

# The influence of anthropometric and basic circulatory variables on count rate in cadmium-zinc-telluride SPECT gated radionuclide angiography

Julie Rydberg, MD,<sup>a</sup> Jannick Andersen, Cand.merc.,<sup>a</sup> Christian Haarmark, MD, PhD,<sup>a</sup> and Bo Zerahn, MD<sup>a</sup>

<sup>a</sup> Department of Clinical Physiology and Nuclear Medicine, Herlev Hospital, University of Copenhagen, Herlev, Denmark

Received Dec 10, 2017; accepted Jul 23, 2018  
doi:10.1007/s12350-018-1402-9

**Aim.** To determine the influence of weight, height, gender, age, heart rate, and blood pressure on count rate in cadmium-zinc-telluride single-photon emission computed tomography (CZT SPECT) gated radionuclide angiography.

**Method.** A total of 1,065 eligible patients referred for routine assessment of left ventricular ejection fraction were registered from August 2015 to November 2016. Data were recorded on heart rate, systolic and diastolic blood pressure, age, gender, height, weight, and count rate. All radionuclide angiographies were performed on a dedicated cardiac CZT SPECT camera, GE Discovery 530c. A dose of 550 MBq <sup>99m</sup>Tc-labeled human serum albumin was administered intravenously to each patient.

**Results.** Count rate varied from 1.2 to 8.9 counts per second. All test variables were significantly associated with count rate. From the preliminary analysis, weight appeared as the main contributing factor for explaining the variations in count rate with and  $R^2$  of 0.68. A model consisting of weight, height, gender, and age explains 75% of the variance in count rate.

**Conclusion.** Patient height, weight, gender, and age have significant impact on count rate when performing CZT radionuclide angiography and may subsequently be used for individualized planning of tracer dosage. (J Nucl Cardiol 2019;26:1974–80.)

**Key Words:** Gated SPECT • RNA • count rate

## Abbreviations

CZT	Cadmium-zinc-telluride	ARSAC	The Administration of Radioactive Substances Advisory Committee
LVEF	Left ventricular ejection fraction	SPECT	Single-photon emission computed tomography
ALARA	As low as reasonably achievable		
MPI	Myocardial perfusion imaging		

## See related editorial, pp. 1981–1983

**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s12350-018-1402-9>) contains supplementary material, which is available to authorized users.

The authors of this article have provided a PowerPoint file, available for download at SpringerLink, which summarises the contents of the paper and is free for re-use at meetings and presentations. Search for the article DOI on SpringerLink.com.

Reprint requests: Julie Rydberg, MD, Department of Clinical Physiology and Nuclear Medicine, Herlev Hospital, University of Copenhagen, Herlev Ringvej 75, 2730 Herlev, Denmark; [julieriydberg@gmail.com](mailto:julieriydberg@gmail.com)

1071-3581/\$34.00

Copyright © 2018 American Society of Nuclear Cardiology.

## INTRODUCTION

Determination of left ventricular ejection fraction (LVEF) is often used as an adjunct for therapeutic decisions and for evaluation of prognosis. Despite a huge variety of available methods there is currently no non-invasive gold standard for LVEF assessment. Each modality has its limitations and potential inborn errors. Among currently available techniques, cadmium-zinc-telluride single-photon emission computed tomography (CZT SPECT) radionuclide angiography ranks high regarding operator independency, reproducibility, and practicability, which makes it an attractive option for routine clinical monitoring of LVEF as it is currently warranted for patients undergoing potentially cardiotoxic treatments.<sup>1-4</sup>

Radionuclide angiography has been used clinically since the 1980s, where a higher radiation dose (25 mSv) and longer acquisition times were necessary. The new dedicated cardiac camera types equipped with CZT detectors<sup>5,6</sup> have higher sensitivity, as well as better spatial and energy resolution giving rise to improved counting statistics and shorter acquisition times. The potentially lower radiation dose (below 4.9 mSv) as well as improved reproducibility may offer important diagnostic benefits.<sup>4,6-10</sup>

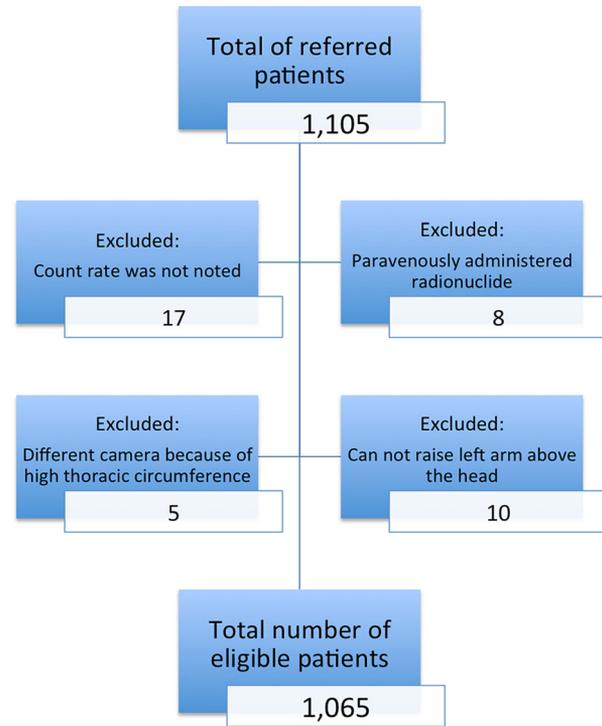
The growing focus on optimizing radiation dose according to the “As low as reasonably achievable (ALARA) principles” has led to weight-adjusted dosing of radiopharmaceuticals for optimizing effective dose in patients undergoing nuclear cardiology imaging.<sup>11</sup>

The aim of the study is to establish a predictive model of count rate based on weight, height, gender, age, heart rate, and blood pressure that would allow prospective standardization of acquired dosage in CZT SPECT camera gated tomographic radionuclide angiography.

## METHOD

A total of 1,105 patients referred for the first time for routine pre-treatment assessment of LVEF were registered from August 2015 to November 2016. Data were recorded on heart rate, systolic and diastolic blood pressure, age, gender, height, weight, and count rate in addition to the standard angiographic variables: left ventricular end systolic and end diastolic volumes and LVEF.

Data were collected as part of routine procedure and no changes were made from routine acquisition procedure. All data were collected for routine quality control assessment of administered activity to achieve best practice for typical adult patients in a routine diagnostic procedure.<sup>12,13</sup> Additional informed consent was redundant, because the study was retrospective and solely aimed at quality control with anonymized patient data.



**Figure 1.** Flow chart of patients excluded from the study.

Forty patients (3.6%) were excluded from the study. Seventeen acquisitions were excluded from the statistical analysis because the count rate was not noted. Another 23 acquisitions were excluded: in 8 acquisitions due to recognized or suspected partially paravenous administration of radionuclide, 5 acquisitions because it was impossible to focus the patients heart within the field of view due to a high thoracic circumference, and 10 acquisitions because the patients were unable to raise their left arm above the head (Figure 1). Thus, the total number of acquisitions eligible for statistical evaluation was 1,065. These patients were diagnosed with varying degrees of cardiomyopathy (18), breast cancer (352), renal cancer (187), diffuse large B-cell lymphoma (80), malignant melanoma (60), ovarian cancer (46), and liver cancer (45), and 277 had other types of cancer.

All radionuclide angiographies were performed on a dedicated cardiac CZT SPECT camera, GE Discovery 530c (GE Healthcare, Milwaukee, WI, USA). A dose of 550 MBq <sup>99m</sup>Tc-labeled human serum albumin was administered intravenously to each patient. The 550 MBq administered to the patients is a target dose based on expected injection time from the daily working schedule. No attempt was made to adjust the injected dose with regard to deviations from the planned time point of injection. An acquisition protocol for multigated acquisition, using 16 frames per R-R interval and requesting 600 accepted beats, was adopted and a 20% energy window centered on 140 keV was performed in all cases. Count rate was read from the work screen during acquisition and calculated as the mean of three readings at the beginning, middle and just before terminating the study. If one or more

readings were missed the cumulated dose at the end of the acquisition was used adjusted for acquisition time and number of missed beats. If this wasn't accomplished no data on count rate were registered. Xeleris 3 Imaging workstation software (GE Healthcare, Milwaukee, WI, USA, Version 3.0562) was used for reorientation of the heart after applying a generic reconstruction algorithm and filtering. Assessment of standard variables was performed with Cedars-Sinai QBS processing software (Cedars-Sinai, Ca, USA: revision 2009.0). Twice two experienced technologists analyzed each acquisition. If LVEF varied more than 2% points between the two analyses a third technologist or physician performed additional analyses until sufficient agreement was obtained.

### Statistical Analysis

Count rate was log transformed in order to obtain normal distribution. A regression model with backward selection was used to determine influence of explanatory variables on count rate. Explanatory variables were rejected if they were insignificant at a 5%-level. We applied the Bonferroni correction to test the significance of the variables. We tested the model performance using a Bland Altman analysis (Figure 3) and perform a variance inflation factor (VIF) calculation to quantify the degree of multicollinearity (Table 3).

Multiple linear regression analysis was performed using the package Stats in R 3.1.2 GUI. The response variable in the model is the logarithmic of count rate ( $Y$ ) and the explanatory variables are: weight (kg) ( $X_W$ ), height (cm) ( $X_H$ ), gender (male = 1, female = 0) ( $X_G$ ), age (years) ( $X_A$ ), systolic blood pressure (mmHg) ( $X_{SB}$ ), diastolic blood pressure (mmHg) ( $X_{DB}$ ), and heart rate ( $s^{-1}$ ) ( $X_{HR}$ ).

$$\text{Log}(Y) = \beta_0 + \beta_1 \cdot X_W + \beta_2 \cdot X_H + \beta_3 \cdot X_G + \beta_4 \cdot X_{HR} + \beta_5 \cdot X_{DB} + \beta_6 \cdot X_A + \beta_7 \cdot X_{SB}$$

Furthermore, we used an unpaired  $t$ -test to test whether the count rate was significantly different between the groups with two processings vs those where three or more processings were needed to obtain a reliable LVEF measurement.

### RESULTS

Basic data of the study population, of which 63% were women, are given in Table 1.

**Table 2.** The test variables correlated with log(count rate)

Test variables	Adjusted $R^2$	$P$ values
Weight	0.681	< .0001
Height	0.045	< .0001
Gender	0.032	< .0001
Age	0.007	< .005
Heart rate	0.015	< .0001
Diastolic blood pressure	0.028	< .0001
Systolic blood pressure	0.021	< .0001

Count rate varied from 1.2 to 8.9 kilocounts per second (kcps). All test variables were significantly associated with count rate (Table 2).

From the preliminary analysis, weight appeared as the main contributing factor for explaining the variations in count rate with an  $R^2$  of 0.68.

The multi linear regression model including all variables explains 76% of the variance (adjusted  $R^2$  0.761) in log(count rate) with coefficients  $\beta_0 = 1.737$ ,  $\beta_1 = -0.020$ ,  $\beta_2 = 0.001$ ,  $\beta_3 = 0.054$ ,  $\beta_4 = -0.003$ ,  $\beta_5 = 0.000$ ,  $\beta_6 = -0.003$ , and  $\beta_7 = 0.001$ .

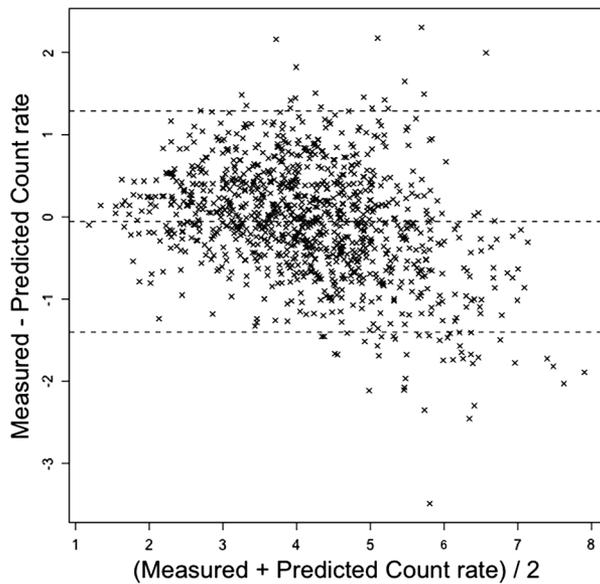
Since radionuclide preparation has to be performed before the patients arrive for their radionuclide angiography, the patients' heart rate and blood pressure are unknown at the production time, which makes these variables unavailable for dosage planning. Subsequently a more practical model for individual dosage planning without significant loss of predictability would be this final model including weight, height, gender, and age:

$$\text{Log}(Y) = \beta_0 + \beta_1 \cdot X_W + \beta_2 \cdot X_H + \beta_3 \cdot X_G + \beta_4 \cdot X_A$$

This model explains 75% of the variance (adjusted  $R^2$  0.748) in log(count rate) with coefficients  $\beta_0 = 1.621$ ,  $\beta_1 = -0.020$ ,  $\beta_2 = 0.008$ ,  $\beta_3 = 0.060$ , and  $\beta_4 = -0.002$ .

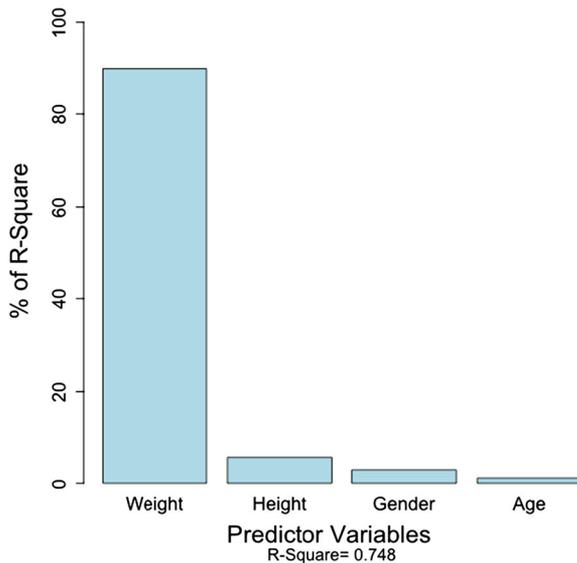
**Table 1.** Mean values of the study population (demographics)

	Mean ± SD	Range
Count rate (kcps)	4.2 ± 1.3	1.2-8.9
Height (cm)	170.6 ± 8.9	142-197
Weight (kg)	75.0 ± 16.1	38-147
Age (years)	62.7 ± 13.8	17.8-91.0
Systolic blood pressure (mmHg)	127 ± 19	86-207
Diastolic blood pressure (mmHg)	76 ± 11	52-122
Heart rate ( $s^{-1}$ )	75 ± 14	42-133



**Figure 2.** Bland Altman plot comparing model predictions with measured count rate.

### Relative Importance of Predictor Variables



**Figure 3.** The relative importance of each predictor variables in the final model defined by the portion of the squared multiple correlation explained by the contribution of each predictor.

A Bland Altman analysis was used to evaluate the performance of the model predictions (Figure 2).

Count rate was significantly higher when initial agreement between the two first analyses of an acquisition varied 2% points or less for LVEF determination compared to those where three or more processing

**Table 3.** The variance inflation factor (VIF) shows how much the variance is inflated.

Test of multicollinearity				
Variable	Gender	Height	Weight	Age
VIF	1.82	2.01	1.37	1.07

procedures were needed for sufficient agreement regarding LVEF [mean (SD) 4.2 (1.1) vs 3.7 (1.3) kcps]  $P = .005$ .

The relative importance of predictor variables in the final model is shown in Figure 3.

Standard model evaluation did not show any violations of the linear regression assumptions and further the VIF showed no existing multicollinearity in the final model (Table 3).

The final model is used to estimate count rate for each patient:

$$Y = \exp(\beta_0 + \beta_1 \cdot X_W + \beta_2 \cdot X_H + \beta_3 \cdot X_G + \beta_4 \cdot X_A).$$

The dosage needed to obtain a specific target count rate ( $CR_t$ ) can be calculated as:

$$\text{Dosage (MBq)} = 550 \cdot \frac{CR_t}{Y}.$$

The standard dose of 550 MBq presently administered to each patient is divided by the target count rate times a target dose. Assuming that the model's assumptions are correct and there is a linear relationship between count rate and dose.

### DISCUSSION

The current study is able to present an algorithm for calculating a patient specific dose while obtaining a target count rate for CZT SPECT gated tomographic radionuclide angiography with 75% certainty. The main factors contributing to this algorithm are body weight and height whereas gender and age only provided minor adjustments. Other minor contributing factors such as blood pressure and heart rate, that is not readily at hand when preparing the individualized dose, can be safely omitted. This algorithm also provides the opportunity to establish an optimal balance between target count rate and image quality in future studies.

Individual dosage planning in nuclear medicine procedures is becoming mandatory and is likely to enable a general dose reduction to the individual patient. Algorithms for patients-specific dosage planning have already been published for myocardial perfusion

imaging (MPI) both using CZT and NaI detectors.<sup>14,15</sup> The single most important variable affecting radiation emitted from the patient in tomographic radionuclide angiography is weight indicating that attenuation by tissue adjacent to the heart can be indirectly evaluated by a simple measurement of body weight accounting for 68% of the variation of count rate. This correlates very well with the studies by van Dijk et al who showed body weight to be the best predictive variable ( $R^2 = 0.61$ ) in MPI and was used to recommend patients-specific tracer dose and/or scanning time.<sup>14</sup> Other studies have demonstrated a similar correlation between injected dose, patient weight, and count statistics.<sup>16,17</sup>

From the relative importance shown, it appears that body weight is the predominant determinant of count rate followed by height. Still, adding further variables such height, gender, age, heart rate, and blood pressure will increase the ability to predict count rate (from 68% to 76%). As data on heart rate and blood pressure are not known at the time of preparation of the radionuclide kit, these variables are not suited for routine clinical practice and these variables can be omitted with the loss of only 1% in predictive power of the algorithm. This study indicated that gender has a significant albeit minor impact on count rate. The count rate variation is conceivably different between males and females, due to the general difference in fat distribution at chest level due to breast attenuation. Similar MPI studies found no significant difference in myocardial counts between gender but a significant increase in image quality with decreasing chest circumference.<sup>14,16</sup> This discrepancy could be due to the difference in tracer distribution (blood pool vs MPI), the number of included patients, patient category (cancer vs coronary artery disease), detector type, and orientation as well as collimation. Looking at tracer distribution, the uptake in MPI is mainly located in the left myocardium where 1% to 2% of the injected tracer is located and to a varying degree in the abdomen, whereas HSA is located in both right and left ventricle and the larger vessels in the thorax. This means that the observed count rate inevitably will vary depending on the tracer. Further as a large portion of the included patients in the current study were women with breast cancer of whom an unknown portion have had mastectomy or breast implants inevitably giving rise to opposite effects on count rate.

Age was significantly correlated with count rate, also with only minor impact. The actual change in count rate with age is minimal. A difference in age of 10 years will change count rate by less than 0.05 counts per second. The relative importance of the variables is given by following example: in order to change count rate 10% from, i.e., 3.0 to 2.7 kcps the following changes are required assuming all other variables remain unchanged;

a height decrease of 13 cm, an age increase of 47 years and a weight gain of 5.4 kg. A count rate of 3.0 kcps will increase by 5% to 3.15 kcps if the person is male compared to female. Gender and age thus only have minor contribution to the model and could be a result of statistical overpowering. However, age and gender is readily available at time of referral and some patients have long or repeated series of therapy. Subsequently, these variables are kept in the model.

Count rate was significantly lower in the group where there was a need for more than two attempts to achieve sufficient agreement for LVEF. Interpreting count rate as an indirect or surrogate measure of image quality means that there might be a lower limit below which the number of processing attempts becomes unacceptably frequent. Given the low frequency (4.7%) of the need for more than two processing attempts with the current dose indicates that it might be possible not only to individualize dosage but also to allow an overall reduction in tracer dosage. This corresponds with van Dijk et al<sup>14</sup> who observed an increase in image quality for patient scans with higher photon counts. Other studies have shown a steady decrease in myocardial counts and image quality with increasing body weight. They generally recommend adjusted injection activity for all patients above 80 kg.<sup>14,16,18</sup> In the present study potential confounders such as patients with high thoracic circumferences and subsequent problems with centering the heart within the camera field of view were recognized beforehand and had their acquisitions performed on a camera with two large field of view heads. This also calls for a dose calculating algorithm specifically derived for the CZT detector camera since both detector system and detector arrangement varies from standard NaI detector based cameras. The VIF showed no multicollinearity in the final model. The Bland Altman plot indicates that the regression model tends to underestimate count rates above 5. This might suggest that an unknown explanatory variable, not included in the model, affects the count rate different from our model predictions at the edge of the range of body size variables analyzed. This substantiates the need to apply and validate our calculated individualized tracer dose in daily clinical practice.

Medical imaging procedures are an important source of exposure to ionizing radiation and even though the long-term risk is still low, procedures are frequently repeated within the same patient.<sup>11,12,19</sup> The Administration of Radioactive Substances Advisory Committee (ARSAC) in January 2017 recommend that the administered activity for cardiac blood pool imaging should be 800 MBq (effective dose 4.9 mSv) per injection of <sup>99m</sup>Tc-human serum albumin. In our department we have until now used a fixed tracer dose of 550 MBq.

The next step to minimize radiation exposure according to ALARA principles is to reduce the individual patient exposure to be the minimum required to achieve the intended diagnostic objective. The final model allows us to calculate a patient specific tracer dose formula for this purpose and test it.

### Limitations

The injected dose was not measured directly before administration, but was estimated at the time of production in the morning. The dose was adjusted to account for decay to match a desired administered dose of 550 MBq at the patients scheduled appointment later the same day. Given the long half-life of  $^{99m}\text{Tc}$  even a 20 minute difference—delay or early start (which is very rare at our institution) will only amount to less than 4% deviation of the desired dosage. Potential left-over activity in the syringes was not assessed in this study. Furthermore, since the derived model will be tested in a prospective manner this potential error will be overcome in our next study.

We have used the number of required processing's to obtain a 2% difference in LVEF as a surrogate for image quality. Nonetheless, there is an indication that a lower count rate is associated with increased number of processing's required and that there is a lower limit of count rate below which the reproducibility will be critically low.

Other limitations are that the scans were performed on more women than men due to inclusion of a large number of patients with breast cancer. Further roughly 50% of the included breast cancer patient were mastectomized and/or had breast implants which could affect attenuation and thus counting statistics. Despite this, the final model is able to account for 75% of the variation in count rate.

### NEW KNOWLEDGE GAINED

This study confirms that also for CZT SPECT gated radionuclide angiography weight is the most important factor influencing count rate. Still height, age, and gender add further prediction power. It has established an algorithm for individualized dosage planning that will enable an overall dose reduction.

### CONCLUSION

Patient weight, height, gender, and age have significant impact on count rate when performing CZT radionuclide angiography and may subsequently be used for individualized planning of tracer dosage to achieve

high quality images with lowest possible dose of administered radioactivity.

### Disclosure

*The authors declare that they have no conflicts of interest.*

### References

1. Foley TA, Mankad SV, Anavekar NS, Bonnicksen CR, Morris MF, Miller TD, et al. Measuring left ventricular ejection fraction—techniques and potential pitfalls. *Eur Cardiol Rev* 2012;8:108-14.
2. Yeh ETH, Bickford CL. Cardiovascular complications of cancer therapy: Incidence, pathogenesis, diagnosis, and management. *J Am Coll Cardiol* 2009;53:2231-47.
3. Mitra D, Basu S. Equilibrium radionuclide angiocardiology: Its usefulness in current practice and potential future applications. *World J Radiol* 2012;4:421-30.
4. Hesse B, Lindhardt TB, Acampa W, Anagnostopoulos C, Ballinger J, Bax JJ, et al. EANM/ESC guidelines for radionuclide imaging of cardiac function. *Eur J Nucl Med Mol Imaging* 2008;35:851-85.
5. Folland ED, Hamilton GW, Larson SM, Kennedy JW, Williams DL, Ritchie JL. The radionuclide ejection fraction: A comparison of three radionuclide techniques with contrast angiography. *J Nucl Med* 1977;18:1159-66.
6. Haarmark C, Haase C, Jensen MM, Zerahn B. Pre-chemotherapy values for left and right ventricular volumes and ejection fraction by gated tomographic radionuclide angiography using a cadmium–zinc–telluride detector gamma camera. *J Nucl Cardiol* 2016;23:87-97.
7. Jensen MM, Haase C, Zerahn B. Interstudy repeatability of left and right ventricular volume estimations by serial-gated tomographic radionuclide angiographies using a cadmium–zinc–telluride detector gamma camera. *Clin Physiol Funct Imaging* 2015;35:418-24.
8. Duvall WL, Croft LB, Godiwala T, Ginsberg E, George T, Henzlova MJ. Reduced isotope dose with rapid SPECT MPI imaging: Initial experience with a CZT SPECT camera. *J Nucl Cardiol* 2010;17:1009-14.
9. Jensen MM, Schmidt U, Huang C, Zerahn B. Gated tomographic radionuclide angiography using cadmium–zinc–telluride detector gamma camera; comparison to traditional gamma cameras. *J Nucl Cardiol* 2014;21:384-96.
10. Acampa W, Buechel RR, Gimelli A. Low dose in nuclear cardiology: state of the art in the era of new cadmium–zinc–telluride cameras. *Eur Heart J Cardiovasc Imaging* 2016;17:591-5.
11. Lindner O, Pascual TNB, Mercuri M, Acampa W, Burchert W, Flotats A, et al. Nuclear cardiology practice and associated radiation doses in Europe: Results of the IAEA Nuclear Cardiology Protocols Study (INCAPS) for the 27 European countries. *Eur J Nucl Med Mol Imaging* 2016;43:718-28.
12. International Atomic Energy Agency, Office IL, International Organization for Medical Physics, Pan American Health Organization, World Health Organization, Medicine WFON, et al. Applying radiation safety standards in nuclear medicine. 2005.
13. Khong P-L, Ringertz H, Donoghue V, Frush D, Rehani M, Appelgate K, et al. ICRP Publication 121: Radiological protection in paediatric diagnostic and interventional radiology. *Ann ICRP* 2013;42:1-63.
14. van Dijk JD, Jager PL, Mouden M, Slump CH, Ottervanger JP, de Boer J, et al. Development and validation of a patient-tailored dose

- regime in myocardial perfusion imaging using CZT-SPECT. *J Nucl Cardiol* 2014;21:1158-67.
15. van Dijk JD, Jager PL, Ottervanger JP, de Boer J, Oostdijk AHJ, Engbers EM, et al. Development and validation of a patient-tailored dose regime in myocardial perfusion imaging using conventional SPECT. *J Nucl Cardiol* 2016;23:134-42.
  16. Notghi A, Williams N, Smith N, Goyle S, Harding LK. Relationship between myocardial counts and patient weight: Adjusting the injected activity in myocardial perfusion scans. *Nucl Med Commun* 2003;24:55-9.
  17. Cerqueira MD, Allman KC, Ficaro EP, Hansen CL, Nichols KJ, Thompson RC, et al. Recommendations for reducing radiation exposure in myocardial perfusion imaging. *J Nucl Cardiol* 2010;17:709-18.
  18. Notghi A, Sundram FX, O'Brien JW, Smith NB. Assessing the effect of increasing injection activity for myocardial perfusion imaging in overweight patients. *BJR* 2008;81:730-4.
  19. Fazel R, Krumholz HM, Wang Y, Ross JS, Chen J, Ting HH, et al. Exposure to low-dose ionizing radiation from medical imaging procedures. *N Engl J Med* 2009;361:849-57. <https://doi.org/10.1056/NEJMoa0901249>.