An Exploratory Study of Washout Rate Analysis for Thallium-201 Single-Photon Emission Computed Tomography Myocardial Perfusion Imaging Using Cadmium Zinc Telluride Detectors

Masaru Ishihara, MS1,2, Masahisa Onoguchi, PhD2, and Takayuki Shibutani, PhD2

Abstract

The aim of this study was to assess the washout rate (WOR) for thallium-201-chloride single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) using cadmium zinc telluride detectors for SPECT (CZT SPECT) versus conventional Anger-type SPECT (conventional SPECT). A total of 52 Japanese patients were examined using CZT SPECT and conventional SPECT, and the global WORs were compared. Additionally, the MPI WORs were compared for patients with a normal MPI versus those in whom MPI reflected the patients’ multivessel disease (MVD) MPI. Washout rates were similar when approximated by CZT SPECT versus conventional SPECT 12.59 ± 2.26%/h vs 12.57 ± 2.27%/h (P = .997), respectively. The WOR values for CZT SPECT versus conventional SPECT were 13.42%/h (1.53%/h) vs 13.93%/h (1.24%/h) (P = .337), respectively, for 7 normal MPI patients, and 10.64 ± 2.20%/h vs 10.84 ± 2.26%/h (P = .848), respectively, for 7 MVD-MPI patients. The WOR values for normal MPI versus MVD-MPI patients for CZT SPECT were 13.42 ± 1.53%/h vs 10.64 ± 2.20%/h (P = .025), respectively. Thallium-201-chloride WOR values obtained with high-efficiency CZT SPECT, which enabled significantly reduced imaging times and use of a low-dose protocol, were similar to those obtained with conventional SPECT.

Keywords
washout rate, thallium-201-chloride, myocardial perfusion imaging, single-photon emission computed tomography, cadmium zinc telluride detectors

Introduction

Thallium-201-chloride (201Tl) is widely used for single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) in many Asian countries.1-3 Thallium-201-chloride is a clinically important radiopharmaceutical for assessing both regional blood flow and the viability of the left ventricular myocardium. Thallium-201-chloride offers several advantages over technetium-99m, including lower extracardiac activity and higher first-pass myocardial extraction. Further, 201Tl can be administered as a single injection for imaging during a stress/rest MPI protocol. The 201Tl washout rate (WOR) is also a valuable tool for assisting MPI when diagnosing coronary artery disease (CAD).4-6

Dedicated cardiac exploratory systems with cadmium zinc telluride detectors for SPECT (CZT SPECT) offer a higher efficiency and resolution than conventional Anger-type SPECT (conventional SPECT), thereby allowing low-dose imaging protocols and reduced acquisition times.7-9 The aim of this study was to assess the WOR for 201Tl SPECT MPI using CZT SPECT versus conventional SPECT.

1 Department of Radiology, Hyogo Cancer Center, Akashi, Japan
2 Department of Quantum Medical Technology, Graduate School of Medical Sciences, Kanazawa University, Kanazawa, Japan

Submitted: 18/11/2017. Revised: 10/05/2018. Accepted: 15/05/2018.

Corresponding Author:
Masahisa Onoguchi, Department of Quantum Medical Technology, Graduate School of Medical Sciences, Kanazawa University, 5-11-80 Kodatsuno, Kanazawa 920-0942, Japan.
Email: onoguchi@staff.kanazawa-u.ac.jp
Materials and Methods

Patients

The final study population for this retrospective study comprised 52 Japanese patients (36 [69.2%] men; mean + standard deviation [SD] age of 73.1 ± 8.5 years; standard body mass index 21.8 ± 2.8 kg/m² [16.0-28.7 kg/m²]) with suspected CAD (n = 26) or known CAD (n = 26). Each patient had undergone stress/redistribution testing during January and February 2015, which included a single injection of 201Tl to assess myocardial ischemia, viability, and scarring of the left ventricle. The patients’ clinical characteristics are shown in Table 1. The ethics committee of Hyogo Brain and Heart Center at Himeji (Himeji, Japan) approved this retrospective study.

Imaging Protocol

The imaging protocol is shown in Figure 1. In all cases, CZT SPECT and conventional SPECT were performed as consecutive acquisitions, with CZT SPECT acquisition performed prior to conventional SPECT to ensure that the interval between the 2 scans was short (to avoid stress and redistribution acquisition). Cadmium zinc telluride detectors for SPECT was performed with a 5-minute acquisition, while conventional SPECT was performed with a 10.0- to 12.5-minutes acquisition. The injected activity was 111 MBq (3 mCi) for stress imaging. Exercise (13 patients) and adenosine (39 patients) stress testing were performed using the same protocol as previously reported.10 The CZT SPECT (D-SPECT Cardiac Scanner; Spectrum Dynamics, Caesarea, Israel) and conventional SPECT (BrightView; Philips Medical Systems, Cleveland, Ohio, USA) imaging systems were similar to those previously reported.10

Quantitative Analysis of WOR

All MPI scans were analyzed using WOR analysis software (CZT SPECT: D-SPECT WOR Software; Spectrum Dynamics; Conventional SPECT: AZE VirtualPlace HAYABUSA Heart Risk View-S; AZE Co., Ltd., Tokyo, Japan). Automated analysis compared the global WOR values for CZT SPECT versus conventional SPECT.

Additionally, WOR values were compared for 7 normal MPI patients and 7 multivessel disease (MVD) MPI patients (of 52 total patients) in each of the 2 SPECT devices. Washout rate values were also compared between 7 normal MPI patients and 7 MVD-MPI patients in the CZT SPECT. Patients with a normal MPI were diagnosed as normal MPI after an experienced nuclear cardiologist ascertained that they had not experienced cardiovascular events during a 1-year period after SPECT MPI. Multivessel disease MPI patients had undergone invasive coronary angiography within 90 days of MPI SPECT, with the angiography showing ≥75% stenosis in the presence of 2- or 3-vessel disease.

Results were calculated as percentage per hour (%/h). The formula for calculating the WOR is as follows:

\[
\text{WOR} = \frac{CZT \text{ mean stress counts}}{\text{CZT mean redistribution counts} \times \text{decay correction factor} \times 100},
\]

where the decay correction factor = 2 (stress and redistribution imaging time interval [hours]/72.97).11

Statistics

Statistical analyses were performed with commercial statistical software (StatView version 5.0 and JMP version 11.2.0; SAS Institute, Inc., Cary, NC, USA). All continuous variables are expressed as mean (SD). Values of \( P < .05 \) were considered statistically significant. Cadmium zinc telluride SPECT and conventional SPECT results are depicted as both scatter plots and Bland-Altman plots. The degree of agreement was calculated according to Bland and Altman.12 Bland-Altman limits were calculated as follows: mean of the difference ± 1.96 × SD of the difference. Pearson’s correlation coefficients were also calculated. Mean WOR values were calculated from the patients’ data. All differences between the 2 groups were assessed using the Mann-Whitney U test.

Table 1. Patients’ Characteristics.

| Characteristic               | Value                      |
|-----------------------------|----------------------------|
| Age (years)                 | 73.1 ± 8.5 (range 40-87)   |
| Men sex, n (%)              | 36 (69.2)                  |
| BMI (kg/m²)                 | 21.8 ± 2.8 (range 16.0-28.7)|
| Prior myocardial infarction | 10 (19.2)                  |
| Prior revascularization     | 26 (50.0)                  |
| Comorbidities               |                            |
| Diabetes                    | 18 (34.6)                  |
| Hypertension                | 30 (57.7)                  |
| Hypercholesterolemia        | 22 (42.3)                  |
| Chronic kidney disease      | 9 (17.3)                   |
| Smoking                     | 14 (26.9)                  |

Abbreviation: BMI, body mass index.

Figure 1. Study protocol for stress/redistribution myocardial perfusion imaging with thallium-201-chloride (201Tl).
**Figure 2.** Linear regression analysis (A) and Bland-Altman plots (B) for cadmium zinc telluride single-photon emission computed tomography (CZT SPECT) and conventional SPECT.

**Figure 3.** An 80-year-old woman was found to have an abdominal aortic aneurysm during a preoperative cardiac evaluation. A, Contrast-enhanced computed tomography shows an infrarenal abdominal aortic aneurysm. B, Cadmium zinc telluride (CZT) single-photon emission computed tomography (SPECT) stress images (top row), redistribution images (bottom row), and washout rate (WOR) (at 15.6%/h) image. C, Conventional SPECT stress images (top row), redistribution images (bottom row), and WOR (at 14.8%/h) image.
Results

In all 52 patients, the global WOR values for CZT SPECT versus conventional SPECT were $12.59 \pm 2.26\%/h$ vs $12.57 \pm 2.27\%/h$ ($P = .997$), respectively. Cadmium zinc telluride SPECT and conventional SPECT results were compared using linear regression analysis (Figure 2A), with a positive correlation for the scores ($r = .91, P < .001$). The Bland-Altman comparison showed a mean difference score of 0.03 (Figure 2B). For factors affecting the $^{201}$Tl WOR values (heart rate, ejection fraction, stress redistribution imaging time interval) for CZT SPECT versus conventional SPECT, the stress heart rates were $70.27 \pm 13.03$ beats per minute vs $66.63 \pm 11.69$ beats per minute ($P = .126$), respectively; the redistribution heart rates were $69.75 \pm 12.87$ beats per minute vs $66.06 \pm 12.50$ beats per minute ($P = .112$), respectively; the stress ejection fractions were $56.48 \pm 16.63\%$ vs $59.63 \pm 15.33\%$ ($P = .269$), respectively; the redistribution ejection fractions were $57.37 \pm 16.73\%$ vs $60.21 \pm 14.96\%$ ($P = .265$), respectively; and the stress redistribution imaging time intervals were 3.47 $\pm$ 0.23 hours vs 3.46 $\pm$ 0.22 hours ($P = .747$), respectively.

Washout rate values for CZT SPECT versus conventional SPECT were $13.42 \pm 1.53\%/h$ vs $13.93 \pm 1.24\%/h$ ($P = .337$), respectively, for the 7 normal MPI patients, and $10.64 \pm 2.20\%/h$ vs $10.84 \pm 2.26\%/h$ ($P = .848$), respectively, for the 7 MVD-MPI patients. The normal MPI versus MVD-MPI patients’ WOR values for CZT SPECT were $13.42 \pm 1.53\%/h$ vs $10.64 \pm 2.20\%/h$ ($P = .025$), respectively. Representative cases are shown in Figures 3 and 4.

Discussion

Cadmium zinc telluride SPECT is a fast and efficient imaging technology that provides high-quality images and high diagnostic accuracy for the detection of CAD. Previous studies have shown that perfusion abnormalities detected with CZT SPECT are highly correlated with those using conventional SPECT. The CZT SPECT image quality with $^{201}$Tl was reported to be superior to that achieved with conventional
SPECT, with significantly reduced imaging times and radio-isotope doses but similar diagnostic accuracy.\textsuperscript{9} Thallium-201-chloride WOR is particularly useful for assisting MPI to diagnose CAD.\textsuperscript{4,6} In particular, in the presence of multivessel or diffuse CAD, \textsuperscript{201}Tl WOR can help identify CAD in patients with apparently normal or slightly abnormal MPI. Cadmium zinc telluride SPECT provides better image quality and higher resolution than conventional SPECT, although there is potential for differences in the WORs. However, the use of \textsuperscript{201}Tl WOR with CZT SPECT has not been reported. Thus, we compared WOR values using CZT SPECT and conventional SPECT in 52 patients with or without CAD, and between 7 normal MPI patients and 7 MVD-MPI patients. We found similar approximated global WOR values and a good correlation score between CZT SPECT and conventional SPECT. Further, WORs approximated by CZT SPECT and conventional SPECT were similar for normal MPI patients and MVD-MPI patients. This relates to the use of the same WOR calculation formula (using decay correction) for the 2 SPECT devices.

Cadmium zinc telluride SPECT and conventional SPECT were not subjected to attenuation correction in the current study as we used a CZT SPECT (D-SPECT cardiac scanner) and a conventional SPECT (BrightView), neither of which had attenuation correction (ie, neither SPECT system had gadolinium-153 transmission line sources or low-dose computed tomography).

A potential limitation of this study was the small sample size and the single-center study design. Further, this study was only based on a Japanese population using a D-SPECT camera. As the participants were Japanese, they had a lower overall body mass index. Thus, a study of Europeans and Americans with a larger body mass index may have produced different results. D-SPECT and other CZT camera system (eg, Discovery NM 530c camera; GE Healthcare, Haifa, Israel) also have different scanning methods and positioning, which may have produced different results. D-SPECT uses rotational wide-angle square-hole tungsten collimators and region of interest–centric scanning, with an upright position imaging used in all cases in the present study. In contrast, the Discovery NM 530c uses stationary multiple pinhole collimators and 19 detectors, usually imaging in a supine position.

**Conclusion**

Clinically, \textsuperscript{201}Tl WOR values obtained with high-efficiency CZT SPECT, which enabled significantly reduced imaging times and use of a low-dose protocol, were similar to those obtained with conventional SPECT. Thallium-201-chloride WOR analysis using CZT SPECT may be useful for identifying MVD and diffuse CAD in patients with apparently normal or slightly abnormal MPI.

**Acknowledgments**

The authors thank the radiological technologists and cardiologists of Hyogo Brain and Heart Center at Himeji for technical support. The authors also thank Edanz Group (http://www.edanzediting.com/ac) for editing a draft of this manuscript.

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The author(s) received no financial support for the research, authorship, and/or publication of this article.

**References**

1. Chen CC, Huang WS, Hung GU, et al. Left-ventricular dys synchrony evaluated by thallium-201 gated SPECT myocardial perfusion imaging: a comparison with Tc-99 m sestamibi. Nucl Med Commun. 2013;34(3):229–232.
2. Shiraishi S, Sakamoto F, Tsuda N, et al. Prediction of left main or 3-vessel disease using myocardial perfusion reserve on dynamic thallium-201 single-photon emission computed tomography with a semiconductor gamma camera. Circ J. 2015;79(3):623–631.
3. Ishihara M, Taniguchi Y, Onoguchi M, et al. Optimal thallium-201 dose in cadmium-zinc-telluride SPECT myocardial perfusion imaging. J Nucl Cardiol. 2018;25(3):947–954.
4. Bateman TM, Maddahi J, Gray RJ, et al. Diffuse slow washout of myocardial thallium-201: a new scintigraphic indicator of extensive coronary artery disease. J Am Coll Cardiol. 1984;1(1):55–64.
5. Koskinen M, Pöyhönen L, Seppänen S. Thallium-201 washout in coronary artery disease using SPECT—a comparison with coronary angiography. Eur J Nucl Med. 1987;12(12):609–612.
6. Yamada M, Chikamori T, Doi Y, et al. Negative washout rate of myocardial thallium-201—a specific marker for high grade coronary artery narrowing. Jpn Circ J. 1992;56(10):975–982.
7. Sharir T, Ben-Haim S, Merzon K, et al. High-speed myocardial perfusion imaging initial clinical comparison with conventional dual detector anger camera imaging. JACC Cardiovasc Imaging. 2008;1(2):156–163.
8. Nakazato R, Slomka PJ, Fish M, et al. Quantitative high-efficiency cadmium-zinc-telluride SPECT with dedicated parallel-hole collimation system in obese patients: results of a multi-center study. J Nucl Cardiol. 2015;22(2):266–275.
9. Songy B, Lussato D, Guernou M, et al. Comparison of myocardial perfusion imaging using thallium-201 between a new cadmium-zinc-telluride cardiac camera and a conventional SPECT camera. Clin Nucl Med. 2011;36(9):776–780.
10. Ishihara M, Onoguchi M, Taniguchi Y, et al. Comparison of conventional and cadmium-zinc-telluride single-photon emission computed tomography for analysis of thallium-201 myocardial perfusion imaging: an exploratory study in normal databases for different ethnicities. Int J Cardiovasc Imaging. 2017;33(12):2057–2066.
11. Flotats A, Carrió I, Agostini D, et al. Proposal for standardization of 123I-metaiodobenzylguanidine (MIBG) cardiac sympathetic imaging by the EANM Cardiovascular Committee and the European Council of Nuclear Cardiology. Eur J Nucl Med Mol Imaging. 2010;37(9):1802–1812.
12. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;1(8476):307–310.

13. Einstein AJ, Blankstein R, Andrews H, et al. Comparison of image quality, myocardial perfusion, and left ventricular function between standard imaging and single-injection ultra-low-dose imaging using a high-efficiency SPECT camera: the MILLISIE-VERT study. *J Nucl Med*. 2014;55(9):1430–1437.

14. Sharir T, Slomka PJ, Hayes SW, et al. Multicenter trial of high-speed versus conventional single-photon emission computed tomography imaging: quantitative results of myocardial perfusion and left ventricular function. *J Am Coll Cardiol*. 2010;55(18):1965–1974.