Cardiovascular Complications of Radiation Exposure

William Finch, MD, Kamran Shamsa, MD, Michael S. Lee, MD
Division of Cardiology, The David Geffen School of Medicine at UCLA, Los Angeles, CA

The cardiovascular sequelae of radiation exposure are an important cause of morbidity and mortality following radiation therapy for cancer, as well as after exposure to radiation after atomic bombs or nuclear accidents. In the United States, most of the data on radiation-induced heart disease (RIHD) come from patients treated with radiation therapy for Hodgkin disease and breast cancer. Additionally, people exposed to radiation from the atomic bombs in Hiroshima and Nagasaki, Japan, and the Chernobyl, Ukraine, nuclear accident have an increased risk of cardiovascular disease. The total dose of radiation, as well as the fractionation of the dose, plays an important role in the development of RIHD. All parts of the heart are affected, including the pericardium, vasculature, myocardium, valves, and conduction system. The mechanism of injury is complex, but one major mechanism is injury to endothelium in both the microvasculature and coronary arteries. This likely also contributes to damage and fibrosis within the myocardium. Additionally, various inflammatory and profibrotic cytokines contribute to injury. Diagnosis and treatment are not significantly different from those for conventional cardiovascular disease; however, screening for heart disease and lifelong cardiology follow-up is essential in patients with past radiation exposure.

© 2014 MedReviews®, LLC

**KEY WORDS**

Radiation-induced heart disease • Cardiotoxicity • Myocardial fibrosis • Coronary artery stenoses • Pericardial disease • Valvular injury

Radiotherapy-induced heart disease (RIHD) is a well-known complication of radiotherapy (RT) for cancer and environmental exposure to radioactive material first described in large-scale human studies in the 1960s.1 The first description of cardiac lesions came from patients who had received mediastinal RT for Hodgkin disease (HD); since then, RIHD has been described in patients who received RT for breast cancer. In patients treated for breast cancer or HD, this may exacerbate and contribute to cardiotoxicity from systemic anthracycline chemotherapy. Additionally, survivors of the atomic bombs in Japan and radiation accidents (such as that in Chernobyl, Ukraine) provide additional evidence...
of the cardiovascular effects of radiation. In this review, grays (Gy) are used as the units of measurement of absorbed radiation dose; units of radiation dosage are described in Table 1.

Involvement of the pericardium, myocardium, coronary arteries, valves, and conduction system has been observed, depending on the type and amount of radiation received (Table 2). In one autopsy series of 16 young patients (age 15-33 years) who had received > 35 Gy to the heart during mediastinal RT, published in 1981, the majority had pericardial and valvular thickening, and many patients also had myocardial fibrosis and coronary artery stenoses. Another autopsy series of patients with likely RIHD found that the majority had pericardial disease, valvular injury, and myocardial fibrosis, whereas a smaller proportion had coronary artery stenoses.

Radiation therapy is frequently used to treat patients with breast cancer. Examination of the US Surveillance, Epidemiology, and End Results (SEER) registry revealed that among patients with early breast cancer, 37% received RT. Meta-analyses of randomized trials of RT for breast cancer have found statistically significant increases in cardiac and vascular mortality. In the SEER registry there was significant laterality of RIHD; that is, women who received radiation to the left breast had significantly higher cardiovascular mortality than those receiving radiation to the right breast. This effect was more prominent as time since radiation increased. In patients who died ≥ 10 years after irradiation, a statistically significant difference in mortality after left versus right breast irradiation was mainly attributed to acute myocardial infarction (MI) and other ischemic heart disease. These findings likely reflect the anterior coronary arteries, including the left anterior descending artery (LAD), being present in the field of radiation of a left breast tumor.

Mediastinal RT is a common treatment for HD. In studies following patients treated long term with RT for HD, cardiovascular causes were the third most common cause of death after HD and other cancers, and accounted for 12% to 16% of mortality. One study that screened patients for cardiac disease by exercise stress test and echocardiography found cardiac disease in 11% of patients. Another study that evaluated patients with echocardiography, radionuclide angiocardiography, and cardiac catheterization found cardiac disease in nearly all patients. The greater prevalence of heart disease in this study may be attributed to the more extensive work-up, and the majority of patients had normal echocardiogram results. Constrictive pericarditis (including overt or occult) was found in 50% of patients, coronary artery disease (CAD) in 12%, and left ventricular dysfunction in 4%. In patients with HD who received irradiation to a portion of the heart or carotid

### Table 1

<table>
<thead>
<tr>
<th>Unit</th>
<th>Type of Unit</th>
<th>Conversion Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>rad(^a)</td>
<td>Absorbed radiation dose</td>
<td>1 rad = 0.01 gray</td>
</tr>
<tr>
<td>gray(^a)</td>
<td>Absorbed radiation dose; SI unit</td>
<td>1 joule/kg = 1 gray = 100 rad</td>
</tr>
<tr>
<td>rem(^b)</td>
<td>Dose equivalent</td>
<td>1 rem = 0.01 sievert; 1 rem = 1 rad(^c)</td>
</tr>
<tr>
<td>sievert(^b)</td>
<td>Dose equivalent; SI unit</td>
<td>1 sievert = 100 rem; 1 sievert = 1 gray(^c)</td>
</tr>
</tbody>
</table>

\(^a\)rad and grays are units of energy per mass.  
\(^b\)rem and sieverts are units of energy per mass adjusted by a dimensionless factor to account for potential for biologic damage.  
\(^c\)rem and rad are equivalent and sieverts and grays are equivalent for radiography and gamma radiation.

### Table 2

<table>
<thead>
<tr>
<th>Cardiac Disease Associated With Radiation Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardial disease</td>
</tr>
<tr>
<td>Pericardial effusion</td>
</tr>
<tr>
<td>Acute pericarditis</td>
</tr>
<tr>
<td>Chronic constrictive pericarditis</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>Vascular injury</td>
</tr>
<tr>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Microvascular injury</td>
</tr>
<tr>
<td>Valvular disease</td>
</tr>
<tr>
<td>Conduction abnormalities</td>
</tr>
<tr>
<td>Bundle branch blocks</td>
</tr>
<tr>
<td>Atrioventricular blocks</td>
</tr>
</tbody>
</table>

Data from International Bureau of Weights and Measures.
Cardiovascular Complications of Radiation Exposure continued

arteries, there was an increased risk of valve surgery, coronary artery bypass grafting (CABG), or percutaneous coronary intervention (PCI) when compared with the US general population.\(^1\)

In addition to RIHD secondary to therapeutic radiation, environmental radiation exposure from nuclear power plant accidents and the atomic bombs dropped in Japan in 1945 has previously caused cardiovascular disease. Longitudinal studies that have followed survivors of Hiroshima and Nagasaki have found statistically significant excess risk for heart disease when compared with the population without radiation exposure.\(^12,13\) Ischemic heart disease was associated with radiation exposure; however, there were stronger associations between radiation and heart failure or hypertensive heart disease. An excess relative risk for heart disease of 14% was found for each Gy of exposure. Patients were at highest risk for MI when exposed at age < 40 years.\(^14\) Workers who were involved in the recovery operation after the Chernobyl accident were also found to have an increased risk in cardiovascular mortality.\(^15\) Risk of disease was found to be increased in those who received doses of \(\geq 150\) mGy over a period of \(< 6\) weeks. Cardiovascular mortality was primarily driven by hypertensive heart disease, and there was no association between radiation dose and ischemic heart disease or acute MI. In addition to those exposed to atomic bomb fall-out and nuclear accidents, workers for British Nuclear Fuels were found to have increased risk for ischemic heart disease, although this is not observed in uranium miners.\(^13\)

The literature regarding radiation exposure from diagnostic studies (ie, conventional films and computed tomography [CT]) focuses primarily on the risk of carcinogenesis rather than discussion of cardiotoxicity.\(^16,17\) However, the dose of a typical CT scan is approximately 10 mGy (0.01 Gy), far less than typical RT doses exceeding 10 Gy. Additionally, in large-scale studies of low-dose radiation exposure, doses < 0.5 Gy did not result in increased risk of heart disease.\(^12\) This indicates that cardiac toxicity as a result of diagnostic radiation is likely not clinically significant.

Relation of Radiation Field, Dose, and Fractionation to RIHD

The total dose of radiation received by the heart, and fractionation (the division of the total dose into smaller fractions separated by time), have both been studied with respect to risk of subsequent RIHD. Early animal studies provided insight into the dose-response relationship of cardiac irradiation. In rats that received unfractinated radiation, higher than the single dose of 20 Gy causing cytolysis in the former study, indicating that fractionation does play a role in the development of RIHD.

In one early autopsy study of RIHD, the mean radiation dose received was 42 Gy (range, 13-75 Gy) in single fractions.\(^3\) Only those who received > 30 Gy developed moderate to severe myocardial fibrosis. The radiation dose that the heart receives varies depending on the type and location of the tumor being treated or environmental exposure. As described above, RT for left-sided breast cancer has resulted in higher risks of cardiac toxicity when compared with RT for right-sided tumors.\(^4\) The estimated whole heart dose for left-sided tumors is more than double that received for right-sided tumors.\(^20\) The LAD received the greatest radiation dose with left-sided irradiation. Anterior radiation fields result in higher cardiac doses than fields that are tangential to the breast.\(^21\) For HD, the historic RT used was mantle field irradiation (lymph nodes in the neck, mediastinum, and axillae) of 35 to 45 Gy.\(^22\) This type of radiation results in 27.5 Gy of radiation to the whole heart, and > 35 Gy to some parts of the heart—above the threshold dose for aortic or mitral radiographic radiation localized to the heart, a dose of 35 to 40 Gy resulted in severe cardiac failure within 15 weeks,\(^18\) and animals that received 10 to 15 Gy developed only minor heart failure after 1 year. It is likely that cardiac disease develops with single radiation doses of < 10 Gy. Larger fractions of radiation led to severe heart failure earlier.\(^19\) Myocardial clytolysis was observed at 50 to 70 Gy of fractionated radiation, higher than the single dose of 20 Gy causing clytolysis in the former study, indicating that fractionation does play a role in the development of RIHD.

RT has previously been used to treat peptic ulcer disease and, in these patients, an average total cardiac dose of 2.8 Gy was the lowest dose that resulted in a statistically significant increase in CAD.

234 • Vol. 15 No. 3 • 2014 • Reviews in Cardiovascular Medicine
Development of RIHD. Studies have demonstrated that greater fractionation of the total dose decreases acute pericarditis and myocardial necrosis. The decrease in non-acute MI cardiovascular mortality in patients who received RT for HD observed at Stanford University Medical Center after 1972 coincided with a reduction in fraction size.

Fractionation schedules of twice weekly rather than five times weekly have been found to result in increased risk of late complications in normal tissues such as pulmonary pneumonitis and fibrosis and pathologic fractures, whereas cardiac effects were not reported. The nonacute MI cardiac death relative risk in the era prior to 1972 was 5.3; this decreased to 1.4 in the period after 1972. A more recent change to RT for HD is involved-field radiation therapy, which only includes the lymph nodes that were enlarged prior to initiation of treatment and their surrounding regions, as opposed to extended-field (mantle) radiation. Similarly, involved-node radiation therapy involves the involved nodes alone. These techniques significantly decrease the total cardiac dose (Figure 2).

Fractionation of radiation doses is another potential factor in the development of RIHD. Studies have demonstrated that greater fractionation of the total dose decreases acute pericarditis and myocardial necrosis. The decrease in non-acute MI cardiovascular mortality in patients who received RT for HD observed at Stanford University Medical Center after 1972 coincided with a reduction in fraction size. Fractionation schedules of twice weekly rather than five times weekly have been found to result in increased risk of late complications in normal tissues such as pulmonary pneumonitis and fibrosis and pathologic fractures, whereas cardiac effects were not reported. The nonacute MI cardiac death relative risk in the era prior to 1972 was 5.3; this decreased to 1.4 in the period after 1972. A more recent change to RT for HD is involved-field radiation therapy, which only includes the lymph nodes that were enlarged prior to initiation of treatment and their surrounding regions, as opposed to extended-field (mantle) radiation. Similarly, involved-node radiation therapy involves the involved nodes alone. These techniques significantly decrease the total cardiac dose (Figure 2).

Studies have demonstrated that greater fractionation of the total dose decreases acute pericarditis and myocardial necrosis.

Figure 1. Planning computed tomography scan prior to radiation of the left breast (A, B, and C are transverse, coronal, and sagittal views, respectively). The light blue line outlines the heart, the green line outlines the left coronary artery. Radiation doses are a color-coded overlay over the left breast: red is 74 Gy, blue is 0 Gy. Treatment delivery may also be restricted to inspiration to maximize the distance of the heart to the radiation field. Reprinted with permission from Topolnjak R et al.
severe coronary artery stenosis (> 75% narrowing) attributable to radiation. Further microscopic examination showed atherosclerosis and intimal fibrosis; however, fibrous tissue dominated in the majority of sections. In addition, in most patients, the media was infiltrated by fibrous tissue.

A complex set of causes contributes to the development of RIHD. There is an early finding of increased vascular permeability and fluid extravasation, as well as inflammatory cell infiltration. This finding correlates with the development of pericardial fibrin exudates and effusions. After 1 year, fibrous tissue within the myocardium is more prevalent. Coagulation necrosis is seen near arteries occluded by fibrointimal proliferation, indicating focal infarctions rather than direct radiation damage to myocardium.

Myocardial fibrosis after radiation exposure is mediated by multiple cytokines and inflammatory cells. Following irradiation there is an increase in both type I and III collagen in the ventricles. Tumor necrosis factor-α and interleukin-1 secreted by macrophages following irradiation contribute to fibrosis in lung tissue. Transforming growth factor-β (TGF-β) promotes fibroblast activity and proliferation, and has been found to correlate with radiation-induced fibrosis in several tissue types. TGF-β gene expression is upregulated after irradiation in cultured endothelial cells, fibroblasts, and myocytes. Expression of other fibrosis-promoting factors, such as fibroblast growth factor-2, is also found to be elevated. The level of gene expression, however, is independent of radiation dose, indicating that this initial change in gene expression may not be the primary insult leading to fibrosis. The authors hypothesize that hypoxia after

Pathology of RIHD and Mechanism of Injury

The distinct gross and microscopic pathology of RIHD has been characterized in human autopsy studies. Many of these patients were young, making it unlikely that age-related degenerative changes or CAD was responsible for the lesions observed. The majority (70%-100%) of RIHD autopsy pericardium specimens had some form of pericardial disease. Pericardial effusion was the most common finding, followed by constrictive pericarditis, fibrinous pericardial adhesions, and oblitative pericardial fibrosis. Pericardial thickening with fibrous tissue was also found in most patients. The mural endocardium and valves were also thickened in the majority of patients. Several valve specimens in one study were surgically removed mitral and aortic valves, and most of these were moderately to severely fibrotic and stenotic. Across the spectrum of autopsied patients, diffuse fibrosis was noted in each of the four valves, with calcification present in some. Interstitial fibrosis of the myocardium was present in > 50% of patients. Damage to or necrosis of myocardial cells was not observed in either study. Finally, 15% to 37% of autopsies revealed severe coronary artery stenosis (> 75% narrowing) attributable to radiation. Further microscopic examination showed atherosclerosis and intimal fibrosis; however, fibrous tissue dominated in the majority of sections. In addition, in most patients, the media was infiltrated by fibrous tissue.

A complex set of causes contributes to the development of RIHD. There is an early finding of increased vascular permeability and fluid extravasation, as well as inflammatory cell infiltration. This finding correlates with the development of pericardial fibrin exudates and effusions. After 1 year, fibrous tissue within the myocardium is more prevalent. Coagulation necrosis is seen near arteries occluded by fibrointimal proliferation, indicating focal infarctions rather than direct radiation damage to myocardium.

Myocardial fibrosis after radiation exposure is mediated by multiple cytokines and inflammatory cells. Following irradiation there is an increase in both type I and III collagen in the ventricles. Tumor necrosis factor-α and interleukin-1 secreted by macrophages following irradiation contribute to fibrosis in lung tissue. Transforming growth factor-β (TGF-β) promotes fibroblast activity and proliferation, and has been found to correlate with radiation-induced fibrosis in several tissue types. TGF-β gene expression is upregulated after irradiation in cultured endothelial cells, fibroblasts, and myocytes. Expression of other fibrosis-promoting factors, such as fibroblast growth factor-2, is also found to be elevated. The level of gene expression, however, is independent of radiation dose, indicating that this initial change in gene expression may not be the primary insult leading to fibrosis. The authors hypothesize that hypoxia after
radiation-induced vascular damage may play a greater role. Indeed, late interstitial fibrosis is often perivascular, and capillary injury precedes fibrosis, providing support that vascular damage causes radiation-induced fibrosis.\(^{18,19,39,42-44}\) There is also evidence that intestinal radiation injury is caused primarily by endothelial apoptosis.\(^{45}\) Deposition of von Willebrand factor (vWF) deposition in myocardial capillaries is followed by fibrosis in the ventricles and atria.\(^{46,47}\) This deposition is further evidence of endothelial damage and may result in capillary obstruction. Additionally, histopathologic findings in RIHD are most evident in the subendocardial layer, as in myocardial ischemia due to CAD. However, the intercalated discs and mitochondria of myofibers are damaged following irradiation, which appears to be unrelated to ischemia.\(^{48-51}\) Additionally, there is evidence of chronic TGF-\(\beta\) activity after irradiation continuing to stimulate fibrosis.\(^{52}\) Cardiac mitochondrial respiration is also inhibited by ionizing radiation, which results in elevated reactive oxygen species (ROS) production.\(^ {53}\) These findings are associated with radiation-induced myocardial dysfunction.\(^ {51,48-54}\) Finally, radiation-induced oxidative stress activates the renin-angiotensin-aldosterone system, and angiotensin II is a potent stimulator of fibrosis.\(^ {55,56}\) Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are protective against radiation-induced fibrosis in multiple tissue types, including heart.\(^ {55-57}\) The kallikrein-kinin system promotes inflammatory cell recruitment within the heart following radiation, although this may have both protective and injurious effects.\(^ {58,59}\)

Cardiac radiation exposure results in endothelial injury and atherosclerosis. Within several days after irradiation of the carotid and coronary arteries, lysosomal enzymes are activated within the intima and media, and cholesterol plaques form in the intimal layer.\(^ {60-63}\) This intimal infiltration of lipids is a result of increased endothelial permeability following radiation.\(^ {64,65}\) The plaques that develop following irradiation are often inflammatory plaques that are vulnerable to thrombosis.\(^ {56,67}\) These lesions contain infiltrates with macrophages and neutrophils, and occasional plaque hemorrhages were present.\(^ {66}\) Microvascular atherosclerosis is also observed.\(^ {68}\) In addition to plaques, fibrosis is present throughout the intima, media, and adventitia.\(^ {7,3}\) Generation of ROS is important to the pathogenesis of radiation-induced endothelial damage.\(^ {69}\) Release of vWF from endothelial cells is increased, thrombomodulin production is decreased, and adhesiveness of endothelial cells is found to increase, contributing to thrombosis.\(^ {46,70-72}\) Additionally, endothelium-dependent vasodilation is impaired by radiation, which may worsen small vessel thrombosis.\(^ {73}\) In patients with whole-body radiation exposure, such as survivors following thoracic radiation, as well as extensive fibrosis of the pericardium resulting in cardiac tamponade.\(^ {77}\) In one of the early series of RIHD patients who had received RT, pericardial disease was commonly observed.\(^ {77}\) The cases consisted primarily of acute pericarditis. Most of these patients subsequently recovered; however, some developed constrictive physiology later on. Their clinical presentation was identical to that of viral pericarditis, including chest pain and a friction rub.\(^ {77,78}\) The onset of acute pericarditis was not necessarily immediately following RT, ranging from immediately after RT to 2 years later.\(^ {77}\) Many patients
developed pericardial effusion, and several of these patients developed tamponade. Treatment was similar to viral pericarditis, consisting of nonsteroidal anti-inflammatory drugs and pericardiocentesis for large effusions.

Some patients develop chronic pericarditis with effusion or constrictive pericarditis. In a series of patients with constrictive pericarditis, up to one-third of cases were caused by RT, although this statistic likely varies by institution. Constrictive pericarditis can occur in patients of any age, including children. Patients with constrictive pericarditis following RT often have jugular venous distention or a pericardial knock on examination, and hepatomegaly was common in children. Many have symptomatic pulmonary congestion or edema. Electrocardiographic findings include low QRS voltage and T-wave abnormalities. The average time from irradiation to clinical presentation ranged from 14 to 88 months in several studies. There have also been cases of constrictive pericarditis developing over 20 years after RT for HD. Diagnosis can be aided with echo-cardiography or CT scan, revealing pericardial thickening, although cardiac catheterization showing elevated end-diastolic pressure is the most sensitive modality. Pericardiocentesis may be indicated for large effusions, especially for stabilization prior to surgery. When fibrosis of the pericardium has progressed to the degree that diastolic filling is significantly impaired, radical or partial pericardiectomy is performed to remove the constrictive portions of the pericardium. The prognosis after pericardiectomy after radiation is significantly worse than that for pericardiectomy performed for other reasons (5-year survival of 64.3% vs 11.0%; P < .001). This is likely because, with radiation-induced constriction, the entire heart is involved rather than the pericardium alone. However, at least one institution has achieved 100% survival in a small cohort after 8 years, and early pericardiectomy is recommended if constrictive pericarditis is diagnosed.

**Cardiomyopathy**

As a result of the involvement of myocardium by vascular compromise or direct radiation injury and fibrosis, cardiomyopathy and heart failure is a potential complication of cardiac radiation exposure. Dogs that developed severe congestive heart failure (CHF) following irradiation often also had myocyte lysis on histopathologic examination. As with CHF due to other causes, orthotopic heart transplantation (OHT) is the final option in cases that are refractory to medical therapy. This may be preferable to CABG or pericardiectomy, given that the severe fibrosis found in the mediastinum or diffuse CAD may impair operative success. One study had a 100% survival rate at a mean follow-up time of 48 months, indicating that OHT has the potential to be safe and feasible. However, OHT in this population also carries significant risks, with 33% of patients dying in the perioperative period in another study. Although OHT is an option for end-stage RIHD, patients should be carefully selected given the significant perioperative risk.

**Valvular Disease**

A wide range of disease affecting any of the cardiac valves may occur as a result of cardiac irradiation. Valvular disease has a high prevalence 20 years or more after mediastinal radiation, affecting the majority of these patients. Most patients are asymptomatic. Aortic regurgitation greater than trace levels was present in 60%, aortic stenosis in 16%, and mitral regurgitation in 52%. Calcification of the aortic valve is common. The treatment for CHF secondary to mediastinal irradiation is similar to treatment for CHF not caused by radiation exposure, including β-blockers and ACE inhibitors. As with CHF due to other causes, orthotopic heart transplantation (OHT) is the final option in cases that are refractory to medical therapy. This may be preferable to CABG or pericardiectomy, even when the two are not administered during the same time period.
The aortic and mitral valves are the most commonly affected, and tricuspid or pulmonary disease is less frequently reported. Risk factors for asymptomatic valvular disease include > 25 Gy of radiation to the heart. In addition to mediastinal RT exposure, valvular disease, including aortic stenosis, aortic regurgitation, and mitral regurgitation, has been reported in a man who was exposed to radiation in Chernobyl. Patients, when symptomatic, often present with heart failure symptoms depending on the valve involved. The presentation is similar to that of non–RIHD-associated valvular disease, and occurs an average of 22 years after radiation exposure.

Treatment of severe radiation-induced valvular disease is primarily surgical, consisting of valve replacement or occasionally percutaneous intervention. In patients with RIHD undergoing valve surgery (including aortic, mitral, tricuspid, and multiple), the 30-day mortality rate is 12%, and the 5-year survival rate is 66%. The most important predictor for perioperative (30-day) mortality was the presence of constrictive pericarditis. These patients had a 30-day mortality rate of 40%. One possible reason for this increased mortality is “frozen mediastinum,” referring to severe fibrosis of the mediastinum that may interfere with the operation. In addition, constrictive pericarditis may be limited to patients who have received higher doses of radiation and have greater overall cardiac injury. In patients with extensive mediastinal fibrosis or who are otherwise poor surgical candidates, transcatheter valve replacement is also an option. One case report described a woman with severe radiation-induced aortic stenosis who was successfully treated with the Edwards SAPIEN XT (Edwards Lifesciences, Irvine, CA) stent-mounted prosthetic valve. Another reported a patient with pulmonary stenosis secondary to RT who was treated with balloon angioplasty and stent placement, achieving reduction in the stenosis and pressure gradient. Intervention for radiation-induced valvular disease should be individually tailored to the valve involved and the patient’s other cardiac disease and noncardiac comorbidities.

**Coronary Artery Disease**

CAD is rapidly accelerated in patients exposed to radiation, and is the most common clinically significant manifestation of RIHD (Figure 3). The majority of patients who develop CAD have at least one Framingham risk factor. However, radiation alone may cause CAD. In multiple cases, young patients without traditional cardiac risk factors who had received mediastinal radiation for HD have had acute MI. The distribution of CAD depends on the areas irradiated, as vessels exposed to higher doses have more stenoses. In patients with left-sided breast cancer treated with RT, the risk of severe stenosis in the mid and distal LAD as well as the distal diagonal is significantly increased. In patients who have received mediastinal RT, over 75% of asymptomatic patients have coronary artery stenoses.

![Figure 3. Coronary angiography images of a patient with coronary artery disease secondary to radiation exposure. (A) There is diffuse atherosclerosis of the right coronary artery with a fractional flow reserve of 0.69. (B) The left circumflex artery had a stenosis in the ostium. (C) The left anterior descending artery had diffuse atherosclerotic disease with a fractional flow reserve of 0.78. (D) Angiography of the right brachiocephalic artery reveals a moderate stenosis.](image-url)
The distribution of CAD in these patients is often extensive; 30% of patients screened for CAD with coronary angiography have two- or three-vessel disease with stenosis of ≥70%.112–114 Ostial lesions in the left, right, or both coronary arteries were also common. In addition to de novo CAD following RT, mediastinal RT for HD can increase the risk of in-stent restenosis following PCI previous to irradiation.115 Interestingly, intracoronary radiation therapy in the form of iridium-192 seeds embedded within a ribbon is being used to treat in-stent restenosis.116 The Washington Radiation for In-Stent Restenosis Trial (WRIST) randomized study evaluating this therapy found a reduced major adverse cardiac event rate at 5 years when compared with placebo (46.2% vs 69.2%; P = .008), primarily driven by reduced target lesion revascularization. The proposed mechanism is inhibition of neointimal proliferation associated with medial fibrosis and cell death of the proliferative cells within the media.116,117 These inconsistencies in the effects of radiation on vasculature may be due to the fact that external RT uses repetitive and higher doses as opposed to the single, lower dose used with intracoronary radiation therapy.117

The clinical presentation of radiation-induced CAD is primarily angina, as with typical CAD.113 This may be exertional angina, rest angina, chest pain due to acute MI, or heart failure secondary to acute MI. Hibernating myocardium associated with a significant stenosis has also been observed in a patient treated for HD.118 Electrocardiographic (ECG) and cardiac biomarkers such as troponin and creatine kinase-MB are useful for the diagnosis of acute MI.119 Coronary angiography is still the standard of care for diagnosis and localization of the lesion in patients who present with angina associated with cardiac irradiation.119 There are also several other validated diagnostic approaches to CAD associated with radiation; perfusion imaging using technetium-99m tetrofosmin is one such method.119,120 However, it should be noted that some lesions observed with perfusion imaging are irreversible or do not correspond to coronary artery territories, suggesting that they are due to damage to microvasculature rather than coronary arteries. CT angiography (CTA) with or without coronary artery calcium (CAC) scoring is another technique.121,122 CAC scoring alone with Agatston and volume scores over 200 was fairly specific for CAD, although not necessarily sensitive.122 Using CTA in addition to CAC scoring adds sensitivity to the test.123

Although guidelines for the medical management of acute coronary syndromes (ACS) and stable CAD do not make mention of RIHD specifically, it is reasonable to follow the existing recommendations for conventional CAD and ACS.124,125 For revascularization of coronary arteries, both PCI and CABG may be used.126 Because radiation may cause multiple types of heart disease in one patient, CABG has the potential of being done during the same operation as pericardiectomy or valve surgery to reduce reoperation.127 As discussed above, mediastinal fibrosis may interfere with cardiac surgery.107 There is concern that the internal mammary artery (IMA) may also be affected by irradiation, and that this makes it an inferior conduit for CABG in patients with radiation-induced CAD.128 However, one study of 125 patients who had previously received RT did not find any evidence of radiation-induced injury to IMA grafts, and the authors state that avoiding use of the IMA as a bypass graft is not necessary.129 Both CABG and PCI are reasonable options and the appropriate use criteria for coronary revascularization should be considered when managing significant coronary artery stenoses in patients with a history of irradiation.130,131

**Conduction Abnormalities**

Damage to myocardium and coronary arteries also can result in conduction abnormalities, such as bundle branch blocks and atrioventricular (AV) block.98,132 In asymptomatic patients, left or right bundle branch block (LBBB, RBBB), and first-degree AV block may be detected incidentally on ECG.98 The prevalence of these defects is comparable with Framingham studies. In a case series of patients with symptomatic conduction defects, clinical presentation was most commonly syncope.132 The average time interval from irradiation until presentation was 12 years, and intermittent complete infranodal AV block was present in all patients, with interval ECGs showing LBBB or RBBB. One reported cause of AV block after RT is exercise-induced ischemia of the AV node, due to ostial stenosis of the right coronary artery.133,134 In addition, fibrosis throughout the heart can disrupt the bundle branches, the AV node, and the conduction system proximal to the AV node.135,136 Pacemaker therapy is indicated for high-degree AV blocks.132,133

In addition to conduction blocks, young patients treated for cancer with anthracyclines and cardiac irradiation were at increased risk for premature ventricular contractions, supraventricular tachycardia, and ventricular tachycardia.137

**Prevention and Screening**

The most important method to prevent RIHD is preventing or
reducing radiation exposure to the heart. This is accomplished with radiation protection blocks covering the heart, decreasing the radiation field, and altering total dose or dose fraction. There is a paucity of literature regarding the prevention of RIHD post-exposure. Several preclinical studies have found that ACE inhibitors and ARBs mitigate injury to noncardiac tissues, and another study found that patients who were incidentally on ACE inhibitors had a decreased risk of radiation pneumonitis.\textsuperscript{138-140} The mechanism of this protective effect appears to be the prevention of fibrosis within these tissues. Given that fibrosis is also commonly observed in the heart following irradiation, the use of ACE inhibitors or ARBs may be similarly protective for RIHD; however, prospective trials would need to evaluate this.

The most important method to prevent RIHD is preventing or reducing radiation exposure to the heart. This is accomplished with radiation protection blocks covering the heart, decreasing the radiation field, and altering total dose or dose fraction.

It is also important to carefully monitor and treat traditional CAD risk factors such as hypertension, dyslipidemia, diabetes, and smoking, even in young patients.\textsuperscript{83} Recommendations for lipid screening include a lipid panel every 3 years, and annual blood pressure and fasting blood glucose testing.\textsuperscript{143} Additionally, screening for valvular disease with echocardiography, and for CAD with CAC scoring and CT angiography, may be warranted. As RT is refined to reduce cardiac doses, the incidence of RIHD may decline.

**References**

Cardiovascular Complications of Radiation Exposure

MAIN POINTS

- The cardiovascular sequelae of radiation exposure are an important cause of morbidity and mortality following radiation therapy for cancer, as well as after exposure to radiation after atomic bombs or nuclear accidents. Involvement of the pericardium, myocardium, coronary arteries, valves, and conduction system has been observed.

- The total dose of radiation received by the heart, and fractionation (the division of the total dose into smaller fractions separated by time), have both been studied with respect to risk of subsequent radiation-induced heart disease (RIHD). Early animal studies provided insight into the dose-response relationship of cardiac irradiation. Studies have demonstrated that greater fractionation of the total dose decreases acute pericarditis and myocardial necrosis.

- A complex set of causes contributes to the development of RIHD. There is an early finding of increased vascular permeability and fluid extravasation, as well as inflammatory cell infiltration. This finding correlates with the development of pericardial fibrin exudates and effusions. Coagulation necrosis is seen near arteries occluded by fibrointimal proliferation, indicating focal infarctions rather than direct radiation damage to myocardium. Myocardial fibrosis after radiation exposure is mediated by multiple cytokines and inflammatory cells. The level of gene expression is independent of radiation dose, indicating that this initial change in gene expression may not be the primary insult leading to fibrosis.

- The most important method to prevent RIHD is preventing or reducing radiation exposure to the heart. This is accomplished with radiation protection blocks covering the heart, decreasing the radiation field, and altering total dose or dose fraction. There is a paucity of literature regarding the prevention of RIHD post-exposure.

Several preclinical studies have found that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers mitigate injury to noncardiac tissues, and another study found that patients who were incidentally on ACE inhibitors had a decreased risk of radiation pneumonitis.


Cardiovascular Complications of Radiation Exposure


