IV Congresso
Novas Fronteiras em Cardiologia

Detecção precoce de cardiotoxicidade no doente oncológico – deve ser efectuada sistematicamente?

7 a 9 de Fevereiro 2014
Hotel Vila Galé Ericeira

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Detecção precoce de cardiotoxicidade no doente oncológico – deve ser efectuada sistematicamente?

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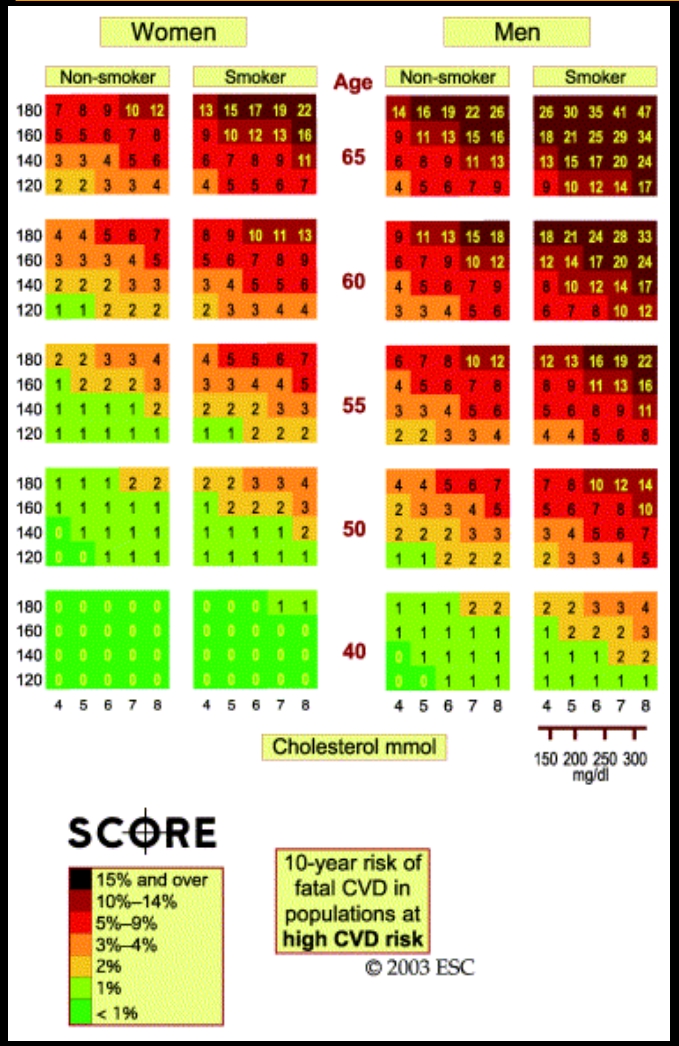
- Quais os doentes que beneficiam?
- Qual o timing da monitorização?
- Como se detecta precocemente?

Porque é importante detectar precocemente?

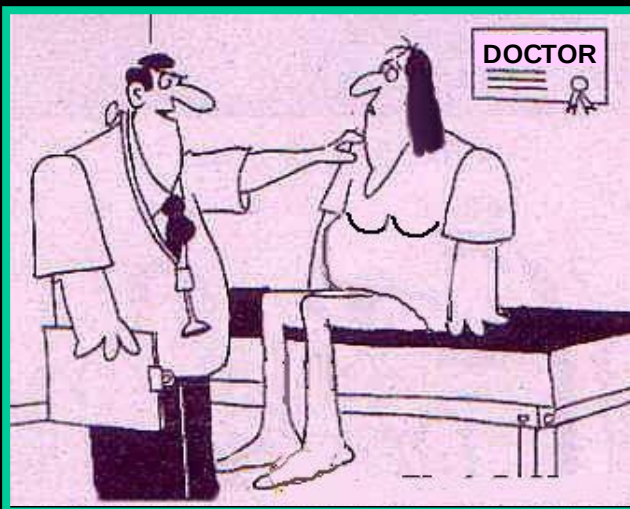
- O número de sobreviventes oncológicos é progressivamente maior
- Diminuir o risco cardiovascular destes doentes
- Tratar precocemente a disfunção sistólica VE

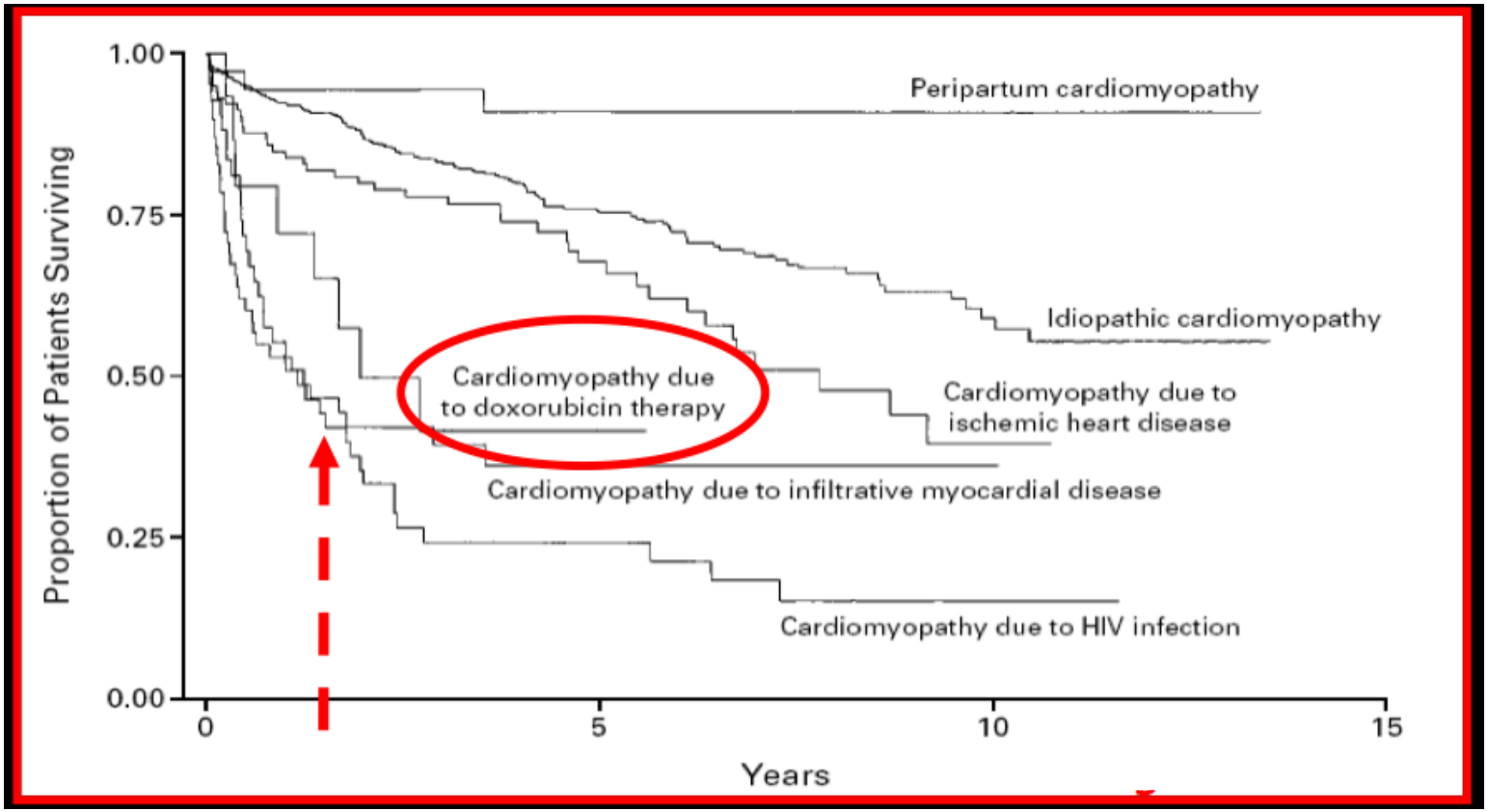
- Impedindo a suspensão de terapêutica oncológica potencialmente curativa
- Prevenir lesão cardíaca irreversível

New cardiologic approach



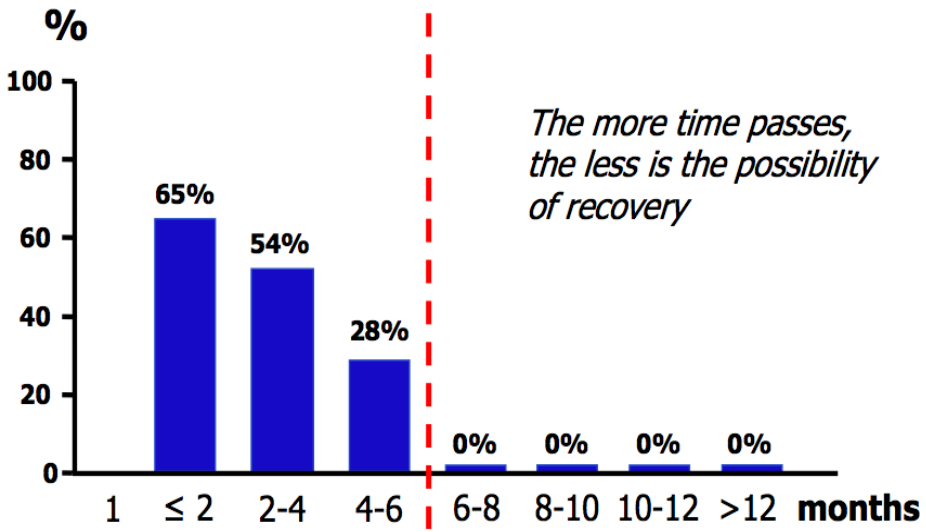
- sex
- age
- family history for CAD
- smoking
- hypertension
- diabetes
- dyslipidemia
- obesity
- sedentariness
- chemotherapy



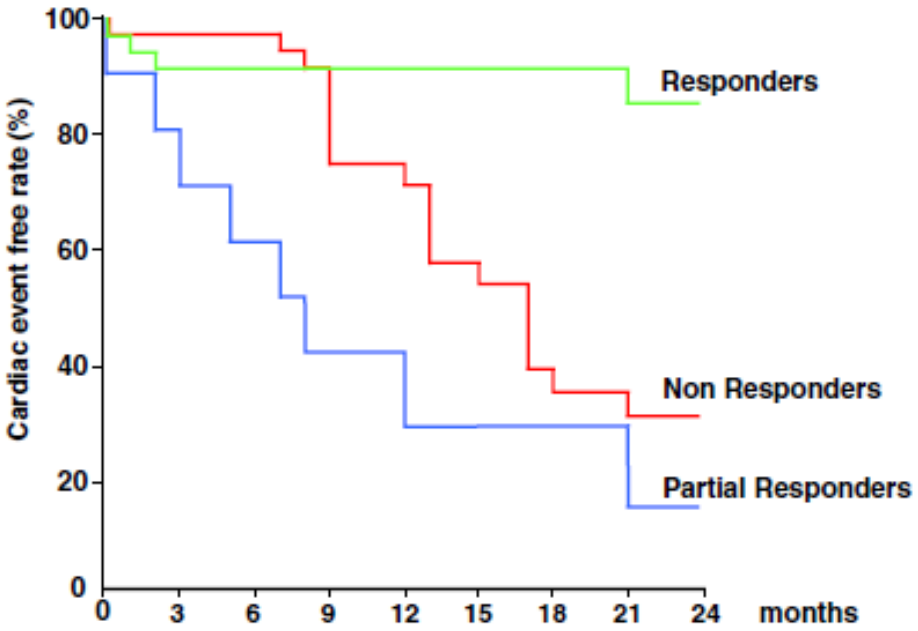


NEJM, 2000, 342:1077 – 1084

Percentage of Responders/ Time-to-HF-treatment



The more time passes, the less is the possibility of recovery



- Responders: ↑ LVEF ≥50% from baseline
- Partial Responders: ↑ LVEF <50 % +10 abs. points
- Non Responders: ↑ LVEF <50 % <10 abs. points

J. Am. Coll. Cardiol. 2010;55;213-220

Cardiotoxicidade

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Hipertensão arterial

Arritmias

Disfunção sistólica VE subclínica

Insuficiência cardíaca

Cardiac Review and Evaluation Committee criteria for the diagnosis of cardiac dysfunction

1. Cardiomyopathy characterized by a decrease in LVEF or changes of contraction most apparent in the interventricular septum
2. Heart failure symptoms
3. Signs associated with heart failure
4. Decline in initial LVEF of at least 5% to less than 55% with signs and symptoms of heart failure or asymptomatic decrease in LVEF of at least 10% to less than 55%

Seidman, *Journal of Clinical Oncology,* Vol. 20, pp. 1215 – 1221

1. Nem todos os fármacos utilizados no tratamento das doenças oncológicas têm o mesmo potencial de cardiotoxicidade

Disfunção ventricular esquerda assintomática / sintomática

Table 1 Chemotherapy Associated With Left Ventricular Dysfunction

Chemotherapy Agents	Incidence (%)	Frequency of Use
Anthracyclines		
Doxorubicin (Adriamycin) (6,7)	3–26*	+++
Epirubicin (Ellence) (10)	0.9–3.3	++
Idarubicin (Idamycin PFS) (8)	5–18	+
Alkylating agents		
Cyclophosphamide (Cytoxan) (8,11–13)	7–28	+++
Ifosfamide (Ifex) (8,14)	17	+++
Antimetabolites		
Clofarabine (Clolar) (10)	27	+
Antimicrotubule agents		
Docetaxel (Taxotere) (10,15,16)	2.3–8	++
Monoclonal antibody-based tyrosine kinase inhibitors		
Bevacizumab (Avastin) (10,18,19)	1.7–3	++
Trastuzumab (Herceptin) (20–28)	2–28	++
Proteasome inhibitor		
Bortezomib (Velcade) (10,17)	2–5	++
Small molecule tyrosine kinase inhibitors		
Dasatinib (Sprycel) (10)	2–4	++
Imatinib mesylate (Gleevec) (34,35)	0.5–1.7	+
Lapatinib (Tykerb) (32)	1.5–2.2	+
Sunitinib (Sutent) (36,37)	2.7–11	+++

Associação de fármacos cardiotóxicos

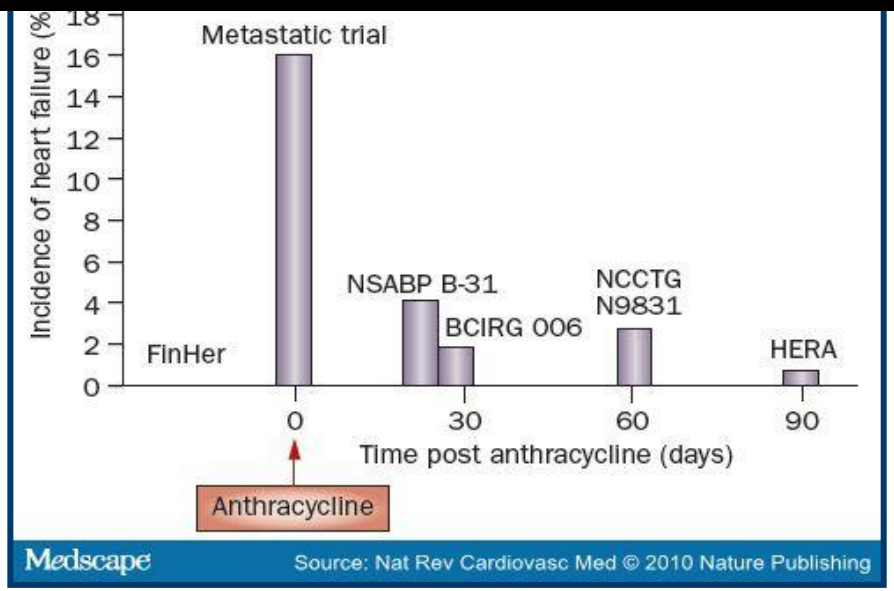
Cumulated dose dependency:

Doxorubicin-induced HF

3-5% at 400 mg/m^2

7-26% at 550 mg/m^2

18-48% at 700 mg/m^2



J. Am. Coll. Cardiol. 2009;53;2231-2247

Detecção precoce de cardiotoxicidade no doente oncológico – deve ser efectuada sistematicamente?

- **Quais os doentes que beneficiam?**
- Qual o timing da monitorização?
- Como se detecta precocemente?

- Doentes tratados com fármacos com maior potencial cardiotóxico (dose e associação)

- Doente

Idade

Factores de risco cardiovascular

Doença cardíaca prévia

Factores genéticos?

Alterações ecocardiográficas subclínicas?

Detecção precoce de cardiotoxicidade no doente oncológico – deve ser efectuada sistematicamente?

- **Quais os doentes que beneficiam?**
- Qual o timing da monitorização?
- Como se detecta precocemente?

- Doentes tratados com fármacos com maior potencial cardiotóxico (dose e associação)
- Doentes com maior risco cardiovascular

Detecção precoce de cardiotoxicidade no doente oncológico – deve ser efectuada sistematicamente?

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- Quais os doentes que beneficiam?
- **Qual o timing da monitorização?**
- **Como se detecta precocemente?**

Guideline statements	Level of evidence	Grade of recommendati
Baseline evaluation		
Patients undergoing chemotherapy should have careful clinical evaluation and assessment of CV risk factors and comorbidities. Strict attention should be paid to patient comorbidities, especially coronary artery disease and hypertension, in those patients receiving multitargeted agents, and these comorbidities should be robustly managed before and during therapy	I	A
Patients should be considered at risk for cardiac toxicity in case they have history of exposure to any of the following cumulative doses of anthracyclines as specified below. • Doxorubicin >500 mg/m^2 • Liposomal doxorubicin >900 mg/m^2 • Epirubicin >720 mg/m^2 • Mitoxantrone >120 mg/m^2 • Idarubicin >90 mg/m^2	I	A
LVEF assessment is mandatory for basal evaluation cardiac function before potential cardiotoxic cancer treatment	I	A
A standard 12-lead ECG should be recorded. The QT time should be corrected for heart rate (QTc) with Bazett's formula ($QTc = QT/\sqrt{RR}$)	I	B
Echocardiography is the standard procedure for basal assessment of cardiac structure, performance and hemodynamics. Multiple gated acquisition (MUGA) scan can reduce interobserver variability with the disadvantages of including the exposure to radioactivity and the limited information than can be obtained on cardiac structure and diastolic function. Magnetic resonance imaging (MRI) is another method used to evaluate myocardial function. Its spatial resolution is higher than that of echocardiography, but its temporal resolution is lower.	I	A

Curigliano et al. *Annals of Oncology* 23 (Supplement 7): 155–66, 2012

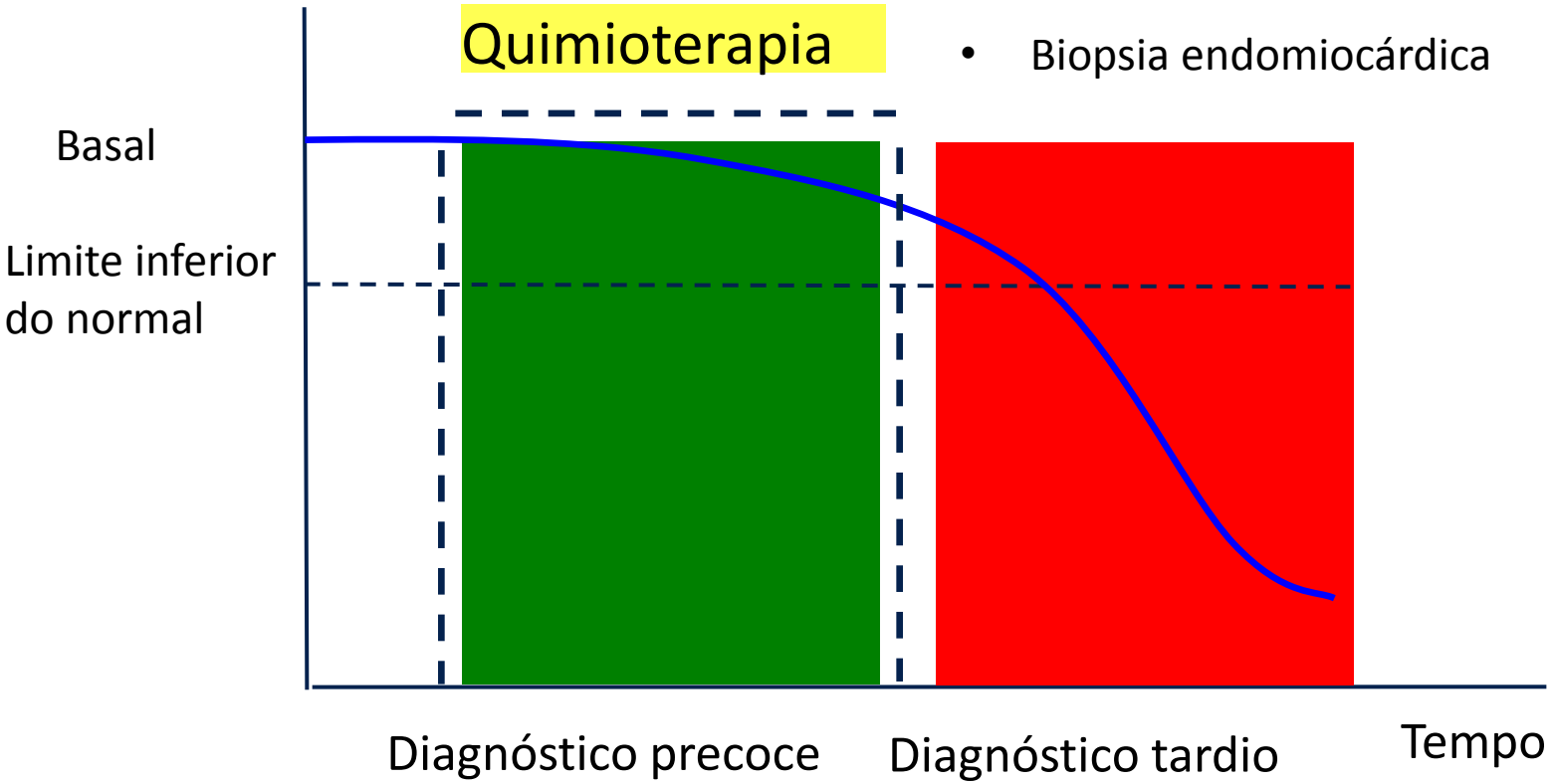
Guideline statements	Level of evidence	Grade of recommendation
Cardiac monitoring		
Patients receiving anthracyclines and/or trastuzumab in the adjuvant setting should perform serial monitoring of cardiac function at baseline, 3, 6 and 9 months during treatment, and then at 12 and 18 months after the initiation of treatment. Monitoring should be repeated during or following treatment as clinically indicated. Limited data are available for elderly patients: increased vigilance is recommended for patients ≥60 years old	I	A
Assessment of cardiac function is recommended 4 and 10 years after anthracycline therapy in patients who were treated at <15 years of age, or even at age >15 years but with cumulative dose of doxorubicin of >240 mg/m^2 or epirubicin >360 mg/m^2	II	B
Cardiac biomarkers such as the troponins and brain natriuretic peptides (BNP), and neutrophil glucosaminidase-associated lipocalin as a marker of renal injury, may be expected to be elevated with significant cardiotoxicity. Although it is not yet established whether their routine monitoring is useful in predicting cardiotoxicity, and this needs to be examined in prospective studies, there is a strong case to incorporate their use in the clinical trial setting	III	B
Aggressive medical treatment of those patients, even asymptomatic, who show LVD at DEcho after anthracycline therapy is mandatory, especially if the neoplasia could have a long-term survival; it consists of ACE inhibitors and b-blockers and the earlier HF therapy is begun (within 2 months from the end of anthracycline therapy), the better the therapeutic response		

Curigliano et al. *Annals of Oncology* 23 (Supplement 7): 155–66, 2012

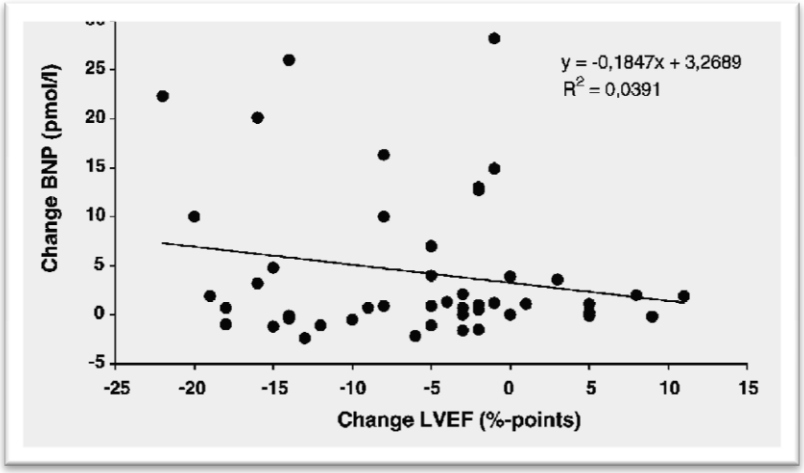
? **Ecocardiograma**
Biomarcadores

Alterações tardias

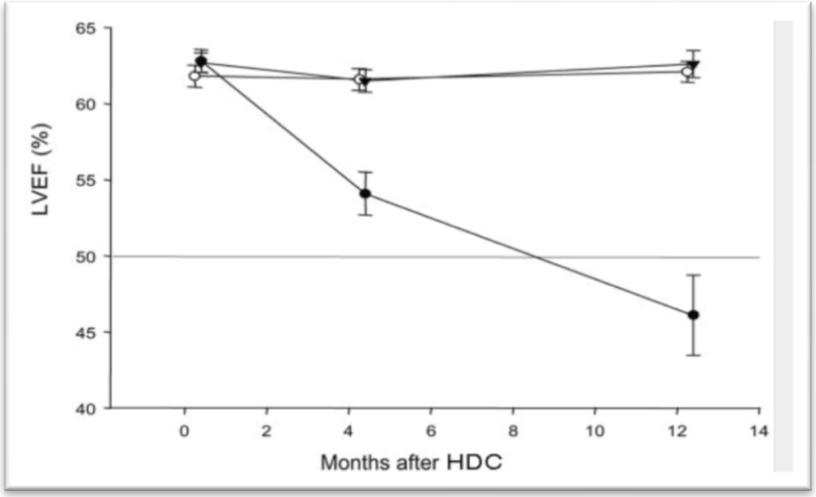
- Avaliação da FEVE
- Biopsia endomiocárdica



NT-proBNP

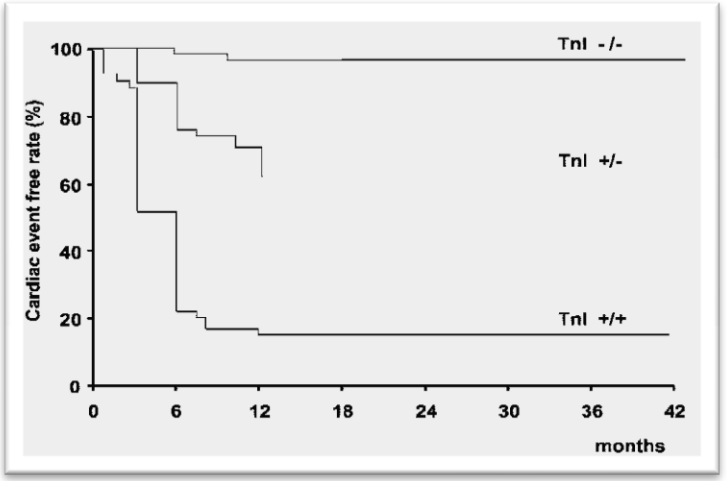


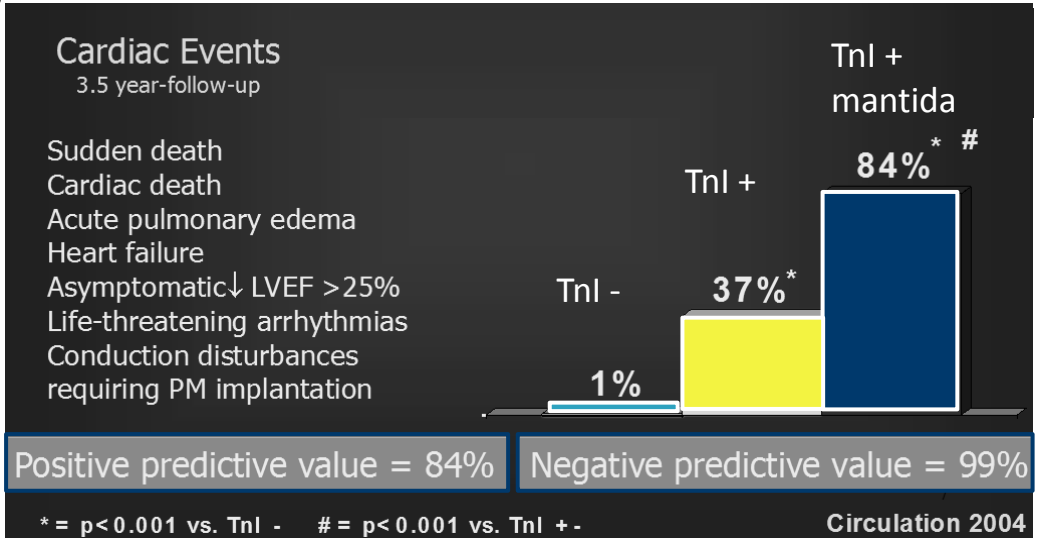
Daugaard,G. *European Journal of Heart Failure*, 2005; 7 87–93



Sandri, M. *Clinical Chemistry. 2005;* 51:8 1405–1410

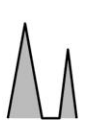
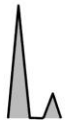
Troponina I



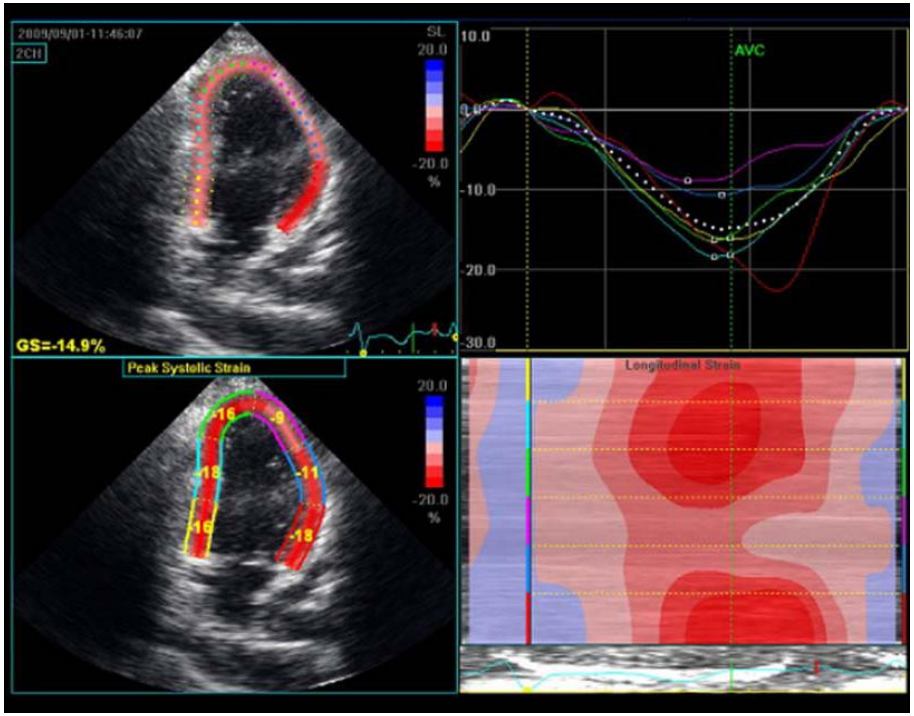


Cardinale, D. *Circulation* 2004, 109:2749-2754

Função diastólica ventricular esquerda

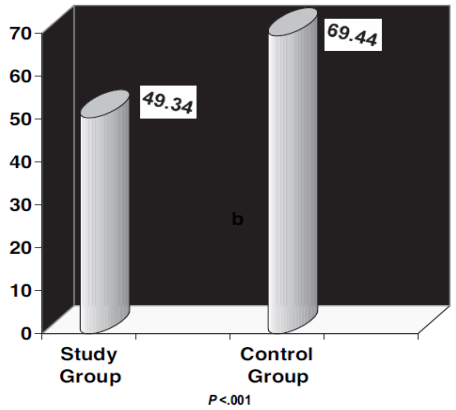
	Normal	Grade 1	Grade 2	Grade 3
PW-Doppler	 DT 140-240 ms E/A 0.75-1.5	 DT >240 ms E/A <0.75	 DT 140-240 ms E/A 0.75-1.5	 DT <140 E/A >1.5
Color M-mode	 Vp >0.45	 Vp ≤0.45	 Vp ≤0.45	 Vp ≤0.45
Tissue Doppler	 E/e´ <15	 E/e´ <15	 E/e´ ≥15	 E/e´ ≥15
LA pressure	Normal	Normal	Moderately increased	Severely increased

Deformação miocárdica ventricular esquerda

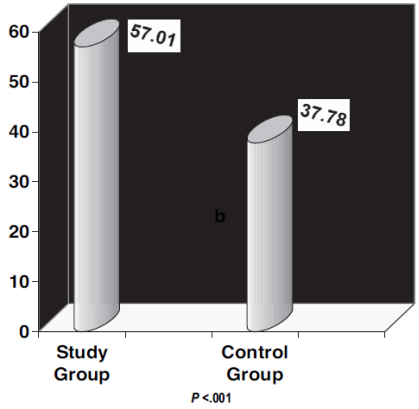


Função diastólica ventricular esquerda

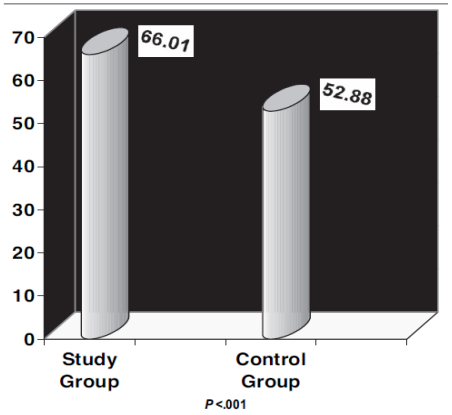
68 doentes submetidos a terapêutica com antraciclinas



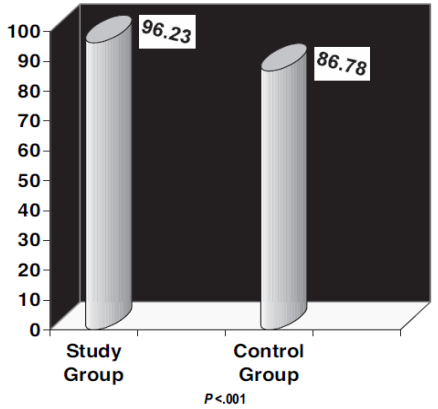
Velocidade da onda E



Velocidade da onda A



Tempo de semi-pressão



Tempo de relaxamento isovolumétrico

A disfunção diastólica representará um estadio precoce de cardiotoxicidade, permitindo predizer uma diminuição posterior da FEVE? Poderá ser utilizada para estratificação de risco nestes doentes?

Congest. Heart Failure, 2007, 13(4):215-220

Avaliação de deformação miocárdica em doentes submetidos a quimioterapia

Autor	Jornal	Ano	Nº doentes
Takenaka et al.	I. J. Cardiology	2001	19
Mercuro et al.	The Oncologist	2007	16
Mantovani et al.	The Oncologist	2008	31
Ganame et al.	Am J Cardiology	2007	13
Ganame et al.	J Am Soc Echocardiography	2007	56
Jurcut et al.	J Am Soc Echocardiography	2008	16
Hare et al.	Am Heart Journal	2009	35
Fallah-Rad et al.	J Am Coll Cardiology	2011	42
Mavinkurve et al.	EHJ – Cardiovascular Imag	2012	60

The Utility of Cardiac Biomarkers, Tissue Velocity and Strain Imaging, and Cardiac Magnetic Resonance Imaging in Predicting Early Left Ventricular Dysfunction in Patients With Human Epidermal Growth Factor Receptor II–Positive Breast Cancer Treated With Adjuvant Trastuzumab Therapy

- 42 doentes

10 doentes que desenvolveram disfunção ventricular esquerda aos 6 meses

Redução do S' lateral e do pico global de strain longitudinal e radial aos 3 meses

Echocardiographic Variables	Normal (n = 32)	CM (n = 10)	p Value
LV dimensions			
LVEF			
Baseline	62 ± 5	64 ± 3	0.31
3 months	60 ± 8	58 ± 4	0.69
6 months	64 ± 4	42 ± 9*†	<0.001
9 months	65 ± 4	39 ± 5*†	<0.001
12 months	61 ± 9	49 ± 4*†	<0.001
TDI parameters			
Mean S′ (cm/s)			
Baseline	8.9 ± 1.4	9.2 ± 1.6	0.47
3 months	9.1 ± 1.6	6.4 ± 0.6*†	<0.001
6 months	8.9 ± 0.8	4.3 ± 0.5*†	<0.001
9 months	9.0 ± 0.7	3.9 ± 0.7*†	<0.001
12 months	8.7 ± 1.1	5.8 ± 0.8*†	<0.001
2D speckle tracking			
Peak global longitudinal strain			
Baseline	−20.2 ± 2.4	−19.8 ± 1.8	0.72
3 months	−19.9 ± 2.3	−16.4 ± 1.1*†	<0.001
6 months	−19.4 ± 2.8	−15.4 ± 1.8*†	<0.001
9 months	−20.1 ± 1.7	−12.4 ± 2.1*†	<0.001
12 months	−19.8 ± 1.9	−15.9 ± 2.7*†	<0.001
Peak global radial strain			
Baseline	40.1 ± 11.1	41.4 ± 10.5	0.57
3 months	42.4 ± 13.2	34.5 ± 15.2*†	<0.001
6 months	41.3 ± 15.4	30.5 ± 16.5*†	<0.001
9 months	40.4 ± 15.2	29.4 ± 12.3*†	<0.001
12 months	44.5 ± 17.2	33.4 ± 16.4*†	<0.001

J. Am. Coll. Cardiol. 2011;57;2263-2270

Multidisciplinary approach to early detection of cardiotoxicity of oncologic treatment for Breast Cancer

TRACE BC

Multidisciplinary approach to early detection of cardiotoxicity of oncologic treatment for Breast Cancer

TRACE BC

IV Congresso Novas Fronteiras em Cardiologia

- 40 mulheres
- Idade média 53 ± 15 anos

Factores de Risco Cardiovascular	%
Hipertensão arterial	33%
Dislipidemia	26%
Diabetes *mellitus* tipo 2	15%
Obesidade	10%

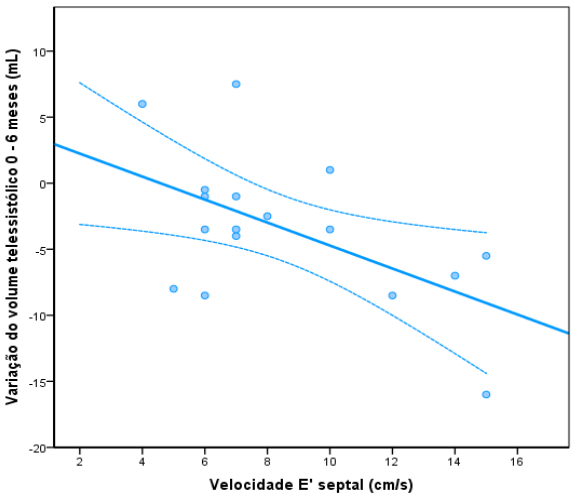
Submetidas a quimioterapia com fármacos cardiotóxicos

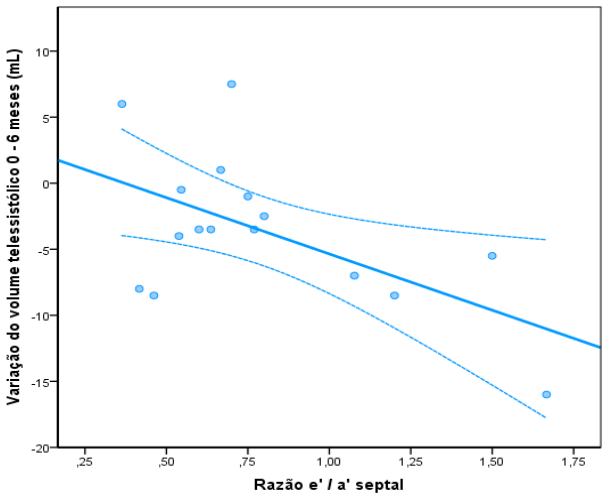
Seguimento 7±5 meses

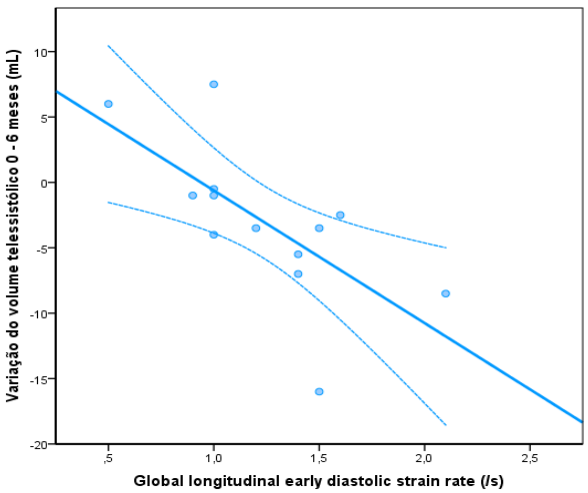
- Sem sintomas atribuíveis a insuficiência cardíaca
- Sem internamentos por causa cardiovascular

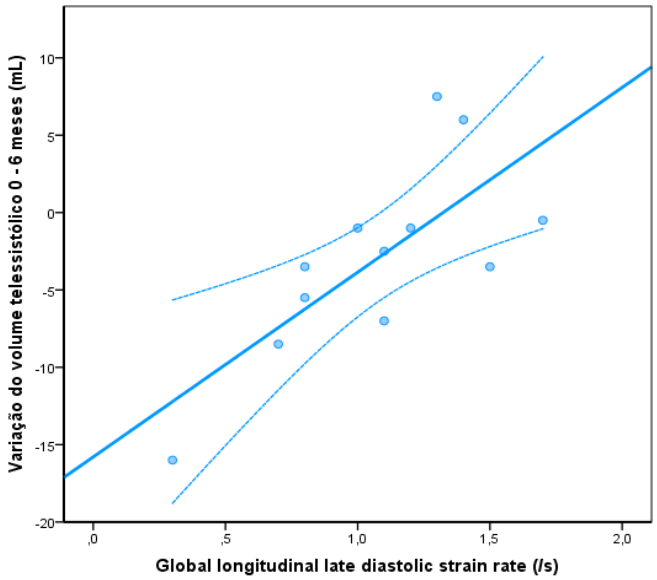
Evolução dos parâmetros ecocardiográficos durante o seguimento

Parâmetros ecocardiográficos	Basal *vs* FUp	Valor-p
Função sistólica		
Fracção de ejecção 2D (%)	69±5 *vs* 62±5%	p=0.011
Fracção de ejecção 3D (%)	62±6 *vs* 58±5%	p=0.023
Volume telessistólico VE (mL)	20±5 *vs* 27±7	p=0.010
Strain longitudinal global VE (s^{-1})	-19.2 ± 2.8 *vs* -17.9 ± 3.5	p=0.013
Função diastólica		
Velocidade E (cm/s)	83±17 *vs* 79±16	p=0.055
Razão E/A	1.09±0.30 *vs* 0.98±0.30	p=0.060
Velocidade E' (cm/s)	10.1±3.1 *vs* 8.4±1.8	p=0.037
Razão E'/A'	1.08±0.66 *vs* 0.93±0.49	p=0.007
Razão E/E'	8.9±3.0 *vs* 10.1±40	p=0.035
Early diastolic strain rate (s^{-1})	1.31±0.37 *vs* 0.95±0.30	p=0.014

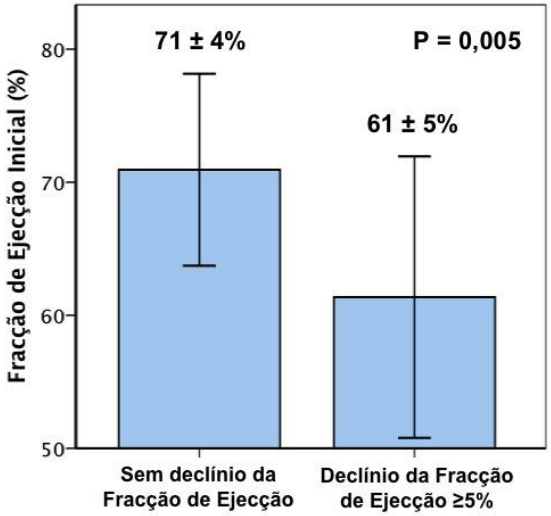


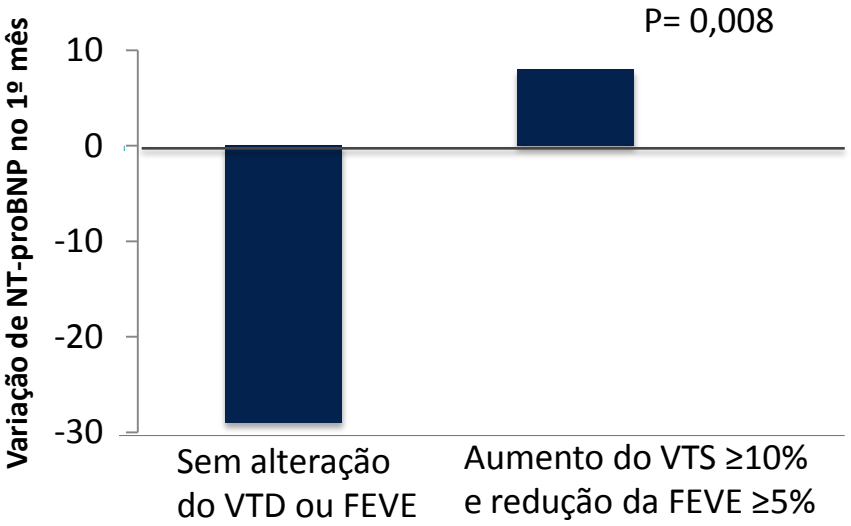


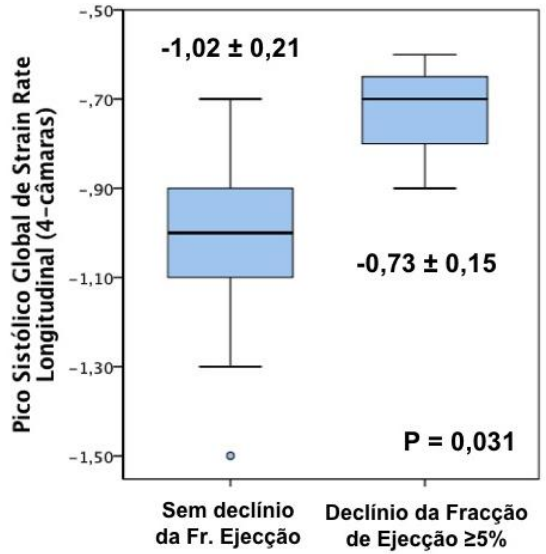


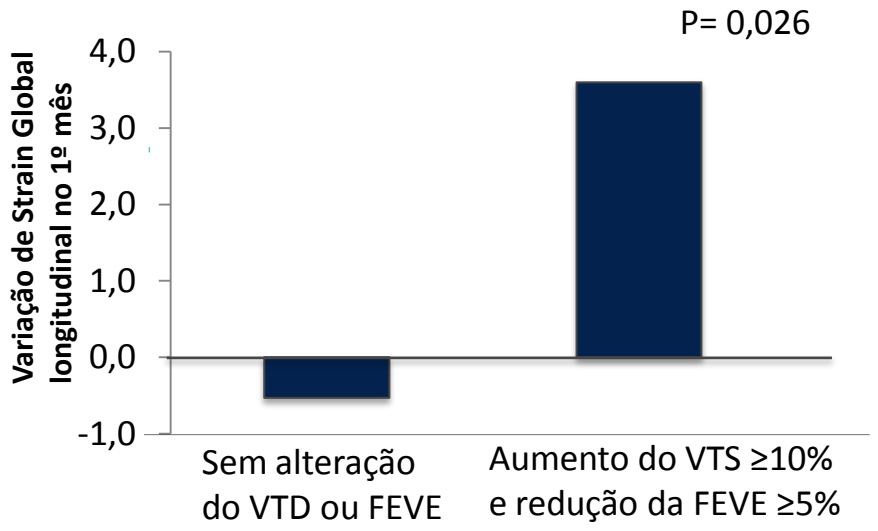


A variação do volume telessistólico aos 6 meses correlacionou-se com parâmetros de função diastólica basais


Fracção de Ejecção Inicial (%)
80
70
60
50
71 ± 4%
61 ± 5%
P = 0,005
Sem declínio da Fracção de Ejecção
Declínio da Fracção de Ejecção ≥5%


P= 0,008
Variação de NT-proBNP no 1º mês
10
0
-10
-20
-30
Sem alteração do VTD ou FEVE
Aumento do VTS ≥10% e redução da FEVE ≥5%


Pico Sistólico Global de Strain Rate Longitudinal (4-câmaras)
-,50
-,70
-,90
-1,10
-1,30
-1,50
-1,02 ± 0,21
-0,73 ± 0,15
P = 0,031
Sem declínio da Fr. Ejecção
Declínio da Fracção de Ejecção ≥5%


P= 0,026
Variação de Strain Global longitudinal no 1º mês
4,0
3,0
2,0
1,0
0,0
-1,0
Sem alteração do VTD ou FEVE
Aumento do VTS ≥10% e redução da FEVE ≥5%

CONCLUSÕES

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- Os doentes oncológicos devem ter uma avaliação clínica cuidada previamente ao início da quimioterapia
- Os doentes submetidos a terapêutica com potencial cardiotóxico e/ou que tenham doença cardíaca prévia devem ser monitorizados por ecocardiografia durante o tratamento
- Os biomarcadores e as modalidades de deformação miocárdica poderão ser úteis para detectar formas subclínicas de lesão cardíaca

Modelos de estratificação de risco cardiovascular baseados na evidência clínica
Maior colaboração entre cardiologistas e oncologistas