# Phase analysis of gated myocardial perfusion SPECT and cardiac resynchronization therapy: The good, the bad, and the ugly

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> ''… the little things are infinitely the most important''
> —Arthur Conan Doyle, The Adventures of Sherlock Holmes

Diffusion of a new technology is determined by five characteristics: relative advantage, compatibility, complexity, opportunity for a trial, and observability. Relative advantage is the superiority over current methodologies and is considered one of the most important attributes for a new technology success but for practical use, complexity, opportunity for a trial, and observability are very important.[1] The use of phase analysis from gated-SPECT myocardial perfusion imaging (MPI) for the evaluation of left ventricular mechanical dyssynchrony (LVMD) is completing 15 years since its first description.[2] The method is count-based and is anchored in the fact that regional maximum counts in myocardium are linearly proportional to myocardial wall thickening based on the partial volume effect. Onset of mechanical contraction of the region (phase angle) is derived from the fitting of first harmonic Fourier curve to the discrete regional maximum counts during the cardiac cycle.[2,3] The relative advantage of this method over radionuclide ventriculography is that it is very reproducible,[4] does not increase radiation exposure or adds any significant change in acquisition protocols and, most important, myocardial perfusion scintigraphy has the advantage of showing, in a single test, both ventricular perfusion disturbances and the phase analysis, also allowing the discrimination of scar areas in the LV that are inappropriate for LV lead implantation during cardiac resynchronization therapy (CRT).[5] All the new gated-SPECT software packages now available in the market have validated capabilities for phase analysis in MPI.[6] The clinical results of the technique are so significant that Port wrote in this journal few years ago: ''Cardiac dyssynchrony: We have the tools. It is time to use them.''[7] Why the adoption of phase analysis from gated-SPECT MPI is not universalized in the clinical practice today? First, evidence is still mounting that phase analysis parameters can be used in clinical decision-making.[8,9] Recently, two studies have shown opposite results. Peix et al. in a non-randomized, international, multicenter trial: ''Value of intraventricular synchronism assessment by gated-SPECT MPI in the management of heart failure patients submitted to cardiac resynchronization therapy'' (IAEA VISION-CRT) with 195 consecutive patients was not able to show that baseline dyssynchrony or on-target lead placement was predictive of better clinical response after CRT implantation.[10] However, Zou *et al*. in a prospective, randomized trial with 194 consecutive patients, demonstrated that the use of gated-SPECT imaging to assess LV latest activation improved the rate of on-target LV lead placement, which increased the CRT efficacy.[11]

The second important issue related to the incorporation of phase analysis in clinical practice is the

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**Table 1.** Variables that influence left ventricular mechanical dyssynchrony measurements by gated-SPECT

| Variables | Type of interference | Impact in Phase analysis | Proposed action/correction | References |
|---|---|---|---|---|
| Signal-to-noise ratio (SNR) | Low SNR due to scar in the myocardium | low SNR, the phase analysis algorithm is unable to accurately measure phases due to errors in the first harmonic approximation | If the SNR is very low ($< 12.0$), then the phase analysis parameters should be interpreted with caution | Cheung *et al.*[3] |
| Heart rate variation during acquisition | Gating errors secondary to non-uniform heart rate | inverse exponential relationship between gating-error magnitude and dyssynchrony magnitude | Post hoc correction of affected studies | Ludwig *et al.*[14] |
| Imaging reconstruction method | OSEM method is susceptible to decreased activity of the last ECG bin secondary to heart rate variation | Decreased activity ratio determines a reduction in the phase analysis parameters obtained from OSEM images but no significant effect on phase analysis parameters from TOSEM images | Reconstructing the data with the TOSEM algorithm in face of heart rate variability | Kortelainen *et al.*[15] |
| Software package for phase analysis | Edge detection of the basal LV myocardium differ among software algorithms | Cutoff values of HBW, PSD, and entropy changes depending on the software programs | All software programs may be used reliably for phase analysis | Okuda et al.[6] |
| Software package for phase analysis | Samples used to for creation of reference standards may suffer several influences | Normal values of phase analysis can vary among software programs and can be different even when the same software is used | Proceed with caution when reporting an abnormal result, consider software reference level and understand the impact of comorbidities on phase parameters | Souza Filho et al.[16] |
| Unit of the phase analysis parameters | Milliseconds measures of LV dyssynchrony are heart rate influenced | Heart rate is strongly correlated to HBW and PSD measured in time, but unrelated when measured in degrees | Phase analysis ought to be measured in degrees | Barron et al.[17] |
| Manual versus automatic selection of base parameters | Automatic reconstruction may select base parameters with very low counts | Low-frequency 'noise' located at the base of the ventricle may create substantial variability in LV dyssynchrony | Place the base parameter at the slice, two slices toward the apex from the basal, most slice with perfusion counts in each of the eight gated image data sets | Trimble et al.[4] |
| Type of study (rest versus stress) and valve plane | Low count studies and misplacement of valve plane may create differences in phase analysis parameters | PSD and HBW significantly differ during rest vs stress and proper valve plane alignment rendered smaller values in both PSD and HBW | Avoid low-dose rest studies to consider LV dyssynchrony to CRT indication and manual select valve plane | Ali et al.[12] |

*SNR*, signal-to-noise ratio; *OSEM*, ordered subsets expectation maximization; *TOSEM*, time-modified OSEM; *LV*, left ventricle; *PSD*, phase standard deviation; *HBW*, histogram bandwidth; *CRT*, cardiac resynchronization therapy understanding of the clinical, physiological, and physical variables that can influence the results of the technique and how they can compromise its use in the decision-making. In this issue of the Journal, Ali et al, present the results of a retrospective study that examines the impact of the test type and alignment of valve plane in dyssynchrony parameters.[12] We must congratulate the authors on the extreme detailed approach that they used and the consistency of their results. The mean standard deviation of left ventricular phase (PSD) and phase histogram bandwidth (HBW) during rest were significantly higher compared to that obtained during stress (33.4 ± 17.4° × 20.7 ± 13.5° and 97.7 ± 59.6° × 59.4 ± 45.4°, respectively). The use rest images could be responsible for falsely labeling 30% of the patients as having significant LVMD. The most probable explanation to this finding is that stress gated images are associated higher tracer uptake due to hyperemia and consequently more counts which allows more precise dyssynchrony parameters secondary to reduced statistical noise.[13] Another important observation is that automatic detection of valve plane by algorithm software increased the PDS and HBW significantly compared to the manual base adjustment. The authors pointed out that improper delineation of the valve plane can lead to accounting of the membranous portion of LV septum and part of the atrial myocardium, both having opposite phase from the remainder of the LV, causing imprecise measurements of LV dyssynchrony parameters.

The results of the study of Ali et al. have immediate clinical implications. First, high-quality studies with good myocardial counts should be preferentially used for the evaluation of mechanical dyssynchrony to reduce inaccuracies. Second, the comparison of LV dyssynchrony parameters ought to use the same protocol settings (both stress or rest gated and similar tracer dose) to assure reproducibility. And, finally, the adequate review of the degree of valve plane exclusion and angular alignment is requested to minimize this potential error. The assessment of left ventricular mechanical dyssynchrony using SPECT is critically influenced for some variables (Table 1) that must be known by physicians reporting their results and for the use in the clinical decision-making: signal-to-noise ratio[3]; heart rate variation during acquisition[14]; method of imaging reconstruction[15]; differences in software packages and in their validation[6,16]; unit used for dyssynchrony measurement[17]; manual versus automatic selection of base slice.[4] Ali et al added new evidence demonstrating that the type of study (rest vs stress) and valve plane are also important in the LV dyssynchrony gated-SPECT results.

Analyzing the recent data and clinical evidence about CRT and phase analysis in gated-SPECT MPI we can perceive the upsides (the good), the downsides (the bad), and the parts that could have been done better, but were not (the ugly). The good: LV dyssynchrony assessed with phase analysis is a robust and mature clinical tool able to generate reproducible and meaningful clinical data that may support and guide clinical decision-making.[18] The knowledge about the best practices for accurate results is mandatory in using this method. The bad: in spite of more than a decade of clinical research phase analysis is not routinely used in clinical practice as no other reliable imaging assessment of mechanical dyssynchrony is used as prerequisite for the selection of candidates for CRT.[19] The ugly: despite of more than two decades of clinical use, several studies continuously show that 30% of patients remain as non-responders to the CRT.[10] This gap represents a very significant unmet clinical need and must be carefully addressed in future studies in order to reduce the costs, the morbidity, the mortality, and futility of using an expensive technology, like CRT, in patients that will not derive any benefit. In this context, machine learning can bring valuable contributions. As an example, it is worth highlighting the work of Tokodi *et al*. who were successful using Random Forests in predicting 1-, 2-, 3-, 4-, and 5-year all-cause mortality from pre-implant variables of patients submitted to CRT.[20]

## Disclosure

*Claudio Tinoco Mesquita received travel grant and participated in advisory board for Pfizer in 2019. Principal Investigator for the ongoing Apollo B trial from Alnylam. Received fees for educational presentations for Bayer in 2017. Erito Marques de Souza Filho has no conflict of interest.*

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