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Reduction of subclinical acute cardiac injury through DIBH radiotherapy: a single-institution real-world clinical cohort analysis

Kun Zhang[1], Jing Shen[1], Yongguang Liang[1], Xiangyin Meng[1], Bo Yang[1], Jiabin Ma[1], Ke Hu[1], Jie Qiu[1*], Xiaorong Hou[1*] and Fuquan Zhang[1,2]

Abstract

Background Radiotherapy for left-sided breast cancer is associated with additional cardiac risks. Deep inspiration breath hold (DIBH) has emerged as the primary cardiac sparing technique, demonstrating significant reduction in mean heart dose (MHD) and left anterior descending coronary artery (LAD) dose. However, the issue of whether dosimetric advantages can be effectively translated into clinically measurable benefits for patients remains to be further elucidated. The study aims to investigate whether DIBH, in contrast to free breathing (FB), could yield a clinical cardiac advantage, beyond dosimetry benefits, for patients with early left breast cancer following breast-conserving surgery combined with whole breast radiotherapy.

Patients and methods The study involved 78 patients with early-stage left breast cancer undergoing radiotherapy between 2021 and 2022 after breast-conserving surgery. 46 patients were treated with DIBH technique and 32 were treated with FB. Patients with previous cardiac disease were excluded. We performed myocardial enzymes, electrocardiogram (EKG), and echocardiograms (ECHO) in all patients within 2 weeks before, during, and 6 months after radiotherapy. EKG and ECHO follow-up extended to 24 months. The results of the two groups were compared using nonparametric tests and chi-square tests, and $P < 0.05$ indicated statistical significance. Subclinical acute cardiac injury was characterized by the emergence of elevated myocardial enzymes beyond normal levels and/or EKG alterations in ST-T or T-wave patterns and/or abnormalities detected in ECHO within a 6-month period following radiotherapy.

Result The average age was 52.3 years for FB and 44.9 years for DIBH. There were no significant differences in staging, molecular subtype, chemotherapy, and endocrine therapy history. The proportion of subclinical acute cardiac injury was lower with DIBH compared to FB (DIBH = 31/46 and FB = 28/32, $p = 0.042$). The most sensitive subclinical acute cardiac injury events were detected by myocardial enzymes, with cardiac troponin I (cTnI, $p = 0.034$) and N-terminal pro-B-type natriuretic peptide (NT-proBNP, $p = 0.023$) appearing significantly lower in the DIBH patients during radiotherapy. The difference of cTnI between 2 groups at 6 months after radiotherapy became non-significant.

*Correspondence:
Jie Qiu
qj_ww@139.com
Xiaorong Hou
hxr_pumch@163.com

Full list of author information is available at the end of the article

Creatine kinase-MB (CK-MB) was higher in DIBH comparedwith FB only 6 months after radiotherapy ($p=0.006$). The differences in EKG and ECHO were not significant between the two groups within 6 months after radiotherapy. Notably, the DIBH group exhibited a significantly lower incidence of abnormal EKG at 12–24 months compared to the 3–6 months ($p=0.003$).

Conclusion The implementation of DIBH has been demonstrated to reduce the proportion of patients experiencing subclinical acute cardiac injury, with a higher proportion of patients returning to normalcy after one year. This finding suggests the potential reversibility of radiation-induced cardiac injury. The monitoring of these early cardiac biomarker changes to identify high-risk patients, followed by the implementation of early interventions, may contribute to a reduction in the incidence of long-term cardiac complications. Future research could integrate cardiac biomarkers, EKG, as well as traditional dosimetric parameters and baseline cardiac risk factors, to construct a more precise, individualized cardiac risk prediction model, thereby better assessing the long-term cardiac risks in patients.

Keywords Breast cancer, Radiotherapy, DIBH, Cardiac enzyme, Electrocardiogram, Echocardiogram, Subclinical injuries

Introduction

Breast cancer is the most common cancer in women and the leading cause of cancer-related death in women [1, 2]. In recent years, the combination of breast-conserving surgery (BSC) and postoperative radiotherapy has become a routine approach to early-stage breast cancer treatment, due to the satisfactory cosmetic and therapeutic outcomes [3]. However, left breast radiation therapy has been found to have cardiotoxic side effects due to the location of the irradiation field adjacent to the heart. Studies have shown that breast radiotherapy can increase the risk of long-term heart disease, including coronary artery disease, ischemic heart disease, arrhythmias, cardiomyopathy, and pericardial disease [4]. The risk of cardiac events increased by 7.4% as the mean heart dose (MHD) per Gy increased, with no threshold [5]. Such side effects partially counteract the survival benefit brought by radiotherapy. Thus, providing cardioprotection and understanding the pathophysiological processes are crucial in breast cancer radiotherapy.

Deep Inspiration Breath Hold (DIBH) is currently one of the mainstream techniques for cardioprotection in radiation therapy. Current research on DIBH focuses on respiratory movement management, as well as dosimetry decline. Various studies have demonstrated that DIBH can reduce cardiac dose by 40–70% [6, 7]. However, it is uncertain whether this dose reduction results in a decrease in the actual risk of cardiac toxicities. In clinical practice, we have observed that the degree of dosimetry decline varies among patients. Due to the uncertainty of its clinical benefit and the inconsistency in the degree of dosimetry decline, further investigation into the actual effects of DIBH is needed.

Our study compared the changes in subclinical cardiac responses in two groups of patients after free-breathing (FB) and DIBH radiation therapy, using cardiac enzymes, electrocardiograms (EKG), and echocardiograms (ECHO). The aim was to clarify the clinical significance of DIBH in addition to dosimetry and provide additional data for future studies on the clinical benefits of DIBH. Also, early detection of subclinical changes in some patients may identify those at high risk of cardiac events.

Patients and methods

The study enrolled patients with early-stage (AJCC 8th) left breast cancer who underwent BCS at our institution between July 2021 and January 2022 and were scheduled to receive postoperative adjuvant radiotherapy. Patients with a history of other cancers or clinically confirmed cardiovascular disease were excluded from the study. The clinical and pathologic information was obtained from the medical records. During the radiotherapy simulation, patients were positioned in the supine position with both arms positioned overhead. Non-contrast-enhanced computed tomography (CT) scans were performed using a Siemens Somatom Emotion 16-slice CT scanner Radiotherapy treatment planning was conducted utilizing the Elekta Versa HD linear accelerator and Monaco Treatment Planning System (TPS) version 5.11. Target volume delineation and organ-at-risk (OAR) contouring were performed in strict adherence to the Radiation Therapy Oncology Group (RTOG) contouring guidelines. Specifically, cardiac substructure delineation was executed according to the standardized cardiac atlas protocol established through collaborative efforts between the University of California and Michigan Medicine [8]. Radiotherapy was delivered using intensity-modulated radiation therapy (IMRT) with a four-field tangential beam arrangement. A total dose of 42.5 Gy was prescribed to the breast parenchyma, administered in 16 fractions of 2.66 Gy over 4 weeks using 6 MV photon beams. The planning acceptability criteria were as follows: 100% of the planning target volume of the breast must be covered by at least 95% of the prescribed dose range, and the dose to any 2 cc volume within the

high-dose region must not surpass 110% of the prescribed dose.

Cardiac enzymes were performed within 2 weeks before the initiation of radiation therapy, during treatment, and at 3 and 6 months after treatment. ECHO and EKG were performed within 2 weeks before the initiation of radiation therapy, 3–6 months, and 12–18 months after radiotherapy. The EKG and ECHO assessments were independently interpreted by board-certified cardiologists who were blinded to all aspects of the study protocol, including patient allocation and experimental interventions. Dosimetry information for radiation therapy was obtained from treatment records. Subclinical cardiac injury was defined as new-onset higher than normal levels of cardiac enzymes or S-T or T wave changes or ECHO abnormalities after treatment initiation.

Data analyses were conducted using SPSS version 27.0. The clinical and pathological characteristics of the two groups were compared using the chi-square test, while the age difference was analyzed with the student's t-test. Nonparametric tests were utilized to compare the differences in cardiac enzymes between the two groups. The chi-square test was employed to compare the number of patients with EKG and ECHO abnormalities, as well as the defined subclinical cardiac injury between the two groups. A comparison of the radiation dose to the heart between the two groups was also conducted using a student's t-test. A p-value of less than 0.05 was considered statistically significant.

Table 1 Patients' characteristics

	FB($n=32$)	DIBH($n=46$)	p
Age	52.28 ± 1.66	44.85 ± 1.35	< 0.001
TNM stage			
Tis	3(9.4%)	8(18.2%)	0.522
T1	24(75.0%)	31(70.5%)	
T2	5(15.6%)	5(11.4%)	
Pathologic stage			
I	26(81.3%)	33(78.6%)	0.776
II	6(18.8%)	9(21.4%)	
Immunohistochemistry			
ER+	26(81.3%)	37(80.4%)	0.928
PR+	24(75%)	31(67.4%)	0.469
Her-2 +	5(15.6%)	7(15.2%)	1.000
Molecular subtype			
Luminal A	10(31.3%)	17(34.6%)	0.950
Luminal B	16(44.4%)	20(43.5%)	
Her-2 enriched	3(9.4%)	4(8.7%)	
Triple negative	3(9.4%)	5(10.9%)	
Adjunctive therapy			
Chemotherapy	12(37.5%)	15(32.6%)	0.655
Targeted therapy	5(15.6%)	3(6.5%)	0.177
Hormone therapy	25(78.1%)	35(76.1%)	0.559
BMI	24.03(20.82–25.39)	22.23(20.07–25.50)	0.323
LDL-C	2.71 ± 0.14	2.74 ± 0.12	0.904
Pre-existing disease			
Coronary heart disease	0	0	-
Hyperlipidemia	3(9.4%)	2(4.3%)	0.396
Hypertension	5(15.6%)	4(8.7%)	0.475
Diabetes	2(6.3%)	2(4.3%)	1.000
Family history of early-onset CVD	0	0	-
Smoking history	0	0	-

BMI, body mass index, CVD, cardiovascular disease, LDL–C, low–density lipoprotein cholesterol

Results

Patients' characteristics

The study involved 78 patients with early-stage left breast cancer who underwent BSC followed by adjuvant radiotherapy. 32 patients received radiotherapy under FB, while 46 patients received radiotherapy using the DIBH technique. None of the patients had a history of coronary heart disease, a family history of early-onset cardiovascular disease, or a smoking history. There were no significant differences in the past medical history of chronic diseases, pathological characteristics, or other adjuvant treatment methods between the FB and DIBH groups. The average age of the FB group was 52.28 ± 1.66, while the average age of the DIBH group was 44.85 ± 1.35 (Table 1).

Changes in cardiac enzyme

The DIBH group had a significantly lower proportion of patients with subclinical cardiac injury within six months after radiotherapy compared to the FB group (DIBH = 31/46, FB = 28/32, $p = 0.042$). There were no significant differences in baseline levels of cardiac enzymes between the two groups. The study revealed that Creatine Kinase-MB (CK-MB) levels in the FB group increased steadily from the start of radiotherapy until 6 months after treatment. In contrast, no increase was observed in the DIBH group. Furthermore, the DIBH group exhibited lower CK-MB values at each time point after the start of treatment compared to the FB group. However, statistical significance was only observed at the 6 months after the treatment ($p = 0.006$). The levels of cardiac troponin I (cTnI) were consistently higher in the FB group than in the DIBH group, but the difference only reached statistical significance during the treatment period ($p = 0.034$). Similarly, N-terminal pro-B-type natriuretic peptide (NT-proBNP) in FB group was significantly higher than that of DIBH group during the treatment ($p = 0.023$). There was also a continuous increase in NTpro-BNP in the FB group (Table 2; Fig. 1).

Changes in EKG and ECHO

There were no significant differences in the proportion of patients with abnormal EKGs between the two groups at

Table 2 Changes in cardiac enzyme

Time		FB	DIBH	*p*
Baseline	CK-MB	0.555 ± 0.073	0.988 ± 0.490	0.965
	CTnI	0.097 ± 0.31	0.017 ± 0.001	0.329
	NTpro-BNP	54.39 ± 5.07	53.09 ± 6.01	0.304
During	CK-MB	0.745 ± 0.112	0.522 ± 0.056	0.238
	CTnI	0.124 ± 0.075	0.044 ± 0.027	**0.034**
	NTpro-BNP	58.03 ± 4.89	42.79 ± 4.48	**0.023**
3 months after	CK-MB	0.924 ± 0.197	0.575 ± 0.069	0.232
	CTnI	0.125 ± 0.33	0.017 ± 0.000	0.067
	NTpro-BNP	59.4 ± 6.91	61.32 ± 6.18	0.827
6 months after	CK-MB	1.080 ± 0.177	0.615 ± 0.064	**0.006**
	CTnI	0.126 ± 0.33	0.044 ± 0.028	0.073
	NTpro-BNP	73.61 ± 10.22	62.00 ± 6.06	0.521

any time point (Supplementary Table 1). However, both the DIBH and FB groups had a significantly higher proportion of patients with abnormal EKGs at 3–6 months compared to the baseline (FB $p = 0.012$ DIBH $p = 0.002$, Fig. 2). At 12–24 months, the number of patients with abnormal EKGs had decreased compared to 3–6 months and did not show a significant difference from the baseline (Fig. 2, Supplementary Table 3). Furthermore, the DIBH group exhibited a significantly lower incidence of abnormal EKG at 12–24 months compared to the 3–6 months ($p = 0.003$, Fig. 2, Supplementary Table 3). There were no significant differences in the proportion of patients with abnormal ECHO or the left ventricular ejection fraction (LVEF) at each time point between the two groups, nor were there any changes over time in either group (Fig. 2, Supplementary Table 2, Supplementary Table 3).

Dosimetry information for radiotherapy

The utilization of the DIBH technique led to a significant decrease in the mean heart dose and all dose parameters, including V5-V40 ($p < 0.001$). The most significant reduction was observed in V40, which decreased from 1.19 Gy to 0.05 Gy, a reduction of 95.8%. Additionally, there was a significant reduction in the maximum and mean doses to the left anterior descending artery and the right coronary artery ($p < 0.001$, Table 3).

Discussion

The present study suggests that the application of the DIBH technique during adjuvant radiotherapy for patients with early-stage left breast cancer after BCS can reduce the risk of subclinical cardiac events from the start of radiotherapy to 6 months after its completion. This is primarily reflected in the improvement of myocardial enzymes and EKG. After extending the follow-up period to 1-1.5 years, it was discovered that the number of individuals with abnormal electrocardiogram results had decreased in both the FB and DIBH groups. However, no significant improvement was observed in ECHO or LVEF in the DIBH group. While the dosimetry benefits of DIBH have been well explained, there is a lack of research on the clinical benefits associated with dose reduction. Our study is the first to demonstrate these advantages from a clinical perspective, providing a new

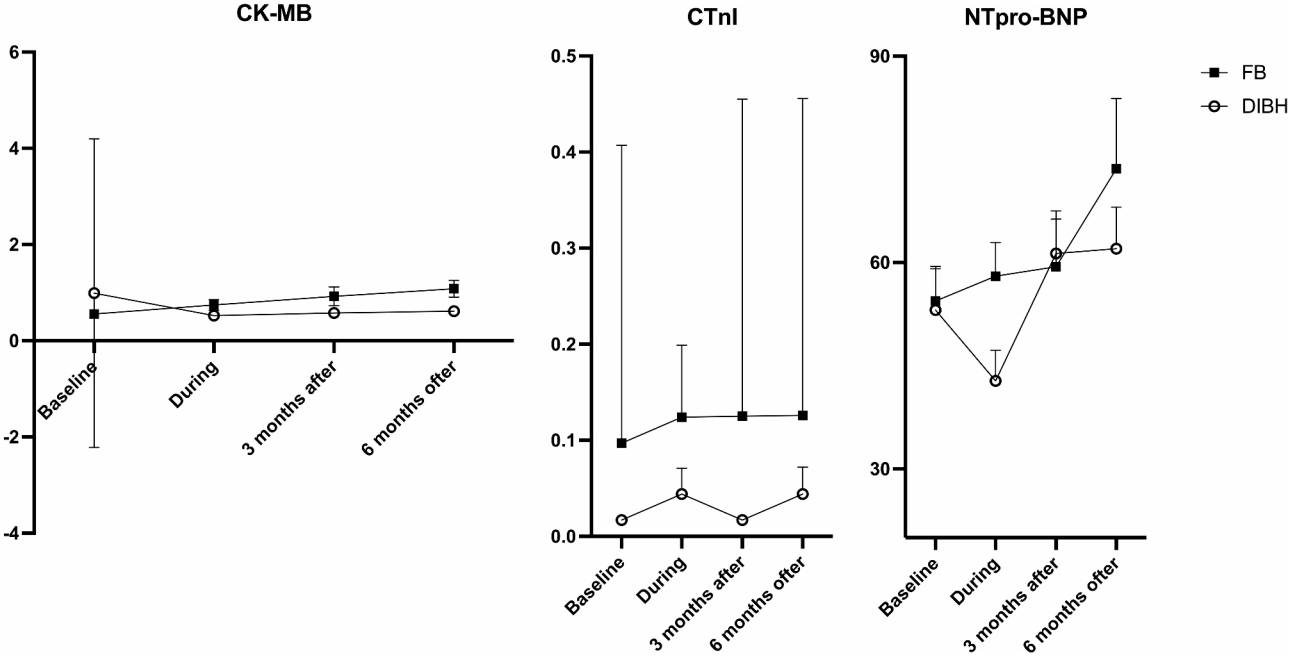

Fig. 1 Changes in cardiac enzyme

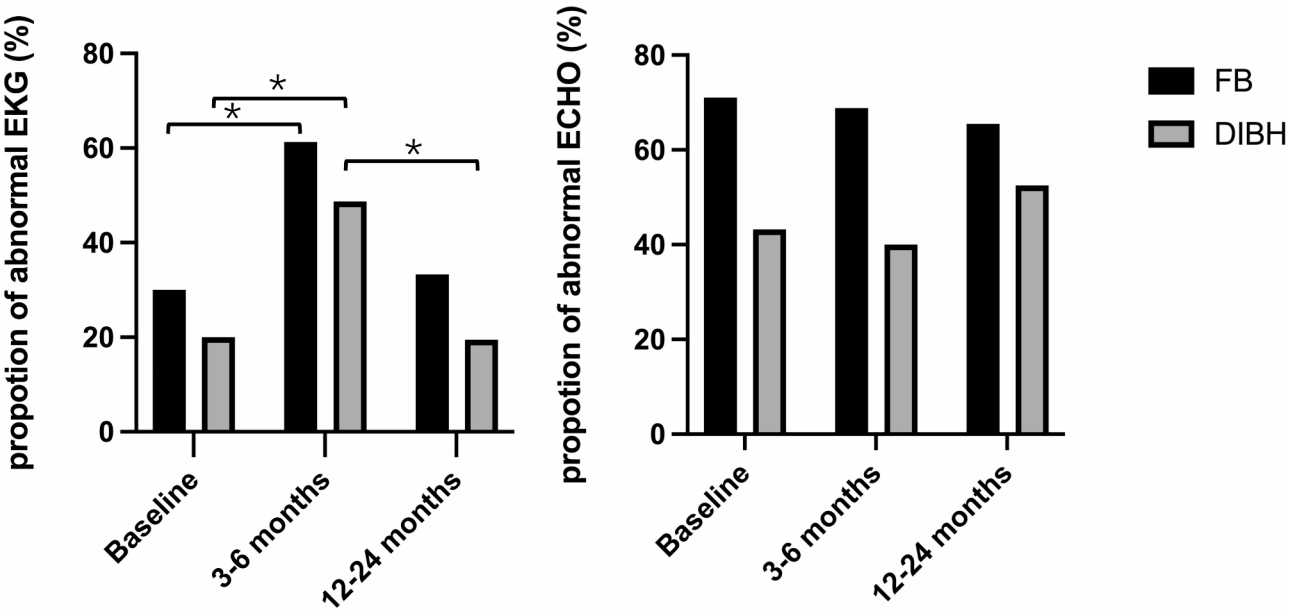

Fig. 2 Proportion of abnormal EKG and ECHO

Table 3 Comparison of dose parameters between the two patient groups

	FB	DIBH	*p*
MHD	3.28 ± 0.35	1.42 ± 0.20	< 0.001
V5	12.03 ± 2.45	4.63 ± 1.48	< 0.001
V10	7.09 ± 1.05	2.15 ± 0.58	< 0.001
V25	3.48 ± 0.49	0.71 ± 0.20	< 0.001
V30	2.91 ± 0.45	0.46 ± 0.13	< 0.001
V40	1.19 ± 0.27	0.05 ± 0.02	< 0.001
LAD dmean	16.17 ± 1.4	6.02 ± 0.75	< 0.001
LAD dmax	38.85 ± 1.77	22.82 ± 2.20	< 0.001
RCA dmean	1.41 ± 0.42	0.57 ± 0.18	< 0.001
RCA dmax	2.69 ± 0.72	1.25 ± 0.32	< 0.001

MHD: mean heart dose, V5: heart volume receiving a dose of over 5 Gy, V10: heart volume receiving a dose of over 10 Gy, V25: heart volume receiving a dose of over 25 Gy, V30: heart volume receiving a dose of over 30 Gy, V40: heart volume receiving a dose of over 40 Gy, LADdmax: maximum dose of the left anterior descending artery, LADdmean: mean dose of the left anterior descending artery, RCAdmean: mean dose of right coronary artery, RCAdmax: maximum dose of right coronary arter

approach to predicting long-term cardiac risks in the future.

The study suggested that after adjuvant radiotherapy, CK-MB in the FB group increased continuously, whereas CK-MB in the DIBH group remained stable throughout the follow-up period. At 6 months after the radiation treatment, a notable difference in CK-MB levels was observed between the two groups. During the treatment, the FB group exhibited significantly higher levels of cTnI and NT-proBNP compared to the DIBH group. At other time points, although cTnI levels were also higher in the FB group than in the DIBH group, the difference did not reach statistical significance. These results suggest that cTnI and NT-proBNP respond more rapidly to radiation exposure, whereas the response of CK-MB becomes more pronounced with time. However, the DIBH technique may attenuate both responses.

CK-MB and cTnI are commonly used markers to detect myocardial injury and are relevant to the prognosis of cardiac disease. Research suggested that cTnI may be a useful predictor of chemotherapy-related cardiotoxicity. Early elevation of cTn is associated with an increased risk of subsequent cardiotoxicity in patients receiving chemotherapy with Adriamycin and Trastuzumab [9]. Patients with elevated CK-MB after percutaneous coronary intervention are at a higher risk of long-term mortality [10]. In addition, the present study demonstrated the different release patterns of CK-MB and cTnI. Similarly, in cases of myocardial infarction, cTnI and CK-MB also demonstrate different release patterns. cTnI is rapidly released within 3–6 h after myocardial injury and continues to be elevated for 10–14 days, whereas CK-MB begins to rise as late as 12 h after infarction and returns to normal within 36–48 h [11]. Previous studies have concluded that the pattern of cTnI elevation is significantly associated with the risk of future cardiac events in patients receiving chemotherapy. Patients with persistent elevations face a higher risk of cardiac events within 3 years [12]. NT-proBNP is a marker of cardiomyocyte stress and has been found to be elevated in patients following radiotherapy [13].

However, the long-term prognostic significance of the elevation remains unclear. Additionally, an increase in NT-proBNP during early pregnancy may indicate improved myocardial adaptation, which could reduce the risk of developing hypertension in late pregnancy and the following 2–7 years [14]. This implies that the significance

of NT-proBNP elevation in the short term needs further clarification regarding long-term outcomes. The present study indicates a change in the cardiac enzyme and EKG that suggests potential cardiac damage and may have prognostic significance. However, more research is needed to determine the association between short-term changes and the risk of long-term heart disease. Longer follow-up is necessary to elucidate this relationship.

Studies have shown that the primary risk factors for developing long-term cardiovascular disease are baseline cardiac risk and cardiac radiation dose. Baseline cardiovascular risk factors and cardiac disease have the potential to impact the development of cardiovascular complications in the long term after radiotherapy [5, 15]. Darby et al. confirmed the effect of cardiac dose [5]. The prediction model was created based on these two factors [16]. However, the model is based on a cumulative risk derived from both the underlying risk factor score and the risk corresponding to the mean heart dose, which lacks actual clinical data support. Predictive models for ischemic heart disease and heart failure were also constructed based on gender, age at diagnosis, chemotherapeutic agents, and radiation dose in survivors of pediatric oncology patients. However, none of these models include biomarkers. In the general population, models are also available for assessing the risk of atherosclerotic cardiovascular disease, with key indicators including age, sex, total cholesterol, HDL-C(high-density lipoprotein cholesterol), systolic blood pressure, diabetes mellitus, smoking, coronary artery calcification, statin therapy, etc [17, 18]. Studies have shown that radiation-associated coronary atherosclerosis has the same morphology as coronary atherosclerosis from general causes. This includes intimal proliferation of myofibroblasts and plaque formation by lipid-containing macrophages, which can lead to thrombosis [19]. This suggests risk prediction in the general population is may be informative for risk prediction after chest radiotherapy. However, it cannot reflect the potential impact of radiotherapy on possible accelerated cardiovascular lesions. The present study demonstrated the onset of cardiovascular effects of radiotherapy in terms of cardiac enzymes and other markers. Incorporating this component of the response into risk prediction will help to more accurately predict the risk of irreversible heart disease in the long term.

The present study also suggests that, in the short term, EKG and cardiac enzymes are more sensitive than ECHO for early injury monitoring. While, there is also a current recommendation suggesting that performing transthoracic ECHO 6–12 months after mediastinal radiotherapy for patients at high risk of cardiovascular disease may be beneficial [4]. In this study, ECHO did not reveal significant changes between FB and DIBH groups, possibly due to the early stage of follow-up. Further data with prolonged follow-up is needed. Moreover, the decrease of EKG abnormalities at 12–24 months after radiotherapy may suggest compensation and repair of some of the damage. Research shows that cardiac stem cell damage is dose-dependent and reversible [20]. This indicates that early detection, followed by pharmacological or lifestyle interventions, may be beneficial for patients.

Overall, this study provides compelling evidence that the DIBH technique significantly reduces radiation exposure to heart and mitigates the risk of subclinical acute cardiac injury. Importantly, our findings suggest a potential for reversibility in radiation-induced cardiac damage within specific dose thresholds. The study demonstrates the clinical utility of serial cardiac enzyme monitoring as a sensitive biomarker for detecting subclinical cardiac injury during and following radiotherapy, complemented by the diagnostic sensitivity of EKG changes in early cardiac injury detection. These observations have several implications for future research directions. First, the integration of cardiac biomarkers and EKG monitoring may facilitate early identification of high-risk patients, enabling timely clinical interventions to minimize long-term cardiac sequelae. Second, the potential role of additional biomarkers, including inflammatory cytokines and oxidative stress markers, in cardiac radiation injury assessment warrants further investigation.Methodologically, future studies should incorporate extended follow-up periods and larger, multi-institutional cohorts to validate the prognostic reliability of EKG parameters and cardiac enzyme profiles in long-term cardiac injury monitoring. Furthermore, the development of comprehensive risk prediction models integrating multiple data streams including dynamic biomarker profiles, EKG, dosimetric data, and baseline cardiovascular risk factors could enhance the precision of individualized risk stratification and improve long-term cardiac risk assessment in radiotherapy patients.

The study's strengths lie in its prospective nature and its focus on the clinical benefits of the DIBH technique for patients, rather than solely on dosimetry. The research presents a comprehensive examination of the acute cardiac response following radiotherapy. However, the study has some limitations. Firstly, the number of patients needs to be expanded. Secondly, it remains unclear whether EKG and cardiac enzymes can serve as a predictive indicator for the future occurrence of Radiation-Induced Heart Disease. Lastly, the selected biomarkers may not fully capture all the changes taking place in the heart. Although these indicators reveal myocardial changes, additional indicators are required for early detection of vascular injury, which is more sensitive to short-term damage.

Abbreviations

BSC	Breast-conserving surgery
NT-proBNP	N-terminal pro-B-type natriuretic peptide
CK-MB	Creatine kinase-MB
cTnI	Cardiac troponin I
HDL-C	High-density lipoprotein cholesterol
EKG	Electrocardiogram
RTOG	Radiation Therapy Oncology Group
ECHO	Echocardiogram
DIBH	Deep inspiration breath hold
FB	Free-breathing
MHD	Mean dose to the heart
CT	Computed tomography
TPS	Treatment planning system
IMRT	Intensity-modulated radiation therapy
V5	Heart volume receiving a dose of over 5 Gy
V10	Heart volume receiving a dose of over 10 Gy
V25	Heart volume receiving a dose of over 25 Gy
V30	Heart volume receiving a dose of over 30 Gy
V40	Heart volume receiving a dose of over 40 Gy
LADdmax	Maximum dose of the left anterior descending artery
LADdmean	Mean dose of the left anterior descending artery
RCAdmean	Mean dose of right coronary artery
RCAdmax	Maximum dose of right coronary artery
LV	Left ventricle
LAD	Left anterior descending artery
OAR	Organs at risk
LVEF	Left ventricular ejection fraction
PCI	Percutaneous coronary intervention

Supplementary Information

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Supplementary Material 1

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No.

Author contributions
ZK and SJ were responsible for data collection and drafted the manuscript; MJB, MXY, YB, HXR, QJ, LYG participated in the design of the study; ZK performed statistical analysis and data interpretation; HK and ZFQ designed the study and revised the manuscript; All authors read and approved the manuscript.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The Institutional Review Board (IRB) of Peking Union Medical College Hospital (PUMCH) reviewed the protocol. This is a prospective study. The protocol is rational and scientific. The study accords with the principle of ethics. The IRB thus approves the protocol. IRB code is ZS-2643, I-23YJ070 and I-23PJ116. The informed consent was obtained from all subjects and/or their legal guardian.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Radiation Oncology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China
[2]Department of Radiation Oncology, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, China

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