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Cardiotoxicidade associada ao tratamento do câncer de mama: o papel do ventrículo direito

Aluno: Géris Mazzutti

Orientadora: Professora Dra Ângela B.S.Santos

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SUMÁRIO

ABREVIATURAS

eGRF	Taxa de filtração glomerular estimada;
FEVE	Fração de ejeção do ventrículo esquerdo;
HER2	Receptor epidérmico humano 2 do fator de crescimento;
RMC	Ressonância magnética cardíaca;
SLG	*Strain* longitudinal global;
SLG VD	*Strain* longitudinal global do ventrículo direito;
SLG VE	*Strain* longitudinal global do ventrículo esquerdo;
TAPSE	Excursão sistólica do ânulo tricúspide;
TTZ	Trastuzumab;
VD	Ventrículo direito;
VE	Ventrículo esquerdo;
VFA	Variação fracional da área;

Introdução

Os avanços no tratamento do câncer são responsáveis por um expressivo aumento na expectativa de vida dos pacientes oncológicos e, de forma concomitante, pelo aumento na incidência de efeitos adversos relacionados a esses tratamentos.[1,2] A disfunção miocárdica resultante da exposição a terapias para o câncer, cardiotoxicidade, adquire especial importância, tanto em decorrência dos paraefeitos precoces, iniciados durante o tratamento, como também por danos tardios, com apresentação clínica meses ou anos após o término do tratamento. Estratégias que busquem prevenção, diagnóstico e tratamento precoces da cardiotoxicidade são de fundamental importância, evitando muitas vezes uma evolução para quadro de insuficiência cardíaca irreversível, com piora da qualidade de vida e redução da sobrevida,[3] assim como, evitando também comprometer a manutenção e o sucesso terapêutico do tratamento contra o câncer.[4] A escolha de estratégias de tratamento oncológico efetivas e com menor potencial cardiotóxico tem se mostrado um desafio para oncologistas e cardiologistas, constituindo-se terreno fértil para a consolidação da Cardio-Oncologia como uma nova área de atuação médica, estando sua existência intimamente ligada ao fato dos pacientes em tratamento oncológico serem considerados um grupo de alto risco cardiovascular, com necessidades e demandas peculiares. [5]

Câncer de mama

O câncer de mama é a neoplasia maligna mais comum do sexo feminino e uma das neoplasias mais prevalentes no mundo.[6] A mortalidade por câncer de mama apresenta redução gradual na América do Norte e Europa, predominantemente em decorrência da detecção precoce do câncer e terapias mais efetivas. Na América do Sul, África e Ásia, a incidência de câncer de mama mantém curva ascendente, muito provavelmente por mudanças no estilo de vida que agregam maior risco, como também pela dificuldade de

implementação de programas de rastreamento populacional. Diferentemente dos países desenvolvidos, nesses continentes a mortalidade pela doença ainda não demonstra sinais de redução, provavelmente devido à dificuldade de acesso ao diagnóstico precoce e tratamento otimizados.[7] O câncer de mama precoce, sem metástases à distância, é uma doença potencialmente curável.[6] Após o diagnóstico, as opções terapêuticas precisam ser definidas em equipe multidisciplinar. O tratamento cirúrgico primário, que por décadas foi o tratamento prioritário, pode não ser a melhor opção inicial para todos os pacientes.[8] Características biológicas do tumor, como presença ou ausência de receptores celulares, influenciam no prognóstico da doença, bem como nas opções terapêuticas. A presença do receptor epidérmico humano 2 do fator de crescimento (HER 2), presente em 15 a 20% das neoplasias malignas de mama, indica que o tratamento sistêmico e direcionado a este receptor agrega benefício prognóstico e revela-se uma terapia potencialmente menos tóxica. [9]

Cardiotoxicidade

Além do tratamento cirúrgico, diferentes regimes terapêuticos envolvendo quimioterapia, radioterapia, hormonioterapia e terapias alvo, são opções consideradas no tratamento do câncer de mama.[6] Doxorrubicina, ciclofosfamida, docetaxel e paclitaxel, entre outros, são quimioterápicos comumente utilizados.[9] O estadiamento da doença, estimativa do risco oncológico e a perspectiva de benefício de cada tratamento, costumam ser avaliados em conjunto com o potencial de toxicidade para a melhor definição da estratégia terapêutica. Esquemas quimioterápicos que incluam antraciclinas e taxanos, pela maior redução de risco oncológico, permanecem como escolhas prioritárias em pacientes com neoplasias de maior volume tumoral ou envolvimento linfonodal.[6] O trastuzumab (TTZ), protótipo da terapia anti-HER2, foi testado em diversos ensaios

clínicos randomizados, demonstrando que, sua adição ao tratamento quimioterápico padrão, por um ano, foi capaz de melhorar de forma significativa a sobrevida livre de doença.[10,11,12]

Antraciclinas

A cardiotoxicidade por antraciclinas, cuja principal representante é a doxorrubicina, decorre de alterações estruturais nos cardiomiócitos levando à morte celular (cardiotoxicidade tipo 1).[13] Esse fenômeno é geralmente irreversível e mediado, em parte, por radicais livres de oxigênio, gerados em reações ferro-dependentes. Os radicais livres de oxigênio levam à peroxidação da membrana do miócito e ao influxo de cálcio para o intracelular, que como consequência, determina o dano permanente ao miócito.[14] Outros mecanismos têm sido identificados, incluindo distúrbios na função da topoisomerase, enzima envolvida na transcrição e replicação do DNA. Existem duas isoenzimas topoisomerases: a topoisomerase 2-alpha (Top 2-α), superexpressa em tumores rapidamente proliferativos e a topoisomerase 2-beta (Top 2-β), expressa em células quiescentes. Em humanos, os cardiomiócitos expressam somente a Top 2- β. A cardiotoxicidade por antraciclina é possivelmente mediada, também, pela sua ligação ao DNA e Top 2- β resultando em um complexo de clivagem que determina a morte celular e consequente dano cardíaco.[15] O risco de cardiotoxicidade por antraciclinas é dose-dependente, aumentando de forma significativa com doses cumulativas elevadas. A incidência de cardiotoxicidade, que varia de 3 a 5% com dose cumulativa de 400 mg/m², aumenta para 7% a 26% com 550 mg/m² e 18% a 48% na dose de 700 mg/m².[16]

Trastuzumab

O Trastuzumab, anticorpo monoclonal com alvo na porção extracelular do receptor HER2, tem demonstrado benefício prognóstico no tratamento de tumores HER2+, principalmente quando associado à quimioterapia.[17,18] O Trastuzumab não está associado a efeitos adversos típicos da quimioterapia como: alopecia, supressão medular, náuseas e vômitos, tendo na cardiotoxicidade seu principal efeito adverso.[19] Alvo primário da ação do trastuzumab, o receptor HER2, é a porção transmembrana do fator de crescimento tirosina kinase ErbB2 e está relacionado ao crescimento, proliferação e reparo celular.[20] Tumores HER2+ tem um fenótipo de elevada proliferação, com aumento na capacidade de disseminação e estímulo à angiogênese. Estes tumores estão associados a menor resposta à terapia hormonal e a elevado risco de metástases, recorrência e morte.[10] De maneira oposta à antraciclina, que determina dano celular direto e irreversível, a citotoxicidade do trastuzumab envolve a inibição de sinais de transdução, neoangiogênese e reparo ao DNA.[16] Estudos prévios sugerem que o trastuzumab bloqueia a ativação da neoregulina-1 (NRG-1) que determina redução de mecanismos intracelulares do cardiomiócito como a capacidade de manter a estrutura e função dos sarcômeros e eliminação de subprodutos proapoptóticos da produção de ATP.[21] A cardiotoxicidade induzida pelo trastuzumab não é dose-dependente e costuma ser reversível com a suspensão do tratamento (cardiotoxicidade tipo 2). A capacidade de exacerbar ou mesmo desencadear o dano miocárdico relacionado à exposição prévia à antraciclina, através da interferência em mecanismos da homeostase e vias fisiológicas do reparo e sobrevivência celular, explicam o risco aumentado de cardiotoxicidade com a associação do trastuzumab e antraciclinas.[16]

Definição de Cardiotoxicidade

A atual definição de cardiotoxicidade relacionada ao tratamento do câncer é baseada prioritariamente na redução da função sistólica do ventrículo esquerdo, avaliada através da fração de ejeção do ventrículo esquerdo (FEVE). O ponto de corte utilizado na maioria dos estudos consiste em uma queda maior que 10 pontos percentuais (10% de redução absoluta na FEVE), ultrapassando o limite inferior da normalidade (<53%)[22] ou um valor < 50%.[23].

O ecocardiograma bidimensional, por ser um exame não invasivo, seguro, com boa reprodutibilidade e de baixo custo, é a modalidade de imagem mais comumente utilizada para monitorar a função cardíaca durante e depois do tratamento com drogas potencialmente cardiotóxicas.[24] No entanto, a avaliação da FEVE apresenta baixa sensibilidade para detectar alterações sutis da função ventricular,[25] seja por presunções geométricas da cavidade ventricular no cálculo da FEVE, inadequada visualização de bordas endocárdicas, variabilidade das medidas e dependência da pré-carga. Além disso, parte do diagnóstico de disfunção miocárdica é feito tardiamente, com quadros de insuficiência cardíaca já irreversíveis.[26] Na busca por medidas mais confiáveis e robustas para diagnóstico precoce de cardiotoxicidade através do ecocardiograma, o *strain* miocárdico por *speckle tracking* tem se destacado.[23] A avaliação do *strain* miocárdico consiste na medida da deformação miocárdica através do rastreamento de mínimas partículas de imagem (*speckles*), que pode ser feita em múltiplos planos (longitudinal, circunferencial e radial), utilizando imagens ecocardiográficas rotineiras, sendo um parâmetro menos dependente de variáveis fisiológicas como a pré-carga ventricular. Particularmente, o *strain* longitudinal global do ventrículo esquerdo (SLG VE) tem se mostrado útil na detecção da disfunção sistólica subclínica, com valor prognóstico adicional à FEVE em diferentes cenários clínicos como valvulopatias, miocardiopatias e

na avaliação de cardiotoxicidade.[27,28,29] Metanálise e revisões sistemáticas, incluindo grande número de publicações na Cardio-Oncologia, sugerem que o SLG VE seja utilizado para detecção de dano miocárdico precoce (cardiotoxicidade subclínica), podendo ser considerado atualmente um dos principais preditores de cardiotoxicidade.[30] Com isso, as diretrizes incorporaram a análise do SLG VE na avaliação de cardiotoxicidade.[22,23] A Sociedade Brasileira de Cardiologia, em seu posicionamento sobre uso de multimodalidades de imagem na Cardio-Oncologia, publicado este ano, sugere que uma queda relativa de 12% do SLG VE em relação ao exame basal, ou ainda, um SLG VE com valor absoluto > -17%, identificaria cardiotoxicidade subclínica no VE.[31] Recente estudo, mostrou que o SLG VE pode, inclusive, ser usado como guia para a terapia cardioprotetiva em pacientes de alto risco para cardiotoxicidade. [32]

Acometimento do ventrículo direito na cardiotoxicidade

A função do ventrículo direito (VD) é reconhecida por ser um importante indicador prognóstico nas doenças cardíacas[33] e um dos principais fatores associados à capacidade de exercício e desenvolvimento de dispneia em pacientes com insuficiência cardíaca.[34] A toxicidade por quimioterápicos no VD foi descrita desde os primeiros estudos que avaliaram, por biópsia endomiocárdica, o efeito cardiotóxico das antraciclinas na década de 1970.[35] Comparativamente ao VE, o VD tem sido pouco estudado e mesmo monitorado, durante e após o tratamento do câncer. O acometimento do VD no paciente oncológico pode ocorrer por diferentes mecanismos. Alguns estudos identificaram alteração na função do VD, previamente ao uso de drogas anti-neoplásicas, provavelmente relacionados à própria neoplasia e ao estado pró-inflamatório.[36] No entanto, o efeito cardiotóxico dessas drogas sobre o VD revela-se o mecanismo mais prevalente e relevante, objeto de grande interesse atualmente na área da Cardio-

Oncologia.[5] Mecanismos fisiopatológicos, tais como estrutura frágil, menor espessura parietal e menor número de miofibrilas, são descritos como potenciais fatores relacionados a uma maior sensibilidade do VD à cardiotoxicidade. [37]

Em decorrência da complexidade anatômica do VD, muitos estudos usaram ressonância magnética cardíaca (RMC) para avaliação da função VD na cardiotoxicidade, considerada o padrão-ouro para avaliação da função ventricular, mas com uso limitado pelo seu alto custo e menor disponibilidade, em relação à ecocardiografia.[38] Barthur *et al.,* estudando pacientes em uso de trastuzumab, demostrou que, mesmo na ausência de cardiotoxicidade sobre o VE, o tratamento com trastuzumab esteve relacionado à redução da função sistólica e aumento dos volumes sistólico e diastólico do VD por RMC.[39] O estudo de Grover *et al.,* avaliou mulheres em tratamento para neoplasia de mama com antraciclinas e/ou trastuzumab, com seguimento de 12 meses e reavaliações periódicas com RMC, demonstrou que uma redução maior que 10% na fração de ejeção foi mais prevalente no VD comparativamente ao VE.[37] Os estudos da função do VD pelos métodos tradicionais da ecocardiografia: excursão sistólica do ânulo tricúspide (TAPSE), onda S´ e variação fracional da área (VFA), mostram dados concordantes com os encontrados pela RMC. Boczar *et al.,* utilizando ecocardiografia, estudaram 49 pacientes com câncer de mama em uso de antraciclina e mostraram uma redução da função do VD avaliada pela alteração da VFA (48,3% para 42,1%; p = 0,01) durante os primeiros 3 meses de terapia oncológica.[40] De forma similar, Calleja *et al.,* avaliaram 40 mulheres com câncer de mama tratadas com trastuzumab, associado ou não à antraciclina, e verificaram um declínio da VFA (47% para 42%; p = 0,01).[41] Tanindi *et al*., durante avaliação da função do VD por TAPSE e onda S´, demonstraram redução da função de VD associado ao uso de drogas anti-neoplásicas.[42] No entanto, buscando medidas ecocardiográficas mais confiáveis, robustas e precoces, que sejam comparáveis ao padrão-ouro (RMC), o estudo

do *strain* de VD vem ganhando espaço na avaliação do VD.[43] Na Cardio-Oncologia, estudos têm demonstrado que tanto o *strain* da parede livre do VD como o *strain* longitudinal global do ventrículo direito (SLG VD), apresentam forte correlação com a fração de ejeção do VD acessada por RMC e demonstram maior sensibilidade na detecção de disfunção miocárdica subclínica, quando comparado a parâmetros ecocardiográficos tradicionais.[39] Keramida *et al.,* em publicação recente, avaliaram de forma longitudinal, por 12 meses, o efeito do trastuzumab sobre o VD através do SLG VD e mostraram que uma variação de −14,8% no valor do SLG VD foi capaz de predizer cardiotoxicidade com uma sensibilidade de 66,7% e especificidade de 70,8%.[44] Estudos como o de Calleja *et al.,* [41] e Boczar *et al.,* [40] embora apresentando um número limitado de participantes e com curto tempo de seguimento, apresentam resultados semelhantes, com redução do SLG VD associado ao tratamento quimioterápico e com valor prognóstico para cardiotoxicidade. A associação entre a redução do SLG VD e sintomas clínicos, como dispneia durante o tratamento oncológico, demonstrada por Chang *et al.,*[45] reforça a importância de uma adequada avaliação do VD no cenário clínico da Cardio-Oncologia.

A identificação de cardiotoxicidade no VD de forma simultânea ao VE,[37] pode sugerir um efeito uniforme das drogas anti-neoplásicas no miocárdico, tornando não apenas o VE, mas também o VD, alvo de monitoramento durante o tratamento oncológico. O número limitado de estudos nessa área, principalmente com monitoramento da função do VD por um tempo maior (acima de 1 ano) e utilização do *strain* mocárdico em cenário de cardiotoxicidade subclínica, ainda deixam lacunas no conhecimento do papel do VD na cardiotoxicidade.

Hipóteses

A função do ventrículo direito reduz gradualmente durante o tratamento com trastuzumab em pacientes com câncer de mama, especialmente quando avaliado por *strain* miocárdico pelo método de *speckle tracking*, e a redução da função do ventrículo direito é maior em pacientes que desenvolvem cardiotoxicidade subclínica do ventrículo esquerdo, comparado aos pacientes que não desenvolvem.

Objetivos

1. Em pacientes com câncer de mama e uso de trastuzumab, avaliar a função miocárdica do ventrículo direito por diferentes métodos ecocardiográficos, incluindo *strain* miocárdico por *speckle tracking*, durante 1 ano de tratamento com essa droga;

2. Em pacientes com câncer de mama e uso de trastuzumab, comparar a função miocárdica do ventrículo direito quanto à presença ou ausência de cardiotoxicidade subclínica no ventrículo esquerdo.

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Right Ventricular Function during Trastuzumab Therapy for Breast Cancer

Running tittle: Right Ventricle and Cardiotoxicity

Géris Mazzutti, MD[1,2], Fernando Pivatto Júnior, MD, MSc[2],

Guilherme Oliveira Magalhães Costa[3], Andreia Biolo, MD, PhD[1,2],

Angela Barreto Santiago Santos, MD, PhD[1,2]

[1]Cardiology Division - Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, Brazil

[2]Post-Graduate Program in Cardiology and Cardiovascular Sciences, Medical School, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil

[3]Medical School, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil

Corresponding author:

Géris Mazzutti, MD

Hospital de Clínicas de Porto Alegre – Cardiology Division

Rua Ramiro Barcelos, 2350, Room 2061. Zip code: 90035-903

Porto Alegre, RS - Brazil

Phone: +55 51 3359-8000

E-mail: gmazzutti@hcpa.edu.br

Abstract

Background. Trastuzumab (TTZ) improves survival of breast cancer patients and cardiotoxicity (CDT) is one of its main adverse effects. The role of the right ventricle (RV) in this context is not clear. We aimed to evaluate the longitudinal changes in RV function during TTZ therapy and to determine the differences in RV function associated with subclinical cardiotoxicity.

Methods and Results. In our study, the patients underwent echocardiograms at the beginning of the TTZ breast cancer treatment (Exam 1) and subsequently every 3 months during the first year of TTZ treatment (Exam 2, 3 and 4) and subclinical CDT was defined as ≥ 12% relative reduction of left ventricle global longitudinal strain (LV GLS). Our sample included 25 women, with a mean age (SD) of 52.1 ± 13.1 years. We found a decrease in left ventricle ejection fraction (LVEF) between the first and fourth exams (64.1% ± 4.9 vs 60.9% ± 4.9, p = 0.003) and the LV GLS gradually decreased during the follow-up (Ex1: -20.6 ± 2.0; Ex2: -19.4 ± 2.1; Ex3: -19.2 ± 1.8; Ex4: -19.0 ± 2.1, all p < 0.05). Regarding the RV parameters, the right ventricle global longitudinal strain (RV GLS) changed from baseline to 3 month (-23.9% ± 1.6 vs -22.5% ± 2.1 p = 0.02) and to 6 month (-23.9% ± 1.6 vs -22.5% ± 2.3 p = 0.01), and the RV Fractional Area Change (RV FAC) was lower in the third exam (Ex1: 44.3% ± 6.6 vs Ex3: 39.9% ± 6.0, p = 0.004) compared to the baseline exam. We found subclinical CDT in 13 of the 25 patients (52%), and the RV parameters had the same pattern of changing with similar values between the group with and without subclinical CDT.

Conclusion. In our sample, the RV function decreased during TTZ therapy with no differences associated with subclinical CDT. The prognostic value of deterioration of RV during the TTZ therapy needs further studies.

Keywords Cardiotoxicity, Trastuzumab, Myocardial strain, Right ventricular

Introduction

The number of cancer treatment survivors is increasing over the past few decades.[1] Adverse cardiovascular effects during and after chemotherapy are revealed to be one of the biggest challenges in the treatment of cancer patients, due to the possibility of compromising the optimal oncological therapy, and by the association with permanent cardiovascular damage and mortality.[2] The spectrum of cardiotoxicity involves from transient and asymptomatic cardiac changes, to permanent structural damage and heart failure.[3] Traditional chemotherapy drugs, as anthracyclines, and new treatments, as target therapies and immunotherapies, are related to cardiotoxicity.[2,3] Trastuzumab, a monoclonal antibody that blocks the human epidermal growth factor receptor type 2 (HER2), significantly improves the survival in patients with breast cancer HER2-positive breast cancar,[4] but it has been associated with the development of left ventricular (LV) dysfunction.[5,6]

Current international guidelines recommended monitoring LV systolic function during the use of trastuzumab, establishing parameters for interruption or modification in chemotherapy treatment when there is a reduction in the left ventricular ejection fraction (LVEF).[2] The search for early diagnosis and cardiotoxicity prevention, before the LVEF changes, remains one of the main objectives of Cardio-Oncology. New echocardiographic technique such as left ventricle global longitudinal strain (LV GLS) allows to detect subclinical LV dysfunction that would be undetectable by traditional measures on echocardiogram,[7] and predicts outcomes in different scenarios such as valvopathies and cardiomyopathies.[8,9] A reduced LV GLS has been shown to be a predictor of anthracycline-cardiotoxicity,[10] and the recent guidelines incorporated these data in order to detect subtle changes in LV function.[7] However, the RV was less studied in the context of Cardio-Oncology. Recent studies demonstrated changes on the RV structure and

function reduction during cancer treatment, especially after protocols with anthracyclines and trastuzumab.[5] Also, reduced RV function was associated with the development of symptoms such as dyspnea after treatment for breast cancer.[11] Pathophysiological mechanisms, such as fragile structure, thinner wall thickness and fewer number of myofibrils, have been described as potential factors related to the greater sensitivity of the RV to cardiotoxicity by chemotherapy.[12]

We aimed to evaluate the longitudinal changes in RV function during trastuzumab therapy for breast cancer and to determine the differences in RV function associated with subclinical LV cardiotoxicity detected by LV GLS.

Methods

Study Population

We prospectively selected patients at the Hospital de Clínicas de Porto Alegre (HCPA), a Brazilian tertiary-care teaching hospital, from June 2019 to May 2020. Inclusion criteria were age ≥ 18 years; diagnosis of early breast cancer (stage I-III) with HER2- positive and treatment plan to use trastuzumab. Patients with current or history of previous heart failure; baseline LVEF < 55%; significant valvopathy, hypertrophic cardiomyopathy, infiltrative cardiomyopathy, estimated glomerular filtration rate (eGFR) < 30mL/min/1.73 m^2) or cirrhose were excluded. The study protocol was approved by the HCPA ethics committee (IRB approval 2019-0010) and all patients signed an informed consent form. The patients underwent echocardiograms at the beginning of the breast cancer treatment (Exam 1) and subsequently every 3 months during the first year (Exam 2, 3 and 4). Out of the 28 screened patients, 25 were included in this analysis with a completed 1 year-follow up.

Echocardiography analysis

All echocardiograms were recorded and analyzed offline on a TOMTEC workstation (TomTec ImagingSystems, Unterschleißheim, Germany) by an experienced echocardiographer (GM), blinded to clinical data. Measurements were obtained according to American Society of Echocardiography (ASE) standards,[13] including septal and posterior wall thicknesses; diameters of the LV, RV, aorta, and left atrium; transmitral flow; mitral and tricuspid annular relaxation velocities; and tricuspid annular excursion.

Echocardiographic measures of RV function were performed using the apical 4-chamber RV-focused view. Tricuspid annular plane systolic excursion (TAPSE) was measured as the vertical displacement of the tricuspid annulus from end-diastole to end-systole using M-mode. The tissue Doppler-derived tricuspid lateral annular systolic velocity wave (S wave) was obtained aligning the basal segment and the tricuspid annulus with the Doppler cursor. Analysis of myocardial deformation (GLS) was performed using specific B-mode speckle-tracking software for the LV and the RV (2D CPA TTA2.20.01, TomTec). This software circumvents angle dependency and identifies cardiac motion by tracking multiple reference points over time. At end-systole, as defined by ECG, three landmarks were established at the endocardial edge (two basal and one apical), with automatic detection of speckles along the endocardial edge of the specified cavity (LV or RV). Manual adjustments were made when necessary. In the LV, peak-systolic strain for each 2D apical view (two-, three-, and four-chamber) was automatically obtained from the mean of the 6 traced segments, while LV GLS was obtained by averaging the peak-systolic strain of apical views. Subclinical cardiac dysfunction related to cancer treatment (GLS-CDRCT) was defined as a relative reduction from the baseline LV GLS of $\geq$ 12% at any follow-up time point, based on the SUCCOUR trial.[14] In the RV, RV GLS was defined as the peak-systolic strain that combined the free wall and the septum (**Figure 1**).

All patients were in sinus rhythm, and a single cardiac cycle was analyzed. Images in which poor quality precluded speckle analysis in two or more consecutive segments, images covering less than one complete cardiac cycle, or excessively tangential views were excluded. RV end-systolic and end-diastolic areas were used to derive other measures of myocardial function, such as RV FAC.

Intraobserver variability for LV GLS and RV GLS was assessed in a sample of 20 randomly selected echocardiograms. The coefficient of variation was 5.5% and 4.5% for LV GLS and RV GLS, respectively. Intraclass correlation coefficients were 0.95 for LV GLS (95% CI: 0.90-0.99) and 0.95 for RV GLS (95% CI: 0.90-0.99).

Statistical analysis

Continuous normally distributed data were displayed as mean ± standard deviation (SD) and categorical data were shown as total sample and proportion. Mean values were compared between groups using Student's t-test for continuous variables or test X^2 for categorical variables. Wilcoxon rank-sum test was used to compare eGFR, which were expressed as median values with interquartile ranges. To assess longitudinal changes of the values of the echocardiographic parameters assessed, we used repeated measures analysis of variance (ANOVA), considering the p-value from the F-test of Huynh-Feldt and followed by a post hoc analysis. To compare the differences in longitudinal changes of the RV echocardiographic parameters between the groups, we used mixed linear regression models followed by parallelism test to obtain the p-value and a post hoc analysis. All statistical analyses were performed with the STATA software package (version 12; Stata, College Station, TX). All tests were 2-sided and P values of < 0.05 were considered statistically significant.

Results

The clinical characteristics of the study population are shown in **Table 1**. All patients included in the study (n=25) were female, with a mean age of 52.1 ± 13.1 years. The prevalence of hypertension was 32%, under treatment with angiotensin-converting enzyme inhibitors in 20% and with beta-blockers in 20%. Twenty-one (84%) patients had been treated with radiotherapy and 46% also used anthracyclines (doxorubicin total dose of 240 mg/m²). None of the patients had significant heart valve disease, ischemic heart disease or renal failure.

Mean values of echocardiographic parameters of the baseline and follow-up exams are shown in **Table 2**. During the follow-up period, LVEF significantly reduced in the last exam compared with the baseline (Ex1: 64.1% ± 4.9 vs Ex4: 60.9% ± 4.9, p = 0.003), while the LV GLS decreased progressively in each follow-up exam compared to the baseline value (Ex1: -20.6% ± 2.0; Ex2: -19.4% ± 2.1, Ex3: -19.2% ± 1.8 and Ex4: -19.0% ± 2.1, all $p < 0.05$). Regarding the RV parameters, RV GLS decreased in the first two follow-up exams (Ex1: -23.9% ± 1.6 vs Ex2: -22.5% ± 2.1 p = 0.02 and Ex1: -23.9% ± 1.6 vs Ex3: -22.5% ± 2.3 p = 0.01) and the RV FAC was lower in the third exam (Ex1: 44.3% ± 6.6 vs Ex3: 39.9% ± 6.0, p = 0.004) compared to the baseline exam (**Figure 2**). The RV dimension, TAPSE and S wave did not differ during the chemotherapy period.

Of the 25 patients, only one of these had LVEF criteria for cardiotoxicity induced by chemotherapy (defined by LVEF drop of > 10% to a value < 53%)[15]. However, we found that 13 of the 25 patients in our study (52%) presented subclinical LV cardiotoxicity (GLS-CDRCT). At baseline, patients with GLS-CDRCT had larger LV dimensions compared to patients without GLS-CDRCT, but most of the clinical and echocardiographic variables were similar between the two groups (**Table 3 and Table**

4). During the chemotherapy treatment, RV dimensions and function had a similar temporal pattern with similar values between the group with and without GLS-CDRCT (**Table 5**), including the parameters that changed over the follow up time (RV GLS and RV FAC). (**Figure 3**).

Discussion

In our study, we observed that RV FAC and RV GLS reduced at around 6 months of TTZ treatment, but not RV dimension and other parameters of RV function. Our sample had a low incidence of clinical cardiotoxicity, with 52% of subclinical GLS-CDRCT, and we found no differences in RV dimension and parameters of RV function, including RV FAC and RV GLS, associated with the subclinical LV dysfunction.

Although the established evidence of the impact of TTZ in LV function,[7,16] the influence of this cancer treatment in the RV function is less well understood. Similarly, to previous studies, our data reinforced the presence of impairment RV function during the TTZ therapy - not by traditional echocardiographic measures as TAPSE and S´wave [17]- but based on reduced RV FAC and RV GLS at 6 months of chemotherapy.[18,19] The RV FAC, such as RV GLS,[20,21] seems to provide a better accurate measure of RV function compared to the gold standard magnetic resonance imaging derived RV ejection fraction,[22] besides that myocardial strain provided a more robust technique for the detection of subclinical myocardial dysfunction.[23] Keramida et al.,[19] found that a percent change of -14.8% of RV GLS predicted TTZ cardiotoxicity with 66.7% sensitivity and 70.8% specificity, a cut-off similar to the percent change of LV GLS to predict cardiotoxicity.[15] Although, the function of the RV is recognized to be an important prognostic indicator in heart disease[24] and one of the main factors associated with the

exercise capacity and development of dyspnea in patients with heart failure,[25] the prognostic implication of RV dysfunction associated with TTZ remains to be determined.

The low incidence of LVEF redution CDT in our sample (only 1 patient out of 25 total sample size) can be related to the lower anthracycline using compared to others studies,[19,26] since the CDT incidence reported in previous studies was 3% to 7% of patients who received trastuzumab monotherapy, reaching around 30% in TTZ combined treatment.[27] However, half of our sample (52%) presented subclinical GLS-CDRCT, detected by decreased of LV-GLS. In this early stage of LV dysfunction, we could not identify subtle changes in RV function associated to the presence or not of subclinical GLS-CDRCT as were observed in studies with LVEF reduction CDT.[19,26] This findings, are aligned with Keramida et al., where LV GLS is significantly decreased earlier than RV GLS in cancer treatment. The mechanism behind that is unknown, but it may justify the role of LV GLS in identifying subclinical cardiotoxicity in advance.[19]

Our results must be interpreted cautiously. The single-center design, our relatively small sample size and the low incidence of clinical cardiotoxicity, defined by decreased LV ejection fraction, are limitations to be considered.

Conclusion

In our sample with a low prevalence of LVEF redution cardiotoxicity, the RV function decreased during the trastuzumab therapy with no differences in patients with and without subclinical LV cardiotoxicity. The prognostic value of deterioration of RV during the TTZ therapy needs further studies.

Competing interests

The authors declare that they have no competing interests

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Abbreviations

ASE, American Society of Echocardiography; CDRCT, cardiac dysfunction related to cancer treatment; GLS, global longitudinal strain; HCPA, Hospital de Clínicas de Porto Alegre; HER2, human epidermal growth factor receptor type 2; LVEF, left ventricular ejection fraction; LV, left ventricular; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle; RV FAC, right ventricle fractional area change; eGRF, estimated glomerular filtration rate; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

Table 1. Clinical characteristics of the study population (n=25).

Age, years	52.1 ± 13.1
Weight, kg	74.3 ± 14.8
Height, cm	157 ± 5.9
BMI, kg/m²	29.9 ± 6.0
SBP, mmHg	130.2 ± 18.7
DBP, mmHg	82.2 ± 12.6
Heart rate, bpm	84.0 ± 11.0
eGFR, mL/min/1.73 m²	102.4 (81.9-129.1)
Hypertension	8 (32%)
Type 2 diabetes	3 (12%)
Smoking	13 (52%)
Obesity	12 (48%)
Radiotherapy	21 (84%)
Anthracyclines	11 (46%)
Angiotensin-converting enzyme inhibitor	5 (20%)
Beta-blockers	5 (20%)

** Values noted as mean ± SD, median (IQR) or N (%).
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGRF, estimated glomerular filtration rate.

Table 2. Mean values of echocardiographic parameters of the baseline and follow-up.

	Exam 1	Exam 2	Exam 3	Exam 4
LVEF, %	64.1 ± 4.9	61.6 ± 6.6	62.3 ± 6.7	60.9 ± 4.9*
LV GLS, %	-20.6 ± 2.0	-19.4 ± 2.1*	-19.2 ± 1.8*	-19.0 ± 2.1*
RV basal, mm	34.4 ± 4.1	35.1 ± 3.7	34.9 ± 3.0	34.6 ± 3.0
RV FAC (%)	44.3 ± 6.6	42.9 ± 5.7	39.9 ± 6.0*	42.1 ± 6.2
TAPSE, mm	21.9 ± 3.0	20.2 ± 2.3	20.8 ± 3.4	21.5 ± 3.8
S´ wave, cm/s	13.1 ± 1.2	12.7 ± 2.0	12.6 ± 2.0	12.5 ± 2.1
RV GLS	-23.9 ± 1.6	-22.5 ± 2.1*	-22.5 ± 2.3*	-23.1 ± 2.2
FW GLS	-26.6 ± 2.5	-25.9 ± 3.0	-24.7 ± 3.8*	-26.1 ± 3.5

Data are presented as the mean + SD.
*$p < 0.05$ compared to Exam 1 (baseline).
Exam 1 baseline echocardiogram; Exam 2 echocardiogram performed between 3 and 6 months; Exam 3 echocardiogram performed between 6 and 9 months; Exam 4 echocardiogram performed between 9 and 12 months.
LVEF, left ventricular ejection fraction; LV GLS, left ventricular global longitudinal strain; RV, right ventricular; FAC: Fractional Area Change, TAPSE, tricuspid annular plane systolic excursion; S´ wave, tricuspid annular peak systolic velocity; RV GLS, right ventricular global longitudinal strain; FW GLS, right ventricular free wall global longitudinal strain.

Table 3. Clinical characteristics in patients with and without subclinical LV cardiotoxicity.

Variable	No LV subclinical cardiotoxicity n=12	LV subclinical cardiotoxicity n=13	P-value
Age, years	50.8 ± 10.1	53.4 ± 15.8	0.633
Weight, kg	72.4 ± 8.0	76.1 ± 19.2	0.533
Height, cm	155 ± 5.1	159 ± 6.8	0.097
BMI, kg/m²	30.0 ± 3.9	29.8 ± 7.6	0.943
SBP, mmHg	132.4 ± 20.7	128.3 ± 17.5	0.613
DBP, mmHg	85.9 ± 12.7	79.1 ± 12.2	0.194
Heart rate, bpm	76.5 ± 12.2	74.9 ± 11.5	0.750
eGFR, mL/min/1.73 m²	105.1 ± 35.4	118.3 ± 56.8	0.491
Hypertension	4 (33%)	4 (31%)	0.891
Type 2 diabetes	1 (8%)	2 (15%)	0.588
Obesity	7 (58%)	5 (38%)	0.320
Smoking	7 (58%)	6 (46%)	0.543
ACEI/ARB	2 (17%)	3 (23%)	0.689
Beta-blockers	3 (25%)	2 (15%)	0.548
Radiotherapy	11 (92%)	10 (77%)	0.315
Anthracyclines use	5 (42%)	6 (46%)	0.682

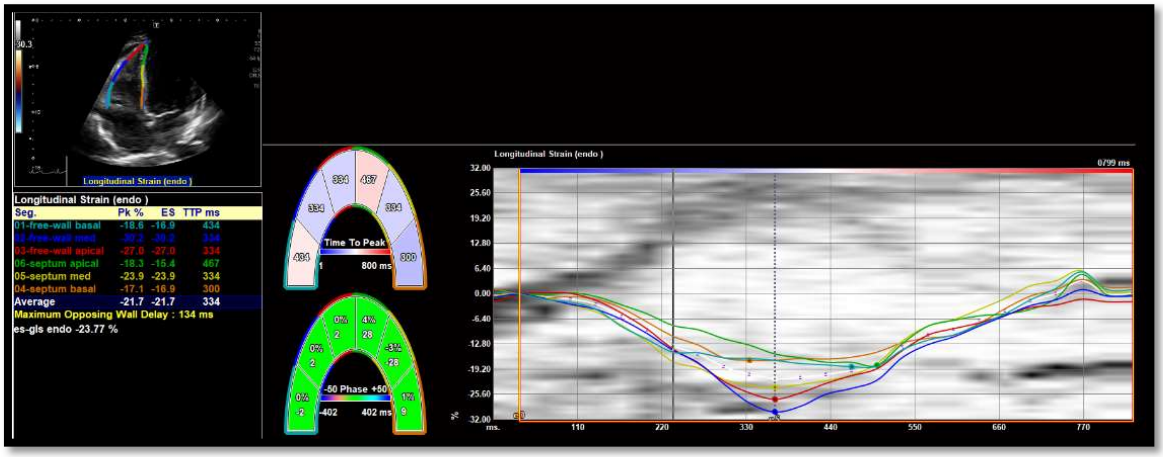
** Values noted as mean ± SD or N (%).
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure eGRF, estimated glomerular filtration rate; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

Table 4. Echocardiographic baseline parameters in patients with subclinical cardiotoxicity and without subclinical cardiotoxicity

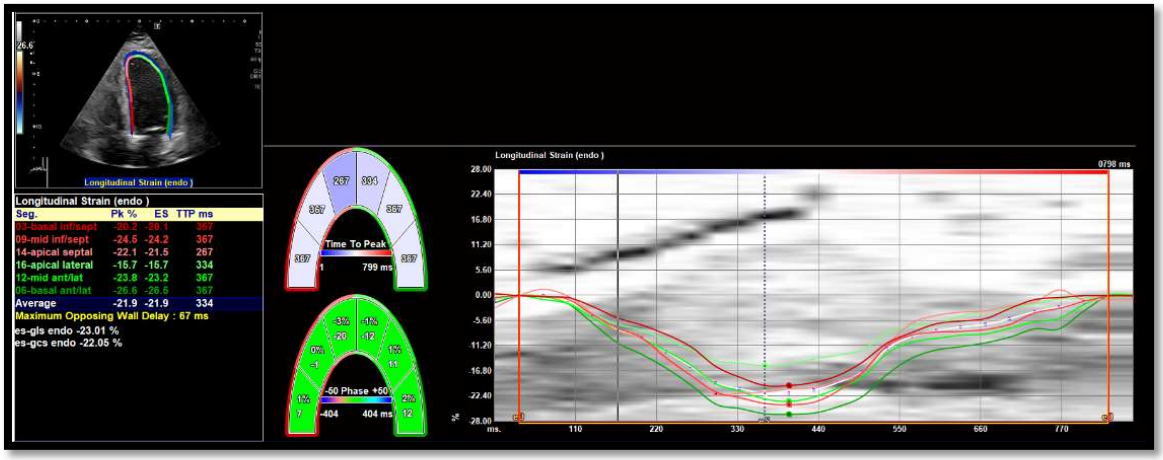
Variable	No LV subclinical cardiotoxicity n=12	LV subclinical cardiotoxicity n=13	P-value
LV diastolic diameter, cm	45.3 ± 2.7	50.5 ± 3.2	0.0002
LV systolic diameter, cm	29.5 ± 2.5	32.7 ± 4.1	0.027
Septal wall thicknesses, cm	8.0 ± 0.7	8.5 ± 1.0	0.214
Posterior wall thicknesses, cm	7.7 ± 0.5	8.1 ± 1.0	0.188
LV Diastolic Volume, mL	86.6 ± 16.6	112.0 ± 31.7	0.02
LV Systolic Volume, mL	37.6 ± 12.1	49.6 ± 15.2	0.039
LVEF, %	64.2 ± 4.4	64.0 ± 5.5	0.934
LA diameter, cm	34.8 ± 3.9	36.9 ± 4.7	0.222
LA volume, mL	52.1 ± 11.2	62.5 ± 22.9	0.191
E/e´ mean	8.4 ± 2.1	7.9 ± 2.9	0.666
Transtricuspid gradient, mmHg	23.2 ± 7.9	24.9 ± 4.6	0.723
RV baseline, mm	34.3 ± 3.7	34.5 ± 4.5	0.938
TAPSE, mm	21.7 ± 2.6	22.1 ± 3.5	0.771
S´ wave, cm/s	13.6 ± 0.9	12.7 ± 1.3	0.116
RV FAC, %	44.7 ± 6.9	43.9 ± 6.5	0.79
RV GLS, %	-23.8 ± 1.8	-24.1 ± 1.4	0.662
FW GLS, %	-26.4 ± 2.8	-26.8 ± 2.3	0.740

Data are presented as the mean + SD.
LVEF, left ventricular ejection fraction; LA: left atrial; RV, right ventricular; FAC: Fractional Area Change, TAPSE, tricuspid annular plane systolic excursion; S´ wave, tricuspid annular peak systolic velocity; RV GLS, right ventricular global longitudinal strain; FW GLS, right ventricular free wall global longitudinal strain.

Figure 1. Right ventricle global longitudinal strain (Figure 1A) and left ventricle global longitudinal strain (Figure 1B).



1A



1B

Figure 2. Mean values of left ventricular global longitudinal strain (figure 2A), right ventricular global longitudinal strain (figure 2B) and right ventricular fractional area change (figure 2C) during trastuzumab therapy.

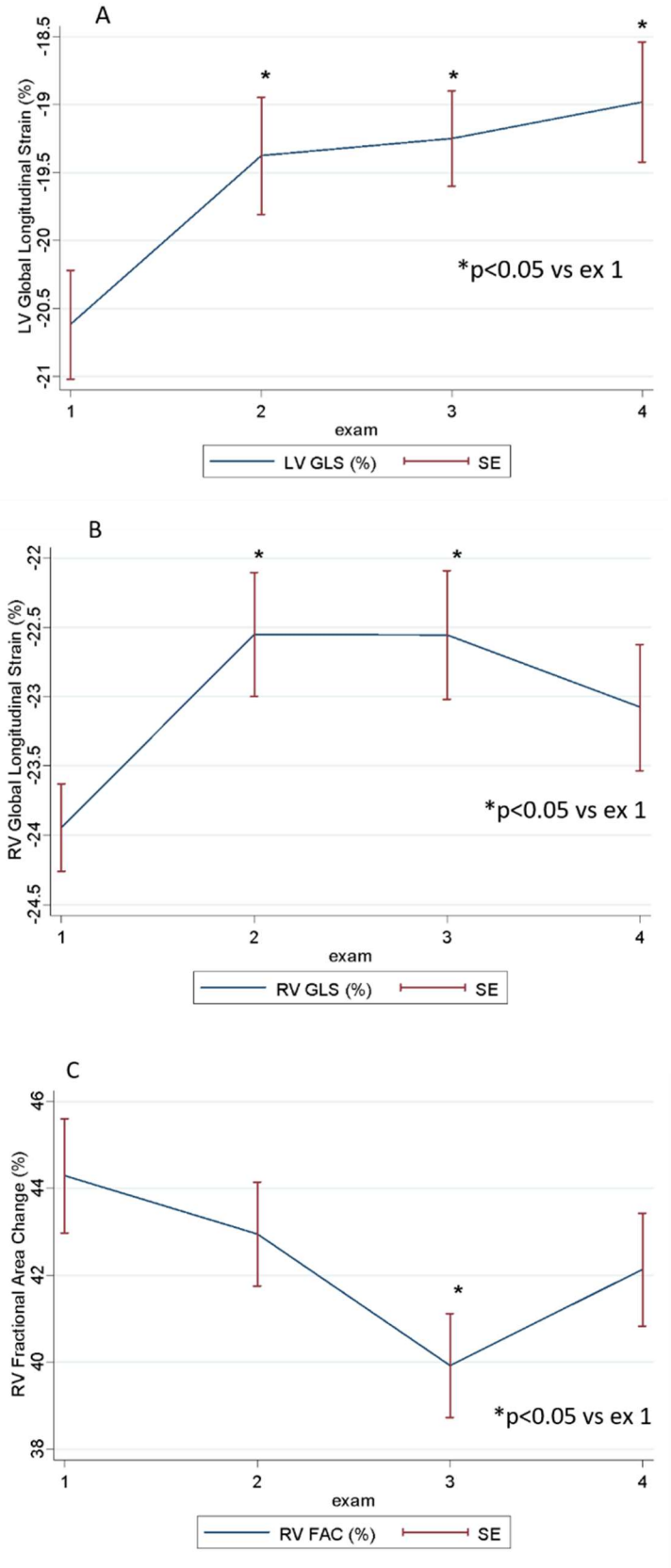
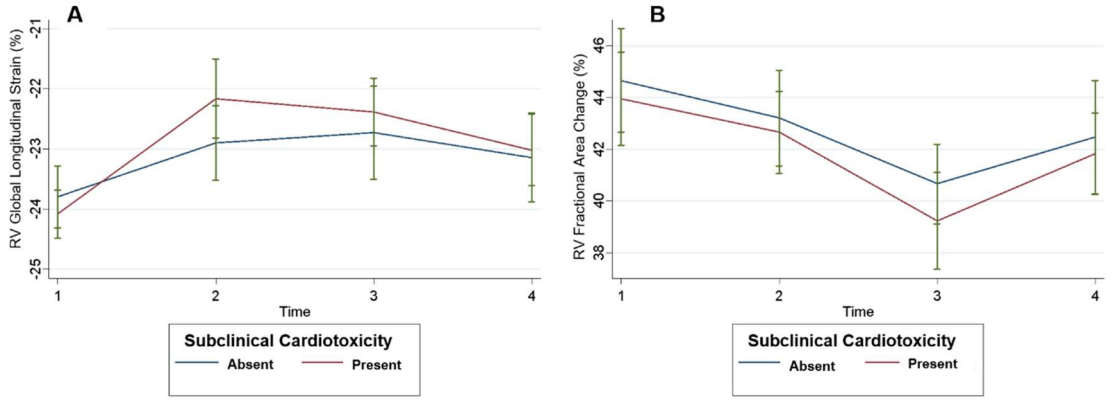


Figure 3: Mean values of right ventricular global longitudinal strain (figure 3A) and right ventricular fractional area change (figure 3B) during trastuzumab therapy in patients with subclinical cardiotoxicity and without subclinical cardiotoxicity.



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CONCLUSÃO

A correta identificação do dano cardíaco em tempo hábil para tratamento sem interferência no prognóstico oncológico é um grande desafio da interação Cardio-Oncologia. Mecanismos de avaliação e acompanhamento da cardiotoxicidade sobre o VE são mais estudados e melhor compreendidos comparativamente ao VD. As características anatômicas e funcionais do VD, além da importância fisiológica da função de VD como preditora de capacidade funcional e de qualidade de vida, constituem um cenário clínico de extrema relevância na Cardio-Oncologia. A limitação dos métodos ecocardiográficos rotineiros na avaliação de VD, além da capacidade do SLG em detectar dano miocárdico precoce, aumentam as perspectivas futuras para sua ampla utilização na prática clínica. Em nosso estudo, a função do VD apresentou redução durante o tratamento com trastuzumab, contudo, sem diferenças quanto à presença ou ausência de cardiotoxicidade subclínica sobre o VE. O valor prognóstico da deterioração da função do VD durante a terapia com trastuzumab ainda necessita de mais estudos.