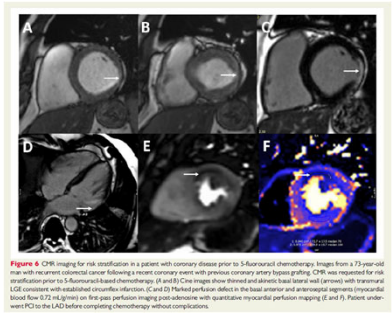

Figure 6 CMR imaging for risk stratification in a patient with coronary disease prior to 5-fluorouracil chemotherapy. Images from a 73-year-old man with recurrent colorectal cancer following a recent coronary event with previous coronary artery bypass grafting. CMR was requested for risk stratification prior to 5-fluorouracil-based chemotherapy. (A and B) Cine images show thinned and akinetic basal lateral wall (arrows) with transmural LGE consistent with established circumflex infarction. (C and D) Marked perfusion defect in the basal anterior and anteroseptal segments (myocardial blood flow 0.72 mL/g/min) on first-pass perfusion imaging post-adenosine with quantitative myocardial perfusion mapping (E and F). Patient underwent PCI to the LAD before completing chemotherapy without complications.

European Heart Journal - Cardiovascular Imaging (2021) 22, 383–396

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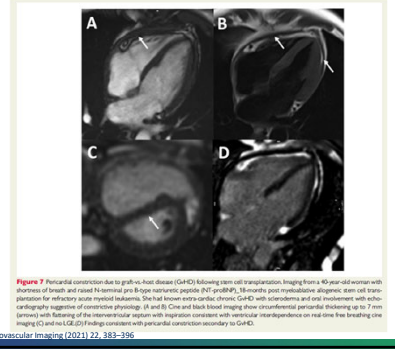

Figure 7 Pericardial constriction due to graft-vs-host disease (GvHD) following stem cell transplantation. Imaging from a 40-year-old woman with shortness of breath and raised N-terminal pro B-type natriuretic peptide (NT-proBNP), 18-months post myeloablative allogeneic stem cell transplantation for refractory acute myeloid leukaemia. She had known extra-cardiac chronic GvHD with scleroderma and oral involvement with echocardiography suggestive of constrictive physiology. (A and B) Cine and black blood imaging show circumferential pericardial thickening up to 7 mm (arrows) with flattening of the interventricular septum with inspiration consistent with ventricular interdependence on real-time free breathing cine imaging (C) and no LGE (D) Findings consistent with pericardial constriction secondary to GvHD.

European Heart Journal - Cardiovascular Imaging (2021) 22, 383–396

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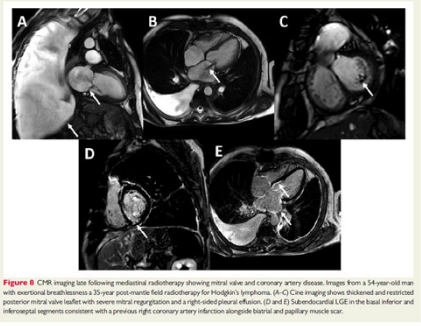

Figure 8 CMR imaging late following mediastinal radiotherapy showing mitral valve and coronary artery disease. Images from a 54-year-old man with exertional breathlessness a 35-year post-mantle field radiotherapy for Hodgkin's lymphoma. (A–C) Cine imaging shows thickened and restricted posterior mitral valve leaflet with severe mitral regurgitation and a right-sided pleural effusion. (D and E) Subendocardial LGE in the basal inferior and inferoseptal segments consistent with a previous right coronary artery infarction alongside biatrial and papillary muscle scar.

European Heart Journal - Cardiovascular Imaging (2021) 22, 383–396

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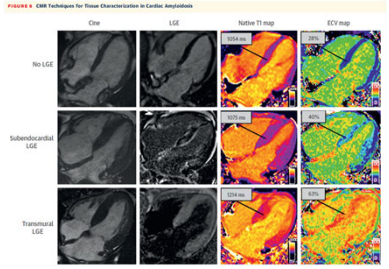
CMR for Infiltrative Cardiomyopathy - Cardiac Amyloidosis



J Am Coll Cardiol Img 2020;13:1221–34

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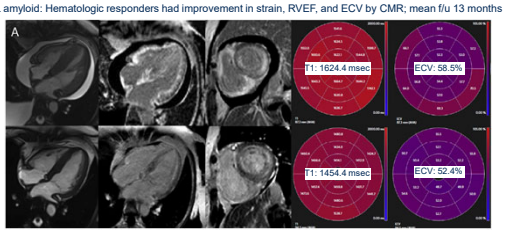
Is CMR the Holy Grail of CV Imaging?
From Diagnosis to Prognosis to Response to Treatment

AL amyloid: Hematologic responders had improvement in strain, RVEF, and ECV by CMR; mean f/u 13 months



J Let al. JACC Cardiovasc Imaging. 2021 Jul;14(7):1485-1487

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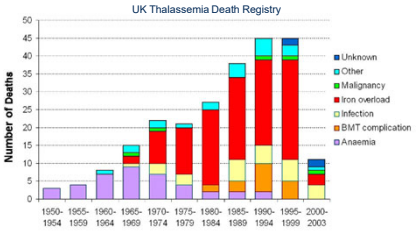
Hematologic Disorders: Iron Overload Cardiomyopathy

- T2* imaging allows quantitative assessment of iron overload for diagnosing and assessing response to treatment
- T2* < 20 msec indicates iron overload
- T2* values are used to guide chelation therapy



Journal of Cardiovascular Magnetic Resonance 2008, 10:42

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CMR for the Diagnosis of Cardiac Masses

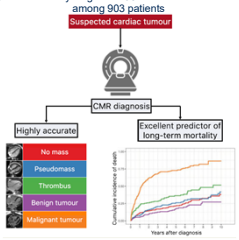
CMR allows thorough interrogation of tissue characteristics of various cardiac masses

MR Imaging Tissue Characteristics of Common Cardiac Masses

Cardiac Mass	T1-weighted Imaging*	T2-weighted Imaging*	After Contrast Enhancement (LGE Imaging)
Pseudotumor			
Thrombus	Low (high if recent)	Low (high if recent)	No uptake[2]
Pericardial cyst	Low	High	No uptake
Benign			
Myxoma	Isointense	High	Heterogeneous
Lipoma	High[2]	High[2]	No uptake
Fibroma	Isointense	Low	Hyperenhancement[6]
Rhabdomyoma	Isointense	Isointense/high	No/minimal uptake
Malignant			
Angiosarcoma	Heterogeneous	Heterogeneous	Heterogeneous
Rhabdomyosarcoma	Isointense	Hyperintense	Homogeneous
Undifferentiated sarcoma	Isointense	Hyperintense	Heterogeneous/variable
Lymphoma	Isointense	Isointense	No/minimal uptake
Metastasis[2]	Low	High	Heterogeneous

Radiology. 2013 Jul;268(1):26-43

CMR accurately diagnosed 98.4% of cardiac masses among 903 patients



European Heart Journal. 2021 Sep 21:ehab635

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Diagnosing Cancer Treatment Related Cardiotoxicity

EXPERT CONSENSUS STATEMENT

Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

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Definition of Cancer Therapeutics–Related Cardiac Dysfunction:
- Decrease in LVEF of >10% points to a value <53%
- **This decrease should be confirmed by repeated cardiac imaging performed 2-3 weeks later**

(J Am Soc Echocardiogr 2014;27:911-39.)

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Guidelines: American Heart Association

Journal of the American Heart Association

SPECIAL REPORT

Cardiovascular Toxicity Related to Cancer Treatment: A Pragmatic Approach to the American and European Cardio-Oncology Guidelines

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ABSTRACT: The considerable progress made in the field of cancer treatment has led to a dramatic improvement in the prognosis of patients with cancer. However, toxicities resulting from these treatments represent a cost that can be harmful to short- and long-term outcomes. Adverse events affecting the cardiovascular system are one of the greatest challenges in the overall management of patients with cancer, as they can compromise the success of the optimal treatment against the tumor. Such adverse events are associated not only with older chemotherapy drugs such as anthracyclines but also with many targeted therapies and immunotherapies. Recognizing this concern, several American and European governing societies in oncology and cardiology have published guidelines on the cardiovascular monitoring of patients receiving potentially cardiotoxic cancer therapies, as well as on the management of cardiovascular toxicities. However, the low level of evidence supporting these guidelines has led to numerous discrepancies, leaving clinicians without a consensus strategy to apply. A cardio-oncology expert panel from the French Working Group of Cardio-Oncology has undertaken an ambitious effort to analyze and harmonize the most recent American and European guidelines to propose roadmaps and decision algorithms that would be easy for clinicians to use in their daily practice. In this statement, the experts addressed the cardiovascular monitoring strategies for the cancer drugs associated with the highest risk of cardiovascular toxicities, as well as the management of such toxicities.

Table 2. Cardiovascular Assessment Included in the "Cardio-Oncological Evaluation"

- Clinical consultation (including BP measurement)
- ECG
- Blood glucose,* lipid profile,* glomerular filtration rate calculation
- Cardiovascular global risk assessment using guidelines[17,18]
- TTE including measurements of LVEF measurements (ideally 3-dimensional but at least 2-dimensional Simpson biplane method) and GLS. In the absence of GLS quantification of LV longitudinal function, use mitral annular displacement by M-mode echocardiography and/or peak systolic velocity of the mitral annulus by pulsed-wave DTI
- LV contrast agents could be potentially useful in 2-dimensional echocardiography
- CMR is recommended if the quality of TTE is suboptimal
- Use the same imaging modality for monitoring
- Actively manage modifiable cardiovascular risk factors and diseases
- Encourage exercise on a regular basis and healthy dietary habits

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Summary – CMR for the Cardio-Oncology Patient

- CMR is a highly accurate and comprehensive imaging modality that is critical for the optimal care of the cardio-oncology patient
- CMR is safe, radiation-free, and cost-effective
  - Medicare reimbursement rates:
    - CMR: $480
    - Echo: $536
- CMR should be considered when:
  - Echo images are suboptimal and LV dysfunction is questionable – ramifications for withholding treatment
  - Evaluating etiology of cardiomyopathy – stress CMR is also an all inclusive examination
  - Myocarditis suspected after exposure to immune-checkpoint inhibitors
  - Pericardial disease and constriction suspected after radiation exposure
  - Cardiac masses are present

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Thank you!

Questions?

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