Imaging cardiac dyssynchrony

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Abstract Myocardial perfusion imaging (MPI) has become a preeminent molecular imaging technique to assess ventricular mechanical dyssynchrony. In this article, we outline the motivation for the assessment of dyssynchrony, briefly review the application of echocardiographic and other non-nuclear imaging techniques for that purpose, and detail the technical aspects and validation of phase analysis by gated single-photon computed emission tomography and positron emission tomography. We also briefly outline differences between phase analysis of MPI and radionuclide angiography. Clinical applications are then reviewed, focusing on cardiac resynchronization therapy.

Keywords Dyssynchrony · Cardiac resynchronization therapy · Phase analysis · Myocardial perfusion imaging

Introduction

Systolic mechanical dyssynchrony of the left ventricle (LV) is commonly defined as the lack, to a varying degree, of synchronous contraction of the myocardium. Impaired systolic function results from dyssynchrony: as regions of

the myocardium contract at different times instead of simultaneously, hemodynamics are adversely affected and a decrease in left ventricular ejection fraction (LVEF) is typically observed. Although it has been shown that electrical dyssynchrony (commonly measured as the duration of the QRS complex) and mechanical dyssynchrony are not equivalent [1], the 2008 American Heart Association (AHA) and American College of Cardiology (ACC) cardiac resynchronization therapy (CRT) eligibility guidelines only mandated sinus rhythm with prolonged QRS duration ($QRS \geq 120$ ms) in addition to advanced heart failure [New York Heart Association (NYHA) functional class III–IV] and depressed systolic LV function ($LVEF \leq 35\%$) [2]. CRT is a widely accepted adjunctive to optimal medical therapy for heart failure (HF) patients, and long-term response rates of approximately 70 % have been reported with the above selection criteria [3, 4], where response is defined using clinical or echocardiographic parameters. Consequently, emphasis has been placed on evaluating the prognostic value of mechanical dyssynchrony in HF patients as well as optimizing patient selection for CRT, and it has been suggested that pre-existing mechanical LV dyssynchrony may contribute to positive response to CRT [4, 5]. The AHA/ACC guidelines were updated in 2012 [6] with new recommendations for patients in NYHA class II and LVEF-based rather than class-based benefit. The recently published European Society of Cardiology (ESC) guidelines [7] differ only slightly from the AHA/ACC guidelines and recommend CRT in patients in NYHA functional class II, III, or ambulatory IV, with left bundle branch block (LBBB), and QRS duration ≥ 120 ms. In the absence of LBBB, the recommendation class is lowered from I to IIa ($QRS > 150$ ms) or IIb ($QRS 120$ – 150 ms), reflecting the decreased consensus on the usefulness of the procedure. It is worth noting that these guidelines

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specifically state that LV mechanical dyssynchrony assessed using imaging techniques should not be used for CRT patient selection.

Echocardiographic assessment of dyssynchrony

Early assessment of dyssynchrony by echocardiography was based on calculations derived from the location of the endocardial surfaces [8]. The advent of pulsed Doppler tissue imaging [or tissue Doppler imaging (TDI)] later provided direct measurement of wall velocity [9], yielding a technique to compare the timing of wall motion across the myocardium. More recently, dyssynchrony assessment based on speckle tracking, both in 2D and 3D, was developed to increase robustness of the technique by eliminating the dependence of the measurements on the angle of incidence, with the 3D approach also providing insight into LV rotational mechanics [10, 11].

Echocardiography, and TDI in particular, had long been the preferred technique for the measurement of dyssynchrony. The PROSPECT trial [12], however, demonstrated that echocardiographically derived dyssynchrony assessment for the purpose of selecting patients for CRT has limited value, with high inter- and intra-observer variability of the measurements suggested as the likely cause. More recently, while the NARROW-CRT trial [13] concluded that patients might benefit from CRT in the presence of marked mechanical dyssynchrony assessed by echocardiography ($n = 120$), the larger Echocardiography Guided Cardiac Resynchronization Therapy multi-center trial (EchoCRT, $n = 1,679$) attempting to evaluate the effects of CRT on mortality and morbidity of HF patients with echocardiographic evidence of ventricular dyssynchrony was halted due to futility [14].

Magnetic resonance imaging and X-ray computed tomography

Both cardiac magnetic resonance imaging (CMR) and cardiac X-ray computed tomography (CCT) have been used to assess LV dyssynchrony [15, 16]. Approaches utilizing these modalities have thus far failed to gain widespread acceptance due to the lack of software automation, which leads to higher complexity of the analysis and increased operator bias; they do, however, have the potential for increased clinical use by providing venous anatomy visualization and scar burden assessment, contingent on the development and validation of adequate tools. In one single-center study, CMR regional vector of circumferential strain variance obtained from tagged

images predicted response to CRT with sensitivity (Ss) of 76 % and specificity (Sp) of 75 % [17].

For a more complete discussion of the evaluation for CRT using non-echocardiographic techniques, we refer the reader to a recent review [18].

Nuclear medicine

The assessment of dyssynchrony has long been a part of nuclear cardiology, since work published in 1980 by Links [19] for planar multi-gated radionuclide ventriculography (MUGA). Compared to MUGA and echocardiography, single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are relative newcomers to the dyssynchrony assessment field. ECG-gated SPECT has long been used for the assessment of myocardial perfusion and function, principally for the purposes of ischemia detection, coronary artery disease (CAD) identification, infarct characterization, viability assessment, and risk stratification. Similarly, PET and gated PET are widely used to assess myocardial perfusion, function, and viability. The first published description of the use of SPECT to assess LV dyssynchrony by Chen in 2005 [20] built both on myocardial perfusion imaging (MPI) SPECT work by Cooke in 1994 [21] and the technique described by Links for MUGA. More recently, dyssynchrony has also been assessed from gated myocardial PET using both ^{82}Rb perfusion imaging [22] and ^{18}F fluorodeoxyglucose (FDG) viability imaging [23]. There is also ongoing research into dyssynchrony assessment using gated blood pool SPECT [24–27] and planar MUGA [28], though there are important differences between these nuclear techniques and phase analysis from MPI, as we shall detail later.

Compared to other techniques, MPI benefits from its wide availability and the fact that quantitative analysis tools are well validated, and commonly used for the assessment of perfusion, function, and viability. Three such commercial software packages, QGS+QPS (Cedars-Sinai, Los Angeles, CA) [29], Emory Cardiac Toolbox (Syntermed, Atlanta, GA) [30], and 4DM (Invia, Ann Arbor, MI) [31] all provide functionality to visually and quantitatively characterize the degree of LV dyssynchrony, in addition to quantifying more traditional function parameters such as LV end-diastolic and end-systolic volumes, ejection fraction, and regional wall motion and wall thickening. High automation of the software offers superior reproducibility over software for other modalities by eliminating or reducing operator input [32], which also decreases study-processing time. At least one other MPI-based dyssynchrony software (cardioGRAF) is also being developed [33]. This tool evaluates endocardial wall motion dyssynchrony and has seen limited validation.

Finally, myocardial sympathetic innervation imaging using ^{123}I -metaiodobenzylguanidine (MIBG) or ^{11}C -epinephrine may offer additional insight. While the prognostic value of the MIBG heart/mediastinum uptake ratio has been shown [34], and it is generally accepted that myocardial innervation improves in responders to CRT [35], the predictive value of baseline innervation for response remains to be demonstrated.

Technical aspects

The technical description we provide applies to the count-based approach used by Cedars-Sinai's QGS. Emory's SyncTool operates in a similar fashion, though we will indicate differences as appropriate. We refer the reader to another manuscript for a description of dyssynchrony calculations performed by Invia's 4DM [36], which includes thickening and wall motion dyssynchrony calculations.

One of the major advantages of nuclear techniques is that they do not require data acquisition protocol changes for the purpose of being able to perform phase analysis, thus allowing the retrospective processing of studies. SPECT calculations are based on systolic myocardial count increases caused by the partial volume effect [37]—for PET calculations, filtering and isotope-specific processing can be applied to take advantage of the same principles. Count values are extracted for each time interval over the entire myocardium, yielding a unidimensional array for each spatial sampling point. This array represents a time-varying, periodic function from which the first Fourier harmonic (FFH) is determined, the phase angle of which forms the basis of all synchrony measurements (Fig. 1).

The phase and amplitude information can be displayed in polar map fashion either separately, using traditional color mapping, or in combined mode, where color is used to indicate timing (phase angle) and brightness is used to denote the amplitude of variation. The frequency distribution of FFH phase angles is also tabulated in global and regional histograms (Fig. 2), using amplitude information to eliminate phase measurements for which the corresponding amplitude was deemed too low to yield accurate measurements, as the FFH phase angle is essentially ill-defined for a signal that exhibits low temporal variations [28]. Histogram metrics are then computed as global and regional measures of dyssynchrony: for global histograms only variability measures are computed, while for regional histograms only means are computed and compared across regions. Variability measures include histogram standard deviation (SD, calculated in the usual fashion for a frequency distribution), bandwidth (BW, the smallest angle range that contains 95 % of the histogram samples), and entropy (E , a variability measure derived from information theory and described in [38], not provided in SyncTool). Because QGS uses filtering and 6° bins to improve histogram noise characteristics while SyncTool uses 1° bins and different filter parameters, metrics obtained by both algorithms differ significantly and are not interchangeable.

The use of a single harmonic to describe count variations implies that one angle describes the timing of contraction, whether one chooses the zero-crossing of the harmonic as SyncTool does, or the peak of the harmonic as QGS does (consequently, these two approaches yield reference angles that differ by 90°). Another advantage is that acquisitions can consist of any number of frames (usually 8 or 16) without major effect on the calculations—indeed, a

Fig. 1 Count variations in an LBBB patient. The *left side* shows a typical mid-ventricular end-diastolic horizontal long axis frame of a SPECT MPI study. *Two arrows* indicate locations on the septum and lateral wall. The *right side* depicts count variations across the cardiac cycle at the marked locations. The first harmonic curve for each

location is superimposed on the counts curve, and the FFH phase angle is indicated. Note that in this LBBB patient, septal contraction is clearly shown to occur earlier than lateral wall contraction. These calculations are repeated for all myocardial sampling points (color figure online)

Fig. 2 Comparison of global and regional thickening phase in a normal vs. an LBBB patient. Global histograms (*top row*) show overall increased dyssynchrony in the patient with LBBB, and polar maps (*middle*) show uniform contraction for the normal patient and clear septal-to-lateral contraction delay for the patient with LBBB. The color scale used for both patients (*bottom*) has been adjusted to emphasize contraction timing differences in middle third of R–R cycle (*deg* degrees) [38] (color figure online)

simulation study showed no impact of the number of frames on the quantification of dyssynchrony in SyncTool [39]. Repeatability (variability for repeat studies) and reproducibility (inter- or intra-observer variability for the same study) have been shown to be high, due to the automated nature of the processing [40, 41]. Though there is evidence that camera type and reconstruction methods do not influence dyssynchrony parameters [42, 43], we would recommend caution when applying phase analysis to images obtained using novel acquisition systems, protocols, or imaging agents. In those situations, a comparison showing close similarity of average parameters obtained from a small normal population imaged with the novel approach to published normal limits for the same parameters would suggest that published thresholds can be applied to the new data, though a more extensive analysis would be needed for full validation purposes.

Count-based phase analysis effectively measures the timing of thickening. While QGS and SyncTool use a single harmonic “onset of contraction” definition of

timing, other software packages such as 4DM may include different definitions, such as parameters derived from a multi-harmonic “peak of contraction” measurement.

Other nuclear techniques that use blood pool imaging, whether SPECT or planar, perform phase analysis on endocardial wall motion by analyzing count variations throughout the blood pool or near the endocardium. In addition, these techniques can provide inter-ventricular as well as intra-LV dyssynchrony by measuring delays between the left and right ventricle (RV). The technical principles of wall motion phase analysis are the same as those of count-based thickening phase analysis, and usually involve FFH phase analysis, histogram generation, and histogram metrics calculations. Clinical interpretation of wall motion phase analysis results, however, requires bearing in mind that endocardial wall motion is a combination of mid-myocardial motion and myocardial thickening. Endocardial wall motion phase analysis measurements may therefore be affected by factors other than those that affect phase analysis measurements from myocardial thickening alone. This consideration applies to blood pool phase analysis as well as to some of the calculations performed by 4DM that are derived from wall motion. In a comparison study [44] between 4DM and SyncTool ($n = 200$, controls $n = 100$, LV dysfunction $n = 100$), the correlation between 4DM endocardial wall motion phase SD and SyncTool phase SD was only moderate ($r = 0.55$, $p < 0.0001$), while correlation between both algorithms was good ($r = 0.88$, $p < 0.0001$) when comparing thickening phase SD.

Of note, though it has been suggested that MPI phase analysis may be susceptible to artifacts in poorly perfused, count-poor myocardial regions [45], a simulation study with SyncTool showed no significant impact on phase measurements in regions with uptake as low as 10 % of normal uptake in other regions [46].

Validation

The fact that phase analysis dyssynchrony parameters such as histogram SD, BW, and E are somewhat arbitrary concepts designed to represent physiological characteristics, instead of physical measurements like LV cavity volumes, renders validation challenging. Despite intrinsic differences, comparisons to TDI dyssynchrony (delay in peak systolic velocity between the basal septum and the lateral wall) in patients undergoing CRT have shown good agreement for QGS ($n = 40$; SD: $r = 0.65$, $p < 0.01$; BW: $r = 0.69$, $p < 0.01$ [47]) as well as SyncTool ($n = 75$; SD: $r = 0.80$, $p < 0.0001$; BW: $r = 0.89$, $p < 0.0001$ [48]). Good agreement with 3D echocardiography (standard deviation of segmental time to peak systolic velocity) in HF

patients was also demonstrated for SyncTool ($n = 40$; SD: $r = 0.74$, $p < 0.0001$; BW: $r = 0.77$, $p < 0.0001$ [49]).

A commonly followed approach has been to confirm that the parameters discriminate as expected between certain patient populations, specifically between normal controls and patients with LBBB (QGS [38], SyncTool SPECT [50, 51], SyncTool PET [22]), right bundle branch block, ventricular paced rhythm, or LV dysfunction (SyncTool SPECT [50, 51]).

CRT and patient selection optimization

The automated, reproducible nature of phase analysis has led to the suggestion that MPI-derived LV dyssynchrony assessment may play a complementary role to the currently available guidelines [52]. While no multi-center trial has yet been conducted, SPECT phase analysis has been shown to predict response to CRT with good sensitivity and specificity in small patients populations both for QGS ($n = 40$, responders [RSP] = 60 %; SD Ss/Sp = 83 %/81 %; BW Ss/Sp = 83 %/81 % [47]) and SyncTool ($n = 42$, RSP = 71 %; SD Ss/Sp = 74 %/74 %; BW Ss/Sp = 70 %/70 % [53]). Response was defined in both studies as an improvement of 1 or more grades in NYHA functional class at 6-month follow-up. Figure 3 shows an example of differences in baseline dyssynchrony in responder and non-responder patients. It is also possible to detect acute changes in LV dyssynchrony after CRT, and a study evaluating the relationship between acute change and patient outcomes [54] demonstrated that deterioration occurs in a significant number of patients ($n = 42$, improved = 41 %, unchanged = 25 %, worsened = 34 %) and that acute changes can be predicted by an algorithm incorporating the presence of baseline dyssynchrony, myocardial scar burden, and lead concordance (acute improvement or no change in LV synchrony: Ss/Sp = 72 %/93 %, positive predictive value = 96 %; deterioration: negative predictive value = 96 % using SyncTool). There is also evidence that myocardial scar burden plays a large part in CRT response, irrespective of LV dyssynchrony: a study investigating the impact of infarct scar burden quantified by rest-redistribution TI-201 MPI and a summed rest score (SRS) derived using a 17-segment model (0 = normal to 4 = absence of uptake) on clinical outcomes [55] found that a scar burden ≥ 40 % (SRS ≥ 27) negatively affected CRT response regardless of baseline dyssynchrony measures. The location of myocardial scar had previously been shown to affect response as well [56], with patients without posterolateral scar tissue (assessed by MRI) and severe baseline dyssynchrony (assessed by TDI) showing a response rate of 95 %, while patients with a posterolateral scar and/or absent LV

dyssynchrony had an 11 % response rate. While there is evidence that transmural scar at the site of LV pacing prohibits CRT response [57], the effect of non-transmural scar remains unclear [58]. One small study [23] evaluated differences between RSP ($n = 7$) and age- and gender-matched nonresponders (NRSP, $n = 7$) using ^{18}F FDG PET/CT, finding statistically significant differences ($p < 0.05$) both in scar burden (RSP scar = 10 ± 8 %; NRSP scar = 30 ± 21 %) and QGS phase entropy (RSP, $E = 77 \pm 4$ %; NRSP, $E = 83 \pm 3$ %). There was no association between lead position in viable myocardium and persistent dyssynchrony by echocardiography, but pacemaker leads in all CRT responders were positioned in viable areas. A study in 90 HF patients with SyncTool [59] demonstrated that patients with lead placement concordant with the site of latest mechanical activation had a significantly higher response rate ($n = 90$, concordant: RSP = 79 %; discordant: RSP = 26 %), exhibiting significant LV systolic function improvement (assessed by echocardiography) at 6-month follow-up, while patients with discordant lead placement showed no significant improvement. To properly account for these factors, a comprehensive approach to CRT patient selection may be needed that combines phase analysis and myocardial scar evaluation, the latter both to assess overall scar burden and to evaluate myocardial viability at possible pacing sites. Patients most likely to respond would also have an LBBB QRS morphology [60] with duration >150 ms, and non-ischemic etiology. A recent study also suggests that within LBBB morphology, distinct activation patterns may have different outcomes [61].

Other clinical applications

There is evidence that dyssynchrony during the relaxation phase of the LV, which causes LV filling abnormalities, may adversely affect CRT response and long-term clinical outcomes in HF patients [62, 63]. Diastolic dyssynchrony can be readily assessed using a technique similar to systolic dyssynchrony, and is implemented in SyncTool using a multi-harmonic fit of the thickening curve [64]. TDI dyssynchrony (time delays in peak diastolic velocities of LV segments) agrees well with SD and BW from SPECT diastolic phase histograms in HF patients ($n = 150$; SD: $r = 0.81$; BW: $r = 0.75$; $p < 0.01$ for both). Diastolic dyssynchrony was also found to be significantly more prevalent than systolic dyssynchrony in patients with end-stage renal disease ($n = 121$; prevalence of dyssynchrony: systolic = 47 %, diastolic = 65 %, $p < 0.0001$ [65]).

Another retrospective study investigated the relation of LV dyssynchrony and cardiovascular events in patients with implantable cardiac defibrillators (ICD) [66],

Fig. 3 Example of phase analysis using SyncTool in a non-responder (**a**) and a responder (**b**) to CRT. **a** Note the absence of dyssynchrony at baseline, as evidenced by the narrow phase histogram. After 6-month follow-up, no response to CRT was observed, as reflected by deterioration in NYHA functional class from III to IV. In addition, LVEF remained unchanged [baseline (32 %) vs. 6-month follow-up (33 %)]. **b** In the responder patient, a wide phase histogram indicates the presence of baseline LV dyssynchrony. After 6-month follow-up, this patient improved in NYHA functional class from III to II, indicating response to CRT, and LVEF increased from 27 % at baseline to 33 % at 6-month follow-up [53]

identifying a threshold (SyncTool, $SD < 50^\circ$) in 70 patients with ICD and LVEF $< 40\%$ below which no events occurred at 1 year, suggesting that presence or absence of dyssynchrony may have long-term outcome implications in such a population.

Conclusions

Nuclear cardiology provides multiple techniques to assess ventricular dyssynchrony, and MPI phase analysis has

recently been the subject of multiple investigations. MPI benefits from high levels of automation and standardization, leading to excellent reproducibility and repeatability, and has the potential to integrate assessment of LV function, viability, baseline dyssynchrony, and optimization of lead placement out of scar tissue and into the area of latest activation, especially in combination with a CCT study providing venous anatomy. Other nuclear techniques (planar or SPECT MUGA) are less automated and have not yet been studied extensively, though it is possible that wall motion-derived dyssynchrony may prove valuable by focusing on

different physiological characteristics of ventricular contraction. MUGA also uniquely provides the ability to assess the relationship between LV and RV contraction, though this advantage may disappear with the advent of PET perfusion imaging agents that allow for improved visualization of the RV [67].

CRT patient selection optimization, a key problem in HF treatment, has proven difficult. Wide adoption of MPI dyssynchrony assessment for this purpose is contingent upon the successful completion of a multi-center trial that would evaluate the value of phase analysis, both to determine the amount of dyssynchrony and optimize lead placement, in a manner similar to what the Imaging CRT trial [68] strives to accomplish.

Conflict of interest S.D. Van Kriekinge and G. Germano receive royalties from the licensing of QGS+QPS by Cedars-Sinai Medical Center.

Human and animal studies This article does not contain any studies with human or animal subjects performed by any of the authors.

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