Mediastinal irradiation and its effect on the cardiovascular system

Mediastinal irradiation for various malignancies can cause radiation injury to mediastinal structures, most importantly the cardiovascular system. This article reviews the effect of radiation on cardiovascular structures and the manifestations of various radiation-induced heart diseases.

Mediastinal irradiation for various malignancies causes an inadvertent injury to the mediastinal structures. This article focuses on the adverse effects of mediastinal irradiation on the cardiovascular system. Its effects on the cardiovascular system are diverse and include pericardial disease, coronary arteriosclerosis, radiation-induced valvular heart disease, aortic calcification, restrictive cardiomyopathy and various conduction abnormalities.

Relationship between radiation dose and extent of radiation-induced heart disease

Any mediastinal structure may sustain the deleterious effects of irradiation. Two groups of cancer patients are particularly susceptible, in Hodgkin's and breast cancer, as the field of radiation involves a significant area of mediastinum. While pericardium is the commonest involved structure, a significant proportion of patients with radiation-induced constrictive pericarditis also develop various types of concomitant cardiovascular diseases (Orzan and Brusca, 1994). The damage includes coronary ostial stenosis, valvular insufficiency and restrictive cardiomyopathy in patients who had received a radiation dose of 30–50 Gy (Orzan and Brusca, 1994).

In a separate study by Adams et al (2004), a median radiation dose of 40 Gy was shown to be adequate to damage various cardiac structures, especially the anterior cardiac structures comprising the right heart chamber and its blood supply. The likelihood of damage and the extent of involvement appear to be dependent on the radiation level. A more extensive radiation dose is required for certain malignancies like Hodgkin's disease, thymoma and testicular tumour and so the risk of developing radiation-induced heart disease is higher, with influence on perioperative morbidity and survival after cardiac surgery (Chang et al, 2007).

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Effect on the pericardium

The pericardium is the most commonly involved structure in the long-term sequelae of mediastinal irradiation. The pathology includes mediastinal fibrosis, pericardial adhesions, pericardial thickening and calcification (Brosius et al, 1981; Jahangiri et al, 1995). These patients commonly develop symptomatic pericardial effusion or severe pericardial constriction (Jahangiri et al, 1995; Stewart et al, 1995; Veeragandham and Goldin, 1998; Banerjee and Swanton, 2002). Pericardiectomy is effective in symptomatic pericardial effusion or constriction (Veeragandham and Goldin, 1998).

Effect on conduction system

Pathological changes to the conduction system are secondary to fibrosis of the conduction system as well as the surrounding tissue. The resulting clinical scenario is variable. Right bundle–branch block and autonomic dysfunction are common manifestations (Adams et al, 2004). More rarely, complete heart block necessitating permanent pacemaker placement may occur (Chen et al, 1991; Adams et al, 2004).

Effect on the coronaries and coronary artery surgery

Radiation can trigger endothelial and fibroblast proliferation leading to atherosclerosis formation. These patients have either premature or accelerated arteriosclerosis of the coronaries (Stewart et al, 1995). The most commonly occurring lesion is an ostial stenosis or a proximal lesion (*Figure 1*) (Kleikamp et al, 1997; Chang et al, 2007). In patients with Hodgkin's lymphoma, 10% developed coronary artery disease a median of 9 years after radiotherapy (Hull et al, 2003). This is more common in patients who have a predisposition to coronary artery disease, i.e. hyperlipidaemia, diabetes or hypertension.

Stents have been used to treat these conditions, but coronary bypass surgery remains the gold standard (Veeragandham and Goldin, 1998). The suitability of the internal mammary artery as a graft may be questionable in the presence of past radiation exposure, but its

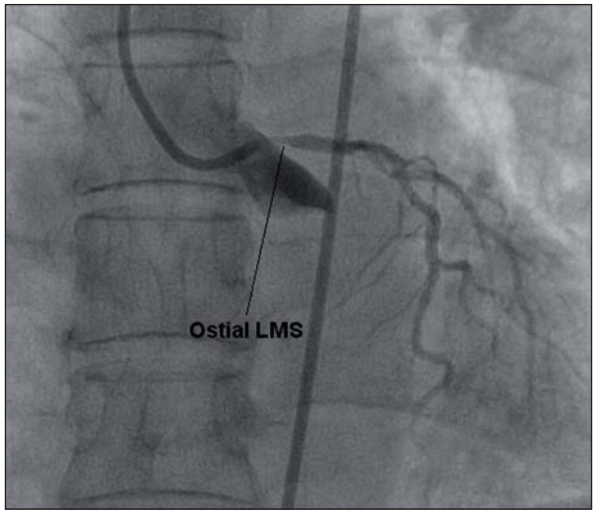


Figure 1. Preoperative coronary angiography showing ostial left mainstem stenosis (LMS) in a patient undergoing coronary artery bypass grafting.

use is advocated whenever feasible (Veeragandham and Goldin, 1998; Nasso et al, 2005). This is supported by the absence of any histomorphological injury to the internal mammary artery harvested in patients with previous mediastinal irradiation (Gansera et al, 2007). Nevertheless, its suitability as a graft requires careful assessment during cardiac catheterization and coronary artery bypass grafting. One should be aware of the concomitant damage from radiation to the rest of the heart. This is especially important in the intra- and postoperative management of a cardiac surgical patient. In the authors' experience, adhesion is not particularly a problem following sternotomy. However, there is some evidence that it may be associated with a slightly increased incidence of sternal instabilities following sternotomy closure (Gansera et al, 2007).

Effect on the heart valves

Valvular dysfunction secondary to radiation is less common. Around 6% of patients developed valvular dysfunction at a median of 22 years post-radiotherapy, i.e. a decade later compared to the onset of coronary artery disease in patients with Hodgkin's disease (Hull et al, 2003). Dystrophic calcification and fibrosis can affect the aortic and mitral valve following radiation injury (Jahangiri et al, 1995; Veeragandham and Goldin, 1998). In a surgical and autopsy study, 71% of patients with radiation heart disease had valvular involvement but just below half (47%) had significant clinical dysfunction (Veinot and Edwards, 1996).

Effect on the aorta

Aortic fibrosis and calcification is common and increases with age. Risk factors for arteriosclerosis play a role in the changes of the aortic wall. This process may be accelerated in patients with mediastinal irradiation. Unusual clinical presentation can sometimes occur. Aorto-oesophageal fistula with massive upper gastrointestinal bleeding is a possible complication of mediastinal irradiation, especially in patients with oesophageal malignancy. However, the use of mediastinal irradiation in non-oesophageal malignancy does not negate the possibility of this life-threatening complication (Sivaraman and Drummond, 2002).

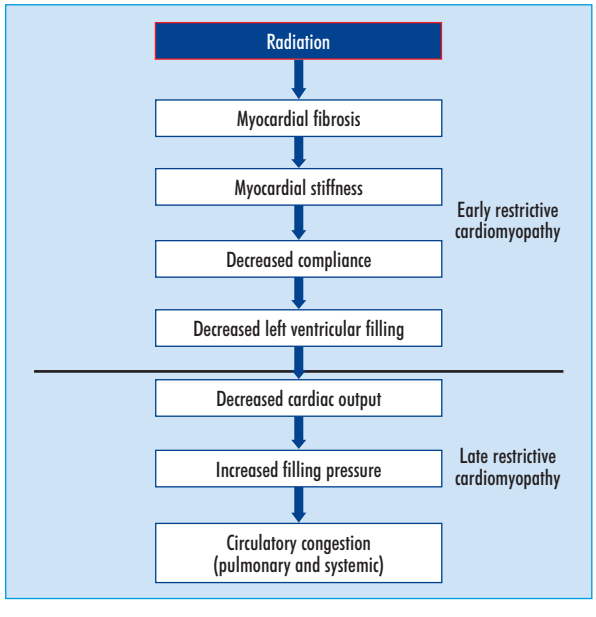
Effect on the myocardium

Restrictive cardiomyopathy is a rare form of cardiomyopathy. Rarer still is the one induced by mediastinal irradiation (Vordermark et al, 2005). It is characterized by restrictive ventricular filling and reduced diastolic volume of either one or both ventricles with a normal or near normal systolic function and wall thickness, as opposed to hypertrophic cardiomyopathy in which the myocardium is thickened. The right ventricle is more commonly involved following radiation injury. The systolic function is also affected in the chronic stage. Clinically, it can simulate constrictive pericarditis.

The primary mechanism of heart failure in restrictive cardiomyopathy is diastolic dysfunction. Myocardial stiffness from the radiation-induced interstitial myocardial fibrosis results in decreased compliance which in turn causes decreased ventricular filling (Brosius et al, 1981). Circulatory congestion subsequently ensues in chronic stage of restrictive cardiomyopathy (*Figure 2*).

Restrictive cardiomyopathy can be associated with other radiation-induced heart disease including constrictive pericarditis (Veeragandham and Goldin, 1998). Therefore, unlike other causes of constrictive pericarditis, there is an underlying dysfunctional myocardium despite surgical release of the pericardial constriction. Perioperatively, the cardiac surgeon and

Figure 2. Pathophysiology of radiation-induced restrictive cardiomyopathy.



anaesthetist should be aware of diastolic dysfunction secondary to restrictive cardiomyopathy as this can cause haemodynamic instability in the postoperative period, necessitating the use of inotropes and mechanical support of the heart despite good left ventricular systolic function.

The development of radiotherapy and cardiovascular protection

The volume of irradiation as well as newer techniques of radiotherapy delivery can confer a higher degree of cardioprotection (Jannifer et al, 2000; Engert et al, 2003). The introduction of mantle radiotherapy in the 1960s to irradiate supra-diaphragmatic lymphatic channels has transformed the outlook of Hodgkin's disease, but many survivors also suffered late myocardial damage and breast carcinoma. Breast cancer survivors showed an excess mortality from radiation-induced cardiac toxicity after 5 years, especially (from meta-analysis) in older radiotherapy regimens with a higher volume exposure than current standard tangential beams (Clarke et al, 2005). The advent of newer radiotherapy concepts like intensity-modulated radiotherapy allows a more precise volume delivery to reduce local toxicity (Veldeman et al, 2008). In addition, with modern chemotherapy, a combined multi-modality approach may see a decline in mediastinal toxicity in future generations.

Conclusions

The deleterious effect of mediastinal irradiation on cardiovascular structure is well supported in the literature. The likelihood of developing radiation-induced heart disease and its extent of involvement is dose and field dependent. The pericardium is the most commonly affected structure while the conduction system is the least affected. The valves, coronaries and myocardium are not spared. Restrictive cardiomyopathy is often underestimated, causing intra- and postoperative haemodynamic instability, resulting in an increased morbidity and mortality. Radiotherapy has transformed the survival outlook of many cancer patients resulting in an increasing number of late survivors. As radiation-induced heart disorder is likely to be encountered more frequently with late survivors from various malignancies, familiarity with its various modes of presentation is essential. Patients with radiation-induced heart disease require vigilant perioperative management. BJHM

KEY POINTS

- Use of mediastinal irradiation to treat various malignancies is associated with a wide range of adverse effects to the cardiovascular system.
- Its effect is often not localized and may involve various cardiovascular components concomitantly, hence a heterogeneous mode of presentation.
- The clinical presentation may be subtle but radiation-induced heart disease should be suspected in patients with previous exposure to significant mediastinal irradiation.
- Diastolic ventricular dysfunction secondary to restrictive cardiomyopathy can result in perioperative haemodynamic instability in patients undergoing surgery. Careful perioperative management is required.
- With late survivors from various malignancies, an increased number of cases of radiation-induced heart disease is likely.

Conflict of interest: none.

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