The very hungry caterpillar and the ongoing effort to reduce radiation in myocardial perfusion scintigraphy: Have we become the beautiful butterfly?

Hein J. Verberne, MD, PhD,^a and Asbjørn M. Scholtens, MD^b

^a Department of Radiology and Nuclear Medicine, F2-238, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

^b Department of Nuclear Medicine, Meander Medical Center, Amersfoort, The Netherlands

Received Jul 20, 2017; accepted Jul 20, 2017
doi:10.1007/s12350-017-1024-7

See related article, pp. 26–35

Single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is a non-invasive test to diagnose coronary artery disease, stratify risk, predict outcomes, guide patient management, and control costs.^{1–5} Over the past 30 years, successive technical innovations including, but not limited to, SPECT acquisition and ECG gating have granted myocardial perfusion imaging the status of a reliable, widely applicable, and increasingly useful technique.^{6,7} Reflecting these benefits, MPI is widely used and its volume has grown rapidly worldwide over the past 2 decades, to approximately 15 to 20 million procedures annually.⁸

Although SPECT MPI is widely used, it is also associated with a relatively high radiation dose. While there is a considerable worldwide variation, SPECT MPI has the highest per capita radiation dose of all medical tests,^{9–11} contributing to approximately 10% of the cumulative radiation dose of medical procedures in the United States.¹² The authors of the IAEA Nuclear Cardiology Protocols Cross-Sectional Study (INCAPS) rightfully concluded that the significant relationship between best-practice implementation and lower doses

indicates numerous opportunities to reduce radiation exposure from MPI globally.¹³ Although exposure to radiation should be handled with care, it is essential to realize that the estimation of risk from ionizing radiation is difficult, especially since no prospective trials focusing on adverse events due to radiation from diagnostic procedures have ever been performed.¹⁴

Despite the (small) possible risk to patients' health, investigations involving radiation are an accepted and fundamental part of medical practice. However, the awareness of medical doctors on the actual radiation doses received by patients of the commonly requested radiological investigations is limited. Using a questionnaire, Shiralkar et al. showed that 97% of the answers were underestimates of the actual dose; six (5%) doctors did not realize that ultrasound does not use ionizing radiation; and 11 (8%) did not realize that magnetic resonance imaging does not use ionizing radiation.¹⁵ Perhaps even more troubling is the fact that even those working in medical imaging are not fully aware of the possible risks of radiation exposure related to medical procedures. In one study of U.S. health care providers using CT in patients with abdominal and flank pain, less than 50% of radiologists and only 9% of emergency department physicians reported even being aware that CT was associated with a possible increased risk of cancer.¹⁶

The latter may partially explain why the awareness of the necessity to reduce radiation doses related to SPECT MPI has been slow to manifest. Additionally, there were historical transatlantic differences and discussions related to concerns whether a reduced administered dose could have the same highly appreciated diagnostic and prognostic properties of higher dose protocols. This is perhaps best illustrated by a reviewer comment (most likely based in the US) from the late

Reprint requests: Hein J. Verberne, MD PhD, Department of Radiology and Nuclear Medicine, F2-238, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands; h.j.verberne@amc.uva.nl

J Nucl Cardiol 2018;25:36–8.

1071-3581/\$34.00

Copyright © 2017 American Society of Nuclear Cardiology.

nineties of the previous century on one of our (European based) manuscripts submitted to the *Journal of Nuclear Cardiology*: “Two-day sestamibi protocol with 400 MBq. In my obsolete units this was about 11mCi. Was the dose really that low?”.

Since that area and post or propter of these transatlantic differences, the awareness to reduce radiation dose from diagnostic procedures has grown rapidly. It is tempting to make an analogy with the illustrated story of the Very Hungry Caterpillar by Eric Carle published in 1969, with its then very innovative design with holes “eaten” through the pages. One Sunday morning, a red-faced caterpillar hatches from an egg, and begins to look for some food. He eats through increasing quantities of fruit on the following 5 days: one apple on Monday, two pears on Tuesday, three plums on Wednesday, four strawberries on Thursday, and five oranges on Friday, and then, on Saturday, he has an enormous feast. By the end of Saturday, the inevitable happens and he is ill. After recovering from a stomach-ache, he returns to a more sensible diet by eating through a large green leaf before spinning a cocoon in which he remains for the following 2 weeks. Later, the “big fat caterpillar” emerges as a beautiful butterfly with large, gorgeous, multi-colored wings. We could call our caterpillar the dose reduction caterpillar and wonder whether the pupal case has been broken and we have emerged as a beautiful butterfly.

The dose reduction caterpillar has been very hungry and many attempts have been made to reduce the relatively high dose associated with SPECT MPI. Introduction of stress-only protocols reduced the radiation dose by 63% without reducing its prognostic value.¹⁷ Moreover, applying attenuation correction can further reduce this dose by an additional 16% due to an increase in normalcy rate and lower need for additional rest imaging.^{18–20} In addition, multiple studies showed that the introduction of new generation cadmium zinc telluride (CZT)-based SPECT cameras allowed for further dose reduction.^{21–23} These new cameras rely on a pinhole collimation design and multiple CZT crystal arrays. Compared to the traditional SPECT camera, this type of collimation provides a three- to five-fold increase in photon sensitivity, thereby reducing imaging times significantly, while providing a 1.7 to 2.5-fold increase in spatial resolution. This makes shorter scans or lower doses (or even both) a reality, without the loss of image quality. Despite these improvements in dose reduction, the caterpillar is still hungry for improvement.

One of the aspects that so far had not been addressed fully is the lowest product of tracer activity and scan time (PAST) that has no effects on the diagnostic outcome in CZT-SPECT MPI. Thus far, previous studies have shown that body-weight dependent activity

protocols not only resulted in an improved image quality but also in the possibility to further lower the tracer activity.^{24,25} However, prognostic evidence that such a low body-weight dependent activity protocol with limited scan time does not affect diagnostic outcome was lacking.

In this issue of the *Journal of Nuclear Cardiology* Van Dijk et al. have addressed this issue and compared a standard fixed-activity protocol (FAP) and a patient-specific low-activity protocol (PLAP) with regard to percentage of scans interpreted as normal, radiation dose, and prognostic value for CZT-SPECT MPI.²⁶

1255 consecutive patients were included retrospectively who underwent CZT-SPECT stress-optional rest MPI. 668 Patients were scanned using FAP (370 MBq) and 587 patients using PLAP (2.25 MBq/kg). The percentage of scans interpreted as normal was 67% in FAP and 70% in PLAP groups ($P = 0.29$). The annualized hard event rates in these patients were 1.0% in the FAP and 0.9% in the PLAP group ($P = 0.86$). However, the mean radiation dose decreased by 23% for stress-only and by 15% to 2.6 mSv for stress-rest MPI after introduction of the PLAP ($P < 0.001$). The authors rightfully concluded that the introduction of a patient-specific low-activity protocol did not affect the percentage of scans interpreted as normal or prognosis but significantly lowered the radiation dose for CZT-SPECT MPI.

Although the relatively low event rates in this study may have introduced statistical variation, this effect is most likely limited as event rates were similar to other publications. In addition, it is important to realize that the study was performed on a CZT-based camera instead of a more commonly used conventional Anger camera. However, it seems safe to assume that introduction of patient-specific activity or scan-time protocols as derived for conventional SPECT cameras may allow radiation dose reductions without affecting diagnostic outcomes in these cameras as well.

Last but not least it is important to realize that the total radiation dose in this protocol is defined by the additional and separate CT scans for attenuation correction and coronary artery calcification scoring. If we assume the cumulated radiation from CT at 3 to 4 mSv this means that the total reduction is less pronounced and almost halved.

Nevertheless the study by Van Dijk et al. has shown that we can further reduce radiation dose for SPECT MPI while maintaining diagnostic and prognostic properties. The question remains whether the Very Hungry Caterpillar has already broken the pupal case to emerge as a beautiful butterfly. The pupal case has not been broken completely yet, but the first cracks are there. The efforts to reduce radiation burden from diagnostic procedures in general and SPECT MPI

specifically are an ever ongoing process that should continue until we finally emerge as a beautiful butterfly.

Disclosure

The authors declare that they have no conflict of interest.

References

1. International Atomic Energy Agency. Nuclear cardiology: Its role in cost effective care. IAEA Human Health Series No. 18. Vienna: International Atomic Energy Agency; 2012.
2. Abraham A, Nichol G, Williams KA, Guo A, deKemp RA, Garrard L, et al. 18F-FDG PET imaging of myocardial viability in an experienced center with access to 18F-FDG and integration with clinical management teams: The Ottawa-FIVE substudy of the PARR 2 trial. *J Nucl Med* 2010;51:567-74.
3. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003;107:2900-7.
4. Jaarsma C, Leiner T, Bekkers SC, Crijs HJ, Wildberger JE, Nagel E, et al. Diagnostic performance of noninvasive myocardial perfusion imaging using single-photon emission computed tomography, cardiac magnetic resonance, and positron emission tomography imaging for the detection of obstructive coronary artery disease: A meta-analysis. *J Am Coll Cardiol* 2012;59:1719-28.
5. Metz LD, Beattie M, Hom R, Redberg RF, Grady D, Fleischmann KE. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: A meta-analysis. *J Am Coll Cardiol* 2007;49:227-37.
6. Henzlova MJ, Duvall WL, Einstein AJ, Travin MI, Verberne HJ. ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress, protocols, and tracers. *J Nucl Cardiol* 2016;23:606-39.
7. Verberne HJ, Acampa W, Anagnostopoulos C, Ballinger J, Bengel F, De Bondt P, et al. EANM procedural guidelines for radionuclide myocardial perfusion imaging with SPECT and SPECT/CT: 2015 revision. *Eur J Nucl Med Mol Imaging* 2015;42:1929-40.
8. Einstein AJ. Multiple opportunities to reduce radiation dose from myocardial perfusion imaging. *Eur J Nucl Med Mol Imaging* 2013;40:649-51.
9. Berrington de Gonzalez A, Kim KP, Smith-Bindman R, McAreavey D. Myocardial perfusion scans: Projected population cancer risks from current levels of use in the United States. *Circulation* 2010;122:2403-10.
10. Einstein AJ, Weiner SD, Bernheim A, Kulon M, Bokhari S, Johnson LL, et al. Multiple testing, cumulative radiation dose, and clinical indications in patients undergoing myocardial perfusion imaging. *JAMA* 2010;304:2137-44.
11. 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.
12. National Council on Radiation Protection and Measurements. Report no. 160 - Ionizing radiation exposure of the population of the United States. Bethesda, MD; 2009.
13. Einstein AJ, Pascual TN, Mercuri M, Karthikeyan G, Vitola JV, Mahmarian JJ, et al. Current worldwide nuclear cardiology practices and radiation exposure: results from the 65 country IAEA nuclear cardiology protocols cross-sectional study (INCAPS). *Eur Heart J* 2015;36:1689-96.
14. Knuuti J, Bengel F, Bax JJ, Kaufmann PA, Le Guludec D, Perrone Filardi P, et al. Risks and benefits of cardiac imaging: an analysis of risks related to imaging for coronary artery disease. *Eur Heart J* 2014;35:633-8.
15. Shiralkar S, Rennie A, Snow M, Galland RB, Lewis MH, Gower-Thomas K. Doctors' knowledge of radiation exposure: Questionnaire study. *BMJ* 2003;327:371-2.
16. Lee CI, Haims AH, Monico EP, Brink JA, Forman HP. Diagnostic CT scans: assessment of patient, physician, and radiologist awareness of radiation dose and possible risks. *Radiology* 2004;231:393-8.
17. Mercuri M, Pascual TN, Mahmarian JJ, Shaw LJ, Dondi M, Paez D, et al. Estimating the reduction in the radiation burden from nuclear cardiology through use of stress-only imaging in the United States and worldwide. *JAMA Intern Med* 2016;176:269-73.
18. Heller GV, Bateman TM, Johnson LL, Cullom SJ, Case JA, Galt JR, et al. Clinical value of attenuation correction in stress-only Tc-99m sestamibi SPECT imaging. *J Nucl Cardiol* 2004;11:273-81.
19. Tragardh E, Valind S, Edenbrandt L. Adding attenuation corrected images in myocardial perfusion imaging reduces the need for a rest study. *BMC Med Imaging* 2013;13:14.
20. van Dijk JD, van Dalen JA, Mouden M, Ottervanger JP, Knollema S, Slump CH, et al. Value of automatic patient motion detection and correction in myocardial perfusion imaging using a CZT-based SPECT camera. *J Nucl Cardiol*. 2016;. doi: [10.1007/s12350-016-0590-4](https://doi.org/10.1007/s12350-016-0590-4).
21. Duvall WL, Guma KA, Kamen J, Croft LB, Parides M, George T, et al. Reduction in occupational and patient radiation exposure from myocardial perfusion imaging: Impact of stress-only imaging and high-efficiency SPECT camera technology. *J Nucl Med* 2013;54:1251-7.
22. Henzlova MJ, Duvall WL. The future of SPECT MPI: Time and dose reduction. *J Nucl Cardiol* 2011;18:580-7.
23. Nakazato R, Berman DS, Hayes SW, Fish M, Padgett R, Xu Y, et al. Myocardial perfusion imaging with a solid-state camera: Simulation of a very low dose imaging protocol. *J Nucl Med* 2013;54:373-9.
24. 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.
25. van Dijk JD, Jager PL, Ottervanger JP, de Boer J, Oostdijk AH, 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.
26. van Dijk JD, Mouden M, van Dalen JA, Ottervanger JP, Jager PL. Effect of a patient-specific minimum activity in stress myocardial perfusion imaging using CZTSPECT: Prognostic value, radiation dose and scan outcome. *J Nucl Cardiol* 2017.