

Phase dyssynchrony and ^{123}I -meta-iodobenzylguanidine innervation imaging towards standardization

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Over the last decades, semi-quantitative analysis has become crucial in the assessment of myocardial perfusion scintigraphy. Through widely available software packages, electrocardiographically (ECG) gated myocardial perfusion single-photon emission computed tomography (SPECT) quantitative parameters of left ventricular (LV) function are easily obtainable. These software algorithms have increased worldwide consistency and improved quality of myocardial perfusion scintigraphy in the assessment of the total ischemic burden, left ventricular (LV) volumes, and left ventricular ejection fraction (LVEF). In general, these software algorithms have standardized the interpretation of ECG gated myocardial perfusion SPECT. However, for other parameters of left ventricular function such as phase analysis of ECG gated myocardial perfusion SPECT and regional analysis of cardiac sympathetic imaging with ^{123}I -meta-iodobenzylguanidine (^{123}I -mIBG), standardization is still not reached. This lack of standardization hampers the widespread clinical use of the potentially

very valuable parameters obtained with phase analysis and ^{123}I -mIBG quantitation methods.

GLOBAL AND REGIONAL ^{123}I -MIBG MYOCARDIAL UPTAKE PARAMETERS

The necessity of standardizing global ^{123}I -mIBG myocardial uptake, has already been emphasized.^{1–3} In particular for the assessment of the heart-to-mediastinum ratio (HMR) on planar images, it has been shown that the accuracy of the HMR is significantly influenced by variations in camera-collimator systems.⁴ However, the recent development of a calibration phantom-based standardization method provides optimal conversion coefficients for most of the Anger-type camera-collimator combinations.^{5,6} The standardization method could be applied to cadmium-zinc-telluride (CZT) cameras, either by empirical conversion equation between two systems with a phantom study^{7,8} or calibration phantom experiments as described for Anger cameras.⁹

On the other hand, the assessment of regional ^{123}I -mIBG uptake with SPECT has not been standardized so rigorously yet. Scoring methods as used in myocardial perfusion SPECT with a 17-segment model and percent of voxels with counts below the lower limit of normal have been described.^{10,11} Important to realize is that the normal distribution of ^{123}I -mIBG on SPECT shows lower uptake in the inferior and apical regions (Figure 1). This lower uptake is not explained by attenuation as seen in myocardial perfusion images. A number of studies used a visual semi-quantitative approach partly aided by percent uptake of each segment and mismatch between perfusion and innervation as well.^{12,13} Normal

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databases as commonly used in myocardial perfusion SPECT could be an option for a standardized ^{123}I -mIBG SPECT analysis. However, the ^{123}I -mIBG databases as used by the Japanese Society of Nuclear Medicine working groups have not been created for clinical use outside of Japan.¹⁴ These databases would be of interest as they use the same approach as used for myocardial perfusion SPECT. However, when there is an overall decreased ^{123}I -mIBG myocardial uptake, myocardial regions corresponding to 100% count cannot be determined appropriately. In other words, this quantification assumes that at least one myocardial region has normal sympathetic activity. In this respect, imaging with CZT could provide high resolution and sensitivity, which could potentially enhance the accuracy of regional scores based on ^{123}I -mIBG SPECT imaging.¹⁵ Obviously, nearly complete decreased ^{123}I -mIBG uptake as seen in Lewy-body disease and very severe heart failure may result in the maximal defect score of 68 (17 segments \times 4 points). In addition, perfusion images combined with ^{123}I -mIBG images may be helpful for a better risk analysis.¹²

Another approach for SPECT is the summation of all myocardial slices to calculate myocardial uptake, and then calculate the uptake in relation to the mediastinal

uptake, similar to the planar approach.^{11,16} Although such whole-heart SPECT analysis has been reported, the impact on the diagnosis or prognosis has not yet been demonstrated.¹⁶ Most promising seems the use of x-ray computed tomography-based attenuation and scatter corrections resulting in absolute quantification in Bq/cm^3 for ^{123}I -mIBG SPECT, similar to the standardized uptake value as used in positron emission tomography. However, the exact role of this exciting methodology for the calculation of absolute ^{123}I -mIBG uptake in establishing diagnosis and prognosis needs to be investigated first before it can be applied to clinical practice.

GLOBAL PHASE VS REGIONAL PHASE ANALYSIS

The principle of phase analysis was developed in 1980s, and subsequently applied to gated SPECT.¹⁷ The application of phase analysis has also been described for modern CZT technology-driven cameras.¹⁸ Whereas phase dyssynchrony parameters have provided potentially promising results, such as for the prediction of response to cardiac resynchronization therapy,¹⁹ it is not yet standardized. Variations of the phase values, namely differences in timing of contraction, using standard deviation (SD) and 95% bandwidth of the phase

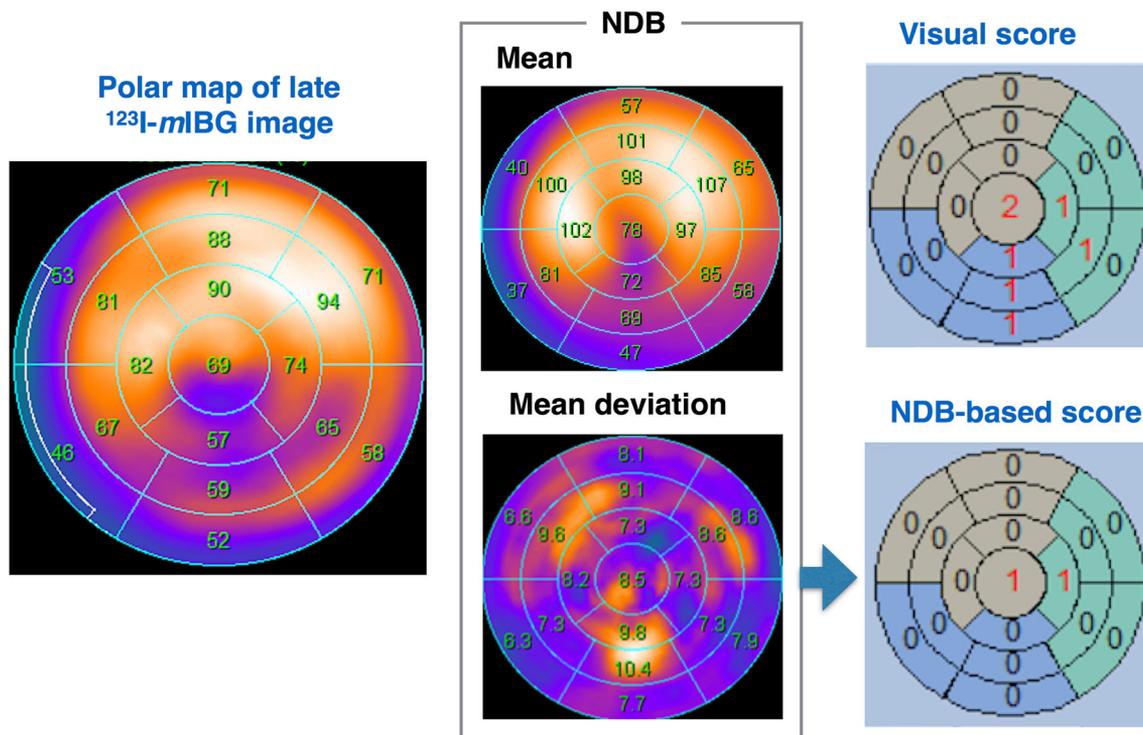


Figure 1. Polar map of late ^{123}I -mIBG and using a normal database (NDB). The mid column shows normal ^{123}I -mIBG database of the Japanese Society of Nuclear Medicine.¹⁴ Due to relatively large mean absolute deviations in the inferior wall, the inferior region was judged as normal, which differed from visual analysis (by KN).

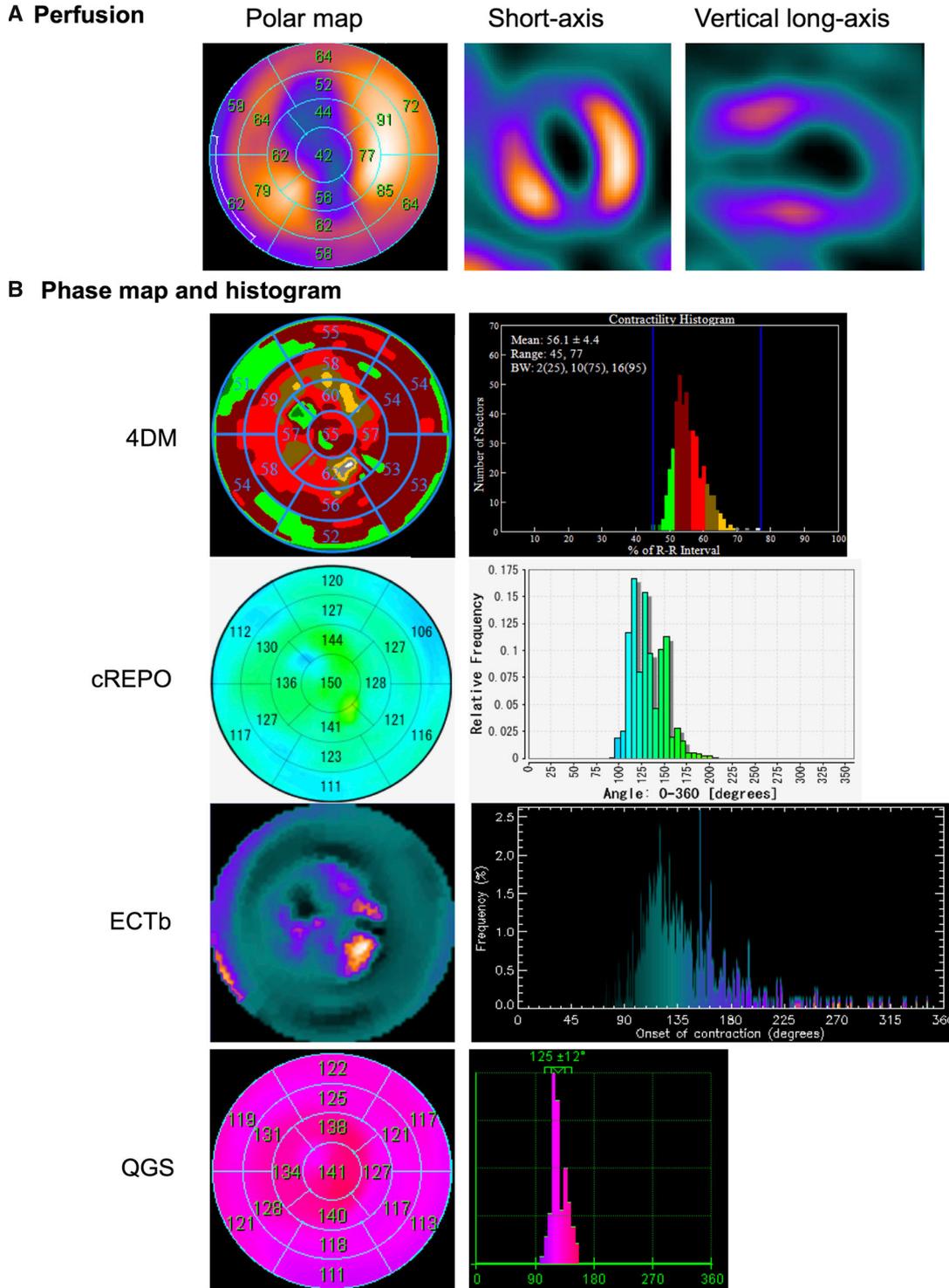


Figure 2. Phase dyssynchrony analysis processed by four software programs in a patient with apical anterior infarction after reperfusion therapy. The top row (A) shows rest ^{99m}Tc-MIBI perfusion images. An area of dyssynchrony is observed near the apex by all phase analysis software programs (B, 2nd to 5th rows), and peaks are split and delayed in all histograms. However, the phase standard deviation of the histogram was 16°, 19°, 41°, and 12° for 4DM, cardioREPO (cREPO), Emory cardiac toolbox (ECTb), and QGS, respectively, and the 95% bandwidth was 58°, 68°, 115°, and 48° degrees, respectively. *The value from 4DM was converted from % of RR interval to degree.

histogram are most often included.²⁰ Time-activity curves in 17 segments may also be used to evaluate regional variations of time to end-systole.²¹ Although phase distribution is usually analyzed using a histogram, peak phase value is influenced by the shape of regional time-activity curves. When the shape is symmetric, the peak value will be around 180° (for example, during tachycardia), and when asymmetric (for example, low heart rate with a long diastolic phase), the peak value will be around 140° - 160° . Therefore, SD and bandwidth are commonly used for the dyssynchrony analysis. However, all these parameters are influenced by the administered tracer dose, body weight, statistical noise, sampling method over the myocardium, filtering, and the number of bins used for the histogram.²²

There are several commercial software programs available, including Emory Cardiac Toolbox (Emory University/Syntermed, Atlanta, GA, USA), QGS (Cedars Sinai Medical Center, Los Angeles, CA, USA), Corridor 4DM (INVIA Medical Imaging Solutions, Ann Arbor, MI, USA), cardioREPO (FUJIFILM RI Pharma, Tokyo, Japan), and Heart Function View (or Heart Risk View-F, Nihon MediPhysics, Tokyo, Japan). It is important to realize that normal values depend on software programs.²¹ Therefore, the characteristics of each software program including normal ranges should be carefully established before use in clinical practice.²³ Figure 2 shows phase maps created in a patient with a myocardial infarction of the apical anterior wall and apex. The images clearly show the variation between the different software programs used.

In order to evaluate regional phase abnormalities, deviance of the mean segmental value of a control segment/region may be analyzed. This kind of analysis may be used to identify the earliest phase in ventricular pacing sites, may help to establish the presence of a pre-excitation syndrome, and to determine the latest phase in a dyssynchronous area.¹⁵

COMPARISON BETWEEN ^{123}I -MIBG AND PHASE PARAMETERS

To integrate parameters of innervation, perfusion, and phase values, various combinations could be selected. When global ^{123}I -mIBG and phase parameters are compared, standardized HMR and “standardized” (but not yet validated) phase values such as SD, bandwidth, and entropy may be used. In typical situations of myocardial infarction, defect score is large, HMR is decreased, ^{123}I -mIBG defect score is high, and phase variations will be large, resulting in some correlation among these parameters.

When regional ^{123}I -mIBG and perfusion are compared, the simplest approach is visual analysis of match

and mismatch. In this issue of the *Journal of Nuclear Cardiology*, Gimelli et al have compared different parameters of perfusion, innervation, and dyssynchrony.¹⁵ LV walls with delayed mechanical activation showed a higher burden of innervation/perfusion mismatch than normally contracting walls. The extent of mismatch was the only predictor of delayed mechanical activation. How this mismatch relates to specific pathophysiology, diagnosis, or prognosis including arrhythmogenicity needs to be further investigated. While the results are intriguing, the dyssynchrony analysis is dependent on the cut-off values used. More importantly, variation between different software algorithms makes extrapolation of the findings troublesome. This only further stresses the necessity for standardized approaches for myocardial perfusion imaging, ^{123}I -mIBG innervation imaging, and assessment of left ventricular dyssynchrony.

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Disclosure

K. Nakajima collaborates with FUJIFILM RI Pharma, Tokyo, Japan to develop cardioREPO and ^{123}I -mIBG software. K. Okuda and H. Verberne have nothing to declare.

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