

Outcomes of Radiation Dose Reduction Protocol in Electrophysiologic and Cardiac Device Procedures

Narawudt Prasertwitayakij, MD¹, Kultida Lertthanaphol, MD¹, Siriwan Meemajam, RN², Wanwarang Wongcharoen, MD¹, Teerapat Nantsupawat, MD¹

¹ Division of Cardiology, Department of Internal Medicine, Chiang Mai University, Chiang Mai, Thailand; ² Maharaj Nakorn Chiang Mai Hospital, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

Background: Exposure to radiation has been demonstrated to be associated with adverse short- and long-term health outcomes.

Objective: To present outcomes before and after the implementation of a radiation dose reduction protocol in electrophysiologic (EP) and cardiac device procedures.

Materials and Methods: The present study was a retrospective comparative study, conducted at Chiang Mai University Hospital in Thailand using 2017 and 2019 data, including all patients who underwent EP and cardiac implantable electronic device (CIED) procedures. Exclusion criteria involved patients with incomplete radiation dose records. The authors compared fluoroscopic time, radiation exposure, and complication rates before and after the protocol.

Results: Among the 458 cases, with 214 Eps and 244 devices, the mean age was 58 years. For device implantation procedures, there was no significant change in fluoroscopic time as median (P_{25} , P_{75}) before and after protocol implementation were 3.1 (0.4, 5.8) versus 4.4 (1.2, 7.6) minutes, respectively ($p=0.117$). However, there was a decreasing trend in dose area product (DAP) at 242.0 (119.2, 766.0) versus 197.9 (71.5, 494.5) $cGy.cm^2$ ($p=0.073$). The reduction in DAP was more pronounced in cardiac resynchronization therapy (CRT) implantation when comparing 2017 to 2019 were 1,933.6 (1,039.4, 7,683.8) versus 1,074.6 (427.2, 2,890.7) $cGy.cm^2$ ($p=0.020$). In EP procedures, fluoroscopic time significantly decreased from 8.1 (3.0, 14.3) minutes in 2017 to 1.0 (0.0, 3.6) minute in 2019 ($p<0.001$), accompanied by a significant reduction in exposure dose of 45.0 (10.8, 153.3) versus 1.7 (0.0, 31.6) mGy ($p<0.001$) and DAP of 1,022.9 (247.2, 2,660.3) versus 38.5 (0.0, 566.9) $cGy.cm^2$ ($p<0.001$). There was no difference in the complication rate between the two periods.

Conclusion: The implementation of the radiation dose reduction protocol resulted in a significant decrease in radiation exposure during EP procedures and showed a trend towards reduction in CIED procedures.

Keywords: ALARA; Cardiac electrophysiology; Cardiac implantable electronic devices; Fluoroscopy; Radiation exposure

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Radiation hazards have the potential to adversely impact biological tissues, leading to conditions such as dermatitis, birth defects, thyroid dysfunction, and tumors. Individuals engaged in interventional cardiology procedures, including coronary intervention, electrophysiological (EP) procedures, and cardiac implantable electronic device (CIED)

implantation, such as patients and healthcare workers, face an elevated risk of exposure. Notably, there have been documented cases of left-sided brain tumors and breast cancer in interventional cardiologists, particularly those who left their left side unprotected and in closer proximity to the radiation source⁽¹⁾. Furthermore, a significant percentage, approximately half, of operators without adequate protection have been reported to develop cataracts^(2,3).

In the cardiac EP laboratory, three factors play a role in modulating radiation doses, patient-related factors, operator-related factors, and technology-related factors⁽⁴⁾. Patients with a lean body habitus and a diagnosis of supraventricular tachycardia tended to exhibit lower radiation doses. Conversely, higher doses were associated with obese patients and those diagnosed with ventricular arrhythmia (VT) or atrial fibrillation (AF). Regarding technology factors, the use of three-dimensional (3D) electroanatomical

Correspondence to:

Nantsupawat T.

Division of Cardiology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, 110 Intawaroros Road, Sripoom, Muang, Chiang Mai 50200, Thailand.

Phone: +66-53-936793, Fax: +66-53-289177

Email: teerapat.nant@gmail.com, teerapat.nant@cmu.ac.th

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mapping systems and the presence of shielding above and below the table were linked to lower radiation doses. Of these factors, the operator is the most modifiable. A skilled and vigilant operator, who consistently records exposure doses, utilizes stored fluoroscopy or short CINE time, and employs adaptive collimation, tends to experience lower radiation exposure doses. Previous studies have shown that educational initiatives, such as limiting cine acquisition and adjusting table height, along with measures like reducing radiation dose per pulse, adopting slower frame rates, employing collimation, integrating with 3D anatomical mapping systems, or using non-gridded single frame location fluoroscopy, can significantly decrease the effective ionized radiation dose without compromising success rates. Importantly, these measures do not impact procedure time or result in higher complication rates⁽⁵⁻⁹⁾.

While there is abundant evidence supporting the advantages of radiation dose reduction strategies, the level of radiation safety knowledge, equipment availability, and awareness among physicians and cardiac catheterization personnel in Thailand remains insufficient⁽¹⁰⁾. Furthermore, there is a lack of data regarding the implementation of radiation safety measures in Thailand. The authors' EP laboratory has been proactive in adopting safety measures for radiation operations. Since 2018, the authors have adhered to the ALARA principles, as low as reasonably achievable, as recommended by the European Heart Rhythm Association^(4,5). Hence, the present study objective was to compare procedural time, fluoroscopic time, radiation dose exposure, and procedural complications both before and after the implementation of the radiation dose reduction protocol in EP and CIED procedures.

Materials and Methods

Study design and patients

The present study was a retrospective comparative study carried out at Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University. The study encompassed all consecutive patients who underwent EP or CIED procedures in 2017 and 2019. The authors excluded data from 2018 because it was a transition year from standard radiation practices to a radiation dose reduction protocol. Patients with incomplete information regarding fluoroscopic time, exposure dose, and dose area product (DAP) were excluded from the analysis. The study protocol received approval from the Research Ethics Committee of the Faculty of Medicine, Chiang Mai University (study

code: MED-2564-07924), and the need for individual consent was waived. The study was conducted in compliance with the Declaration of Helsinki and the International Conference for Harmonisation-Good Clinical Practice (ICH-GCP) guidelines.

Radiation strategies

In 2017, physicians and personnel in the EP laboratory adhered to standard radiation practices, utilizing fluoroscopic guidance with 15 frames per second and CINE acquisition.

However, in 2019, the EP laboratory introduced a radiation dose reduction protocol in line with EHRA recommendations, using the ALARA principles, which included the following:

1. Optimizing frame rate from 15 to 7.5 or 3 frames per second depending on the limitation of radiation source technology
2. Using "stored fluoroscopy" over "CINE acquisition"
3. Regularly adjusting collimation of image only to the region of interest
4. Routinely using electroanatomical mapping system (EnSite NavX™ navigation system) in EP cases and aiming for zero fluoroscopy when possible

Outcomes

The primary outcome of the present study was the radiation dose exposure before and after the application of the radiation dose reduction protocol. Secondary outcomes included procedural time, fluoroscopic time, and procedural complications.

Definitions

Radiation dose is a measure of the amount of exposure to radiation. There are four forms of doses commonly reported⁽⁴⁾:

1. Absorbed dose is the amount of energy deposited by radiation in a mass such as air, or human tissue. It is expressed in milligrays (mGy).
2. Equivalent dose is calculated based on the absorbed dose to an individual organ, accounting for the effectiveness of the type of radiation. It is expressed in millisieverts (mSv). Because all radiation used in diagnostic medicine has the same low-harm potential, the absorbed dose and the equivalent dose are numerically the same. Only the units are different.
3. Effective dose is calculated for the whole body. It is the addition of equivalent doses to all organs, each accounting for the sensitivity of the organ to radiation. Different body parts have different

sensitivities to radiation. Effective dose relates to the overall long-term risk to a person from a procedure.

4. DAP is a measure of the total amount of radiation absorbed by a specific area of tissue, calculated by multiplying the dose by the area of tissue irradiated, usually expressed in cGy.cm². It is commonly used for estimating stochastic risk to patients.

In the present study, the authors reported radiation dose exposure in absorbed dose and DAP.

Statistical analysis

Since the data were not normally distributed, median and interquartile range (IQR) were utilized to represent center of the data. Mann-Whitney U test (nonparametric test) was used to compare differences of procedural time, fluoroscopic time, exposure dose, and DAP. Chi-square or Fisher's exact test was used to compare complication rates between the two periods. All analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA). A p-value of less than 0.05 was considered statistically significant.

Sample size calculation

For CIED implantation procedure, Bork et al. showed DAP was significantly reduced by 62% after a reduced frame rate protocol from 7.5 to 3.8 frames per second for a median of 369 (IQR 154 to 1,207) cGy.cm² with the reduced frame rate protocol versus a median of 970 (IQR 400 to 1,906) cGy.cm² with the standard frame rate, $p < 0.01$ ⁽¹¹⁾. According to this data, the authors would require 92 patients, with 46 patients in each group, to achieve a type I error of less than 0.05 with a power of 80%. For the EP procedure, Marini et al. demonstrated a 65% DAP reduction after primarily using a 3D mapping system guidance from 58.18 Gy.cm² (95% CI 41.8 to 71.0) to 20.19 Gy.cm² (95% CI 14.2 to 29.7), $p < 0.001$ ⁽¹²⁾. The authors require 132 patients, with 66 patients in each group, to obtain a type I error of 0.05 and a power of 80%. Therefore, by combining CIED and EP procedures, the present required 224 patients.

Results

Five hundred sixty-one cases underwent EP or CIED procedures in 2017 and 2019. Patients with age less than 18 years, thus 12 cases, pulse generator change, thus 43 cases due to no fluoroscopy required by the nature of the procedure, and no radiation dose recorded, thus 48 cases were excluded.

The analysis included a final cohort of 458 patients, comprising 244 cases of CIED procedures

and 214 cases of EP procedures. The mean age of patients was 58 years, with an equal distribution between male and female. The average body mass index (BMI) was approximately 23 kg/m². There were no significant differences in age, gender, BMI, underlying diseases, medications, preprocedural basic laboratory results, left ventricular ejection fraction (LVEF), and left atrial size between patients in the pre-implementation (2017) and post-implementation (2019) periods of the radiation safety protocol. The only notable distinction was a higher usage of beta blockers in 2017 compared to 2019 at 42.4% versus 27.8% ($p = 0.001$) (see Table 1). The overall number of CIED and EP procedures performed in 2017 and 2019 were comparable, with 126 versus 118 cases for CIED and 102 versus 112 cases for EP procedures, respectively.

Among all CIED implantation procedures, there was a significant increase in median procedural time in 2019 compared to 2017 to 45 (24, 66) versus 35 (24.5, 45.5) minutes, respectively, ($p < 0.001$), with no significant change in fluoroscopic time at 4.4 (1.2, 7.6) versus 3.1 (0.4, 5.8) minutes, respectively, ($p = 0.177$) (Table 2). Overall, exposure dose slightly decreased in 2019, but this change was not statistically significant at 12.2 (6.6, 42.3) versus 14.5 (6.8, 45.5) mGy, ($p = 0.98$). In comparison with 2017, 2019 exhibited a trend towards decreased DAP in overall CIED procedures at 242.0 (119.2, 766.0) versus 197.9 (71.5, 494.5) cGy.cm², ($p = 0.073$). Among all procedures in the present study, cardiac resynchronization therapy (CRT) implantation had the longest fluoroscopic time, using 17.5 (10.2, 25.5) minutes in 2017 and 19.3 (9.1, 26.7) minutes in 2019. Consequently, the impact of the radiation dose reduction protocol was more pronounced in CRT cases than in other CIED procedures. This was evidenced by the significant reduction in DAP in 2019 compared to 2017 at 1,074.6 (427.2, 2,890.7) versus 1,933.6 (1,039.4, 7,683.8) cGy.cm², respectively, ($p = 0.020$), as shown in Table 2.

In EP procedures, the procedural time had significantly increased from a median time of 51.5 (34.5, 70.5) minutes in 2017 to 60.0 (45.2, 74.5) minutes in 2019 ($p = 0.034$). However, the median fluoroscopic time had markedly decreased from 8.1 (3.0, 14.3) minutes in 2017 to 1.0 (0.0, 3.6) minute in 2019 ($p < 0.001$), attributed to the routine use of 3D anatomical mapping (see Table 3). Notably, 45 out of 112 (41%) EP procedures in 2019, including 32 cases of atrioventricular nodal reentrant tachycardia (AVNRT), eight cases of VT/premature ventricular

Table 1. Demonstrate baseline characteristics of patients underwent CIED and EP procedures before (2017) and after the radiation dose reduction policy (2019)

Characteristic	Year 2017 (n=228)	Year 2019 (n=230)	p-value
Age (years); mean±SD	58.9±16.8	58.8±16.0	0.953
Male sex; n (%)	118 (51.8)	122 (52.6)	0.855
Body mass index (kg/m ²); mean±SD	22.9±4.3	23.3±4.5	0.222
Underlying diseases; n (%)			
Diabetes mellitus	33 (14.5)	35 (15.2)	0.463
Hypertension	88 (38.6)	97 (42.2)	0.435
Dyslipidemia	53 (23.2)	61 (26.1)	0.275
Peripheral arterial disease	3 (1.2)	3 (1.2)	0.653
Atrial fibrillation	45 (19.7)	39 (17.0)	0.259
Chronic kidney disease	26 (11.4)	19 (8.3)	0.165
Cancer	6 (2.6)	4 (1.7)	0.370
Previous myocardial ischemia	23 (10.1)	21 (9.1)	0.419
Previous valvular heart disease	13 (5.7)	9 (3.9)	0.253
Previous heart failure	50 (21.9)	41 (17.8)	0.163
Left ventricular ejection fraction (%); mean±SD	35.6±30.1	31.6±30.1	0.175
Left atrial size (mm); mean±SD	20.7±20.9	19.6±20.3	0.476
Medication; n (%)			
Antiplatelet	57 (22.8)	46 (18.9)	0.291
Warfarin	46 (20.2)	39 (17.0)	0.222
Non-vitamin K oral anticoagulant	4 (1.8)	10 (4.3)	0.089
Beta blocker	95 (42.4)	64 (27.8)	0.001
Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers	60 (26.3)	53 (23.0)	0.417
Statin	61 (26.8)	72 (31.3)	0.160
Basic laboratory			
Hemoglobin (g/dL); mean±SD	12.7±2.2	12.4±3.2	0.322
Hematocrit (%); mean±SD	38.6±7.5	37.5±9.9	0.203
White blood cell (×10 ³ μL); median (P ₂₅ , P ₇₅)	7450.0 (6,125.0, 8,790.0)	6790.0 (5,780.0, 8,057.5)	0.953
Platelet (cu.mm); mean±SD	229,746.9±87,228.9	249,839.6±241,283	0.237
International normalized ratio; mean±SD	1.2±0.6	1.2±0.6	0.462
Blood urea nitrogen (mg/dL); median (P ₂₅ , P ₇₅)	16.0 (11.0, 22.0)	14.8 (11.0, 20.0)	0.389
Creatinine (mg/dL); median (P ₂₅ , P ₇₅)	1.0 (0.7, 1.3)	1.0 (0.8, 1.3)	0.669
Potassium (mmol/L); median (P ₂₅ , P ₇₅)	4.0 (3.7, 4.4)	4.0 (3.7, 4.4)	0.542

SD=standard deviation

contraction (PVC), four cases with atrioventricular reentrant tachycardia (AVRT) or pre-excitation syndrome, and one atrial arrhythmia case, were performed exclusively under 3D anatomical mapping guidance with zero fluoroscopy. This resulted in a drastic reduction in exposure dose in 2019 compared to 2017 at 1.7 (0.0, 31.6) versus 45.0 (10.8, 153.3) mGy, respectively, ($p<0.001$), as well as in DAP at 38.5 (0.0, 566.9) versus 1,022.9 (247.2, 2,660.3) cGy.cm², respectively ($p<0.001$) (see Table 3).

The overall complication rate in 2017 and 2019 was similar at 2.2% versus 3.0%, respectively, ($p=0.771$). In CIED implantation procedures, there were four complications in 2017 including one

coronary sinus dissection, two lead dislodgements, and one atrial lead perforation. In 2019, there were five complications comprising two lead dislodgements, two device infections, and one lead perforation. In EP procedures, one complication occurred in 2017, a coronary sinus ostial trauma, and in 2019, two complications including a transient ischemic attack and atrioventricular block requiring permanent pacemaker implantation. Most patients spent a day hospitalized after the procedure, with similar durations in both groups.

Discussion

The present study demonstrated a trend toward

Table 2. Number of cases, procedural time, fluoroscopy time, exposure dose, and dose area product before and after policy change in CIED implantation cases

	Number of cases	Procedural time (minutes) median (P ₂₅ , P ₇₅)	Fluoroscopy time (minutes) median (P ₂₅ , P ₇₅)	Exposure dose (mGy) median (P ₂₅ , P ₇₅)	Dose area product (cGy.cm ²) median (P ₂₅ , P ₇₅)
Total case					
Pre	126	35.0 (24.5, 45.5)	3.1 (0.4, 5.8)	14.5 (6.8, 45.5)	242.0 (119.2, 766.0)
Post	118	45.0 (24, 66)	4.4 (1.2, 7.6)	12.2 (6.6, 42.3)	197.9 (71.5, 494.5)
p-value		<0.001†	0.117	0.980	0.073
Single chamber pacemaker					
Pre	10	44.0 (30.0, 58.0)	3.9 (1.2, 6.6)	16 (8.5, 30.6)	224.8 (134.4, 565.1)
Post	9	39.0 (29.5, 48.5)	2.8 (1.3, 4.3)	8 (6.7, 48.6)	162.7 (79.5, 280.1)
p-value		0.720	0.842	0.780	0.356
Dual chamber pacemaker					
Pre	58	30.5 (27.2, 38.5)	2.6 (1.5, 4.6)	12.5 (5.0, 22.5)	191.3 (83.7, 299.3)
Post	54	43.0 (32.8, 58.5)	4.4 (2.2, 7.2)	11.2 (6.4, 29.4)	188.2 (65.6, 385.9)
p-value		<0.001†	0.003*	0.476	0.556
Implantable cardioverter defibrillator					
Pre	33	33.0 (26.0, 44.5)	2.9 (2.0, 5.3)	10.0 (5.5, 23.8)	214.3 (104.9, 579.2)
Post	26	44.0 (30.8, 75.0)	2.9 (1.8, 5.8)	11.4 (5.8, 26.3)	181.9 (68.7, 367.4)
p-value		0.013*	0.443	0.397	0.563
Cardiac resynchronization therapy					
Pre	20	91.5 (70.0, 115.0)	17.5(10.2, 25.5)	224.8 (75.0, 675.5)	1933.6 (1,039.4, 7,683.8)
Post	20	99.0 (69.2, 168.8)	19.3 (9.1, 26.7)	101.9 (37.2, 223.8)	1074.6 (427.2, 2,890.7)
p-value		0.547	0.862	0.060	0.020*

* p<0.05, † p<0.001

Table 3. Number of cases, procedural time, fluoroscopy time, exposure dose, and dose area product before and after policy change in electrophysiologic procedure

	Number of cases	Procedural time (minutes) median (P ₂₅ , P ₇₅)	Fluoroscopy time (minutes) median (P ₂₅ , P ₇₅)	Exposure dose (mGy) median (P ₂₅ , P ₇₅)	Dose area product (cGy.cm ²) median (P ₂₅ , P ₇₅)
Total case					
Pre	102	51.5 (34.5, 70.5)	8.1 (3.0, 14.3)	45.0 (10.8, 153.3)	1,022.9 (247.2, 2,660.3)
Post	112	60.0 (45.2, 74.5)	1.0 (0.0, 3.6)	1.7 (0.0, 31.6)	38.5 (0.0, 566.9)
p-value		0.034*	<0.001†	<0.001†	<0.001†
Atrioventricular nodal reentrant tachycardia					
Pre	41	45.0 (29.0, 57.0)	4.9 (1.8, 11.2)	24.0 (4.8, 135.0)	400.6 (131.1, 1,558.0)
Post	42	54.0 (38.8, 68.5)	0.0 (0.0, 0.1)	0.0 (0, 0)	0.0 (0, 0)
p-value		0.036*	<0.001†	<0.001†	<0.001†
Atrioventricular reentrant tachycardia, pre-excitation syndrome					
Pre	25	52.0 (40.0, 59.5)	9.4 (4.6, 13.7)	63.0 (20.7, 232.8)	1,961.6 (404.1, 5,136.5)
Post	31	61.0 (45.0, 76.0)	2.5 (0.9, 5.7)	20.6 (0.2, 95.7)	369.9 (5.6, 1,470.1)
p-value		0.222	<0.001†	0.016*	0.001*
Atrial arrhythmia					
Pre	18	74.0 (47.5, 111.2)	18.4 (11.1, 25.4)	85.1 (37.8, 126.5)	1,733.8 (1,002.2, 2,811.0)
Post	23	69.0 (50.0, 90.0)	2.1 (1.0, 8.3)	13.9 (5.0, 50.8)	313.2 (69.9, 879.6)
p-value		0.979	<0.001†	0.027*	0.007*
Ventricular tachycardia/premature ventricular contraction					
Pre	10	85.5 (49.5, 109.5)	9.0 (5.0, 23.0)	47.8 (8.8, 177.3)	1,118.6 (188.8, 3,796.0)
Post	10	60.0 (59.0, 82.5)	0.0 (0.0, 3.4)	0.0 (0.0, 4.9)	0.0 (0.0, 33.7)
p-value		0.796	0.001*	0.004*	0.002*

* p<0.05, † p<0.001

lower DAP among CIED implantation cases in 2019 when the radiation reduction protocol was implemented, although it did not reach statistical significance. Notably, only CRT implantation procedures showed a significant reduction in DAP in 2019. This could be attributed to the fact that the fluoroscopic time in other CIED procedures was too short to exhibit a significant difference.

Regarding EP procedures, the adoption of 3D electroanatomical mapping played a crucial role in the radiation reduction policy, particularly with specific features enabling the visualization of all catheters. This system facilitated mapping and radiofrequency ablation with zero fluoroscopy in 41% of cases, resulting in a substantial decrease in overall radiation exposure during EP procedures. The remaining 59% of procedures inevitably required fluoroscopic guidance for transeptal puncture, managed challenging catheters or manipulating long/steerable sheaths, or utilizing a retrograde transaortic ablative approach. These findings aligned with the latest research data⁽¹³⁾, all of which support the recommended protocol suggested by the European Heart Rhythm Association.

The procedural time for both device and EP procedures was significantly higher in 2019. This increase may be attributed to factors such as case complexity and the involvement of a fellow-in-training operator, which began in 2019. In that year, two device infections were noted, whereas none were observed in 2017. The prolonged procedure time in 2019 compared to 2017 may explain this observation, as longer procedure times had been shown to be associated with increased risk of CIED infection⁽¹⁴⁾.

The variations in radiation dose could be attributed to differences in frame rate, energy per frame, and fluoroscopic time between the two time periods. Despite these differences, the present study findings indicated a lower DAP without a significant difference in complication rates and length of hospital stay when the radiation reduction protocol was applied. These results were consistent with previous studies, reinforcing the effectiveness of the radiation reduction protocol in minimizing radiation exposure without compromising patient outcomes^(5,9,15).

The authors' EP laboratory operated with three different fluoroscopic systems. The oldest system had a lowest frame rate limit of 7.5 frames per second, whereas the newest one can be lowered to 3 frames per second. Another system was specifically set for coronary angiograms, which require high-quality images. It could be challenging to remember to reduce

the frame rate for device implantation, as it was not routinely used in this context.

The present study has notable limitations. As a retrospective study, the data were not uniformly recorded, resulting in missing information on exposure dose and DAP in some patients. The authors did not have data on the long-term clinical outcomes of radiation exposure for operators and patients. However, the harmful effects of radiation exposure, including both deterministic and stochastic effects, have been well documented in previous literature. Furthermore, details such as the actual frame rate used, the number of recorded CINE frames, energy per frame, collimation use, and radiation badge information were lacking. Consequently, the authors were unable to definitively assess the extent of compliance with the radiation reduction protocol in 2019.

Conclusion

The present study demonstrates that an ALARA-based radiation reduction protocol, incorporating various optimization strategies, significantly decreases radiation exposure for both patients and staff without compromising outcomes. The findings underscore the importance of not only implementing dose-reducing measures but also cultivating a strong radiation safety culture to minimize risks effectively.

What is already known on this topic?

Radiation hazards have the potential to adversely impact biological tissues. Individuals engaged in interventional cardiology procedures, including coronary intervention, EP procedures, and CIED implantation, consisting of patients and healthcare workers, face an elevated risk of exposure.

What this study adds?

This study demonstrated that the implementation of the radiation dose reduction protocol resulted in a significant decrease in radiation exposure during EP procedures and showed a trend towards reduction in CIED procedures.

Authors' contributions

NP performed statistical analysis, wrote the manuscript and tables. KL, WW performed statistical analysis, the data analyses, and data interpretation. SM collected and re-checked the data prior to the analyses. TN designed the cohort, conception of the data analyses, data interpretation and critically revised the manuscript. All authors agreed to be

accountable for all aspects of the work to ensure that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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