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REVIEW

Mechanisms of Radiation-induced Cardiovascular Complications

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SUMMARY

Radiation therapy (RT) has contributed to significant improvements with respect to the survival times in many cancers, including Hodgkin's Lymphoma (HL), breast cancer, lung cancer, and other thoracic region tumors. In addition, the advances of anti-cancer therapies result in greater numbers of long-term survivors after thoracic irradiation as well. Therefore, it has become more important to understand the long-term complications of RT. Radiation-induced cardiovascular complications (RICC) have become an increasingly recognized side effect of RT, which can cause non-malignant death in patients particularly suffering from HL and breast cancer. The spectrum of RICC is broad, potentially involving any component of the heart, including pericardium, myocardium, heart valves, coronary arteries, capillaries, and conducting system that underwent RT, most often occurring decades after the treatment. Numerous studies of RICC show that the injury of endothelial cells is the key point in most tissues that ultimately leads to fibrosis or necrosis. Ionizing radiation directly modifies DNA, including single- and double-strand breaks on a molecular level. Indirectly ionizing radiation also produces reactive oxygen species, which can lead cellular stress and death. Radiation directly affects the vasculature by causing endothelial cell apoptosis and senescence and by changing aspects of normal vascular homeostasis. The mechanism of RICC has not been clearly defined yet. A better understanding of the biological mechanisms of RICC is very important to clarify the exact pathogenesis of this important disease spectrum, and it will also provide to develop novel treatment strategies.

Keywords: Cardiotoxicity; cardiovascular complications; inflammation; radiation therapy; radiation-induced heart disease.

Introduction

Radiation therapy has contributed to significant improvements with respect to the survival times in many cancers, including Hodgkin's Lymphoma (HL), breast cancer, lung cancer, and other thoracic region tumors. Although the use of modern radiotherapy (RT) techniques, including intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), and stereotactic body radiotherapy (SBRT), have greatly improved the radiation-related side effects by minimizing the irradiated heart volume, it is impossible to spare whole nearby tissues during irradiation. In addition, the advances of anti-cancer therapies result in greater numbers of long-term survivors after thoracic irradiation as well. Analyses have been shown that the therapeutic benefits from RT may be offset to some extent by delayed effects on the heart, thereby reducing the benefits of RT.[1,2] Particularly, early-stage breast cancer and HL patients who have excellent prognosis may suffer from radiation-induced cardiovascular complications (RICC) in a dose-dependent manner.[1-6]

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Estimates of relative risk of fatal cardiovascular events after mediastinal irradiation for Hodgkin's disease ranges between 2.2 and 12.7.[3,7] An estimated aggregate incidence of RICC is between 10% and 30% by 10-year post-treatment, with up to 88% of patients demonstrating asymptomatic cardiac abnormalities.[8] Estimates of relative risk of fatal cardiovascular events after chest irradiation for left-sided breast cancer ranges between 1.0 and 2.2.[3] Among breast cancer patients, the incidence of RICC varies greatly in different studies, ranging from 0.5% to 37%.[9-11] Possible relationships between RICC and internal mammary chain irradiation, left-sided breast irradiation, irradiated volume of heart, mean heart dose, RT volume, RT dose, RT technique, and the use of chemotherapy have been demonstrated.[11,12] RICC is a late effect of RT that may become apparent many years after RT and it may be progressive. Other risk factors for cardiovascular disease, including hypertension, smoking, hyperlipidemia, and preexisting cardiovascular disease, may also increase the risk of RICC.[9,13] The incidence of symptomatic RICC is higher in lymphoma patients when compared with that of breast cancer patients, reaching 49.5-54.6%, and the incidence of various heart diseases ranges from 11% to 31%.[14-16] Due to the short survival times and follow-up time, a true morbidity of RICC cannot be estimated for other thoracic region tumors.

The cardiac effect of irradiation has been manifested as coronary artery disease (CAD), cardiomyopathy, pericardial disease, valvular heart disease, and conduction system abnormality. There is not any defined minimum dose that is entirely safe during thoracic irradiation and the effects of radiation on the cardiovascular structures increase with increasing doses of irradiation.[17] Cardiovascular disease is the most common non-malignancy cause of death in cancer survivors who underwent radiation therapy, most often occurring decades after RT.[7] To date, no effective treatment has been established for RICC, partially because the underlying mechanisms of the RICC remain largely unknown.[2,18] Therefore, it has become increasingly important to profoundly understand RICC mechanisms. This review focuses on the possible radiobiological mechanisms of RICC.

Clinical Manifestations of RICC

The spectrum of RICC is broad, potentially involving any component of the heart, including pericardium, myocardium, heart valves, coronary arteries, capillaries, and conducting system (Table 1). Pericarditis can be an acute manifestation of radiation complication, while chronic pericardial disease, CAD, cardiomyopathy, valvular disease, and conduction abnormalities manifest years after the radiation exposure. These complications may result in significant mortality and morbidity. The radiation dose correlates linearly with the morbidity of the RICC, and the location of the tumor makes it highly variable. The left anterior myocardium, pulmonary valve, and atrioventricular structure are strongly affected by left-sided irradiation.[16] Awareness and early detection of potential cardiac complication induced by RT are crucial in cancer survivors.

Pericardial Disease

Pericardial abnormalities can be detected up to 70% of radiation-induced heart disease patients in necropsy studies.[19] The clinical spectrum of radiation-induced pericardial disease ranges from acute pericarditis to delayed chronic pericarditis, fibrinous pericarditis, tamponade, and constrictive pericarditis according to the severity and development of the disease.[20] The most common manifestation is acute exudative pericarditis.[21] Acute pericarditis may be associated with a large mediastinal tumor contagious to the heart and some chemotherapy agents, including cyclophosphamide.[22] Pericarditis is usually self-limiting; however, approximately 10-20% of the patients may develop a chronic or constrictive pericarditis 5-10 years after radiation exposure.[23] Pericarditis can remain clinically silent or present with sudden onset of pleuritic chest pain, dyspnea, friction rub, fever, ST-segment, and T-wave changes and decreased QRS voltage.[1]

Cardiomyopathy

Radiation-induced cardiomyopathy is related to a combination of structural changes in myocardial tissue and perfusion deficit due to microvascular and macrovascular changes. Most of the cardiomyopathies related to irradiation have no clinical symptoms, so the clinically diagnostic rate is low, only about 10%.[1,22] The clinical symptoms of myocardial injury caused by RT are long-term systolic and diastolic left ventricular dysfunction due to myocardial fibrosis. Clinically, most patients suffer from restrictive cardiomyopathy that is characterized with a diastolic dysfunction which is partially accompanied by a slight reduction of systolic function in the left ventricle.[2,24] Dilated cardiomyopathy accompanied with left ventricular ejection fraction may develop in <5% of the patients.[25] Myocardial injury is common in patients who have received >60 Gy doses

Table 1 The clinical spectrum of radiation-induced cardiovascular complication

Manifestation	Comments
Pericardial disease	
• Acute pericarditis • Chronic pericarditis • Fibrinous pericarditis • Pericardial tamponade • Constrictive pericarditis	• The pericardium is one of the most commonly affected structures of the heart • Acute pericarditis may be associated with mediastinal tumor and some chemotherapy agents including cyclophosphamide
Cardiomyopathy	
• Systolic dysfunction/systolic heart failure • Diastolic dysfunction/heart failure with preserved ejection fraction • Restrictive cardiomyopathy • Myocardial fibrosis	• The clinically diagnostic rate is low (~10%), since most of the radiation-related cardiomyopathies have no clinical symptoms • Restrictive cardiomyopathy is the most common form and it is characterized with a diastolic dysfunction which is partially accompanied by a slight reduction of systolic function in the left ventricle
Vascular disease	
• Coronary artery disease • Microvascular coronary disease • Carotid artery disease • Radiation-induced atherosclerosis	• "Ischemic heart disease" has become the most common reason for cardiac death in patients with a history of mediastinal radiation
Valvular heart disease	
• Mitral stenosis and insufficiency • Aortic stenosis and insufficiency	• The clinically evident radiation-induced valvular disease is uncommon • Autopsy studies report a prevalence of valvular fibrosis up to 70-80% after >35 Gy of RT doses
Conduction system abnormality	
• Bundle branch blocks • Atrioventricular nodal block • Sick sinus syndrome • Prolongation of the corrected QT interval • T-wave changes and ST depression • Ventricular ectopic beats	• "Life-threatening arrhythmia" and "conduction disturbances" occur years after radiation exposure, and they are distinct from the common, asymptomatic, nonspecific, and transient repolarization abnormalities seen soon after irradiation • Can progress to complete heart block and congestive heart failure

or anthracycline chemotherapy. Patients who have received chemo-RT are prone to diastolic myocardial damage while, who have received a high dose of RT are prone to restrictive myocardial damage.[16,26] Although there are many studies investigating the relation-associated myocardial injury, the exact mechanism of myocardial injury has not been clearly defined yet.

Vascular Disease/CAD

Radiation-induced vascular complications, including CAD, have become a serious reason for morbidity in patients who received thoracic irradiation. Ischemic heart disease has become the most common reason for cardiac death in patients with a history of radiation exposure to mediastinal structures.[27] It has been demonstrated that the incidence of CAD in patients is up to 85%, and it is closely related to radiation dose, location, time, and other patient-related factors.[1,28-30] Radiation-induced coronary artery damage is consistent with coronary atherosclerosis due to additional factors. The key point is still an endothelial injury and the infiltration of monocytes into the intima, inducing low-density lipoprotein deposition and eventually the formation of fatty streaks.[16,28] Clinical presentation of CAD in cancer survivors with a history of mediastinal irradiation is similar to that in the general population. The clinical scenarios are board from an asymptomatic CAD to angina pain and sudden death. When compared to general population, cancer survivors with a history of mediastinal irradiation have more frequent silent myocardial infarction.[1,30]

Valvular Heart Disease

Ionizing radiation may cause an increased risk of cardiac valve injury that is characterized by valve fibrosis and calcification. Valvular fibrosis reported up to 70-80% after >35 Gy of RT doses in autopsy studies. However, clinically evident radiation-induced valvular disease is sparse.[31] Although valvular insufficiency seems to be more common, valvular stenosis is more

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serious than valvular insufficiency and more often leads to hemodynamic significance that requires intervention.[1,31] Clinically significant cardiac valvular disease usually develops after a latent period of 10-20 years. The radiation-induced cardiac valvular disease risk is related to the radiation dose, time from exposure, and use of concomitant chemotherapy. The signs and symptoms of radiation-related valvular regurgitation and stenosis due to the progressive thickening of atrial and mitral valves are not different than that in the general population with atrial and mitral insufficiency.

Conduction System Abnormality

Life-threatening arrhythmias and conduction disturbances may be encountered years after exposure to irradiation and are different from common, asymptomatic, non-specific, and transient repolarization abnormalities seen immediately after radiation.[32] The reported conducting system abnormalities related to mediastinal irradiation include atrioventricular nodal bradycardia, all levels of heart block, including complete heart block,[30,33,34] and sick sinus syndrome,[35] prolongation of the corrected QT interval,[30] and T-wave changes and ST depression.[32] Infra-nodal blocks occur more often than nodal blocks and right bundle branch block is common as well.[36] So far, the exact mechanism of radiation-induced conduction system abnormality has not been clearly defined yet. Conduction abnormalities may not occur until years after exposure, so demonstrating causation is difficult. Unfortunately, it is challenging to establish a radiation-induced conduction system abnormality in an animal model.

Possible Mechanisms of RICC

Although the heart was initially thought to be relatively resistant to radiation, endothelial cells, which differ from less sensitive cardiomyocytes, are particularly radiation-sensitive and are suspected of being a key point for RICC. There may be also a causal relationship between endothelial dysfunction and the development of muscular, valvular, and arrhythmogenic complications besides from vascular damage.[1,37,38] The human and animal data indicate the important role of endothelial dysfunction and vascular injury,[39,40] but also of myocardial remodeling, degeneration, and dysfunction[40-42] in the mechanism of RICC. Endothelial dysfunction contributes to pro-fibrotic and pro-inflammatory environments, which are common aspects of RICC. There are many cytokines involved in the process and regulation, and control mechanisms are affected with various factors.[16,40] At present, it is believed that RICC is associated with oxidative stress, increased levels of endothelial adhesion molecules, vascular inflammation, and cellular senescence are all consequences of the normal aging process (Fig. 1).[42-44] However, all of these are observed early in irradiated tissues, including the cardiovascular structure, and it suggests an intensification and acceleration of these molecular processes. A better understanding the biological mechanisms of RICC is very crucial to clarify the exact pathogenesis of this important disease spectrum, and it will also provide to develop novel treatment strategies.

The Endothelial Cell Injury

Radiation-induced changes in cardiovascular structures have been known since Gassmann.[45] Estimates of relative risk of fatal cardiovascular events after mediastinal irradiation for left-sided breast cancer from 1.0 to 2.2. Numerous studies of radiation injury show that the injury of endothelial cells is the key point in most tissues that ultimately leads to fibrosis or necrosis.[46-49] Irradiation to mediastinal structures may influence cardiac capillary endothelial cells causing to their proliferation, injury, swelling and degeneration, and significantly reduce the number of capillaries. Although endothelial cells can regenerate, capillary network damage is irreversible;[50] this may reduce the blood supply of myocardium.

In addition to endothelial cell damage, exposure of the heart to radiation can alter coagulation function and platelet activity. The accumulation and release of von Willebrand factor (vWF), a blood glycoprotein involved in hemostasis, in endothelial cells increased after the heart was exposed to irradiation. Changes in vWF expression eventually result in increased platelet adhesion and capillary thrombosis.[51,52] It was shown in experimental studies that the inflammatory thrombotic plaque emerged in the blood vessels after the exposure of high doses of irritation to rat heart.[53] The combination of thrombosis and reduced cardiac blood flow can lead to myocardial ischemia.[16,54]

Besides from adult endothelial cells, endothelial progenitor cells can also be injured because of irradiation. The injury of these progenitor cells can be resulted in disturbed vascular remodeling and thus contribute the development of endothelial dysfunction.[55] Lee et al.[56] demonstrated that radiation exposure in either mice-or human-cultured endothelial progenitor cells induces senescent growth arrest and functional defects, which lead to attenuated vascular regeneration.

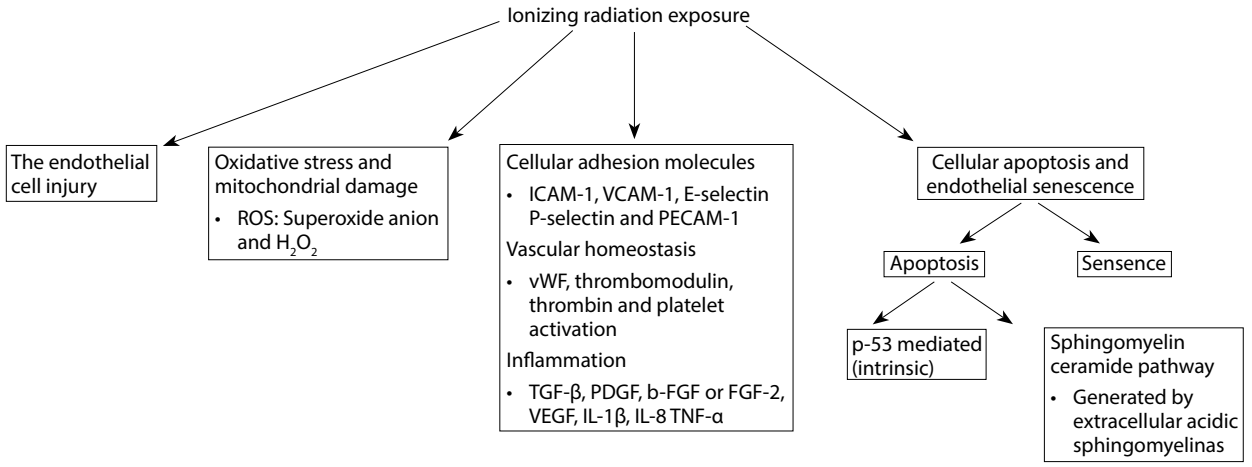

Fig. 1. Radiation-induced cardiovascular changes.
ROS: Reactive oxygen species, ICAM-1: Including intracellular adhesion molecule 1, VCAM-1: Vascular cell adhesion molecule 1, PECAM-1: Platelet endothelial cell adhesion molecule, vWF: von Willebrand factor, TGF-β: Transforming growth factor-β, b-FGF or FGF-2: Fibroblast growth factor, VEGF: Vascular endothelial growth factor, IL-1β, IL-8: Including interleukin, TNF-α: Tumor necrosis factor α, PDGF: Platelet-derived growth factor.

Oxidative Stress and Mitochondrial Damage

Cardiomyocyte mitochondria involve a critical role in cardiac function, with each cardiomyocyte comprising substantial mitochondria that makeup to 30-40% of cell volume.[57,58] Mitochondrial reactive oxygen species (ROS) in the cardiomyocytes including superoxide anion and hydrogen peroxide (H_2O_2) play an increasing role in cellular signaling pathways, including immune response, microbial defense, cell signal transduction, cell adhesion, differentiation, and apoptosis and take place in the maintenance of redox homeostasis and various cellular signaling pathways in the cardiovascular system.[57-59] Therefore, the mitochondrial ROS generated at low to moderate concentrations under normal physiological conditions has been recognized as a beneficial non-toxic by-product of cellular metabolism that can mediate physiological signaling.[16,59,60]

In the late 1960's, it was demonstrated that radiation can substantially alter the structural appearance of mitochondria.[61] The electron microscopic finding includes swollen mitochondria, decrease in number, and disorganization of cristae, often with fused outer double membranes. These findings have led to a better understanding the role of mitochondrial damage in cardiomyocytes. Ionizing radiation directly modifies deoxyribonucleic acid (DNA), including single and double-strand breaks on a molecular level. Indirectly ionizing radiation also produces ROS, which can lead cellular stress and death.[57,62] DNA damage after the radiation exposure is likely to occur when intracellular antioxidants cannot remove ROS adequately. DNA damage has many forms, which can significantly change the structure of DNA and eventually lead to cell cycle arrest, apoptosis, mutation, and other effects.[63,64] It has been shown that increased levels of the most reflected mutation have been noted in human cardiac cells undergoing oxidative stress secondary to atrial fibrillation.[65] ROS can also lead to peroxidation of lipids and proteins and activate multiple signaling pathways.[66,67] In addition to direct damage of the DNA, ROS can alter the expression of multiple proteomes in the cytoplasm which leads to activation of pro-inflammatory factors.[68] ROS acts as a second messenger to activate nuclear factor kappa-B (NF-κB) and induce the production of inflammatory cytokine.[69] The pro-inflammatory environment is also a powerful initiator for cardiac fibrosis. Thus, while pro-inflammatory cytokines and chemokines are believed to be closely related to the formation of oxidative stress, oxidative stress-enhanced inflammation also leads to disease progression, leading to a vicious circle.[37,69]

In the heart, cardiomyocytes' membrane structures are rich in phospholipids that are susceptible to oxidative stress. Lipid peroxidation in the cardiomyocyte membrane results in structural and functional damage.[70] It has been shown that cardiac muscle is particu-

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larly sensitive to the oxidative activity of free radicals that are produced by radiation.[40,70,71] It has been demonstrated in cardiac tissues exposing to free radicals that the free radicals cause depressed contractile function, impaired energy production, increased resting tension, and enhanced levels of lipid peroxidation.[72] Both the inflammation and the oxidative stress may act independently in the development and progression of cardiac failure. However, their interactions are also evident throughout the period from initial injury to cardiac remodeling and failure.[40,73] Upregulation of several cytokines, including interleukin-6 (IL-6), IL-8, and tumor necrosis factor-α (TNF-α), has been seen after endothelial cell high-dose irradiation in a time and dose-dependent manner.[40,74]

Cellular Adhesion and Vascular Homeostasis

NF-κB activation induced by ionizing radiation leads to increased expression of adhesion molecules, including intracellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), E-selectin, and platelet endothelial cell adhesion molecule (PECAM-1), and P-selectin.[75-79] The expressions of these adhesion molecules vary in different tissues since they are tissue-specific. ICAM-1 is primarily expressed in the microvasculature, E-selectin in the endothelium of large blood vessels and, P-selectin in the Weibel-Palade bodies of the endothelium.[40,80] Ionizing radiation reduces the level of thrombomodulin and increases the level of pro-inflammatory tissue factor, thereby causing loss of thromboresistance.[81-83] The accumulation and release of vWF in endothelial cells increased after the heart was exposed to irradiation. Changes in vWF expression eventually result in increased platelet adhesion and capillary thrombosis.[51,52] Alterations of endothelial cell integrity and function influence normal hemostasis, causing thrombotic occlusion of capillaries, enhanced arteriosclerosis in larger vessels, and the release of pro-inflammatory and fibrogenic mediators. It has been shown previously that increased immunoreactivity of transforming growth factor-β (TGF-β), a key cytokine in abnormal tissue fibrosis.[81,84,85] In addition, the free radicals produced by macrophages can stimulate TGF-β and accelerate the profibrotic milieu in the vasculature. This may lead to vessel stenosis, leading to an increased risk of ischemic events in the long term.[40,81,84]

In the vascular endothelium, as an immediate response to injury, TGF-β, PDGF, basic fibroblast growth factor (b-FGF or FGF-2), vascular endothelial growth factor (VEGF), IL-1β, IL-8, and TNF-α are produced and subsequent healing responses that perpetuate coagulation, inflammation, recruitment and activation of blood leukocytes, mesenchymal cell migration and proliferation, and matrix synthesis. The extent of intimal hyperplasia is determined by these growth factors and cytokines.[81,84,86,87]

It was demonstrated in cellular studies that up-regulation of endothelial cell adhesion molecules in addition to chemokines was detected in both normal and radiation-induced atherosclerosis. This upregulation results in monocyte attachment, transmigration, and finally foam cell formation.[75,79,80] Therefore, inflammation and oxidative damage play a role in radiation-induced atherosclerosis, as the response can be mitigated by the overexpression of Cu-Zn-superoxide dismutase (SOD1), an enzyme responsible for destroying free superoxide radicals in the body.[47,79]

Cellular Apoptosis and Endothelial Senescence

Radiation-induced DNA damage in the endothelial cells can be repaired or trigger apoptosis, which can be mediated either P-53 or sphingomyelin-ceramide pathway.[37,88] Although the early stages of p53-mediated apoptosis are reversible, it is unclear that whether activation of the sphingomyelin-ceramide pathway is reversible or not.[38] The mechanisms of apoptosis are very sophisticated, involving an energy-dependent cascade of molecular events. To date, studies show that there are two main apoptotic pathways: The exogenous or death receptor pathway and the intrinsic or mitochondrial pathway.[88] P53-mediated apoptosis of endothelial cell is mediated predominantly by the intrinsic pathway. In p-53 mediated intrinsic pathway, cytochrome c-mediated mitochondrial dysfunction and irreversible damage are the key links of cell apoptosis and necrosis, and the occurrence of mitochondrial dysfunction is closely related to endoplasmic reticulum stress.[88]

After high-dose single-fraction irradiation, apoptosis in endothelial cells is modulated primarily by the sphingomyelin-ceramide pathway.[88] Ceramide is produced through the enzymatic cleavage of sphingomyelin due to activation of TNF by ionizing radiation in the sphingomyelin-ceramide pathway. Ceramide is a bioactive molecule involved in the regulation of cell death, differentiation, and inflammation and may sensitize radiation insensitive cells to undergo cell death. Ceramide is a second messenger that serves as a key mediator in the rapid apoptotic response to various cell stressors.[89] Radiation-induced, ceramide-mediated endothelial cell apoptosis

is generated by extracellular acidic sphingomyelinase.[90] Ceramide serves as a second messenger in diverse signaling pathways, including those for cell death and differentiation.[91]

Radiation-induced DNA damage also triggers in endothelial cells. It causes to a change in the cellular phenotype of endothelial cells and hence the secretion of cytokines, proteins, and other factors. Together, apoptosis and senescence of endothelial cells lead to an imbalance in the vascular environment between pro- and anti-coagulatory and pro-inflammatory and anti-inflammatory factors. This leads to increased adhesion of leukocytes and macrophages, chronic inflammation, a pro-thrombotic status, and the increased occurrence of ROS.[37,38]

Pathology and Pathophysiology of Disease Formation

Pericardium

It has been demonstrated that in addition to capillary endothelial cell damage, stenosis or occlusion of lymphatics plays a role in the mechanism of radiation-induced pericarditis. The small blood vessel proliferation is detected throughout the irradiated pericardium at microscopic level. The microvasculature is usually damaged, causing increased permeability. Eventually, ischemia and vascular fibrosis are encountered. Fibrosis of the venous and lymphatic channels decreases the extracellular fluid drainage ability of the heart and mediastinal structures.[46,47] Therefore, radiation-induced pericarditis is marked by both protein-rich exudates in the pericardial sac and fibrin accumulation in the mesothelial lining of the pericardial cavity.[92,93]

Myocardium

Microcirculatory damage seems to be the common pathophysiological pathway of damage to the heart. Stewart and Fajardo demonstrated that the injury to the myocardium develops through three phases in experimental work conducted on rabbits.[46,47] After 6 hours of radiation exposure, acute inflammation begins, characterized by neutrophilic infiltration of all heart layers. This inflammation process causes an increased permeability in the endothelial cells of the capillary network which is seen usually within hours of radiation. Due to the increased permeability in capillary endothelium, functional parameters including blood flow and perfusion pressure alter. The latent phase with slight progressive fibrosis begins 2 days of exposure. Electron microscopy demonstrates progressive damage leading to obstruction of the lumen and thrombi of fibrin and platelets (Fig. 2).[94,95] Further injury causes detachment of the basement membrane and formation of the microthrombi. Therefore, the blood flow reduction exacerbates. Although healthy endothelial cell replication occurs in the vicinity, it is often insufficient and inevitable ischemia leads to progressive fibrosis. Animals begin to die at 70th day due to extensive fibrosis. The hallmark of this late stage is extensive fibrosis.[1,46,47]

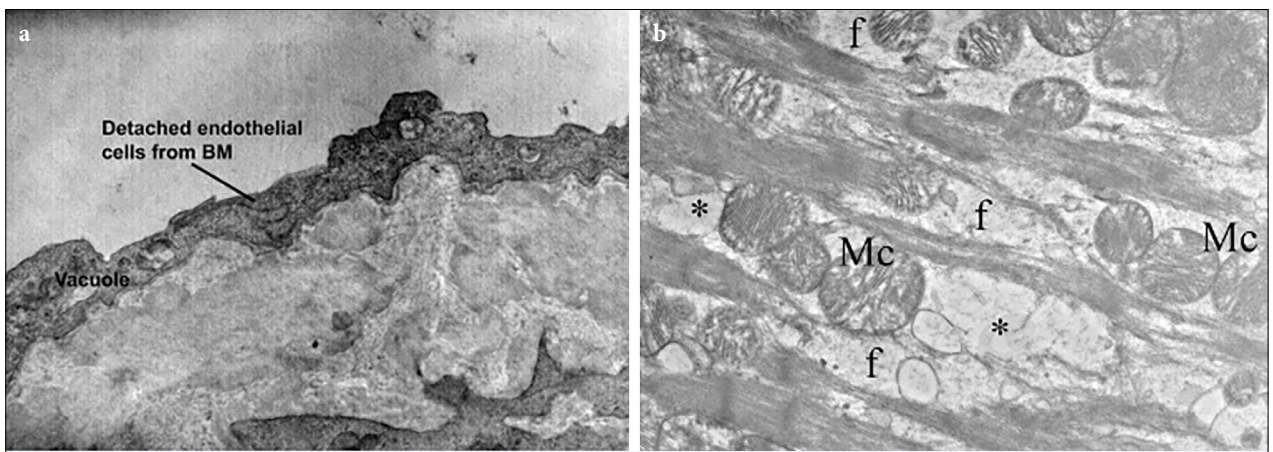

Fig. 2. (a) Electron microscopical appearance of 15-Gy radiotherapy (RT) to thoracic aorta. 70 days after RT. Endothelial cells are obviously thin and in some areas, they lost their cytoplasmic organelles. Detachment from basement membranes in some areas is also seen. BM, basement membrane,[94] (b) heart sample of 12-Gy radiotherapy at 16th week of radiotherapy: Electron micrograph showing separations in myofibrils (*), mitochondria with prominent cristae (Mc) and fibrosis (f) (Original magnification ×7500)[95].

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Valves

Different from other parts of the heart, the exact mechanism of radiation-induced valvular changes is not understood fully and cannot be explained as a result of microvascular damage, since the heart valves are avascular. In radiation-induced valvular damage, the leaflets/cusp of the cardiac valves may undergo fibrotic changes with or without calcification.[1,19,96] The damage is likely related to another myocardial disease. Regardless of dose distribution, the left-sided irradiation causes more common and severe damages to valves suggesting that the higher pressures of the systemic circulation play a role in pathogenesis.[19,31] The patient with the radiation-related valvular disease is usually asymptomatic or moderately symptomatic.

Coronary Arteries

The mechanism of radiation-induced CAD appears to be slightly different from that of CAD in the general population. This is shown by the location of lesions and their morphology.[1,97] The mostly effected coronary arteries are the left anterior descending and the right coronary arteries.[97-100] The initiation of radiation-induced CAD is similar to that of most other tissues as ionizing radiation causes to microvascular damage, inflammation, and fibrosis. The endothelial lining of the coronary arteries is probably damaged like the microvascular damage seen in the myocardium. This causes fibrointimal thickening, which causes thrombus formation and potentially lipid deposition.[101] The atherosclerotic plaques in coronary arteries caused by ionizing radiation are morphologically same with that of regular atherosclerotic plaques.

Conduction System

There are limited data with respect to the mechanism of radiation-induced conduction system abnormality. Radiation-induced arrhythmias are caused by either microvascular damage, leading to cardiac myocyte conduction abnormalities or direct damage to critical structures such as the sinoatrial or atrioventricular nodes.[97] As in the case of radiation-induced valvular abnormality, radiation-induced conduction system abnormality may be related to other myocardial diseases caused by irradiation.

Conclusion

Although modern techniques, including IMRT, IGRT, and SBRT, have allowed minimizing the irradiated heart volume during thoracic RT, RICC remains an important risk. The spectrum of RICC both in clinical manifestation and severity varies extensively. The key point of RICC is most probably the endothelial dysfunction and vascular injury; however, also myocardial remodeling, degeneration, and dysfunction also take part in the mechanism of RICC. Endothelial dysfunction contributes to pro-fibrotic and pro-inflammatory environments, which are common aspects of RICC. Many clinical and preclinical studies have widely investigated the RICC to clarify the excite mechanism of the heart injury. However, present knowledge is insufficient to explain the whole mechanism. A profound understanding of the biological mechanisms underlying radiation-induced damage in cardiovascular tissue is essential to prevent cardiac damage. There is a need of novel preclinical studies investigating the radiation-induced changes on a cellular and molecular level, with the hope of discovering new targetable pathways.

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