Radiation-Induced HFpEF Model as a Potential Tool for the Exploration of Novel Therapeutic Targets

#1 Osamu Tsukamoto, MD, PhD, #2 Masafumi Kitakaze, MD, PhD,

#1 Department of Medical Biochemistry, Osaka University Graduate School of Medicine, Suita 565-0871, Japan

#2 Department of Clinical Medicine and Development, National Cerebral and Cardiovascular Center, Suita 565-8565, Japan

Mailing address: Osamu Tsukamoto, MD, PhD
Department of Medical Biochemistry, Osaka University Graduate School of Medicine, Suita 565-0871, Japan
Fax: ±81-6-6879-3493, Tel: ±81-6-6879-3492
E-mail: tsuka@medbio.med.osaka-u.ac.jp

Word count: 1,937 words
The prognosis of patients with breast cancers has improved: Five-year survival has been about 90% in recent years(7) partially because the increased use of adjuvant therapies such as chemo- 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 provide a deleterious impact on 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 the previous studies 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 this issue of the American Journal of Physiology-Heart and Circulatory Physiology, Saiki et al. 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 the current study did not assess the earliest morphological changes following radiation exposure, the previous studies demonstrated that radiation primarily damages the microvasculature followed by inflammatory and thrombotic changes, resulting in capillary loss, and thus myocardial low tissue perfusion(14). The current 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 the nitric oxide (NO)-cyclic guanosine monophosphate (cGMP)-protein kinase G (PKG) signaling from
Paulus WT and Tschope C 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(10). We also have previously confirmed the involvement of NO less in HFpEF in rats(15). Coronary microvascular inflammation induces high oxidative stress and decreases NO bioavailability, resulting in stiff and hypertrophic cardiomyocytes through the 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 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 the metabolic risk-related HFpEF models. Especially, the current radiation exposure-related HFpEF model significantly increases myocardial fibrosis, while 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 myocardium in patients with breast cancer following the radiation therapy, indicating the development of both perivascular and pericellular fibrosis, although a direct evaluation for the collagen deposition in myocardium has not performed(9).

The current study also demonstrated that radiation exposure induces both slowed/incomplete left ventricular 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). The several questions arise as to whether the alternations in the Ca\(^{2+}\)-sensitivity of the myofilaments and/or Ca\(^{2+}\)-handling contribute to the impaired relaxation in this model, whether the stiffness of collagen matrix depends not only on the amount of collagen but also the extent of collagen crosslinking(8), and whether there is any change in the extent of collagen crosslinking. The expression ratio of titin isoforms (N2B and N2BA)
varies greatly among the different species (3) and human 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 similar expression ratio of titin isoforms with human (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 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 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 reflects the severity of and/or the 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 are urged to the
establishment of the animal HFpEF models that mimic the pathophysiology of human HFpEF and
allow us to test the drugs for human use. Although a wide range of the HFpEF models related to
various metabolic risks have been recently established (6), it is difficult to make an animal model of
HFpEF that encompassing all etiologies, because HFpEF is clinically a 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 current model of the radiation
exposure-related HFpEF seems to faithfully mimic the HFpEF observed in breast cancer patients
after radiation therapy, such as a development of HFpEF followed the radiation therapy caused by
microvascular rarefaction, myocardial fibrosis, oxidative stress and suppressed PKG activity (9).
Even though we have to remember that cardiovascular risk may differ even among the individuals
receiving the same radiation dose depending on the preexisting age- and comorbidity-related
myocardial abnormalities, the current radiation exposure-related HFpEF model will provide us the
opportunity to reveal novel signaling cascades and therapeutic targets against HFpEF cause by not
only radiation-driven but also comorbidity-driven coronary microvascular endothelial inflammation.

Disclosures

No conflicts of interest, financial or otherwise, are declared by the authors.


12. Saiki, H., Petersen, I. A., Scott, C. G., Bailey, K. R., Dunlay, S. M., Finley, R. R., Ruddy, K. J., Yan,


Figure legend

Fig. 1. Proposed mechanism of the radiation exposure-related HFpEF. Cardiac radiation exposure induces coronary vascular inflammation followed by microvascular rarefaction, cardiac fibrosis, and depressed NO-PKG signaling in cardiomyocytes, all of which contribute to the development of HFpEF. Abbreviations used are: sGC, soluble guanylate cyclase; cGMP, cyclic guanosine monophosphate; HFpEF, heart failure with preserved ejection fraction; NO, nitric oxide; PKG, protein kinase G.
cardiac radiation exposure

coronary microvascular vascular damage
inflammation and thrombotic change
oxidative stress
NO bioavailability (↓)
capillary loss
microvascular rarefaction
microvascular dysfunction
ischemia during exercise
leukocytes
TGF-β
fibroblasts
myofibroblasts
fibrosis
increased passive stiffness
impaired relaxation
hypertrophy
sGC (↓)
cGMP (↓)
PKG activity (↓)
collagen content (?)
collagen crosslinking?
phosphorylation of titin?
Ca²⁺ handling?
Ca²⁺ sensitivity?

cardiomyocytes