Review Article

Right Ventricular Dysfunction in the Cancer Patient

Marina Macedo Kuenzer Bond,[1,2,3] *Fernando Pivatto Júnior,*[4,5] *Andreia Biolo*[4,6,7]

Centro Paulista de Oncologia – Grupo Oncoclínicas,[1] *São Paulo, SP – Brazil*
Hospital do Coração (HCOR),[2] *São Paulo, SP – Brazil*
Faculdade de Medicina da Universidade de Santo Amaro (UNISA),[3] *São Paulo, SP – Brazil*
Hospital de Clínicas de Porto Alegre (HCPA),[4] *Porto Alegre, RS – Brazil*
Programa de Pós-Graduação em Ciências da Saúde: Cardiologia e Ciências Cardiovasculares – Universidade Federal do Rio Grande do Sul (UFRGS),[5] *Porto Alegre, RS – Brazil*
Hospital Moinhos de Vento,[6] *Porto Alegre, RS – Brazil*
Faculdade de Medicina – Universidade Federal do Rio Grande do Sul (UFRGS),[7] *Porto Alegre, RS – Brazil*

Abstract

Right ventricular dysfunction (RVD) is present in several clinical conditions, and its clinical impact and prognosis in cardiology has been more studied in recent years. In oncology, some studies have tried to determine the role of RVD in cardiotoxicity caused by some therapies including anthracyclines, trastuzumab, cyclophosphamide and dasatinib. In the present study, we made a literature review on the subject, trying to highlight the challenges for the coming years.

Introduction

The assessment of the right ventricle (RV) can be challenging due to its anatomical and functional features. Recently, more attention has been paid to the understanding of conditions that affect the RV, either alone or in combination with the left ventricle (LV), their clinical and prognostic impact, and to interventions that may reduce their clinical effects.

Cardio-oncology is a growing field with well-defined strategies for the detection, follow-up and prevention of cancer treatment-related cardiotoxicity. However, the RV is little mentioned in most guidelines that address cardiotoxicity. Recently, several studies have tried to establish the prevalence and the impact of right ventricular disfunction (RVD) in this context. In this paper, we will discuss some fundamental aspects of the mechanisms, clinical manifestations, and therapeutic approach of RVD, and summarize the main findings from studies evaluating the RV, either alone or in combination with the LV, in the context of cardiotoxicity. The prevalence, clinical impact and diagnostic methods to identify the involvement of the RV will be reviewed as well as the challenges that still exist in this scenario that has received growing attention in the last years.

Keywords

Right Heart Failure; Cardiotoxicity; Cardio-Oncology; Cardiac Dysfunction

Mailing Address: Marina Macedo Kuenzer Bond •
Rua Bento de Andrade, 346. Postal Code 04503-001, Jardim Paulista, São Paulo, SP - Brazil
E-mail: mmkbond@gmail.com
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Right ventricular dysfunction

The increase in right ventricular afterload is the main pathophysiological mechanism of RVD, which may be caused by cardiac, pulmonary, and other diseases. Cardiac diseases of various etiologies have been related to RVD, including ischemic disease (myocardial infarction), myocarditis, takotsubo cardiomyopathy, dilated cardiomyopathy, hypertrophic cardiomyopathy, amyloidosis, Chagas disease, arrhythmogenic right ventricular cardiomyopathy (in which right ventricular myocardium is replaced by fibro-adipose tissue), Uhl's anomaly (which involves aplasia or hypoplasia of most of the right ventricular myocardium), Ebstein's anomaly (defined as apical displacement of the septal and posterior tricuspid leaflets, which induces severe tricuspid regurgitation), and congenital disease (Fallot, atrial septal defect with left-to-right shunt or pulmonary regurgitation). These encompass conditions that affect the RV only, others that affect predominantly the RV and also the LV in more severe cases, and others that affect both ventricles. Other causes of RVD include pulmonary thromboembolism, chronic obstructive pulmonary disease, pulmonary arterial hypertension (PAH), obesity, and sleep apnea.[1]

Clinical signs of RVD result mainly from systemic congestion (lower limb edema, jugular turgescence, congestive hepatopathy, ascites, edematous bowel loops). In severe cases, the right heart dilates and, due to interventricular dependence, can compromise left ventricular filling, reducing the performance of the LV and causing low cardiac output. The diagnosis is based on clinical history, physical examination and complementary tests, including electrocardiography (ECG) with axis deviation to the right, and signs of right ventricular hypertrophy, echocardiogram (ECHO), which is an easily accessible tool that provides important information, including assessment of right ventricular function by tricuspid annular plane systolic excursion (TAPSE) and signs of venous congestion, and cardiac magnetic resonance (CMR), which is the best method for evaluation of right ventricular function and etiological definition.[2]

The crucial role of the right ventricular function in establishing the prognosis in several diseases has been increasingly recognized. In general, RVD is associated with poor clinical outcomes, regardless of the underlying mechanism. Patients with heart failure (HF) and reduced left or right ventricular ejection fraction had an increased risk of mortality, urgent transplantation or urgent assist device placement compared to those without RVD.[3]

The initial evaluation of patients with RVD aims to assess the clinical severity and identify the causes of right ventricular failure, focusing on those that require specific therapy. The management of acute insufficiency of the RV requires not only the understanding of anatomical and physiological particularities of the RV, but also the rapid identification and treatment of underlying causes and related pathophysiological disorders.[4,5]

The objectives of RVD treatment include reduction of RV afterload, optimization of RV preload and possibly improvement of right ventricular contractility.[6] However, current evidence indicate that right ventricular afterload reduction is the most appropriate approach, especially in the scenario of PAH.[7]

Afterload reduction

Adaptive changes favor vasoconstriction, thrombosis and proliferation of endothelial cells in PAH, contributing to increased peripheral vascular resistance (PVR) and right ventricular afterload, disadaptive hypertrophy, and eventually RVD. Advances in the pharmacotherapy in the last two decades increased mean survival time from 2.8 years to approximately eight years after the diagnosis. Aiming to augment arterial vasodilation and inhibit platelet aggregation to reduce PVR, the treatment includes: (a) oxygen administration as appropriate, since hypoxemia increases pulmonary vasoconstriction; (b) prostacyclin agonists (epoprostenol, treprostinil, iloprost, selexipag); (c) endothelin receptor antagonist (endothelin 1, bosentan, ambrisentan, macitentan); (d) increase of nitric oxide production (sildenafil, tadalafil, riociguat); (e) calcium channel blockers (anlodipine, levamlodipine, nimodipine); (f) combined therapy.[8] In the randomized study AMBITION, the efficacy of the combination therapy with ambrisentan and tadalafil was evaluated in 605 patients, and compared with their use as monotherapy; there was a 50% reduction in the primary end point (death, hospitalizations for PAH, disease progression, unsatisfactory response to therapy) ($p<0.001$), and improvement in exercise capacity ($p<0.001$).[9] Based on results from this trial, the European Cardiology Society and the European Respiratory Society recommend the combination of ambrisentan and tadalafil as initial therapy for patients with PAH and symptoms class I or II (WHO (class I recommendation, level of evidence B. In addition, the guidelines recommend intravenous prostacyclin in functional class II patients with rapid disease progression or poor prognosis and functional class IV patients.[10]

Afterload optimization

RVD is frequently associated with increased overload, leading to dilation of the RV, tricuspid regurgitation, and congestion. In more severe cases, interventricular septal deviation may be seen towards the RV, with consequent reduction of left ventricular filling and low cardiac output. Therefore, optimization of blood volume to prevent right ventricular dilation is crucial and achieved by non-pharmacological measures (fluid and salt restriction) and diuretics, although there are no randomized study evaluating the benefit, type or dose of diuretics in the management of RVD.[8] High doses of loop diuretics (e.g. furosemide) are usually required, mainly due to concomitant neurohormonal activation, diuretic resistance and impaired absorption of medications related to visceral edema. Combined therapy of loop diuretics plus thiazide diuretics, aldosterone antagonist and/or acetazolamide may be needed. A common mistake is to believe that most patients with RVD are preload-dependent and should be treated with volume supplementation to promote elevated right ventricular filling and an ideal cardiac output; conversely, most clinical exacerbations are caused by right ventricular volume overload that causes systemic venous congestion, that may lead to cardiorenal syndrome and cardiac output reduction.[6]

Contractility increase

Contractility can be increased by inotropic agents or circulatory assist devices. Inotropic therapy is indicated for patients with acute HF and reduced cardiac output However, there are no studies investigating the efficacy of chronic inotropic therapy in right HF. Potentially beneficial inotropic agents include milrinone, levosimendan and dobutamine. Apart from an acute case of HF decompensation with low cardiac output, inotropes should be avoided in patients with right HF due to limited evidence of benefit and associations with increased mortality. Right ventricular assist devices are mechanical pumps that take over the right ventricular function and are used in refractory cases. Examples of these devices include Thoratec PVAD (Thoratec, Pleasanton, CA) and Impella RP (Abiomed,Danvers, MA) approved for temporary support of the RV for two weeks, and CentriMag up to four weeks. Thirty-day and one-year survival after implantation of CentriMag was 72,1% e 54,6%, respectively, in a retrospective study with 55 patients. Cardiac transplant, however, remain the definite therapy for refractory right ventricular failure.[8]

Right ventricular dysfunction in cancer patient

Cardio-oncology is an emerging area in cardiology aimed at protecting the cardiovascular system, reducing mortality, and improving the quality of life of cancer patients, and enabling them to receive the best treatment available without interruptions. Although position statements and guidelines on prevention and management of cancer-related and treatment-related cardiotoxicity address mainly the LV, the involvement of the RV has been a subject of intense research recently. Since the prognostic role of the structure and function of the RV has been proved in several cardiovascular conditions, such as HF, coronary artery disease, pulmonary hypertension and hypertrophic cardiomyopathy, the assessment of the RV in oncologic patients has gained space.[4]

Radiotherapy (RT) to the chest area can damage the heart in a dose-dependent manner.[11] Evidence has shown that high-dose RT (>30Gy), combined with chemotherapy, may induce fibrosis and narrowing of right ventricular myocardium at long term.[12] Other potential pathophysiological mechanisms that could explain right ventricular remodeling include microvascular and macrovascular ischemia, accelerated atherosclerosis, and oxidative stress.[4]

Some anticancer drugs are known to cause PAH (e.g. dasatinib) and/or RVD (anthracyclines, trastuzumab, cyclophosphamide, and dasatinib).[13] We will now review important aspects and studies focusing on the effects of these interventions on the RV and their diagnosis.

Anthracyclines and Trastuzumab

Recent studies have shown structural changes and reduced right ventricular function during cancer treatment, especially with anthracyclines and trastuzumab.[14] Currently no guideline explicitly incorporates right ventricular parameters into the definitions of cancer therapy-related cardiac dysfunction (CTRCD).[15]

Although the mechanisms of right ventricular remodeling induced by chemotherapy have not been elucidated, the direct destructive effect of chemotherapy on the myocardium, oxidative stress, endothelial dysfunction and the negative impact of pulmonary circulation seem to significantly contribute to right ventricular failure.[16] The higher sensitivity of the RV to cancer therapy-related cardiotoxicity may be explained by the thinner structure of this ventricle, with fewer myofibrils.[17]

Most studies with analysis of the RV in cardio-oncology have involved breast cancer patients and childhood cancer survivors.[4] Evidence has suggested that the RV is affected as frequently as the LV,[4] and even earlier in some situations.[18] To confirm the possibility of assessing the RV to early detect subclinical cardiotoxicity and to define its criteria, larger studies, preferably multicentric ones, are still warranted.[18]

CMR and echocardiography are the techniques of choice to evaluate right ventricular systolic function in cancer patients.[16] CMR is the gold standard to assess right ventricular diameter and function.[4] There are few studies, with a limited number of patients, regarding right ventricular function following chemotherapy, but all studies agree that its ejection fraction reduces with anthracyclines in adults who had survived childhood cancer,[19,20] and with anthracyclines[21] and trastuzumab[4,22] in breast cancer patients.

An accurate evaluation of the RV by conventional echocardiography is still challenging.[18] Right ventricular shape and geometry limit the capacity of conventional echocardiographic indexes like right ventricular ejection fraction, fractional area change (FAC), and tricuspid annular plane systolic excursion (TAPSE), to reliably detect subtle changes in right ventricular systolic function in cancer patients.[4]

Right ventricular strain seems to be a reliable, robust and easy-to-use indicator in cardio-oncology.[4] Right ventricular global longitudinal strain (RVGLS) is the only index of systolic performance with consistent and homogenous data in oncological patients,[4] and apparently a better indicator of right ventricular function than the right ventricular free wall longitudinal strain (RVFWLS).[4] Shi et al.[11] recently published a systematic review and meta-analysis of 21 studies including 1355 patients, evaluating the RV by echocardiography at the beginning of treatment and follow-up of cancer patients who underwent chemotherapy and/or radiotherapy. The authors found an increase in pulmonary artery systolic pressure (PASP), as well as reductions in TAPSE, S', RVGLS and RVFWLS.[11]

Further studies are needed to determine the prognostic value of the assessment of the RV in oncologic patients.[23] In breast cancer patients receiving epirubicin, the decrease in the RVFWLS was significantly correlated with the development of dyspnea, regardless of systolic and diastolic function in both ventricles.[24] In patients with stage III non-small cell lung cancer receiving concurrent chemoradiotherapy, baseline RVFWLS and its variation was an independent predictor of all-cause mortality.[25]

Desatinib

Desatinib is an oral tyrosine kinase inhibitor approved as a first-line treatment in patients with chronic myeloid leukemia and acute lymphocytic leukemia. It induces endothelial cell damage, oxidative stress, and changes the proportion between proliferation and antiproliferation of the endothelial and pulmonary arterial smooth muscle cells, which leads to higher susceptibility to pulmonary hypertension.[16] In the DASISION (DASatinib versus Imatinib Study in treatment-Naïve chronic myeloid leukemia patients), 5.4% of patients randomized to desatinib were diagnosed with PAH, as compared with 0.4% in those randomized to imatinib.[26]

Symptoms of PAH are nonspecific, like dyspnea and fatigue. In more advanced stages, signs and symptoms of right HF may emerge. Echocardiography is the first choice to assess the risk of PAH in patients with suggestive symptoms and/or signs during cancer treatment. In patients with chronic myeloid leukemia treated with drugs that potentially cause PAH, treatment should be discontinued in case of signs suggestive of PAH (peak tricuspid regurgitation velocity > 3.4 m/s, corresponding to a pulmonary artery systolic pressure ≥ 50 mmHg) until the diagnosis is confirmed or ruled out by right heart catheterization.[27] Most patients have clinical and functional improvement after dasatinib discontinuation.[16]

Cyclophosphamide

Cyclophosphamide is an alkylating agent that interferes with DNA replication.[16] The metabolism of cyclophosphamide in the lungs is partially responsible for its pulmonary toxicity. Evidence suggests that cyclophosphamide and its metabolites cause peroxidation of cell membrane lipids.[28]

A systematic review of the role of alkylating agents in the development of pulmonary hypertension, published in 2015 established that these compounds, including cyclophosphamide, are a risk factor for pulmonary veno-occlusive disease. In experimental models, cyclophosphamide exposure leads to venous remodeling, which, in turn, leads to the development of pulmonary hypertension.[29] Pulmonary veno-occlusive disease is extremely rare, with an incidence of 0.1-0.2 cases per million per year, and difficult to be differentiated from PAH. The gold-standard for the diagnosis of PAH, as previously mentioned, is right heart catheterization.[28]

Challenges and perspectives

Although the role of the RV in the development of cardiovascular diseases has been increasingly recognized, the best diagnostic and therapeutical approach in cardio-oncology has been poorly defined. Important challenges need to be addressed, as listed in Chart 1, including: definition of RVD in the context of cardiotoxicity, selection of the most appropriate method for its correct diagnosis, prognostic impact of RVD (either alone or in conjunction with the LC), and identification of specific therapies to prevent, attenuate and even reverse RVD associated with cancer therapy-induced cardiotoxicity.

The development and availability of diagnostic tools, as the use of strain echocardiography and wider use of CMR, opens the way to a better assessment of the RV. Cardio-oncology and new multicentric studies must include them to promote the understanding of the real impact of the RV and the development of interventions in cardiovascular care of oncologic patients.

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Chart 1 – Challenges related to right ventricular dysfunction (RVD) in the cancer patient

- The condition is poorly recognized, but highly prevalent and even prior to left ventricular dysfunction;
- Diagnosis: diagnostic methods (strain, cardiac magnetic resonance) should be validated;
- Prognostic impact: multicentric studies, to assess the role of the right ventricle alone;
- Detection, interventions, and follow-up: not defined yet

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