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CURRENT VIEW ON RADIATION-INDUCED HEART DISEASE AND METHODS OF ITS DIAGNOSIS

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In recent years, cardiologists and cardiovascular surgeons are increasingly encountering radiation-induced heart disease (RIHD) in their practice. This complication is described in literature but is poorly understood and clinically challenging. Radiation therapy (RT) is widely used in the treatment of many cancers. Despite the considerable risk of RT complications, it is used in 20–55% of cancer patients. Radiation-associated cardiotoxicity appears to be delayed, typically 10 to 30 years following treatment. Mediastinal irradiation significantly increases the risk of non-ischemic cardiomyopathy. Recent reviews estimate the prevalence of radiation-induced cardiomyopathy at more than 10%. Therefore, it is important to understand the pathophysiology of RIHD, consider risk factors associated with radiation injury, and detect the condition early.

Keywords: mediastinal tumors, radiation therapy, radiation-induced cardiomyopathy.

In recent years, cardiologists and cardiovascular surgeons are increasingly encountering radiation-induced heart disease (RIHD) in their practice. This complication is described in literature but is poorly understood and clinically challenging. Radiation therapy (RT) is widely used in the treatment of many cancers. Despite the considerable risk of complications, this method is used in 20–55% of cancer patients. Its basic principle consists of inhibiting proliferation or inducing apoptosis of cancer cells [4].

When using high doses of mediastinal irradiation, almost any component of the heart – myocardium, pericardium, valves, coronaries or conduction system – can be damaged. Basically, the cardiotoxic effect is caused by irradiation in such diseases as mediastinal lymphoma, esophageal cancer, thymoma, lung cancer (especially left-sided), and breast cancer (especially left-sided). The cumulative dose of mediastinal irradiation is a major risk factor for subsequent heart disease. Although complications can occur at any dose, there is a linear increase in the risk of valvular disorders at doses above 30 Gy/m^2 [1]. Radiation-induced cardiotoxicity is delayed, usually occurring 10 to 30 years after treatment. For example, in patients with a history of Hodgkin's lymphoma who have undergone RT, the average time from diagnosis of malignancy to onset of cardiac complications is about 19 years [2]. Hodgkin's lymphoma is one of the most common cancers in young adults, with an estimated incidence of 3 cases per 100,000 population. The cumulative long-term incidence of RIHD is nearly 60% in Hodgkin's lymphoma survivors 40 years after exposure with a relative risk of 3.2 times that of the general population, and 51.4% of patients develop 2 or more cardiovascular events [13]. Many studies have confirmed that cardiovascular risk factors such as hypertension, diabetes mellitus, dyslipidemia, and obesity significantly increase the risk of heart disease and related complications of RT [3]. Risks also increase after chemotherapy and/or when two or more cardiovascular risk factors are present.

Mediastinal irradiation significantly increases the risk of non-ischemic cardiomyopathy; these include direct myocardial fibrosis, myocardial hypertrophy secondary to valvular disorders, and diastolic dysfunction due to constrictive pericarditis. Reviews of the problem estimate the prevalence of radiation-induced cardiomyopathy at >10%. Therefore, it is important to understand the pathophysiology of RIHD, to consider risk factors associated with radiation injury, and to diagnose the condition early enough.

The walls of the heart are composed of three layers: endocardium, myocardium and epicardium. The myocardium is a highly vascularized tissue with capillary density approaching 2,800 capillaries per square millimeter. In comparison, the capillary density of skeletal muscle is much lower, approximately 350 capillaries per square millimeter. The myocardial subunit consists of cardiac myocytes, capillaries, and stromal tissue. Each myocardial subunit has a network of capillaries and depends on diffusion for nutrient metabolism because there are no arterioles in the tissue. Capillaries completely surround individual myocytes and are normally always open to perfusion. Myocardial blood supply is crucial for cardiac muscle function and depends on the degree of development of the capillary system.

Radiation injury is characterized by both acute and chronic changes in cardiac tissue [11]. Within minutes after exposure to ionizing radiation, cellular damage causes vasodilation and increased vascular permeability.

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Cardiomyocytes themselves are known to be resistant to radiation. However, when combined radiation/chemotherapy treatment is used, the risk of complications increases significantly. According to Suter and Ewer classification, all cytostatics are divided according to the nature of their damaging effect on the cardiovascular system. There are two types of cardiotoxicity: type I cardiotoxicity (irreversible myocardial dysfunction due to cardiomyocyte death; anthracyclines have such an effect; the degree of myocardial damage in this case depends on the cumulative dose) and type II cardiotoxicity (reversible cardiomyocyte dysfunction due to mitochondrial and protein damage; this type is most typical for trastuzumab and does not depend on the cumulative dose). High cumulative dose, intravenous bolus administration of drug, high single dose, co-administration of other cardiotoxic drugs (cyclophosphamide, trastuzumab, paclitaxel, etc.), previous RT, female gender, <15 years old and >65 years old, existing heart disease (especially hypertension and coronary heart disease), obesity, elevated biomarker levels (troponin) during or after anthracycline treatment are all risk factors for type I cardiotoxicity. Risk factors for type II cardiotoxicity are previous or concurrent anthracycline therapy, left ventricular (LV) ejection fraction <55%, existing cardiovascular disease (especially hypertension and ischemic heart disease), >50 years old, and body mass index >25 kg/m^2.

One of the most understood pathophysiological mechanisms of radiation exposure is macrovascular damage. Radiation burn of coronary artery endothelium causes an inflammatory response in the vessel wall, resulting in the release of a large number of cytokines responsible for macrophage activation and, consequently, lipoprotein deposition. Plaques may crack and cause thrombosis. This process reduces the arterial lumen to varying degrees, leading to the clinical manifestations of coronary heart disease: stable and unstable angina, myocardial infarction. The mechanism is essentially similar to the formation of atherosclerotic plaques, which we observe in traditional coronary heart disease, but with radiation damage the event occurs at an accelerated rate.

From 1998 to 2001, 114 patients were enrolled onto an IRB-approved prospective clinical study to assess changes in regional and global cardiac function after RT for left-sided breast cancer. Perfusion imaging by technetium-99m myocardial scintigraphy were performed before and after RT. The incidence of new perfusion defects 6, 12, 18, and 24 months after RT was 27%, 29%, 38%, and 42%, respectively. There was also a significant difference in myocardial perfusion between patients whose LV radiation lesion volume was less or more than 5%. New defects occurred in approximately 10% to 20% and 50% to 60% of patients with less than 5%, and greater than 5%, of their left ventricle included within the RT fields, respectively. The rates of wall motion abnormalities in patients with and without perfusion defects were 12% to 40% versus 0% to 9%, respectively [5].

In addition to large vessel damage, microvascular myocardial damage occurs. Radiation-induced endothelial cell damage is considered the primary and major cause of myocardial damage [8]. It is characterized by both acute and chronic changes in cardiac tissue. Within minutes of exposure to ionizing radiation, cell damage causes vasodilation and increased vascular permeability. Damaged endothelial cells trigger an acute inflammatory response. Inflammatory cytokines include monocyte chemotactic factor, tumor necrosis factor and interleukins including IL-1, IL-6 and IL-8. The predominant cells in the acute phase are neutrophils, which appear in all layers of the heart in areas exposed to RT. There is proliferation, damage, edema and degeneration of capillaries, and their number is significantly reduced. Although endothelial cells can regenerate, capillary network damage is irreversible, and this naturally leads to a significant reduction in myocardial blood supply.

Radiation exposure to the heart not only causes endothelial cell damage and reduction of capillaries, but also alters coagulation function and platelet activity, leading to immediate fibrin deposition. Deposition and release of von Willebrand factor in endothelial cells increases. This eventually leads to increased platelet adhesion and capillary thrombosis [9]. The acute phase takes place within a few days after RT. After this acute infiltration, there is a quiescent period when there are no obvious microscopic changes in the tissue. The acute proinflammatory environment is a powerful initiator of fibrosis [10]. Fibroblasts are recruited from a variety of sources: from mesenchymal cells, from bone marrow, or from transitional epithelial-mesenchymal cells.

However, radiation alters the biology of pro-fibrotic cells. It turned out that ionizing radiation induces premature differentiation of fibroblasts. Normal fibroblast differentiation requires 25–35 cell division cycles. After ionizing radiation, progenitor fibroblasts differentiate into post-mitotic fibroblasts within 2–3 weeks, which is only 3–4 cell cycles. The lifespan of these terminally differentiated radiation-induced fibrocytes is nearly 40–45% shorter than that of naturally differentiated cells. These post-mitotic cells are shown to be five to eight times more active in the production of interstitial collagens I, III, and IV compared to progenitor fibroblasts. Myofibroblasts are permanently activated in these tissues [12]. Chronic deposition of collagen and other components of other extracellular matrix components can produce a fibrotic scar, reducing the functionality of the affected tissue. Pathologic examination of these lesions show elevated inflammatory cells, fibroblasts, and excessive extracellular matrix, such as collagens, proteoglycans, and fibronectin. Extracellular matrix deposition by fibroblasts results in late pathologic dysfunction of myocytes, vascular endothelial cells, and the pericardium

[11]. Progressive myocardial fibrosis eventually leads to decreased tissue elasticity and extensibility.

The cardiovascular system responds differently to RT-related myocardial damage compared with ischemia-related heart failure. In RT-unrelated myocardial damage, the body activates the sympathetic nervous system continuously, while simultaneously down-regulating β-adrenergic receptors. In contrast, RT-related myocardial damage results in no augmentation of the sympathetic nervous system in the adrenal glands, but β-receptors initially are upregulated in the heart. This upregulation of the receptors may allow the heart to stabilize cardiac output despite damage. Eventually, as damage progresses, further reductions in cardiac output occur near the onset of congestive heart failure [11].

Restrictive cardiomyopathy is a late stage of myocardial damage due to fibrosis with severe diastolic dysfunction and symptoms of heart failure. Most radiation-induced myocardial lesions have no clinical symptoms for a long time; therefore, the rate of early diagnosis of the disease is low, only about 10% [6]. Transthoracic echocardiography is the optimal imaging modality for the diagnosis of LV systolic and diastolic dysfunction. The most common echocardiographic features are regional wall motion abnormalities (usually lower LV wall), moderate LV hypertrophy, and diastolic dysfunction, which can manifest as severe congestive heart failure [7].

In a study by Paul A Heidenreich et al. [14], the prevalence of LV wall motion abnormalities was 13% (12/89) for individuals with a latency period of 2 to 10 years, 18% (24/132) for a latency period of 11 to 20 years, and 29% (21/73) for a latency period greater than 20 years post-RT (at least 35 Gy) for mediastinal Hodgkin lymphoma. Regional wall motion abnormalities were independently associated with a greater biologically equivalent dose (odds ratio 1.07 per one-unit increase, 95% CI 1.02–1.13) and older age (odds ratio 1.7 per 10-year increase, 95% CI 1.2–2.4) in addition to time following irradiation.

The authors investigated the effect of irradiation on LV myocardial mass. The LV mass was lower for irradiated patients than for those of similar sex and age in the general population (Framingham Heart study [15]). LV hypertrophy (defined as more than 163 g/m for men and 121 g/m for women) was present in 6% (7/121) of female and 2% (2/104) of male patients compared with 19% of women and 16% of men in the Framingham Heart Study. The difference in myocardial mass was due to lower LV diastolic volume in patients after irradiation, as systolic volume and wall thickness were similar to the Framingham cohort.

It was also found that the age-adjusted ventricular mass remained constant or slightly decreased over time following irradiation. This is in contrast to the usual increase in LV myocardial mass that occurs with aging [16]. When the authors stratified changes in LV myocardial mass by age, there was a clear trend toward lower mass with greater latency period . In multivariate analysis, ventricular mass decreased by 0.6 g/m ($p = 0.001$) for each year following exposure, but increased by 0.8 g/m ($p < 0.0001$) for each year increase in age. Similar findings were observed for interventricular septal and LV posterior wall thickness, which decreased by 0.05 mm ($p = 0.08$) for each year following irradiation but increased by 0.1 mm ($p < 0.001$) for each year increase in age.

Modern imaging techniques for examining myocardial deformation have shown that they may be more sensitive to detect early subclinical LV dysfunction than standard measures such as ejection fraction measurement. Strain is a dimensionless value reflecting the change in length relative to the initial state [17]. Longitudinal strain reflects the change in length of a section of myocardium along the long axis. Short-axis circular strain shows the contraction of circularly arranged myocardial fibers. Transverse (radial) strain describes the processes of thickening/thinning of myocardial fibers in different phases of the cycle, which occurs due to the principle of incompressibility of cardiac muscle.

Global longitudinal strain (GLS) and strain rate assessed using automated 2D spectral echocardiography reveal minimal changes in LV systolic function. The prospective BACCARAT study was designed to examine the association between cardiac radiation doses and subclinical LV dysfunction based on reduced GLS. The study included 79 breast cancer (BC) patients (64 left-sided BC, 15 right-sided BC) treated with RT without chemotherapy. Echocardiographic parameters including GLS were measured before RT and 6 months after.

The association between subclinical LV dysfunction, defined as GLS decrease >10%, and cardiac radiation doses, was performed using logistic regression. Non-radiation associated with subclinical LV dysfunction included age, body mass index, hypertension, hypercholesterolemia, and endocrine pathology. These were also considered in the multivariate analysis but were found not to be significant. The authors conclude that subclinical LV dysfunction can be detected early after RT for BC with GLS measurement based on 2D speckle-tracking echocardiography.

Reduction in longitudinal deformity in a period of a few days to 14 months after RT has also been observed by other authors in patients with left-sided BC [18, 20]. Suvi Sirkku Tuohinen et al. also draw attention to RT-induced regional changes. The study showed that the changes corresponded to the RT fields. Patients with left-sided BC showed apical changes, whereas patients with right-sided BC showed basal changes in the anterior and anteroposterior regions, which corresponds to the area most vulnerable to RT [18].

AF Yu et al. also conducted a study to determine whether RT leads to early changes in LV function. The study was based on 2D echocardiographic assessment of such

parameters as LV ejection fraction, myocardial strain indicators including longitudinal (GLS), radial (GRS) and circular deformation (GCS), LV diastolic indices and high-sensitivity troponin. There appeared to be no predictors of changes in LV ejection fraction or changes in longitudinal strain indicators during the immediate period of RT. Similarly, age, hypertension, baseline systolic blood pressure, and intake of cardiac medications were not predictors of changes in LV function [19].

Electrocardiography rarely has specific changes [14]. However, resting heart rate is higher in patients with longer latency after RT (70 ± 13 beats/min for a period ≤10 years, 74 ± 12 for 11 to 20 years, and 81 ± 10 for >20 years). In multivariate analyses controlling for age, gender, diabetes, hypertension, and dose of irradiation, a 10-year increase in latency period was independently predictive of a higher resting heart rate (increase of 3.7 beats/min, 95% CI 1.3 to 6.1), right bundle branch block (odds ratio 7.3, 95% CI 1.2 to 45), and abnormal Q-waves (odds ratio 4.9, 95% CI 1.7 to 14).

Magnetic resonance imaging of the heart, detecting both functional and structural changes simultaneously, allows the diagnosis of radiation-induced coronary, valve, myocardial, and pericardial disease. Features of the method include myocardial tissue characterization based on various tissue relaxation properties such as fat, muscle, and areas of inflammation. The use of gadolinium has significantly improved the diagnosis of altered myocardium of non-ischemic genesis. Images obtained 5–20 minutes after gadolinium injection at a dose of 0.1–0.2 mmol/kg allow to describe nonischemic cardiomyopathic processes and provide valuable diagnostic and pathophysiological information with unprecedented resolution and highly specific images of fibrosis and myocardial scarring [21].

Development of modern imaging methods allows for early identification of patients with potential risk of cardiotoxicity who require further cardiovascular monitoring or cardioprotective therapy. Evaluation of parameters using echocardiography and magnetic resonance imaging over time can contribute to early diagnosis of heart damage before overt heart failure develops.

Evaluation and early treatment of traditional cardiovascular risk factors is the first step towards preventing cardiotoxicity. Finally, in patients with high-risk heart disease, primary prophylaxis, including cardioprotectors and/or drugs commonly used to treat cardiovascular disease, should be used. According to recent studies [22], early initiation of ACE inhibitors and β-blockers and modification of anti-cancer therapy can prevent cardiac fibrosis and decrease in LV ejection fraction in the terminal stage of a disease. However, further multicenter studies are needed to establish prevention and treatment protocols.

Due to the direct toxic effects of RT, myocardial fibrosis and vasculopathy lead to ventricular remodeling, which, in turn, may increase the risk of developing valvular dysfunction [23]. Although the precise pathophysiologic mechanisms of radiation-induced valvulopathy are not completely understood, irradiation is thought to have a direct effect on the pathologic fibrosis and calcification of the valvular apparatus. Due to the avascular nature of valve tissue, the mechanism of injury is believed to be distinct from radiation-induced damage to the myocardium and vasculature. There is a lack of histological markers of chronic inflammation or neovascularization on tissue specimens removed during surgery [24]. Interestingly, there are histopathological differences noted in the affected valves. Thus, patients who have undergone RT for BC show a degenerative calcific process as opposed to a predominantly fibrotic process in lymphoma patients who have received RT. This difference is probably due to the young age at which irradiation for Hodgkin's lymphoma was performed.

Risk stratification of surgical treatment for valvular pathology using modern scales does not take into account side effects and complications associated with previous RT and may underestimate the true risk. A retrospective analysis by Wu et al. [25] on the surgical outcomes of 173 patients (75% women; age, 63 ± 14 years, mean EuroSCORE 7.8 ± 3) with RIHD, compared with 305 operated patients matched on the basis of age, sex, and procedure type, revealed a higher mortality rate in the RIHD group than in the comparison group (55% vs 28%; $p < 0.001$) over a mean follow-up of 7.6 ± 3 years, despite comparable EuroSCORE scores. Analysis of the results of surgical treatment of valvular pathology in 60 patients with previous RT in the Handa et al study showed an increased rate of early mortality in patients with constrictive pericarditis (40% vs. 6%, $p = 0.011$). In the same cohort, lower preoperative LV ejection fraction and longer aortic constriction time were also associated with early mortality [26].

Among 230 patients in a study by Chang ASY et al. [27] who underwent cardiac surgery after thoracic irradiation, the proportion of perioperative complications, in-hospital and long-term mortality was significantly higher in patients who received extensive radiation exposure. Therefore, an understanding of the nature of radiation exposure to the heart and its structure is primarily necessary to determine the degree of surgical risk prior to cardiothoracic surgery, which will determine the most appropriate treatment tactics, emphasizing the need for interdisciplinary collaboration between the radiation oncologist, cardiologist, cardiac surgeon, and other specialists.

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