EDITORIAL FOCUS

Radiation-induced HFpEF model as a potential tool for the exploration of novel therapeutic targets

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The prognosis of patients with breast cancers has improved: 5-yr survival has been ~90% in recent years (7), partially because the increased use of adjuvant therapies such as chemotherapy and radiotherapy. Recent advance in radiotherapy techniques substantially reduces the radiation exposure to hearts during radiotherapy of breast cancers, which reduces the incidence of cardiovascular diseases caused by atherosclerosis. However, even a low level of radiation exposure to the hearts during contemporary radiotherapy of breast cancers still provides a deleterious impact on the coronary microvasculature, which is associated with the increased risk of heart failure with preserved ejection fraction (HFpEF) with the mean cardiac radiation dose (12). Thus, radiation-induced cardiovascular disease, especially HFpEF, emerges as the most important competing mortality risk for breast cancer survivors (1).

The effects of cardiac radiation on left ventricular (LV) diastolic function remain to be poorly characterized, so far. Although previous studies have demonstrated the link between cardiac radiation exposure and subsequent microvascular rarefaction in both animal models and patients with breast cancer, LV diastolic function has not been assessed (9, 14). In a recent report from the American Journal of Physiology-Heart and Circulatory Physiology, Saiki et al. (11a) established a novel model of diastolic dysfunction without reduced ejection fraction by experimental global cardiac radiation exposure, in which the diastolic functional abnormalities were correlated well with the extent of microvascular rarefaction. Although this study did not assess the earliest morphological changes after radiation exposure, a previous study (14) has demonstrated that radiation primarily damages the microvasculature followed by inflammatory and thrombotic changes, resulting in capillary loss, and thus myocardial low tissue perfusion. The Saiki et al. study showed, for the first time, the causal link between microvascular dysfunction and increased risk of HFpEF after breast cancer radiation therapy. Interestingly, although the initial trigger is totally different, the radiation exposure-related HFpEF model appears to share the same underlying mechanism with metabolic risk-related human (4, 10, 16) and animal model of HFpEF (5, 13), the disturbance in nitric oxide (NO)-cGMP-PKG signaling from the microvascular endothelium due to the microvascular inflammation (Fig. 1).

Paulus and Tschöpe (10) proposed the hypothesis that a systemic proinflammatory state induced by metabolic comorbidities followed by coronary microvascular endothelial inflammation plays critical roles in and primary cause for the development of HFpEF. We (15) have also previously confirmed the involvement of NO less in HFpEF in rats. Coronary microvascular inflammation induces high oxidative stress and decreases NO bioavailability, resulting in stiff and hypertrophic cardiomyocytes through reduced PKG activity in cardiomyocytes (10). Indeed, microvascular inflammation, high oxidative stress, and depressed NO-PKG signaling were observed in both HFpEF patients (4) and the HFpEF model with obese ZSF1 rats (4, 5). At the same time, we have to recognize the different characteristics of the current radiation exposure-related HFpEF model from metabolic risk-related HFpEF models. Especially, the current radiation exposure-related HFpEF model significantly increases myocardial fibrosis, whereas the obese ZSF1 rat, a prevalent HFpEF model with the metabolic syndrome, lacks myocardial fibrosis (5). Indeed, two-thirds of patients with metabolic risk-related HFpEF do not show an elevated fraction of collagen volume in their myocardial biopsy sample (2). On the other hand, the radiation therapy induces dose-dependent perfusion defects in the myocardium in patients with breast cancer after the radiation therapy, indicating the development of both perivascular and pericellular fibrosis, although a direct evaluation of collagen deposition in the myocardium was not performed (9).

The Saiki et al. study also demonstrated that radiation exposure induces both slowed/incomplete LV relaxation and increased passive chamber stiffness through coronary microvascular endothelial inflammation with rarefaction and fibrosis. However, the molecular and cellular mechanistic insights remain to be addressed (Fig. 1). Thus, several questions arise as to whether the alternations in the Ca2+ sensitivity of the myofilaments and/or Ca2+ handling contribute to the impaired relaxation in this model, whether the stiffness of the collagen matrix depends not only on the amount of collagen but also the extent of collagen cross-linking (8), and whether there is any change in the extent of collagen cross-linking. The expression ratio of titin isoforms (N2B and N2BA) varies greatly among different species (3), and humans express much higher levels of N2BA titin than rodents, which affect the stiffness of cardiomyocytes (3). Accordingly, it seems to be important to use swine models that express a similar expression ratio of titin isoforms with humans (3) to investigate the effect of titin on diastolic properties. The relative contributions of changes in both collagen and titin to passive myocardial stiffness (16) also

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need to be addressed in this model. Systemic effects of radiation exposure such as elevated cholesterol, renal damage, and hypertension on the development of HFpEF also need to be addressed. Furthermore, the question of whether there is a threshold below which coronary microvascular damage and inflammation are not present should be clarified in the future. Finally, useful biomarkers that reflect the severity and/or efficacy of the treatments for radiation exposure-related HFpEF should be explored.

There are no approved therapies to reduce mortality and morbidity of patients with HFpEF so far, and the deeper understanding of the cellular and molecular mechanisms for the development of HFpEF is necessary to identify new effective therapies (11). To achieve it, we urge the establishment of animal HFpEF models that mimic the pathophysiology of human HFpEF and allow us to test drugs for human use. Although a wide range of HFpEF models related to various metabolic risks have been recently established (6), it is difficult to make an animal model of HFpEF that encompasses all etiologies, because HFpEF is a clinically diverse syndrome initiated by inflammatory mediators from a combination of variety of comorbidities that modify clinical presentation and course (10, 11). From this aspect, however, the Saiki et al. model (11a) of radiation exposure-related HFpEF seems to faithfully mimic the HFpEF observed in breast cancer patients after radiation therapy, such as the development of HFpEF followed the radiation therapy caused by microvascular rarefaction, myocardial fibrosis, and depressed nitric oxide (NO)-PKG signaling in cardiomyocytes, all of which contribute to the development of HFpEF. TGF, transforming growth factor; sGC, soluble guanylate cyclase.

also comorbidity-driven coronary microvascular endothelial inflammation.

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