Radiotherapy-induced heart disease: a review of the literature

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Abstract

Radiotherapy as one of the four pillars of cancer therapy plays a critical role in the multimodal treatment of thoracic cancers. Due to significant improvements in overall cancer survival, radiotherapy-induced heart disease (RIHD) has become an increasingly recognized adverse reaction which contributes to major radiation-associated toxicities including non-malignant death. This is especially relevant for patients suffering from diseases with excellent prognosis such as breast cancer or Hodgkin’s lymphoma, since RIHD may occur decades after radiotherapy. Preclinical studies have enriched our knowledge of many potential mechanisms by which thoracic radiotherapy induces heart injury. Epidemiological findings in humans reveal that irradiation might increase the risk of cardiac disease at even lower doses than previously assumed. Recent preclinical studies have identified non-invasive methods for evaluation of RIHD. Furthermore, potential options preventing or at least attenuating RIHD have been developed. Ongoing research may enrich our limited knowledge about biological mechanisms of RIHD, identify non-invasive early detection biomarkers and investigate potential treatment options that might attenuate or prevent these unwanted side effects. Here, we present a comprehensive review about the published literature regarding clinical manifestation and pathological alterations in RIHD. Biological mechanisms and treatment options are outlined, and challenges in RIHD treatment are summarized.

Key words: Radiotherapy; heart injury; thoracic cancer; radiation-induced heart injury; cancer treatment

Background

Thoracic irradiation is a fundamental part of the standard therapy for lung, breast, esophageal and thymic carcinoma, and one of the most common uses of radiotherapy. Although modern planning and irradiation techniques have greatly improved since the introduction of intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT) and stereotactic radiotherapy, adjacent organs at risk limit the application of high
radiotherapy doses. Simultaneous chemoradiotherapy and combination of radiotherapy with novel agents including monoclonal antibodies, tyrosine kinase inhibitors and checkpoint inhibitors can increase radiation-induced toxicities. Especially patients suffering from diseases with excellent prognosis such as breast cancer or Hodgkin’s lymphoma may suffer from delayed side effects including radiation-induced heart disease (RIHD) in a dose-dependent manner. The number of long term survivors after radiotherapy is increasing even for lung cancer patients due to new targeted therapies and checkpoint inhibitors. Therefore, a profound understanding of RIHD is becoming more important in the future. While numbers do vary, an increased risk with up to 62% of cardiac deaths was reported among breast cancer patients after radiotherapy and 4% (50/1261) of Hodgkin’s lymphoma patients receiving radiotherapy died from cardiovascular diseases including ischemic heart disease and myocardial infarction. Patients who received thoracic radiotherapy in their childhood have a 5.0 to 18.4-fold increase in the risk to develop RIHD when average cardiac radiation dose exceeded 5 Gy.

The pathological spectrum of RIHD includes conduction abnormalities, valvular disease, coronary artery disease, pericarditis and pericardial constriction or effusion, cardiomyopathy and myocardial fibrosis. Although physical progress allowing for more conformal radiation techniques have decreased radiation doses to normal tissues, significant heart doses still can not completely be avoided. Until now, no effective treatment has been established for RIHD, partially because the underlying mechanisms of the RIHD remain largely unknown.

Here, we present the clinical manifestations and possible radiobiological mechanisms of RIHD. Furthermore, we discuss how a deeper understanding of RIHD might help to discover strategies in order to reduce the risk of cardiovascular diseases in thoracically irradiated cancer patients.

Clinical manifestation

Coronary artery disease

Radiation-induced coronary artery changes have become a serious reason for morbidity in breast cancer and other mediastinal malignancy patients treated with radiotherapy. For example, ischemic heart disease has become the most common reason for cardiac death in cancer patients after thoracic radiotherapy. A retrospective analysis involving 2168 breast cancer patients who received radiotherapy showed a linear correlation between radiation dose and coronary artery changes, showing the risk of coronary events increasing by 7.4% per Gy without obvious ceiling. Symptoms of radiation-induced coronary artery disease are the same as for regular coronary artery disease including angina and myocardial infarction, thereby complicating the differential diagnosis between radiation-induced coronary artery disease and conventional coronary heart disease. The diagnosis of radiation-induced coronary artery disease depends mainly on the history of thoracic radiotherapy.

Valvular disease

Thoracic radiotherapy may directly affect heart valves, leading to both stenotic and regurgitant valve diseases. Pathologic changes involve not only leaflet retraction but also fibrotic thickening and finally calcification. Aortic and mitral valves are affected more frequently compared to tricuspid and pulmonic valves. Although valvular heart changes are found in up to 81% of RIHD patients, over 70% of affected patients show no symptoms. Mean development time of asymptomatic valvular lesions is estimated to be 11.5 years, while the average time to symptomatic dysfunctional valvular disease is about 16.5 years. Until now, no specific radiation-induced valvular damage model has been established in vivo, and further animal data about the radiation-induced valvular disease are needed.

Conduction system disease

For radiation-induced conduction system injuries, it is difficult to confirm the causal link to radiotherapy and to determine the incidence, because conduction abnormalities typically are not detected until many years after radiation. However, reported conduction system diseases after thoracic irradiation include all degrees of atrioventricular block (AV block), atrioventricular nodal bradycardia and sick sinus syndrome. Other conduction anomalies reported to be connected with radiotherapy include right bundle branch block, prolongation of the corrected QT interval, T-wave changes and ST depression. So far, the biological mechanisms underlying radiation-induced conduction system disease remain unclear as it is challenging to establish the disease model in animals.

Pericardial disease

In necropsy studies, 70% of RIHD patients were found to have pericardial abnormalities. Hereby, radiation-induced pericarditis is marked by both protein-rich exudates in the pericardial sac and fibrin accumulation in the mesothelial lining pericardial cavity. Clinical spectrum of pericardial disease ranges from acute pericarditis to delayed chronic pericardial effusion, tamponade and constrictive pericarditis, according to the severity and the development of the disease.

Myocardial injury

Microvascular impairment by chest radiotherapy may lead to chronic ischemia, which eventually can result in myocardial fibrosis. Clinically, most patients suffer from restrictive cardiomyopathy leading to diastolic dysfunction which is partially accompanied by a slight
reduction of systolic function in the left ventricle.\textsuperscript{35} Less than 5\% of patients develop a dilated cardiomyopathy accompanied by reduction of left ventricular ejection fraction.\textsuperscript{37} Although the majority of studies associated with RIHD focus on the myocardial damage, the underlying mechanisms of the myocardial injury itself remain largely unknown. Elucidation of biological mechanisms underlying RIHD may give the opportunity to attenuate RIHD both in the early and delayed stage after thoracic irradiation.

**Mechanisms of RIHD**

Finding the biological mechanisms of RIHD is challenging due to many confounding factors, including the difficulty of sampling and the long observation time of over 10 years for clinical development of RIHD. However, preclinical studies may yield information on pathologic changes and potential treatments.

The response of tissues to radiotherapy can be estimated using a dose-response model, the so-called linear quadratic model,\textsuperscript{39} where the \(\alpha/\beta\)-ratio indicates the fractionation sensitivity of irradiated cells.\textsuperscript{39} Cardiomyocytes exhibit a low \(\alpha/\beta\)-ratio (about 2) which is typical for late-responding normal tissues. Most preclinical research about mechanisms of RIHD has been performed using a single high dose (20-30 Gy) or a low number of fractions, which is an increasingly used fractionation method for many tumors. However, many clinical irradiation protocols still use multiple fractions (~30) with a relatively low dose (~2 Gy) per fraction.\textsuperscript{39-42} High radiation doses show different biological effects compared to doses used in normal fractionated treatments; thus, available data from animal models in which high doses were used are difficult to compare with the majority of clinical situations. Moreover, although pathological findings in animals appear to be similar to those in cardiac tissue samples of human beings, it remains uncertain how well preclinical in vivo findings correspond to RIHD in humans.\textsuperscript{43}

**Coronary artery disease and vessel injury**

Radiation-induced atherosclerosis plays an essential role in the development of RIHD. While myocardial changes in response to a high dose of radiotherapy are alike to those detected in human beings, atherosclerosis does not occur in regular laboratory animals. Therefore, additional vascular risk factors are included in these models to accelerate atherosclerosis formation such as apolipoprotein E (ApoE) knock-out, high lipid diet, or high levels of troponin in plasma.\textsuperscript{43-46} Heart irradiation in ApoE knock-out mice was found to induce both elevated microvascular detriment and atherosclerotic plaque formation in coronary arteries.\textsuperscript{47} The transcription factor peroxisome proliferator-activated receptor alpha (PPAR\(\alpha\)), an important regulator of lipid metabolism in heart tissue, was activated in wild-type mice after exposure to a single radiation dose of 16 Gy\textsuperscript{40,48}; and reduced activation of PPAR\(\alpha\) resulted in the sudden death of 40 weeks old mice.\textsuperscript{49} Analogously, the increment of PPAR\(\alpha\) activity by administering simvastatin partly prevented the progress of cardiac fibrosis and hypertrophy in hypercholesterolemic and atherosclerosis-prone apolipoprotein E knock-out (ApoE/-) mice, which exhibited elevated cholesterol levels and developed age-related atherosclerosis and fibrosis.\textsuperscript{50} These in vivo findings are consistent with observations in both tissue specimens and ultrasound examination from patients showing vessel wall lesions after radiation.\textsuperscript{51,52}

Both perivascular and interstitial collagen deposition in rat myocardium was found increased for several months after a single radiation dose or a limited number of fractions.\textsuperscript{53,54} Irradiation-related myocardial fibrosis was accompanied by altered microvascular density, leading to impaired myocardium microvasculature function.\textsuperscript{55} Mice with an endothelial cell-specific deletion of \(\alpha\) showed a significant increase of cardiac dysfunction and myocardial necrosis in response to local heart radiation with 12 Gy, indicating the importance of myocardial vessels in sustaining cardiac structure and function after heart irradiation.\textsuperscript{56}

Eventually, atherosclerotic lesions in coronary vessels caused by irradiation are morphologically identical to those in patients with regular atherosclerosis and are marked by intimal proliferation, lipid-rich macrophages accumulation, and finally plaque formation.\textsuperscript{57} Risk of radiation-caused coronary artery alteration is known to be correlated with radiation dose and duration of radiotherapy.

Compared to thoracic radiation alone, 10 Gy whole body irradiation was found to result in pronounced cardiac vascular density reduction,\textsuperscript{58} suggesting that RIHD may be enhanced by irradiation of non-cardiac structures in the body. This might reflect an “abscopal” irradiation effect against normal tissue, which is then not in favour of patients as is the “abscopal” effect against tumors in the standard literature about radiation immune effects. However, this hypothetical negative systemic “abscopal” phenomenon against cardiac tissue has not yet been systematically investigated.

**Conduction system disease and pericardial disease**

Few researchers have focused on the mechanisms of the conduction system and pericardial disease in RIHD. Cardiac arrhythmia induced by exposure to ionizing radiation is a long-term consequence. The beat rate of differentiated cardiomyocytes derived from human induced pluripotent stem cells (iPS) decreased at 48 hours after irradiation with 5 Gy or 10 Gy. With higher irradiation doses, alterations in electrophysiological function were observed.\textsuperscript{59} In contrast, the beat rate of chicken cardiac cells raised in a dose-dependent manner for more than one week after irradiation with 0.5 Gy to 7 Gy. Dura-
irradiation, thickening of the left ventricular anterior wall was observed reducing both the inner diameters and the volumes of the left and right ventricle.66,67 Both fractional shortening and ejection fraction were increased in the irradiated hearts, whereas stroke volume was not changed.55,67

In animal models, a single dose of up to 8 Gy led to a significant increase in cardiac fibrosis, although higher total doses with lower dose per fraction seemed to be less harmful to cardiomyocytes than a lower single dose.57-69 Rat cardiac fibroblasts isolated from irradiated hearts displayed cytoskeletal remodelling such as actin filament changes and stress fibres formation.70 Formation of cytoplasmatic actin stress fibres was associated with an increased number of myofibroblasts producing collagen, leading to impaired myocardial contractility.65,67,71 Additionally, cardiomyocytes responded to stress signals by launching an inflammatory reaction activating macrophages, which resulted in reduced myocyte contractility both in vitro and in vivo, eventually leading to impaired diastolic and systolic function.73,74 This inflammatory response also reduced the capillary density of irradiated hearts, which may contribute to myocardial injury.47,75

Oxidative stress induced by various cytokines and growth factors including TGF-β,76,77 TNF-α,78-80 IL-1,81 IL-11,82-84 CTGF,85 PDGFs,86,87 VEGF and FGF88,89 has been demonstrated to contribute to the induction of fibrosis (Fig. 1). Many of these factors as well as CK-MB and BNP were considered to qualify as potential markers in predicting and evaluating RIHD.90 Overexpression of TGF-β1 was associated with radiation-induced cardiac fibrosis, suggesting that increased growth factor levels may deteriorate RIHD.91-93 Another important mediator of heart fibrogenesis are factors belonging to the PDGF family. Some studies have shown that overexpression of cardiac PDGF-C and PDGF-D by transgenic technology resulted in extensive cardiac fibrosis,86,87,94 whereas the PDGF-receptor blocker imatinib (which blocks also other kinases) significantly attenuated fibrosis in mice.95 Antifibrotic effects of PDGF signalling inhibitors such as imatinib have also been published for other organs including the lung and the kidney.96-99 PDGF signalling generally seems to play an important role in fibrogenesis. The small molecule PDGF tyrosine kinase inhibitor BIBF 11200 (Ofev) has been approved by the Food and Drug Administration (FDA) in the USA for the treatment of idiopathic lung fibrosis. Furthermore, in vivo experiments revealed beneficial effects regarding RIHD when the pro-fibrotic protein CTGF was blocked.100 Recently, an interesting study identified circulating microRNAs (pre-treatment c-miRNA) as biomarkers of radiation-induced cardiac toxicity in non-small-cell lung cancer, highlighting the important role of microRNA in RIHD.101

In rodent hearts receiving single high dose irradiation, long term pathological changes are associated with altered protein expression and impaired cardiac mitochondria function.102-104 The mitochondrial transcription factor, nuclear factor erythroid 2 [NF-E2]-related factor 2 (Nrf2), regulates the expression of various anti-oxidant enzymes.105 Although the exact mechanisms of the interaction between the Nrf2 pathway and mitochondrial alterations in RIHD are unclear, deficiency of Nrf2 was observed to reduce the life span of mice receiving thoracic radiation, suggesting that increment of Nrf2 levels may reduce radiation damages including RIHD.45,106-108

Some researchers proposed that cardiac irradiation can increase the number of mast cells which could be associated with progression of RIHD53; however, in other studies, mast cell-deficient rats showed more severe alterations than controls.109 Furthermore, high throughput transcriptomic and genetic studies have identified new molecular signals and pathways related to the whole fibrotic process after irradiation. Pathogenesis of cardiac fibrosis includes several molecular pathways, which can be activated by ionizing radiation110 (Table 1). However, the exact roles for the various cytokines and transcription factors in RIHD still need to be clarified, and it is unlikely to find a unique driver biological mechanism of RIHD.
Figure 1. Putative pathway overview how radiation therapy is involved in the development of cardiac fibrosis upon thoracic radiotherapy for cancer. RT, radiation therapy; PPA, protein phosphatase; AKT, protein kinase B; TGF-β, transforming growth factor beta; PI3K, phosphatidylinositol Biphosphatate; PISK, phosphoinositide 3-kinases; ROS, reactive oxygen species; ERK, extracellular signal-regulated kinase; TAK, TGF-β-activated kinase; MKK, mitogen-activated protein kinase kinase; JNK, the c-Jun NH2-terminal protein kinase; ATP, activating transcriptional factor; CTGF, connective tissue growth factor; α-SMA, α smooth muscle actin; Ang II, angiotensin II; AMPKα, AMP-activated protein kinase α; MAPK, mitogen-activated protein kinase; P38, P38 mitogen-activated protein kinase; JIP/JNK-interacting protein; AP-1, activating protein-1; CCN, the first number of CYR61, CTGF & NOV family; IL, interleukin; INF-α, interferon-α; RhoA, Ras homolog gene family, member A; ROCK, Rho-associated protein kinase; MRTF, myocardin-related transcription factor; YAP, yes-associated protein; PLC-2, Phospholipase C 2; PKD, Protein kinase D; PKC, Protein kinase C; SRF, serum response factor; C/EBPβ, CCAAT-enhancer-binding protein β; VEGFR, vascular endothelial growth factor receptors; NF-κB, nuclear factor-κB; COX-2, cyclooxygenase-2; TNF-α, tumour necrosis factor alpha; I KK, NF-κB kinase; MMPs, matrix metallopeptidases; ECM, extracellular matrix.

Table 1. Cytokines, signalling pathways and transcription factors involved in cardiac fibrosis.

| Cytokines | Pathway | Transcription factors |
|-----------|---------|----------------------|
| TNF-α78-80 | Smad-independent pathway112 | Smad113 |
| CTGF100 | AMPKα signaling pathway117 | PPAR-γ114 |
| MCP-1111 | Wnt signaling pathway123 | Nrf212,105-108 |
| ET-1110,115,116 | Smad-dependent pathway113 | |
| IL-1β111 | MRTF118,119 | |
| Ang II111 | AP-1120 | |
| VEGF88 | ERK121 | |
| IL-16,77,91,92 | FGF88 | |
| PDGF86,87,94 | SRF119 | |
| Nf-κB120 | ATF2127 | |
| JNK125,126 | C/EBPβ128 |

IL, interleukin; TNF-α, tumour necrosis factor alpha; CTGF, connective tissue growth factor; ET-1, endothelin-1; Ang II, angiotensin II; MCP-1, anti-monocYTE chemotactic protein-1; TGF-β, transforming growth factor beta; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor; AMPKα, AMP-activated protein kinase α; MRTF, myocardin-related transcription factor; YAP, yes-associated protein; JNK, c-Jun N-terminal kinase; SRF, serum response factor; PPAR-γ, peroxisome proliferators-activated receptor gamma; AP-1, activating protein-1; NF-κB, nuclear factor-κB; ATF2, activating transcriptional factor 2; Nrf2, Nuclear factor erythroid 2 (NFE2)-related factor 2; ERK, extracellular signal-regulated kinase; C/EBPβ, CCAAT-enhancer-binding protein β.
Potential countermeasures

Since early RIHD is mostly asymptomatic, pathologic changes are often diagnosed in late stages, generally over 10 years after irradiation. Currently, the only eligible approach for prevention of RIHD is by reducing cardiac irradiation doses. Since some exposure will remain inevitable, pharmacological treatments have been studied in order to attenuate RIHD.

Previous studies have shown that oxidative stress plays a significant role in the progression of RIHD. Antioxidants like pentoxifylline (PTX) and α-tocopherol applied 24 hours to one week prior to local heart irradiation significantly attenuated radiation-induced increments of left ventricular diastolic pressure in vivo. Furthermore, mast cell number in the left ventricle, collagen deposition and myocardial degeneration were found to be reduced after application of antioxidants. Regardless of clinical suitability, these studies suggested that antioxidants in principal may be able to reduce radiotherapy-caused collagen deposition and cardiac fibrosis. In another study, colchicine was prophylactically used against radiation-induced coronary artery impairment by reducing inflammation and hindering platelet aggregation. Additionally, the cytoprotective agent amifostine was reported to protect against myocardial fibrosis and loss of function by scavenging free radicals when applied before single high dose heart irradiation. Amifostine is one of few clinically approved drugs for radiation protection but is rarely used due to significant adverse effects such as hypotension, Stevens-Johnson syndrome, erythema multiforme and epidermal necrolysis. Oral administration of molecular hydrogen saturated water or black grape juice prior to local heart irradiation reduced RIHD in animal models, probably by free radical scavenging. Similarly, melatonin application 15 minutes before radiation decreased both necrosis and fibrosis by free radical scavenging in a rat model. L-carnitine has also been found to attenuate radiation-induced cardiac function loss in mice by activating the p38MAPK/Nrf2 pathway, triggering the expression of NQO1 and HO1. Additionally, L-carnitine exhibited anti-apoptotic and anti-oxidative effects in irradiated mice hearts.

Cardioprotective drugs, which are used in ischemic heart disease and chronic heart failure, have been investigated for RIHD, too. In some studies, statins have shown promising effects for RIHD, but in other studies, atorvastatin (and the anti-platelet drug clopidogrel) did not ameliorate atherosclerosis induction after 14 Gy irradiation in ApoE-/- mice. Nitric oxide-releasing aspirin (NCX 4016) and aspirin are known to attenuate age-related atherosclerosis; however, both NCX 4016 and aspirin did not significantly reduce number of atherosclerosis lesions when a single irradiation dose of 14 Gy was delivered. Moreover, the angiotensin-converting enzyme inhibitor (ACEI) captopril has demonstrated beneficial effects regarding RIHD in vivo. With rheological agent PTX in combination with α-tocopherol, cardiac fibrosis was mitigated, and cardiac function was preserved. The authors reported about inhibition of pathways in which TGFβ and CTGF were involved. However, induction of arrhythmia and bradycardia neutralized these beneficial effects. Thalidomide was used to reduce infiltration of inflammatory cells by inactivating macrophages but did not change long-term radiation damage in mice receiving a single radiation dose of 16 Gy. The tyrosine kinase inhibitor sunitinib reduced systolic left ventricular inner diameter and volume, when administered once a day for 14 days after irradiation. Rabender and colleagues investigated the effects of IPW-5371, a TGF-β receptor 1 inhibitor. Administration of 30 mg/kg IPW-5371 for 20 weeks preserved cardiac contractile reserve and resulted in significantly decreased cardiac fibrosis. Furthermore, IPW-5371 treatment at either 10 mg/kg or 30 mg/kg for 6 weeks extended the survival time of irradiated mice. Mesenchymal stem cells (MSC) are known for their regenerative abilities in radiation-induced tissue injuries. Tail vein injection of bone marrow MSC improved RIHD and may be a new therapeutic option for myocardial injured patients after chemo- or radiotherapy. Whether bone marrow MSCs or adipose tissue MSCs are superior regarding their regenerative effects for RIHD is unknown; at least, radioresistance was shown to be independent of their tissue of origin. In a rat model, palladium alpha-lipoic acid complex (POLY-MVA) was administrated after irradiation with 45 Gy delivered in 5 fractions of 9 Gy. POLY-MVA reduced inflammatory infiltration markers such as CD2 and CD68 in irradiated hearts and attenuated radiation effects on mitochondria. However, the reversal of cardiac remodelling was not observed. Moreover, chronic intermittent hypobaric hypoxia promoted cardiac function in RIHD and decreased interstitial and perivascular cardiac fibrosis by reducing oxidative stress. Some other agents such as tetrahydrobiopterin might protect cardiomyocytes from radiation-induced injury by decreasing oxidative stress in vitro. Potential countermeasures to mitigate RIHD are summarized in Table 2. Currently, it seems far away to find an effective therapy for attenuation of RIHD and simulataneous tumor sensitisation.

Clinical management

Countermeasures for radiation-induced coronary artery disease in patients are challenging. Potential therapeutic concepts are similar to those used in patients with regular coronary artery disease which include lifestyle modifications, medical therapy, percutaneous coronary intervention and coronary artery bypass grafting. Regarding RIHD, percutaneous coronary intervention is generally preferable to coronary artery bypass grafting.
since radiation-induced lung injuries, valvular diseases, internal thoracic artery stenosis and fibrosis of surrounding structures may increase the risk of surgical procedures.29,159,160 For patients with irradiation-caused valvular disease, surgical valve replacement is generally recommended. Due to perioperative risk factors, increased long-term morbidity and death associated with open heart surgery, transcatheter aortic valve implantation (TAVI) might also be an appropriate alternative.161

Furthermore, patients with acute pericarditis are often treated with diuretics and non-steroidal anti-inflammatory drugs for symptom control, whereas chronic pericarditis can be treated surgically.17,29 Management of radiation-caused cardiomyopathy is similar to treatment of other types of cardiomyopathy and is typically based on symptomatic treatment. Heart transplantation may be a choice for highly selected patients in the terminal heart failure stage.162–164 Most mechanical interventions for fibrosis-related diseases are helpful to a certain degree, but a more biological approach that can interfere with fibrogenesis on a cellular level seems mandatory. Clearly, further preclinical and clinical research is needed to develop new compounds for RIHD.159,165,166

**Conclusion**

Despite significant technical and physical improvements of thoracic radiotherapy such as IMRT, IGRT, stereotactic radiotherapy, proton and heavy ion irradiation, RIHD remains a relevant risk. Preclinical and clinical studies have widely investigated various manifestations of RIHD including coronary vessel, heart valve, conduction system, pericardium and myocardium injuries. However, present knowledge of the underlying biological mechanisms is insufficient, and reported data from clinical studies are scarce, hampering a personalized and effective treatment approach for RIHD.

A deeper understanding of RIHD mechanisms is essential to initiate appropriate non-invasive screening methods for diagnosis and monitoring. Potential diagnostic modalities are specific biomarkers and radiological techniques such as echocardiography, high resolution computed tomography (HRCT), magnetic resonance imaging (MRI), positron emission magnetic resonance imaging (PET-MRI) and positron emission computed tomography (PET-CT). Beneficial effects of several compounds have been demonstrated in preclinical studies but data regarding these drugs in RIHD patients are limited. Some pharmacological drugs may provide new approaches to treat or prevent RIHD; however, randomized trials are essential to evaluate the role of these biological approaches.

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Conflict of interest
The authors declare that they have no competing interests.

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