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Journal of Radiology & Radiation therapy

Short Communication

Quality Control for Quantitative Evaluation of Cardiac Sympathetic Nerve Function with 123i-Metaiodobenzylguanidine

Yusuke Inoue*

Department of Diagnostic Radiology, Kitasato University School of Medicine, Japan

Corresponding author

Yusuke Inoue, Department of Diagnostic Radiology, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0374, Japan, Tel: 81-42-778-8111; Fax: 81-42-778-9436; E-mail: inoueys34@gmail.com

Submitted: 10 August 2013

Accepted: 10 September 2013

Published: 12 September 2013

Keywords

- ^{123}I-metaiodobenzylguanidine (MIBG)
- Heart-to-mediastinum (H/M) ratio
- Quantitative evaluation
- Collimator

Abstract

Cardiac imaging with ^{123}I-metaiodobenzylguanidine allows assessing cardiac sympathetic nerve function and aids the prediction of prognosis in heart failure and the differential diagnosis of neurodegenerative diseases. The heart-to-mediastinum (H/M) ratio is widely used as a quantitative indicator of cardiac accumulation; however, it is susceptible to the instrumentation, imaging parameters, and data-processing methods, and quality control is essential. This article briefly discusses technical considerations, including collimator choice, correction methods, energy window settings, and selection of regions of interest, for reliable evaluation of cardiac accumulation of ^{123}I-metaiodobenzylguanidine.

Cardiac sympathetic nerve function can be assessed using iodine-123 metaiodobenzylguanidine (^{123}I-MIBG), a radioiodinated analog of norepinephrine. Anterior chest images are acquired with a gamma camera 15 minutes and 4 hours after intravenous injection of the agent. ^{123}I-MIBG is taken up by the abundant sympathetic nerve endings in the left ventricular wall and this uptake decreases, accompanied by accelerated washout, in patients with impaired cardiac sympathetic function. The heart-to-mediastinum (H/M) ratio, the ratio of count density in the left ventricle to that in the upper mediastinum, is calculated to quantitatively assess cardiac accumulation, and a decreased H/M ratio at a late phase (*i. e.* , 4 hours postinjection) is regarded as an indicator of impaired cardiac sympathetic function. The H/M ratio reflects disease severity in patients with heart failure, and cardiac ^{123}I-MIBG imaging is used to predict their prognosis [1]. Patients with Parkinson's disease and dementia with Lewy bodies have impaired sympathetic function, and this can be used for the differential diagnosis of neurodegenerative diseases [2,3]. ^{123}I-MIBG was recently approved by the US Food and Drug Administration to predict prognosis in heart failure. In Japan, it has long been used in routine clinical practice to evaluate cardiac diseases including heart failure, and now its main indication has been changed to the diagnosis of neurodegenerative diseases.

Although many studies have suggested the usefulness of cardiac ^{123}I-MIBG imaging in heart failure and neurodegenerative diseases, the large variability in the estimated H/M ratios limits its clinical use [4]. The Japanese guidelines for chronic heart failure published in 2005 state that no consensus exists regarding the quantitative value of cardiac ^{123}I-MIBG imaging despite its potential usefulness. The 2010 version omitted the description about this examination, reflecting reduced expectations. The estimated H/M ratio depends on the instrumentation, imaging parameters, and data-processing methods, which causes difficulty when comparing values from different institutions and establishing a cutoff value for diagnosis. To overcome this problem, a proposal for standardization of cardiac ^{123}I-MIBG imaging was published by the EANM Cardiovascular Committee and the European Council of Nuclear Cardiology in 2010 [5].

Collimator choice is a critical factor in cardiac ^{123}I-MIBG imaging. The radionuclide ^{123}I has great potential in nuclear medicine with versatile labeling capability and an appropriate half-life; however, it has tricky physical characteristics. It emits high-energy photons of more than 400 keV, in addition to 159-keV photons to be measured. A gamma camera relies on a collimator, typically a large lead plate with many small holes, to determine the position of radioactive sources. The collimator is attached to the surface of the detector (scintillator) and faces the patient. A gamma ray can travel though the holes and reach the scintillator only when its path is parallel to the axis of the hole. Otherwise, it is stopped by the septa of the holes. This mechanism is essential for

position detection; however, high-energy photons from ^{123}I can penetrate the thin septa of a low-energy high-resolution (LEHR) collimator designed for imaging 140-keV photons from ^{99m}Tc. The sources of the photons passing through the septa are located erroneously, degrading image quality and quantitative accuracy. Medium-energy (ME) collimators have thicker septa and are less susceptible to septal penetration than LEHR collimators. The proposal for standardization [5] comments superior accuracy using ME collimators; however, LEHR collimators are still used in many centers probably because of their wide availability and the presence of much literature using this type of collimator.

Previously, we investigated the effect of collimator choice on the assessment of H/M ratios [6]. Phantom experiments indicated better quantitative accuracy using the ME collimator than using the LEHR collimator, and clinical comparisons in eight patients demonstrated that large underestimation of H/M ratios actually occurred using the LEHR collimator. Recently, we examined 40 patients using LEHR and ME collimators for a more detailed comparison [7], and confirmed image degradation (Figure 1) and severe underestimation of H/M ratios using the LEHR collimator. We propose that all values be reported with the type of collimator used because of the large influence of collimator choice on H/M ratios. Moreover, we determined a regression equation to convert the H/M ratio using the LEHR collimator to an equivalent H/M ratio using the ME collimator. After conversion using this equation, the collimator-dependent differences decreased greatly despite obvious residual errors. Although the use of an ME collimator is recommended for accurate measurement, conversion of values obtained with an LEHR collimator facilitates comparisons among institutes. A cutoff value defined based on LEHR studies can be converted to an ME-based value using the same equation. We compared the LEHR and ME collimators using a 5/8-inch crystal camera and are now studying using a 3/8-inch crystal camera, which is commonly used in nuclear medicine. The collimator specifications differ among manufactures, and the conversion equation needs to be determined for each collimator. We also examined the use of a low-medium-energy (LME) collimator, which has characteristics intermediate between LEHR and ME collimators and are widely used for ^{123}I imaging in Japan. Although H/M ratios were still underestimated using the LME collimator, the underestimation was much smaller than that using the LEHR collimator. When the width of the energy window was reduced from the standard 20% window to a 15% window, underestimation was almost eliminated. This indicates that the width of the energy window affects the estimated H/M ratios and that measurement with an LME collimator and a 15% window is an acceptable alternative to that with an ME collimator and a 20% window.

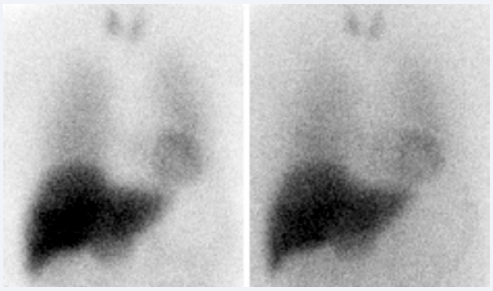

Figure 1 Anterior chest images acquired 4 hours after ^{123}I-MIBG injection using ME (left) and LEHR (right) collimators. Background counts are elevated in the image obtained using the LEHR collimator, reducing the contrast between the left ventricular wall and mediastinum.

Additional energy windows can be set for estimating photons contaminating into the main window. The triple-energy-window method, used for scatter correction, was proven to be inaccurate for estimating H/M ratios [6]. The ^{123}I-dual-window (IDW) method assesses the degree of contamination by high-energy photons based on counts in an energy window set at a high energy level. The IDW correction neglects scatter counts from 159-keV photons and attempts to eliminate the effect of high-energy photons exclusively. In our study [7], the IDW correction partially reduced the underestimation of the H/M ratio using the LEHR collimator; however, considerable underestimation remained. Energy-window-based corrections cannot replace the use of optimal collimators.

Septal penetration still occurs using an ME collimator, although to a much lower degree than using an LEHR collimator. If its effect on H/M ratios is significant, differences in the specifications of ME collimators among manufacturers might cause differences in H/M ratios. High-energy collimators are designed for imaging 364-keV photons from ^{131}I and are less transparent than ME collimators. Although extensive use of an HE collimator in routine clinical practice is not realistic because of its low availability, comparison between ME and HE collimators would be informative to determine whether penetration through the septa of an ME collimator has significant effects on H/M ratios.

To calculate H/M ratios, an operator draws regions of interest (ROIs) for the heart and upper mediastinum, which introduces operator-dependent variability in the estimated values. In a recent study regarding cardiac ROIs, significant changes in the size of ROIs produced only minimal changes in the H/M ratios [8]. Acceptable reproducibility in calculating H/M ratios from a given image has been stated in other reports; however, substantial operator dependence has been shown in one report [9]. The results of operator-dependent reproducibility are operator-dependent, and operator dependence is better investigated using many operators. The background of and instructions given to the operators should be defined in such studies. The borders of the organs are unclear on images acquired using an LEHR collimator due to septal penetration, which may cause difficulty in drawing ROIs. The effect of collimator choice should be considered when assessing operator-dependent reproducibility. We assume that well-defined standardization of ROI setting and instruction followed by some training would provide acceptable reproducibility in calculating H/M ratios from images obtained with LME or ME collimators, which should be tested in the future.

Typically, the heart ROI is drawn manually covering the left ventricle and includes not only its wall but also its cavity. Since the count density, total counts divided by the area, is used to calculate H/M ratios, a dilated cavity reduces the H/M ratio, even with a fixed accumulation per gram of myocardium. The effect of dilatation may not be a substantial problem in neurodegenerative diseases, but should be considered in the assessment of heart failure. Successful treatment would reduce the cavity volume,

increasing the H/M ratio even without a change in accumulation. The H/M ratio in a patient with heart failure may be regarded as a combined indicator of cardiac sympathetic nerve function and left ventricular dilatation, and correction for dilatation may provide a better indicator of sympathetic function itself.

Single photon emission computed tomography (SPECT) is commonly used in cardiac nuclear medicine and is also described in the proposal for the standardization of cardiac ^{123}I-MIBG imaging [5]. The utility of SPECT with ^{123}I-MIBG has been indicated for the assessment of arrhythmogenic foci; however, it is questionable in heart failure and neurodegenerative diseases. Regional differences in accumulation and washout are common especially in elderly patients, and their clinical significance is unclear. Omission of SPECT is a valid option substantially reducing the burden on patients and nuclear medicine facilities. Nominal spatial resolution is better for an LEHR collimator than for an ME collimator, and one might prefer an LEHR collimator to detect focal hypoactivity clearly on SPECT images. Actually, because of marked septal penetration, the use of an LEHR collimator gives poorer SPECT images [10]. The use of an LME collimator may offer the best balance between estimation of H/M ratios and regional assessment with SPECT, if SPECT is meaningful. In this case, an ME-equivalent H/M ratio can be obtained using a 15% energy window in planar imaging.

Normal values of H/M ratios can be determined after appropriate conversion to ME-equivalent values. However, it is desirable to establish the normal range and cutoff values using the method standardized in terms of image acquisition and data processing. In establishing reference values, age-related reduction in H/M ratios should be considered [11].

In addition to the emission of high-energy photons, ^{123}I has other tricky physical characteristics. The physical decay of ^{123}I produces ^{123}Te, emitting characteristic X-Rays of 27-32 keV. A dose calibrator can detect such low-energy photons, and low-energy photons are stopped by a glass container but not by a plastic syringe. As a result, the readings on a dose calibrator vary depending on the container material [12]. This effect should be considered when measuring injection doses.

Quality control is essential in all clinical practices and has paramount importance in quantitative assessment. Cardiac ^{123}I-MIBG imaging has a great potential for contributing to patient management in cardiology and neurology, but is susceptible to technical variance. We hope that standardization of the protocol and adherence to best practices will realize its potential.

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Cite this article

Inoue Y (2013) Quality Control for Quantitative Evaluation of Cardiac Sympathetic Nerve Function with ^{123}i-Metaiodobenzylguanidine. J Radiol Radiat Ther 1(2): 1010.