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Assessment of dyssynchrony by gated myocardial perfusion imaging does not improve patient management

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Abstract

Clinical trials have demonstrated improved outcomes with cardiac resynchronization therapy in patients with heart failure and electrical evidence of dyssynchrony. There has been intense effort at developing imaging markers of dyssynchrony with the aim of improved risk stratification.

However, these efforts have not been fruitful to date. This article discusses mechanisms of cardiac dyssynchrony, reviews clinical data supporting resynchronization therapy, and addresses the lack of convincing evidence to support the use of noninvasive imaging measures of dyssynchrony in improving patient management.

Keywords

Cardiomyopathy; Heart failure; Dyssynchrony; Cardiac resynchronization therapy; Dyssynchrony imaging

INTRODUCTION

Heart failure (HF) is the most common cause for hospitalization in patients over 65 years of age, affecting more than 5 million individuals in the United States and costing in excess of \$50 billion a year.^{1,2} Despite significant advances in medical therapy,³ progressive HF despite optimal medical therapy remains a significant source of cardiovascular morbidity. Mechanical dyssynchrony is highly prevalent in HF, occurring in approximately 20%–30% of HF patients,⁴ reducing cardiac efficiency,⁵ worsening symptoms, and leading to poorer prognosis.^{6,7} Efforts to mitigate electromechanical dyssynchrony in HF (cardiac resynchronization therapy, or CRT) have led to significant reductions in cardiovascular events and improved quality of life.^{8,9}

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MECHANISMS OF CARDIAC DYSSYNCHRONY

Mechanical dyssynchrony arises in the context of abnormal intraventricular conduction and/or myocardial scar. Temporally distinct activation of sections of the left ventricular (LV) myocardium may compromise diastolic filling and systolic emptying.¹⁰ In the setting of induced dyssynchrony by right ventricular (RV) pacing, LV end-systolic volume increases, diastolic filling interval shortens, and LV contractility decreases (see Figure 1).^{11,12} In addition, dyssynchrony may lead to increased mitral regurgitation,^{13,14} imposing a further volume load on the failing LV and exacerbating HF over time.¹⁵ These factors combine to further reduce the mechanical efficiency of an already failing LV. Indeed, metabolic studies of patients with NYHA class III-IV HF with evidence of electrical dyssynchrony (QRS duration ≥ 150 ms) who underwent implantation of CRT (using ^{11}C -acetate PET) have shown that restoration of mechanical synchrony leads to improved myocardial efficiency.^{16–18}

METHODS OF ASSESSING DYSSYNCHRONY

The crudest but most commonly used tool to estimate cardiac dyssynchrony is the QRS duration on the electrocardiogram. The presence of abnormal intraventricular delay (from either right or left bundle branch block or non-specific conduction delay) alters the timing and activation sequence of LV contraction. Electrical dyssynchrony is classically defined by a QRS duration ≥ 120 ms, though more recent guideline statements suggest a higher QRS duration threshold (>150 ms) as a cutoff for CRT implantation, particularly in those individuals with advanced HF and left bundle branch block QRS morphology.¹⁹

There are several echocardiographic methods of assessing mechanical dyssynchrony. Using M-mode to measure the time to peak systolic contraction of both anteroseptal and inferolateral walls, delay of >130 ms defines mechanical dyssynchrony.¹⁰ Doppler techniques to measure dyssynchrony include pulse-wave measurements of time from QRS onset to beginning of ventricular systole at different levels of the myocardium, e.g., pulmonic and aortic valves, with interventricular mechanical delay defined as a difference >40 ms.¹⁹ Tissue Doppler imaging (TDI), which is often the most accepted echocardiographic technique, captures time to peak systolic velocity of multiple myocardial segments, with dyssynchrony defined by regional differences in the time from QRS onset to peak of systolic velocity.¹⁹

Left ventricular dyssynchrony can also be measured with nuclear imaging techniques including gated myocardial perfusion imaging (MPI) using single-photon emission computed tomography (SPECT) or positron emission tomography (PET) as well as equilibrium radionuclide angiography (ERNA). In a small study of patients with NYHA III-IV HF, LVEF $< 35\%$, and QRS > 120 ms, gated SPECT parameters such as phase standard deviation analysis and phase histogram bandwidth were compared with dyssynchrony measures by TDI.²⁰ These two parameters showed the strongest correlation with dyssynchrony analysis by TDI. Phase distribution analysis is performed by evaluating the distribution of time to peak wall thickening across multiple myocardial segments. The standard deviation and bandwidth of the resulting histograms have been widely used in this

literature.²⁰ Importantly, the temporal resolution of gated SPECT is substantially lower than echocardiographic methods.²¹ Conversely, MPI based methods offer complete 3D visualization of the left ventricle which may better integrate the global burden of dyssynchrony across the ventricle than 2D metrics generally used in echocardiography.

EVIDENCE FOR CARDIAC RESYNCHRONIZATION THERAPY

The seminal MIRACLE and CARE-HF trials demonstrated symptomatic, clinical, and mortality benefit from cardiac resynchronization therapy (CRT) in severe HF. These studies demonstrated improved New York Heart Association (NYHA) functional status, lower rates of recurrent hospitalizations, and improved all-cause mortality in those randomized to CRT.^{8,9} Generally, clinical trials of CRT have focused on patients with heart failure with reduced ejection fraction with LVEF < 35%, NYHA III or IV symptoms, and QRS > 120 ms (see Table 1). Importantly, studies in lower-risk heart failure populations, such as REVERSE and MADIT-CRT, have also shown similar benefits.^{22,23}

Across these studies, up to 1/3rd of patients do not have improved LVEF or symptoms after CRT. It is believed that non-response to CRT is related to suboptimal LV lead placement (either due to anatomical limitation of coronary venous anatomy or presence of LV scar over a pacing site), suboptimal intraventricular or interventricular delay programming, high atrial or ventricular arrhythmic burden that limits effective pacing (e.g., atrial fibrillation), or overall suboptimal frequency of biventricular pacing.¹⁰ Consequently, there has been interest in using imaging to optimize treatment and minimize non-response.

ROLE OF NON-NUCLEAR DYSSYNCHRONY IMAGING

Several echocardiographic methods have been evaluated in trials of CRT. In single-center studies, echocardiographic measures such as tissue Doppler imaging (TDI) performed well in identifying responders.²⁴ However, when echocardiographic measures were evaluated in a large, international multicenter study of 498 patients who met indications for CRT based on aforementioned criteria, a wide range of sensitivity (9–77%) and specificity (31–93%) was observed for the prediction of end-systolic volume response as well as for improved clinical status.^{24, 25} No single parameter was deemed sufficiently powerful to influence clinical decision-making.

Furthermore, utilization of echocardiographic parameters to identify potential responders to CRT based on imaging evidence of mechanical dyssynchrony without electrical dyssynchrony (i.e., a QRS < 120 ms) failed to show benefit in a multicenter randomized control trial.²⁶ Among these patients with echocardiographic evidence of mechanical dyssynchrony, resynchronization therapy did not reduce rates of death or hospitalization compared to controls. Indeed, an increase in deaths in the CRT group was observed (11.1% vs 6.4%; HR 1.81; 95% CI, 1.11–2.93, $P = 0.02$).²⁶

PROSPECT and EchoCRT attempted to identify predictors of CRT benefit utilizing echocardiographic imaging evidence of mechanical dyssynchrony. They showed no significant difference in HF clinical composite score, LV end-systolic volume, or rate of death or hospitalization.^{24–26} Regardless, single-arm prospective cohort studies have

demonstrated that echocardiographic markers are associated with favorable long-term event rates (e.g., time to death, time to LVAD implantation, time to heart transplant) after CRT.²⁷ Higher survival rates were seen among those with favorable echo markers such as the 12-site SD (Yu Index) -32 ms ($P=0.003$), speckle tracking radial strain anteroseptal:posterior wall delay -130 ms ($P=0.003$), and interventricular mechanical delay by pulsed Doppler -40 ms ($P=0.019$).²⁷

Although echocardiographic parameters are prognostically relevant, because of a lack of strong evidence relating these metrics to treatment selection, current ACC/AHA guidelines do not generally recommend their routine use to arbitrate CRT implantation decisions.^{28, 29} Contemporary indications for CRT include individuals in sinus rhythm with electrical dyssynchrony (QRS >150 ms) and left bundle branch block with NYHA class II-IV symptoms and LV ejection fraction $<35\%$ on guideline-directed medical therapy.²⁹ For those with lesser degrees of electrical dyssynchrony and LBBB (QRS between 120 and 149 ms), or non-LBBB morphologies and QRS >150 ms, with otherwise the same indications, CRT implantation may also be reasonable based on available data.²⁹

EVIDENCE SUPPORTING CLINICAL USE OF SCINTIGRAPHIC ASSESSMENTS OF MECHANICAL DYSSYNCHRONY

A prospective follow-up study in 42 patients underwent both gated myocardial SPECT phase analysis and echocardiographic TDI, with a higher percentage of responders demonstrating higher histogram bandwidth values when compared with those who did not respond to CRT ($175^\circ \pm 63^\circ$ vs $117^\circ \pm 51^\circ$, $P<0.01$) and phase SD ($56.3^\circ \pm 19.9^\circ$ vs $37.1^\circ \pm 14.4^\circ$, $P<0.01$).³⁰

There has also been interest in identifying prognostic scintigraphic markers of mechanical dyssynchrony in patients with LV dysfunction, independent of response to CRT. A single-arm retrospective study looking at 324 patients with nonischemic cardiomyopathy, LVEF $35\text{--}50\%$, and QRS <150 ms who underwent gated SPECT MPI at a tertiary academic center showed variables such as phase SD were independently related to all-cause mortality.³¹

Recently, novel scintigraphic methods using ERNA have been applied to small populations of advanced HF, with specific measures such as LVS (left ventricular synchrony) and IVS (interventricular synchrony) correlating well with those who responded to CRT therapy ($29/32$, $P<0.01$).³²

Outside of the general HF population, phase standard deviation (SD) and histogram bandwidth (BW) have recently been evaluated in patients with chronic kidney disease, a common comorbid condition with advanced HF. In a prospective study, assessing the rate of major adverse cardiac events such as sudden cardiac death, fatal arrhythmias, or acute coronary syndrome requiring revascularization among patients with chronic kidney disease, those with higher phase SD and wider histogram BW had a higher event rate ($P=0.002$).³³ Phase SD was found to be associated with major adverse events (OR 1.33, 95% CI 1.05–1.69, $P=0.01$).

While such scintigraphic methods of LV mechanical dyssynchrony assessment hold promise in identification of poor prognosis in HF, their role in selecting patients who will benefit from resynchronization therapy has not been defined. Large randomized prospective studies using scintigraphic methods of dyssynchrony assessment remain to be conducted to show a change in patient outcomes.

CONCLUSIONS

Although treatment of electrical dyssynchrony has been demonstrated to improve outcomes in HF, to date no high-quality evidence supports the use of imaging markers of mechanical dyssynchrony in patient selection. Until high-quality data supporting the use of imaging in this role are available, multi-society guidelines are unlikely to endorse a role for dyssynchrony assessment in clinical practice. Nonetheless, nuclear and other imaging methods remain important research tools in this arena and may eventually evolve to have a more prominent clinical role.

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Figure 1.

Pressure–volume loop with and without mechanical dyssynchrony.^{11,12} Right ventricular free wall pacing was used to induce dyssynchrony.¹² Atrial pacing was used as a control. In the setting of induced dyssynchrony, stroke volume decreases and end-systolic volume increases while the end-systolic pressure–volume relationship (ESPVR) shifts to the right.¹¹

Table 1.

Major CRT trials

Study	Question	Patients (n)	Inclusion criteria	Therapy	Primary end point	P value
MUSTIC-SR (NEJM 2001) ³⁴	CRT benefit in HF+EF	58	NYHA III LVEF < 35% QRS > 150 ms	Active vs inactive CRT after implant	6 minute walk	<0.001 ^c
MIRACLE (NEJM 2002) ⁸	CRT benefit in HF+EF	453	LVEDd 60 mm NYHA III–IV LVEF 35% QRS 130 ms LVEDd 55 mm 6 MW 450 m	Active vs inactive CRT after implant	NYHA, QOL score, 6 minute walk	<0.001 ^a 0.001 ^b 0.005 ^c
MIRACLE-ICD (JAMA 2003) ³⁵	CRT-D benefit in HF+EF	369	NYHA III–IV LVEF 35% QRS 130 ms	Active vs inactive CRT after implant	NYHA, QOL score, 6 minute walk	0.007 ^a 0.02 ^b 0.36 ^c
CARE-HF (NEJM 2005) ⁹	CRT-D benefit in HF+EF	814	LVEDd 55 mm NYHA III–IV LVEF 35% QRS 120 ms LVEDd 30 mm	CRT vs optimal medical therapy	Death or hospitalization	HR 0.63; CI 0.51–0.77; P < 0.001
REVERSE (JACC 2008) ²²	CRT-D benefit in HF+EF	610	NYHA I–II LVEF 40% QRS 120 ms LVEDd 55 mm	Active vs inactive CRT after implant	HF clinical composite response, hospitalization	0.10 ^d HR 0.47 ^e P = 0.03 ^e
MADIT-CRT (NEJM 2009) ²³	CRT-D benefit in HF+EF	1820	NYHA I–II LVEF 30%	CRT-D vs ICD alone	Death or non-fatal HF event	HR 0.66, CI 0.52–0.84, P = 0.001

Study	Question	Patients (n)	Inclusion criteria	Therapy	Primary end point	P value
RAFT (NEJM2010) ³⁶	CRT-D benefit in HF _{rEF}	1798	QRS 130 ms NYHA II–III LVEF 30%	CRT-D vs ICD alone	Death, hospitalization for CHF	HR 0.75, CI 0.62–0.91, P=0.003
			QRS 120 ms			

^aNYHA class improvement
^bQOL or quality of life score improvement
^c6-minute walk improvement
^dHF clinical composite response
^eTime to first hospitalization