Review Article

My Approach to the Echocardiographic Assessment of a Pediatric Patient with Cancer

Como eu faço Avaliação Ecocardiográfica do Paciente Oncológico Pediátrico

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What is the importance of cardiovascular assessments in pediatric patients with cancer?

Pediatric oncology has greatly progressed in recent decades due to the development of more effective treatment protocols; in fact, 5-year disease-free survival rates now exceed 80%. However, despite improved survival rates, the cardiovascular risks arising from these therapies are 5- to 6-fold greater in long-term surviving oncology patients than the general pediatric population.[1,2] Thus, cardiovascular events, such as myocardial infarction, heart failure, and stroke, are the major cause of non-cancer death in these patients.[1]

Cardiotoxicity is defined as any structural or functional damage incurred by the heart and circulation during or after cancer treatment. These changes may be caused by chemotherapeutic agents, radiotherapy, or even the disease itself (Table 1). Cardiotoxicity may present as symptomatic or asymptomatic heart failure, pericardial changes, arrhythmias, thromboembolic events, arterial hypertension, or valve and coronary diseases[3,4] and can be classified by time of onset as follows:[5]

- Acute cardiotoxicity: occurs soon after treatment initiation but is rare; may be reversible; most commonly presents as arrhythmias and ventricular dysfunction (Figure 1).
- Early-onset cardiotoxicity: occurs in the first year after the end of cancer treatment; usually progressive, featuring ventricular dilation and dysfunction.
- Late-onset cardiotoxicity: diagnosed after the first year of the end of treatment and is more common; characterized by dilated or restrictive cardiomyopathy (Figure 2).

What are the main risk factors for cardiotoxicity?

- Age, especially in children younger than 5 years of age, and a high risk of cardiotoxicity in children younger than 1 year of age;
- Female sex;
- Accumulated anthracycline doses greater than 240 mg/m^2, but it depends on individual susceptibility, with reports of cardiotoxicity at doses lower than 100 mg/m^2, and THERE IS NO SAFE DOSE;
- Thoracic radiotherapy at doses above 30 Gy greatly increases the risk of cardiotoxicity, as does associated use of anthracyclines;
- Combined therapies, such as cyclophosphamide, vincristine, mitoxantrone, among others, can potentiate toxic effects on the cardiovascular system. Special attention should be directed to new-generation drugs (tyrosinase inhibitors, chimeric antigen receptor T-cell therapy, immune checkpoint inhibitors, etc.) and its impact on the myocardial units;
- Pre-existing risk factors include arterial hypertension, valvular heart disease, cardiomyopathy, congenital heart disease, and previous high-risk treatment for cardiotoxicity;
- Alcohol, tobacco, and illicit drug use;
- Comorbidities including diabetes, obesity, kidney disease, endocrinopathy, infection, and previous thrombosis; and
- Others include trisomy 21, African descent, and genetic predisposition.[6]

How to proceed with echocardiographic follow-up?

These patients should be followed up using multimodal imaging methods, electrocardiography, metabolic screening, and specific biomarkers whenever available. The patient should always be assessed before (initial tests), during, and after treatment (long-term follow-up). The objective is the early detection of cardiovascular changes. Thus, echocardiography is a useful tool due to its high accessibility, noninvasive nature, and low cost in addition to diagnosis of any subclinical dysfunction.

Cardiotoxicity is traditionally diagnosed by echocardiography as a 10-point drop in left ventricular (LV) ejection fraction (LVEF) compared to the initial assessment test (<55% is reference for pediatric patients).[10] However, this diagnosis by LVEF or shortening fraction alone is suboptimal, as it does not include preclinical myocardial injury changes but is affected by common conditions such as sepsis, pulmonary hypertension, and hyperhydration. Thus, volumetric LVEF (two- or three-dimensional), myocardial deformation, and diastolic analyses are fundamental to better follow-up.

Keywords

Cadio-Oncology, Echocardiography, Pediatrics.

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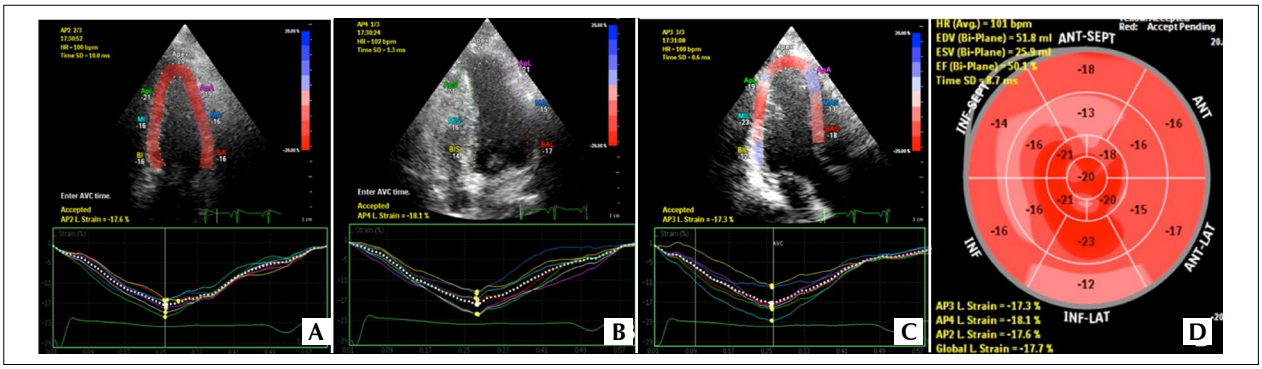

Figure 1 – *Acute cardiotoxicity. Images of a 10-year-old female patient diagnosed with acute lymphocytic leukemia. Left ventricular global longitudinal strain (GLS) was obtained from four- (A), two- (B), and three-chamber (C) images. Bullseye plot (D) showing discreet ventricular dysfunction. Left ventricular ejection fraction (LVEF) = 50%. Reduced GLS = -17.7% with changed segmental contractility.*

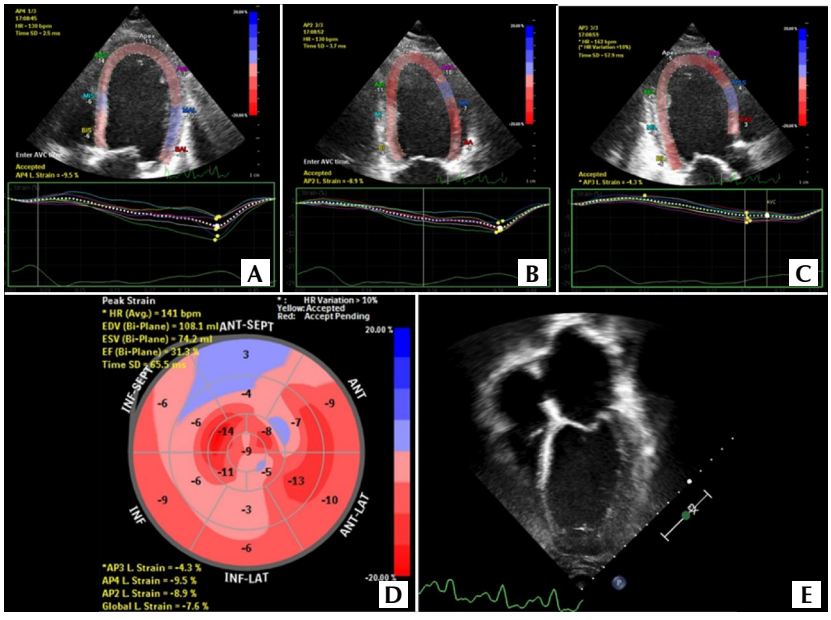

Figure 2 – *Late-onset cardiotoxicity. Images of a 22-year-old woman with a history of acute lymphoblastic leukemia taken 18 years after the end of cancer treatment. Left ventricular global longitudinal strain (GLS) obtained from four- (A), two- (B), and three-chamber (C) images. Bullseye plot (D) showing ventricular dysfunction. Left ventricular ejection fraction = 31%. Very reduced GLS = -7.6% with changed segmental contractility and areas of dyskinesia (blue). (E) Left heart chamber dilation.*

Echocardiographic assessment:

LV systolic function

Volumetric LVEF analysis

The biplane Simpson's method (Figures 3A, 3B) for estimating myocardial function from LV volumes overcomes the limitations of shortening methods and the Teichholz formula derived from linear M-mode or two-dimensional measurements. It should be the test of choice for myocardial function analyses in patients with cancer. Most popular volumetric techniques to obtain LVEF are Simpson's method. In younger patients, this could be shortened in the two-chamber apical view and the area-length or bullseye method using the formula V = 5/6 of the short-axis basal area × LV length (Figure 3C) as an alternative.

Three-dimensional LVEF analysis (Figure 3D) is a promising method. The software currently performs semi-automated calculations to estimate the three-dimensional volume with improved image acquisition and data processing. However, this remains challenging to perform in the pediatric population.

LV global longitudinal strain

Myocardial strain analysis derived from two-dimensional speckle tracking is growing in popularity that is less dependent

Table 1 - Cardiovascular system damage caused by main oncological treatments used in pediatric oncology patients.[7,8]

Agent	Examples	Cardiovascular damage
Anthracyclines	Doxorubicin Daunorubicin *Mitoxantrone	Arrhythmia Ventricular dysfunction Myocardial fibrosis Endothelial dysfunction
Alkylating agents	Cyclophosphamide Busulfan	Arrhythmia Endothelial dysfunction Pericardial effusion Thrombosis
Antimetabolites	Cytarabine (Ara-C) Cisplatin Methotrexate 5-Fluorouracil	Arrhythmia Myocardial ischemia
Tyrosine kinase inhibitors	Imatinib Dasatinib Pazopanib	Arterial hypertension Endothelial dysfunction Prolonged QTc Thrombosis Ventricular dysfunction Pericardial effusion
Vinca alkaloids	Vincristine	Myocardial ischemia
Radiotherapy		Pericarditis Valve disease Coronary artery disease Systemic arterial hypertension Ventricular dysfunction
Immunotherapy	Immune checkpoint inhibitors CAR T-cell therapy	Arterial hypertension Endothelial dysfunction Prolonged QTc Thrombosis Ventricular dysfunction Pericardial effusion

**Mitoxantrone is usually allocated to the anthracycline class, but studies show a different cardiotoxicity mechanism. It is 10× more cardiotoxic than doxorubicin.[9]*

on angle and easier to calculate than that from tissue Doppler. It also has low intra- and interobserver variability.[11] A global longitudinal strain (GLS) reduction of 15% compared to the initial baseline test appears to be a good cutoff value for the early detection of anthracycline-induced cardiotoxicity.[10] In the absence of an initial assessment for comparison, GLS values lower than -17% increase the sensitivity for diagnosing cardiotoxicity when associated with biomarkers, mainly high-sensitivity troponin.[12]

Strain to detect subclinical ventricular dysfunction in patients with preserved global myocardial function (EF%) can be an excellent method for the early diagnosis of cardiac compromise by oncological treatment.

LV diastolic function

Diastolic function changes in the adult population with cancer may precede systolic dysfunction; therefore, it represents an early sign of LV functional changes. However, further studies of this topic are needed in the pediatric population in clinical practice using Doppler indices such as mitral valve E/A ratio, deceleration time, E/e' ratio (Figures 4A, 4C, 4D), and indexed left atrial volume (Figure 4B).

The left atrium (LA) plays an important role in LV filling pressures and LV diastolic function. Although the focus of myocardial function is the LV, currently studies suggest that the LA assessment may be related to the early detection of LV dysfunction. Furthermore, LA function is associated with prognosis in heart failure. Adults treated with anthracycline showed a significant change in LA strain (LAS). A small study of children showed that changes in LA function demonstrated by LVEF, strain, and strain rate were mild in children and young

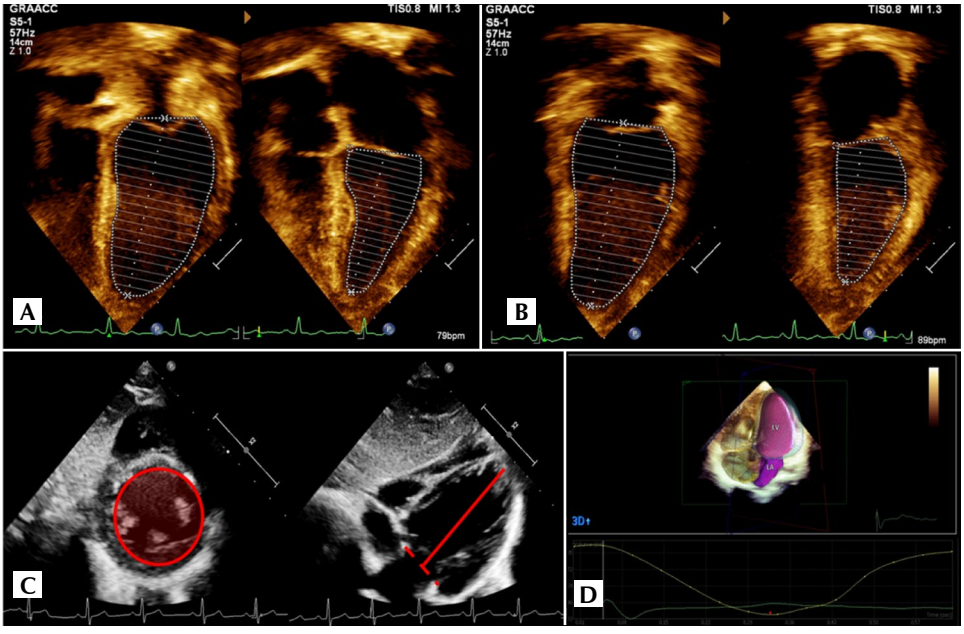

Figure 3 – *(A, B) Biplane Simpson's method. Apical four- (A) and two-chamber (B) left ventricular volumetric analysis. (C) Area-length or bullseye method used to determine left ventricular ejection fraction (LVEF). (D) LVEF analysis performed using the three-dimensional method.*

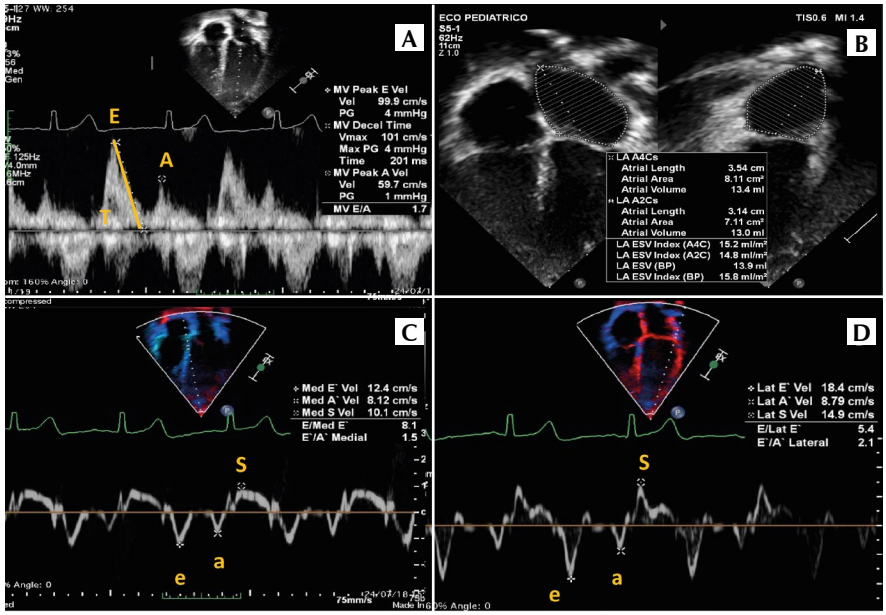

Figure 4 – *ALeft ventricular (LV) diastolic assessment. (A) Pulsed Doppler of mitral valve flow showing peak velocities during early ventricular diastole (E), atrial contraction (A), and deceleration time. (B) Left atrial volume assessment performed at the end of systole in the apical four- and two-chamber planes. (C) Tissue Doppler with septal mitral annulus velocities. (D) Tissue Doppler with mitral annulus velocities on the lateral wall of the LV.*

adults exposed to anthracyclines. In pre-adolescence, the effects of anthracyclines were more significant in this population.[13,14] Another study compared survivors of childhood cancer exposed to anthracyclines who were ≥1 year out from completing chemotherapy with controls. Those exposed to higher anthracycline doses had worse peak LAS (reservoir phase). The authors suggested that further studies of LAS as a potential marker of cancer therapy–related cardiac dysfunction are indicated and may provide insight into the prompt detection, treatment, and recovery of myocardial function.[15]

This new echocardiographic option such LAS is encouraging but still under investigation; for the time being, there is no evidence in the pediatric population of its predictive value of clinical outcomes.

Right ventricular function

The American Society of Echocardiography recommends the use of fraction area change (FAC), tricuspid annular plane systolic excursion (TAPSE), and Doppler analysis for the assessment of right ventricular (RV) systolic function in children.[16]

FAC assesses the RV area in end-diastole and systole on apical four-chamber view of the modified RV (Figure 5A). Values < 35% indicate RV systolic dysfunction.[17] TAPSE measures RV longitudinal shortening on an apical four-chamber view by M-mode in the tricuspid valve annulus (Figure 5B).[17]

On tissue Doppler imaging, the RV lateral wall S' wave velocity is easy to measure, reliable, and reproducible; moreover, it is highly correlated with other RV systolic function measurements (Figure 5C). Velocities < 10 cm/s indicate right systolic dysfunction.[17]

New techniques such as three-dimensional echocardiography (Figure 5D) have been useful for obtaining more accurate volume and LVEF measurements that have excellent correlation with magnetic resonance imaging (MRI), the gold standard for evaluating RV EF and volume.[18] RV strain was also validated to assess RV function (Figure 5E).[19]

Further studies in the pediatric population with cancer are needed to define the usefulness of RV strain for the early diagnosis of cardiotoxicity.

Guidelines are lacking regarding how often imaging screening should be performed at each stage of pediatric cancer treatment; thus, further studies are needed to enable standardization. The Children's Oncology Group[20] published long-term follow-up guidelines for standardization. However, individualizing follow-up based on treatment history is the best strategy in cases of early diagnosis.

Role of multimodality

Cardiac MRI, an important diagnostic tool in the follow-up of pediatric cancer patients, features excellent reproducibility and is unaffected by a limited acoustic window or complex ventricular geometry.

Cardiac MRI, which plays an important role in preclinical lesion detection, allows the diagnosis of early interstitial edema on a T2-weighted view and of the subsequent myocardial fibrosis by T1 mapping and late gadolinium enhancement.

The disadvantages of routine use of this method are its low availability in national medical services, high cost, and need for sedation in young children.[3]

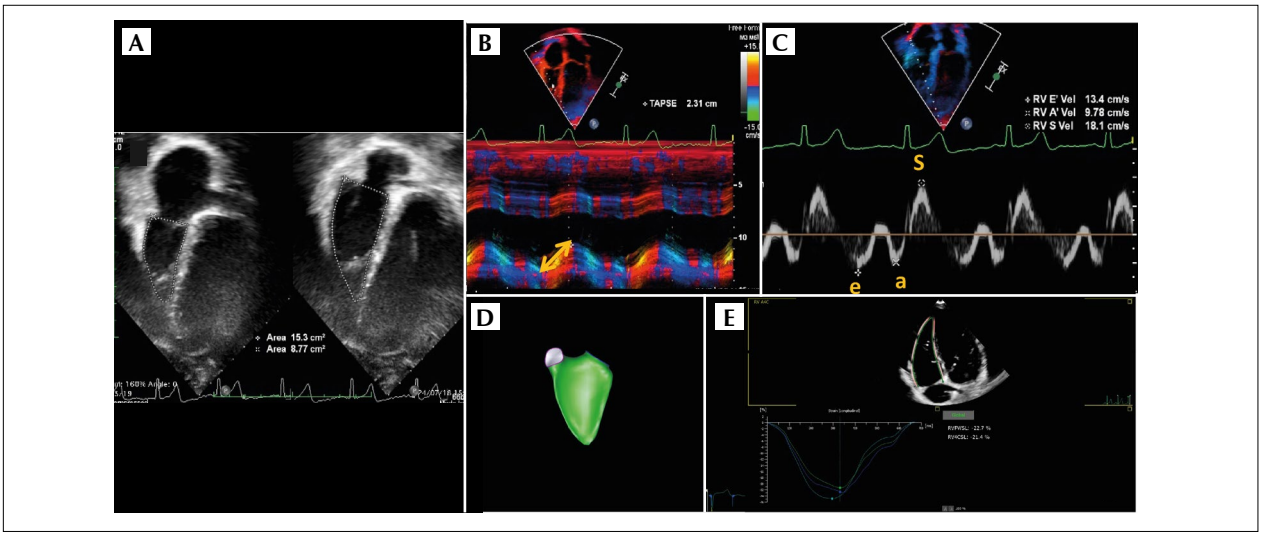

Figure 5 – *Right ventricular (RV) systolic function assessment. (A) RV fraction area change. (B) Tricuspid annular plane systolic excursion. (C) Tissue Doppler showing tricuspid annulus velocities on the lateral wall of the left ventricle. (D) Three-dimensional analysis of RV volumes and ejection fraction. (E) Apical four-chamber plane focusing on the RV for calculation of the RV global longitudinal strain.*

Conclusion

Despite the growing number of cardio-oncology studies, imaging guidelines and robust longitudinal scientific studies of pediatric populations are lacking. Echocardiography has become an important imaging method for diagnosing cardiotoxicity.

We strongly recommend volumetric EF% as the primary tool for following these patients. Independent of which method is being used to obtain EF%, a quality control program should be instituted to avoid a variability higher than 10% in each echocardiology laboratory. We also strongly support LV GLS measurements as an early sign of subclinical manifestation of cardiotoxicity.

We encourage left atrial strain analysis, but it should be recognized that it remains an early phase of research requiring more data.

Cardiac MRI is a solid technique that is underused mostly due to economic reasons and scarce availability to requesting physicians. Cardiac MRI should be considered when echocardiographic evaluation results are questionable or conflicting values are obtained. MRI tissue evaluations offer a promising aspect of this technique.

Authors' contributions

Research conception and design: Gallafrio CG, Pignatelli RH; data collection: Gallafrio CG, Pignatelli RH; data analysis and interpretation: Gallafrio CG, Pignatelli RH; manuscript writing: Gallafrio CG; critical review of the manuscript for important intellectual content: Pignatelli RH.

Conflict of interest

The authors have declared that they have no conflict of interest.

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