Applicability of Myocardial Perfusion Scintigraphy in the Evaluation of Cardiac Synchronization

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Abstract

To systematically assess the literature on the applicability of myocardial perfusion scintigraphy with phase analysis in the investigation of cardiac dyssynchrony and in the selection of patients for cardiac resynchronization therapy (CRT), manuscripts published on the PubMed database over the past five years have been reviewed. The following MeSH terms were used: heart failure, left ventricular, dyssynchrony, gated-spect, phase analysis and resynchronization therapy. Altogether, 99 manuscripts were included for discussion. Speckle-tracking echocardiography is still widely used in the evaluation of dyssynchrony, but the advent of myocardial perfusion scintigraphy with the phase analysis technique has been gaining ground, as besides being operator-independent, it can evaluate myocardial viability in the same test. Its use became more widespread in patients with left bundle branch block, with recommendation of CRT. Phase analysis also allows evaluating, in a highly reproducible way, the last ventricular segment to contract, hence allowing the best positioning of the CRT electrode. Knowing that the presence, location and extent of fibrosis in the left ventricle, associated with dyssynchrony are determinants of response to resynchronization therapy, gated-SPECT can provide this information in a single test and in a reproducible and accurate way. Phase histogram offers several parameters that provide greater sensitivity and specificity to the method. It seems that the technique is able to add value both in the selection and in the evaluation of response of patients eligible to CRT. Further studies are being conducted to demonstrate its clinical applicability.

Introduction

Myocardial perfusion scintigraphy is a well-established technique for the investigation of coronary artery disease having applicability in the detection of myocardial ischemia, evaluation of therapeutic response, risk stratification, measurement of the infarcted area and evaluation of myocardial viability.[1] The introduction of gated SPECT as a tool for assessing cardiac contractile function added more diagnostic accuracy by allowing to obtain further analysis data such as left ventricular motility and muscular thickening, as well as quantification of ejection fraction and ventricular volumes. More recently, diastolic function has also been assessed by gated SPECT quite successfully.[2]

Ventricular synchronism is defined as a coordinated electrical activation of the heart which leads to harmonic and synergistic contraction.[3] The loss of ventricular synchrony started to get increasing attention in patients with heart failure (HF) with the development of cardiac resynchronization therapy (CRT), where an implantable device makes ventricular contraction more homogeneous. This treatment is now established as a reducer of mortality and morbidity in patients with advanced HF[4] and is class I indication in major international and national guidelines on the treatment of advanced heart failure.[5]

Electrocardiogram has been used as a method for detecting patients with dyssynchrony due to the correlation of QRS complex widening (electric dyssynchrony) with mechanical dyssynchrony. Although echocardiography is the most widely used imaging method to evaluate mechanical dyssynchrony, this evaluation needs to be improved, as Chung et al.[6] demonstrated the great variability of the technique and low predictive power in the selection of patients for CRT.[6] There are other methods to assess left ventricular (LV) mechanical dyssynchrony, such as magnetic resonance imaging and radionuclide ventriculography.[7]

In the last decade, technological advances made it possible to study the parameters of intraventricular dyssynchrony using gated SPECT phase analysis, expanding the use of the method for the evaluation of patients with heart failure and allowing to understand its pathophysiology.[1] Although tissue Doppler echocardiography is an easy technique to investigate dyssynchrony, the main advantage of gated SPECT is its high reproducibility intra- and interobserver[1] and it does not require changes in the technique employed in myocardial perfusion. Myocardial perfusion scintigraphy has been playing a new role in the evaluation of patients with heart failure eligible to resynchronization therapy, as it allows not only the assessment of myocardial viability in the area where the resynchronization electrode will be deployed, but it also evaluates dyssynchrony through the phase analysis technique.[1]

The objective of this review is to systematically review the literature on the applicability of myocardial perfusion scintigraphy with phase analysis in the investigation of cardiac dyssynchrony and selection of patients for CRT.

Keywords

Heart Failure; Myocardial/radionuclide imaging; Myocardial Perfusion Imaging; Cardiac Resynchronization Therapy; Echocardiography, Doppler.

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Methodology

A literature review was conducted on the articles published on the PubMed database. The following MeSH terms were used: heart failure, left ventricular, dyssynchrony, gated-spect, phase analysis and resynchronization therapy. Through the evaluation of abstracts, any articles that did not address the subject (Figure 1) have been excluded.

Results

The combined search of all terms resulted in 176 articles on searches conducted until August 4, 2016. From 2006 to 2016, 99 articles were selected according to the analysis of correlation with the subject studied. About 65% of the articles are original and the other ones are review articles. In view of the above, from now on, we will analyze the evidence of the use of myocardial perfusion scintigraphy in the evaluation of ventricular dyssynchrony in patients with heart failure.

Imaging techniques for synchrony analysis

Left ventricular dyssynchrony has been evaluated by various forms of cardiovascular imaging, including: tissue Doppler echocardiography or strain rate;[8] magnetic resonance imaging;[9] or nuclear imaging by radionuclide ventriculography or single-photon emission computed tomography.[10] Phase analysis of left ventricular contraction was initially successfully analyzed by radionuclide ventriculography, but with the addition of gated SPECT phase analysis and its subsequent validation, this technique has proven to have a greater potential in determining left ventricular mechanical dyssynchrony. Gated SPECT allows to assess left ventricular dyssynchrony using Fourier harmonic functions to estimate wall thickness over the cardiac cycle and determine the regional start time of ventricular mechanical contraction, obtaining a three-dimensional quantitative analysis of the entire left ventricle.

Tissue Doppler echocardiography allows to assess segmental contraction rate and to compare different segmental times and determine ventricular dyssynchrony,[8], and specifically the presence of left ventricular dyssynchrony of 65 ms or more and was able to predict the response to CRT.[8] The most important study of the tissue Doppler technique was the multicenter, prospective, non-randomized Prospect study with 498 patients that met the criteria currently accepted for the indication of resynchronization therapy. The Prospect study was intended to determine which echocardiographic parameters were able to predict response to treatment with CRT. Clinical improvement assessed using a score and left ventricular reverse remodeling (reduction of LV end-systolic volume by ≥ 15%) in 6 months was considered response to CRT. The echocardiographic predictive ability ranged

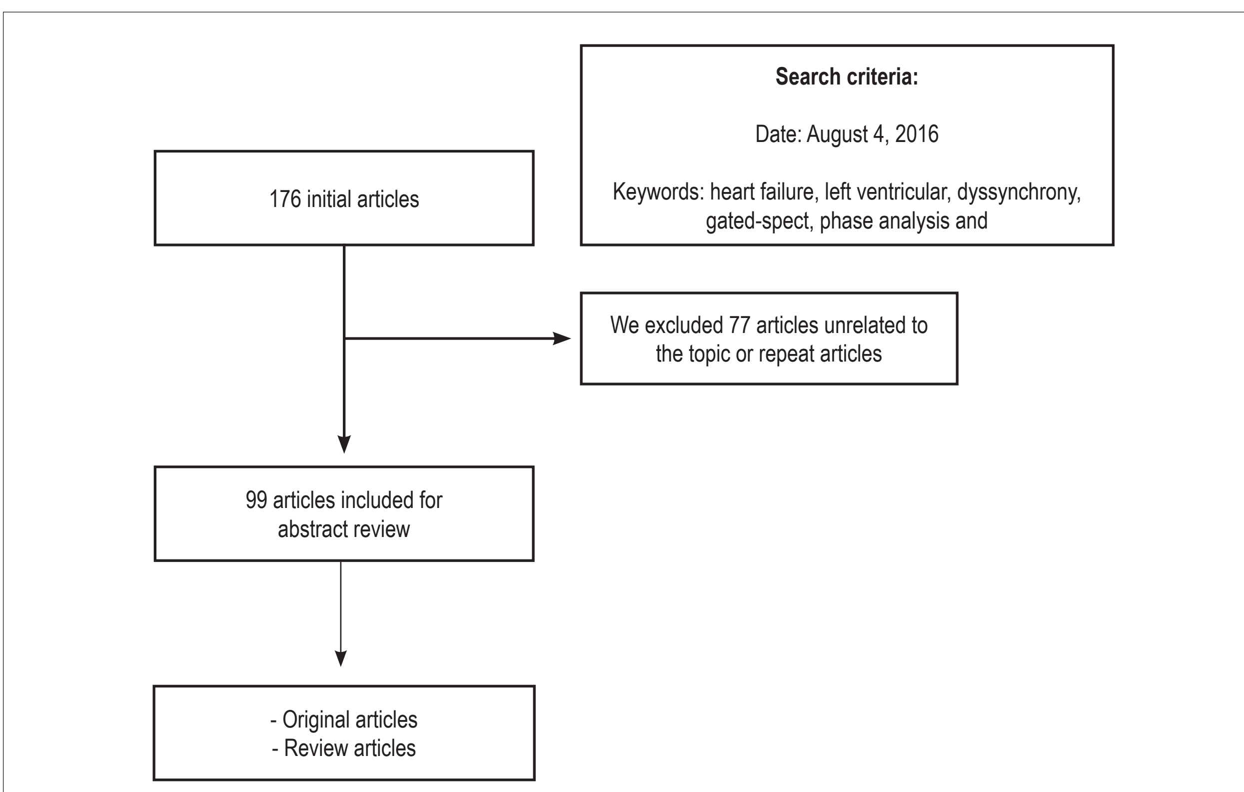

Figure 1 – *Flowchart showing the number of initial articles found on the databases according to the search criteria described above, on August 4, 2016, and the final number of articles after exclusion, for being repeat articles or unrelated to the topic.*

from a sensitivity of 6% to 74% and from a specificity of 35% to 91%.[6]

Analyzing this study from a critical perspective, Belém and Salgado3 proposed the development of new imaging technologies to assess dyssynchrony.[3] One is the Speckle Tracking technique,[11] involving the evaluation of regional and global myocardial strain, which can be measured by speckle tracking using two-dimensional echocardiography (2D - STE) (Figure 2). The strain obtained by speckle tracking is superior to that obtained with the tissue Doppler, mainly due to a smaller intra and interobserver variability.[11] Dohi et al.[12] demonstrated that the difference in time to reach the peak radial strain between the septum and the LV posterior wall ≥ 130 ms is a predictor of LVEF improvement after CRT.[12] The randomized multi-center Target study was proof of this concept,[13] as the use of speckle tracking to identify patients with dyssynchrony and the site of the last ventricular mechanical activation (which is not the fibrotic area) has provided greater improvement probability after CRT therapy compared to electrode deployment without using speckle tracking as a guide.

Cardiac magnetic resonance imaging is an imaging method that does not use radiation and can accurately quantify left ventricular contraction and its temporal course. Speckle tracking can also be used to evaluate dyssynchrony. Its main limitations are higher cost, reduced availability and it is difficult to use after the deployment of metal devices.[8]

Radionuclide ventriculography

Radionuclide ventriculography, also known as MUGA scan, uses Technetium-99m labeled red blood cells to provide an accurate and reproducible left ventricular ejection fraction. As a prerequisite, acquisition is synchronized with electrocardiography to correlate the ventricular activation time with moments of dynamic acquisition. This process is called gated acquisition (acquisition of synchronized images). The scan takes about 30 minutes, where both a qualitative and a quantitative evaluation is conducted. By selecting an area of interest, left ventricular ejection fraction, regional ejection fraction and many other parameters are obtained, including parametric images.[14]

An important advantage of the radionuclide test is assessing the movement of the left ventricular regional wall and regional ejection fraction in addition to the global ejection fraction. Regional values may be abnormal even when the global ejection fraction is still preserved, as in the scenario of a dyskinetic ventricular segment. The analysis of radioactive counts allows to determine a left ventricular activity curve, and from this curve, two important parameters (Figure 3) are obtained in the assessment of left ventricular diastolic function: 1) the peak filling rate (PFR) and 2) the time from the start of diastole to this filling peak (time to PFR).[14] Studies have shown the importance of MUGA in the determination of left ventricular synchronism in patients selected for resynchronization therapy. MUGA was proven

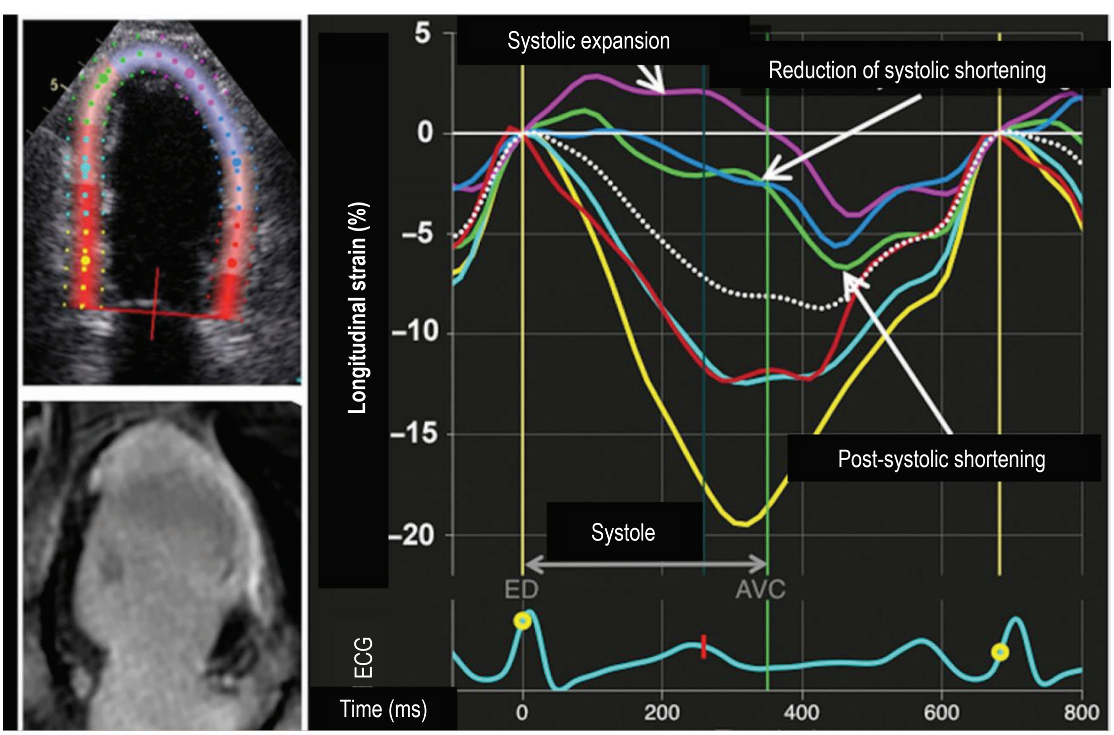

Figure 2 – *Echocardiography with speckle-tracking showing the graphic reproduction of the parietal strain. ECG: electrocardiography; ED: end of diastole; AVC: aortic valve closure.*

efficient in determining left ventricular dyssynchrony and collaborating in decision-making in cardiac resynchronization therapy. Through the phase analysis, MUGA has the potential to determine the last segment to contract, bringing useful information to the resynchronization therapy, such as the electrode site. The amplitude image shows quantitatively the spatial changes of ventricular margins in systole and diastole, representing the motility of ventricular walls. With this, different parameters are obtained, including: left ventricular volume curve, left ventricular ejection fraction, right ventricular ejection fraction, left and right ventricular emptying, and left ventricular synchronicity.

Phase analysis by GATED SPECT

Phase analysis for the assessment of LV dyssynchrony was incorporated by myocardial perfusion scintigraphy with gated SPECT.[15] This technique can have a clinically significant impact, as it allows gated SPECT — the nuclear imaging procedure mostly used for the diagnosis of CAD — can also evaluate cardiac dyssynchrony.[16] Despite the inconvenience of exposing the patient to radiation, as it requires intravenous administration of radioactive material, as most patients with HF at some point undergoes a gated SPECT scan during diagnostic investigation, patients can benefit from the additional phase analysis to measure LV dyssynchrony in the same test.

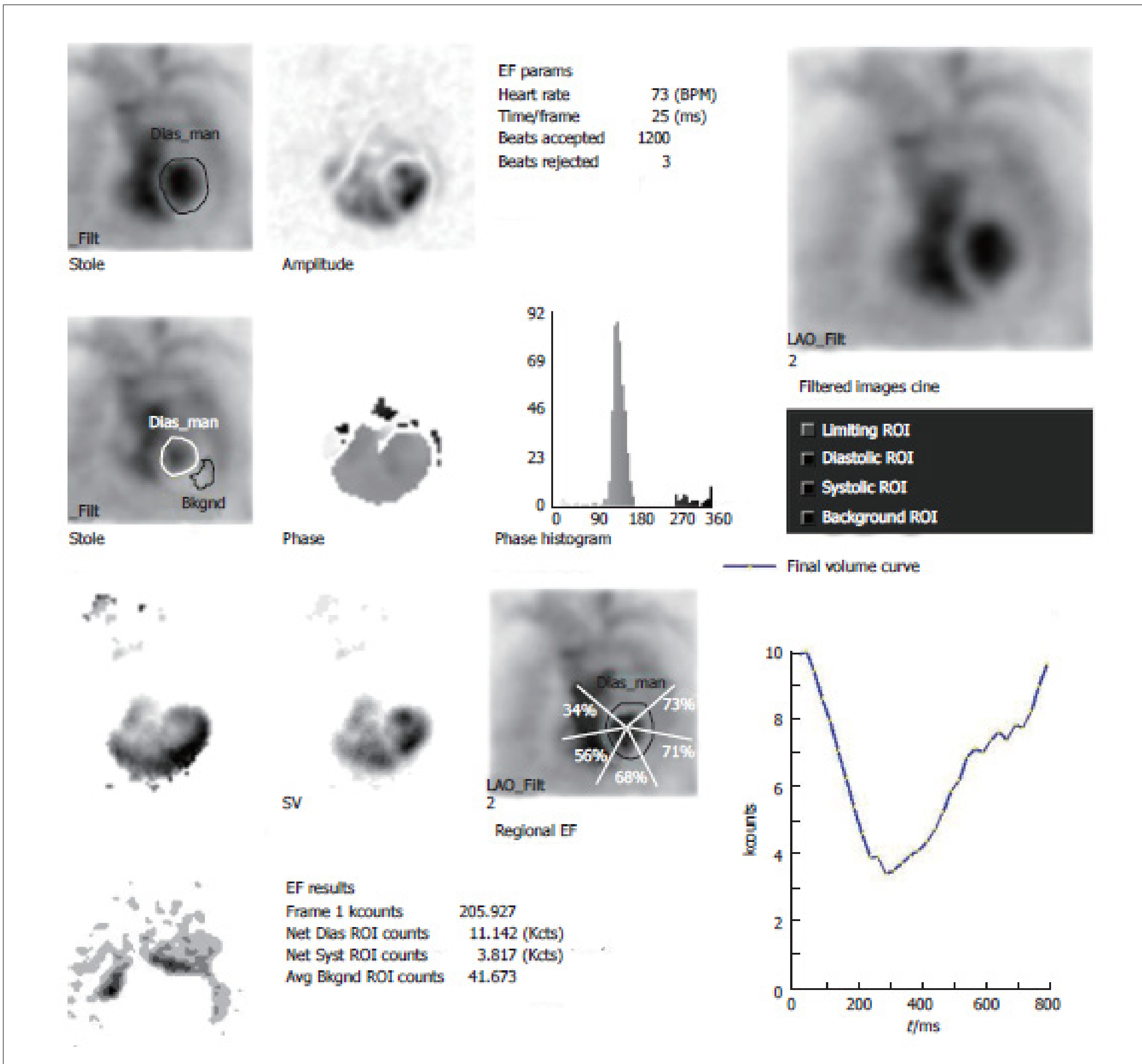

Figure 3 – *Normal radionuclide ventriculography with 66% ejection fraction. The phase image shows a synchronous contraction of the left ventricle (LV) with a narrow bandwidth in the phase histogram. The LV phases are in synchrony with those of the right ventricle and in dyssynchrony with the atrial phases. The amplitude images show the maximum count variation in the LV lateral wall suggesting maximal contraction by the side wall. The LV time-activity curve is normal. AOI: area of interest; EF: ejection fraction; LAO: left anterior oblique; SV: stroke volume; Syst: systolic; Days: diastolic; Avg Bkgnd: average background count. Adapted from D. Mitra and Basu (2012).[14]*

The basic principle that allows Fourier phase analysis in myocardial perfusion scintigraphy is due to the partial volume effect, where the physical properties of the nuclear test will generate a possibility of identifying with extreme precision the exact moment at which the ventricular wall begins to contract. This moment is identified by an increase in regional count/pixel rates. This technique that is used in cardiac perfusion images by gated SPECT is the same employed to study LV dyssynchrony in radionuclide ventriculography. However, instead of focusing on the radioactive counts of radiolabelled blood, the heart muscle is analyzed. It is an automatic technique that correlates well with echocardiographic techniques, predicting response to CRT in patients with HF.[17]

The phase analysis technique has the ability to transform the 4D image (three spatial plans + time) into 2D paired images. Therefore, we have a photograph of cardiac contractility (amplitude) and a photograph of contraction sequence (phase). Each cardiac imaging pixel has its own cycle, having an amplitude and its characteristic temporal relationship (phase) related to the R wave (Figure 4). The amplitude is related to the maximum count variation for each pixel in the cardiac cycle. The phase is related to the time between two R waves for each pixel. More recently, studies have shown that gated SPECT with phase analysis has sufficient spatial and temporal resolution to examine specific LV mechanical activation sites to optimize the CRT electrode deployment in patients with HF.[10]

Left ventricular dyssynchrony assessed by gated PECT shows a correlation with dyssynchrony assessed by tissue Doppler. The histogram with bandwidth and the phase analysis showed better results in the evaluation of left ventricular dyssynchrony.[8] Findings correlated as for the assessment of left ventricular dyssynchrony,[1] as well as good accuracy for the prediction of response to CRT using the evaluation of bandwidth and phase histogram were found.[18]

Phase analysis by gated SPECT in patients with left bundle branch block

Left bundle branch block (LBBB) has a low prevalence in the general population, occurring in 0.05 to 2.4%. This condition increases with age and is more common in men, but may also occur in patients without any structural heart diseases. However, in patients with heart failure, left bundle branch block negatively influences myocardial contractile dynamics. The simultaneous evaluation of perfusion and ventricular function by gated SPECT allows greater diagnostic accuracy and is often the non-invasive method of choice for evaluating synchrony in this group of patients.

In patients with LBBB, there is a significant change in the left ventricular activation sequence: the interventricular septum has an early contraction in the cardiac cycle followed by a later activation of the side wall, producing a broad contractile heterogeneity which, in the long run, determines a left ventricular remodeling (increased end-systolic volume) and reduced intraventricular pressure, adversely affecting patients with heart failure.[19]

In addition to the intraventricular dyssynchrony, interventricular (mechanical) asynchrony is also noted in the presence of LBBB. There is contraction asynchrony between the ventricles, with the left ventricle (LV) contracting about 85 ms after the onset of right ventricular contraction (RV), a much longer delay compared to the physiological delay, in the absence of block; decreased LV diastolic time and abnormal septal motility, as depolarization in this area only occurs at the end of LV systole.[20]

Most patients with an ejection fraction of 35% or less, with advanced symptoms of heart failure and prolonged QRS, present electrical dyssynchrony and left ventricular mechanical dyssynchrony. However, studies have shown that the presence of perfusion abnormalities in patients with

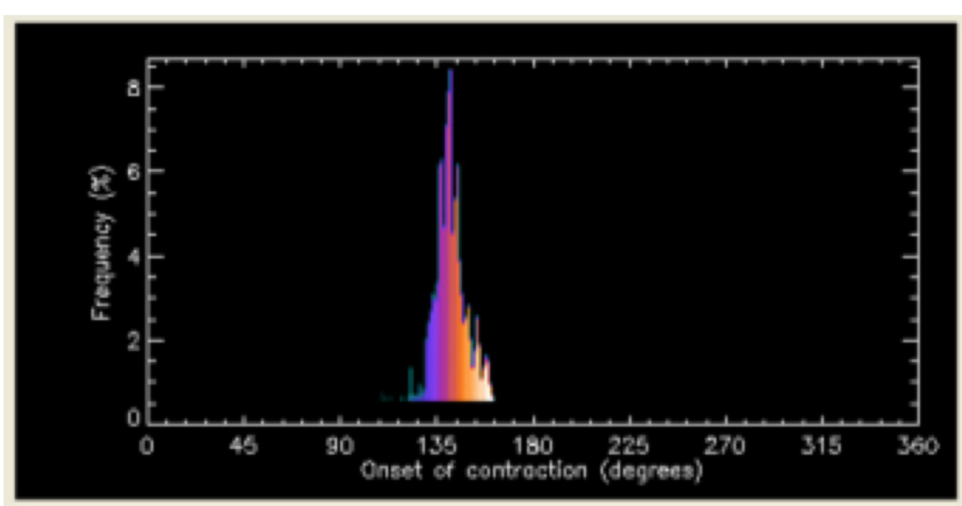

Figure 4 – *Normal phase histogram. On axis X, representation of a cardiac cycle time (RR interval) in degrees. On axis Y, myocardial percentage in the beginning of mechanical contraction in a specific phase of the cardiac cycle. The color map has 256 levels, where black corresponds to the minimum and white corresponds to the maximum.*

left ventricular dysfunction also play a role in the production of myocardial dyssynchrony,[21] even in those with normal electrocardiography scans. Myocardial perfusion scintigraphy has the advantage of showing, in a single test, both ventricular perfusion disturbances and the phase analysis. Patients with larger fibrotic areas tend to have higher dyssynchrony.[22] The presence of ventricular dyssynchrony as assessed by gated SPECT is an independent risk factor for increased mortality in patients with coronary artery disease and left ventricular dysfunction who have not undergone resynchronization therapy (Figure 5). [22]

Use of gated SPECT with phase analysis for cardiac resynchronization therapy

CRT has recently emerged as a therapeutic strategy for a subgroup of patients with advanced heart failure (NYHA functional class III and IV), with severe systolic dysfunction (ejection fraction <35%) and wide QRS (> 120ms). Although these are the clinical criteria of CRT indication, initial studies have shown that 20-30% of patients do not respond to treatment, and may even present unfavorable outcomes. Widened QRS itself indicates an electric left ventricular dyssynchrony. However, this is not always associated with mechanical dyssynchrony (around 30% of patients with QRS > 120ms). The presence of mechanical dyssynchrony is not yet part of the criteria for the indication of resynchronization therapy. Therefore, it is of great value to study ventricular synchrony before CRT in order to estimate its response, since it is a costly procedure.

The phase analysis of myocardial perfusion scintigraphy uses two main variables for the prediction of response to CRT. The 135° bandwidth cutoff value (histogram bandwidth — HBW) can predict clinical response with 70% sensitivity and specificity, while the 43° cutoff value for standard deviation (phase SD) has a 74% sensitivity and specificity for this prediction.[1,22] The presence, location and extension of myocardial fibrosis of a previous infarction also proved to influence the response to CRT. Adelstein et al.[23] demonstrated that the presence of myocardial fibrosis adjacent to the left ventricular electrode position was negatively correlated with increased left ventricular ejection fraction (LVEF) 6 months after CRT. Similarly, Bleeker et al.[24] demonstrated that patients with transmural infarction adjacent to the left ventricular electrode (most commonly in the posterolateral region) have a lower response to CRT compared to patients without fibrosis.[24] The presence of myocardial viability demonstrated by positron-emission tomography (PET) using fluorine-18 fluorodeoxyglucose, myocardial perfusion scintigraphy with thallium-201 or technetium-99m has shown to be predictive of response in patients with indication for cardiac resynchronization therapy.[25,26]

The phase analysis allows to evaluate the dyssynchrony parameters and, in a highly reproducible manner, the last ventricular segment to contract. Patients with left bundle branch block tend to have early onset of LV mechanical contraction in the septal wall cardiac cycle, and later in other myocardial areas due to a slowing spread of the nerve impulse by the conduction system, causing delayed activation, with the last contraction site most commonly located on the inferior or lateral wall.[1] Studies in which the resynchronization electrode was deployed consistently with the last segment to contract by the phase analysis in gated SPECT have shown significant clinical improvement.[1] The parameters that indicate acute change in synchrony after CRT are: (a) presence of baseline dyssynchrony defined by SD and HBW > 2SD above normal limits, (b) presence of fibrosis < 40% of the left ventricle and (c) consistency in the electrode position, defined as left ventricular electrode deployment in the last segment to contract, based on the polar map.[7,27] Previous studies have demonstrated a

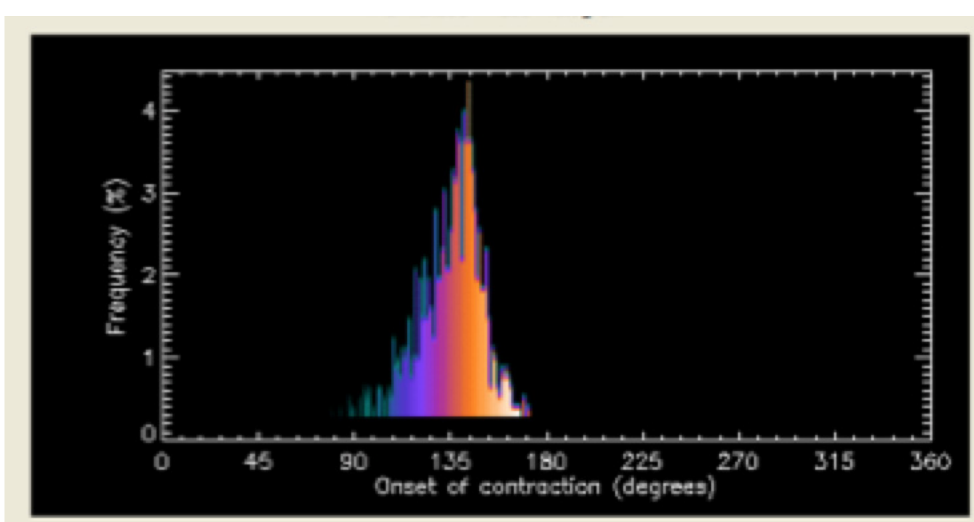

Figure 5 – *Abnormal phase histogram showing an increased bandwidth suggesting delayed onset of myocardial contraction, determining a significant left ventricular dyssynchrony.*

low CRT response in patients with > 40% of left ventricular fibrotic area. Improvement in ventricular synchrony occurs when all of the above criteria have been met.

The International Atomic Energy Agency has recently published a guide on the use of nuclear medicine in patients with heart failure,[25] and the use of gated SPECT was specifically emphasized with a 135º cutoff value for bandwidth (BW) and 43º for standard deviation (SD) for the patient to be considered a potential responder (which occurs in 71% of the cases). The document also emphasizes that only the presence of dyssynchrony by gated SPECT is not enough to consider the patient a good responder. The patient needs to have a fibrotic area smaller than 50% of the left ventricle and the pacing electrode must be deployed — if technically possible — in the last viable contractile segment.[25] Figure 6 shows a case of our series in which the patient has severe intraventricular dyssynchrony and after resynchronization electrode is deployed, there is significant improvement of these parameters, of the functional capacity and left ventricular function.

By knowing that the presence, location and extension of fibrosis in the left ventricle associated with dyssynchrony are determinants of the response to resynchronization therapy, gated SPECT can provide this information in a single scan and in a reproducible and accurate way.

Use of gated SPECT with phase analysis in the evaluation of dyssynchrony in hypertensive patients and patients with chronic kidney disease

Systemic arterial hypertension (SAH) is a multisystem disease and one of the main risk factors for left ventricular hypertrophy (LVH) and heart failure. A study conducted

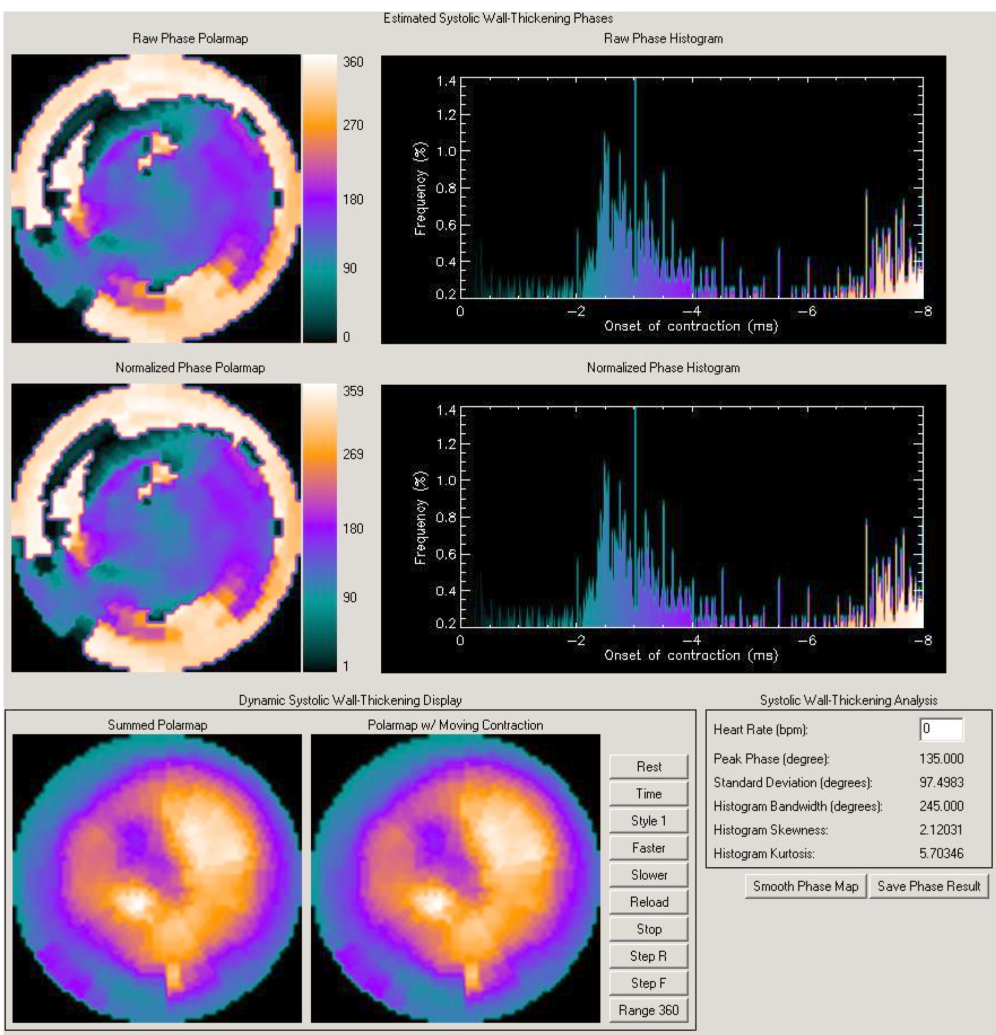

Figure 6A – *Scintigraphy with gated SPECT with phase analysis in patients with dilated cardiomyopathy and left bundle branch block. There was an increase in bandwidth and standard deviation, characterizing sharp dyssynchrony (BW 245º and SD 97º).*

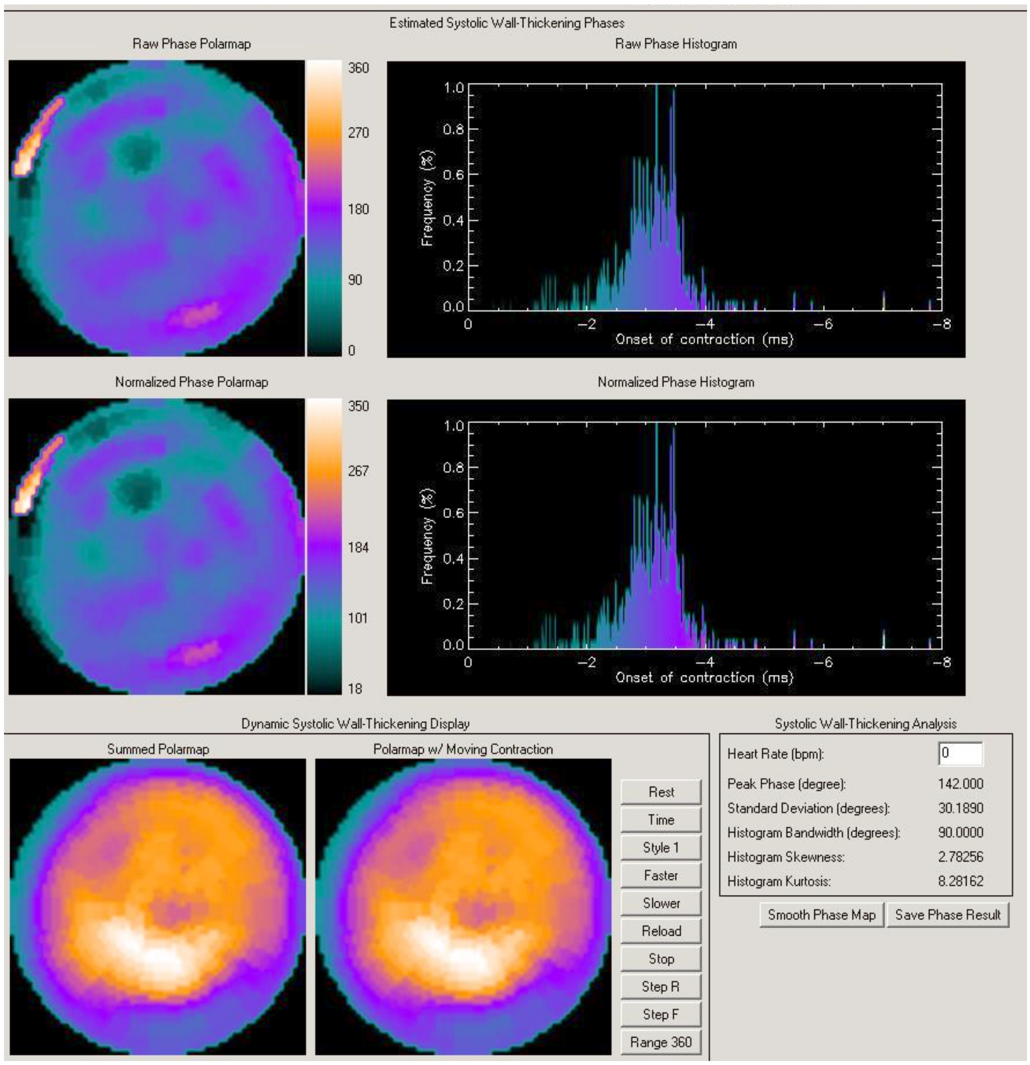

Figure 6B – *Gated SPECT scintigraphy of the same patient as in Figure 6A after resynchronization electrode deployment demonstrating improved dyssynchrony by reducing the BW and SD values (90º and 30º, respectively).*

by Ozdemir evaluated 196 normal myocardial perfusion scintigraphy scans of patients with and without SAH and showed statistically significant differences between the groups. The SAH group showed higher standard deviations (SD) and histogram bandwidth (HBW) ($p < 0.005$ and $p < 0.001$, respectively)[28]. Besides, by analyzing the subgroup of patients with SAH and diabetes mellitus (DM), we observed higher levels of SD and HBW than in the SAH subgroup only.

Another interesting area of study is the presence of intraventricular dyssynchrony in patients with chronic kidney disease (CKD). The presence of left ventricular hypertrophy, retention of solutes not eliminated by the urine and neuro-humoral mechanism activation seems to determine dyssynchrony in patients with CKD and this seems to be reversed by increased dialysis, as assessed by gated SPECT in a recent publication.[29]

Conclusion

The use of gated SPECT with phase analysis has become a powerful tool in the analysis of ventricular synchronism, especially in patients with heart failure. It seems that the technique is able to add value both in the selection and evaluation of response of patients eligible to cardiac resynchronization therapy. Larger studies, underway, are needed to explore the relative effectiveness of the scintigraphy scan in the selection of patients for cardiac resynchronization.

Authors' contributions

Research creation and design: Reis CCW, Nascimento EA, Dias FBR, Ribeiro ML, Wanderley APB, Batista LA, Nunes THP, Mesquita CT; Data acquisition: Reis CCW, Nascimento EA, Dias FBR, Ribeiro ML, Wanderley APB, Batista LA, Nunes THP, Mesquita CT; Data analysis and interpretation: Reis CCW, Nascimento EA, Dias FBR, Ribeiro ML, Wanderley APB, Batista LA, Nunes THP, Mesquita CT; Statistical analysis: Reis CCW, Nascimento EA, Dias FBR, Ribeiro ML, Wanderley APB, Batista LA, Nunes THP, Mesquita CT; Manuscript drafting: Reis CCW, Nascimento EA, Dias FBR, Ribeiro ML, Wanderley APB, Batista LA, Nunes THP, Mesquita CT; Critical revision of the manuscript as for important intellectual content: Reis CCW, Nascimento EA, Dias FBR, Ribeiro ML, Wanderley APB, Batista LA, Nunes THP, Mesquita CT.

Potential Conflicts of Interest

There are no relevant conflicts of interest.

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Academic Association

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