Selection of candidates for cardiac resynchronization therapy: late gadolinium enhanced cardiac magnetic resonance as a new and promising predictor of intraventricular dyssynchrony

Kardiyak resenkronizasyon tedavisi adaylarının seçimi: İntraventriküler dissenkroninin yeni ve ümit verici öngördürücüsü olarak geç gadolinyum tutulumlu kardiyak manyetik rezonans

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ABSTRACT

Cardiac resynchronization therapy (CRT) is an important therapeutic option for patients with intraventricular conduction delay and has been shown to reduce mortality and morbidity in selected heart failure patients. Several echocardiographic methods have been proposed to define intraventricular delay and to select candidates for CRT, such as color coded tissue Doppler echocardiography and speckle tracking. Since, up to 30% of these carefully selected patients do not receive benefit; predictors of response to CRT still remain a topic of ongoing investigations. Recently, myocardial fibrosis defined by late gadolinium enhancement on cardiac magnetic resonance (CMR) imaging has been introduced as promising predictor of both intraventricular dyssynchrony and response to CRT. The focus of the present review is the major echocardiographic modalities to select CRT candidates, the potential role of cardiac fibrosis detected by CMR in this respect, and the possible relation of it with the presence of intraventricular dyssynchrony. *(Anadolu Kardiyol Derg 2011; 11: 263-8)*

Key words: Myocardial fibrosis, dyssynchrony, cardiac magnetic resonance

ÖZET

Kardiyak resenkronizasyon tedavisi (KRT) ventrikül içi ileti gecikmesi olan hastalar için önemli bir tedavi seçeneği olup, seçilmiş kalp yetmezliği hastalarında mortalite ve morbiditeyi azalttığı gösterilmiştir. Ventrikül içi gecikmeyi tanımlamak ve KRT adaylarını seçmek için, renkli doku Doppler ekokardiyografi ve benek takibi gibi, çeşitli ekokardiyografik yöntemler önerilmiştir. Bu dikkatlice seçilmiş hastaların yaklaşık %30'u yanıt vermediğine göre, KRT'ne yanıtın öngörücüleri hala araştırma konusu olarak kalmaya devam etmektedir. Son zamanlarda kardiyak manyetik rezonans (KMR) görüntülemelerdeki geç gadolinyum tutulumu tarafından gösterilen miyokardiyal fibrozis, hem intraventriküler dissenkroninin hem de KRT'ne cevabın gelecek vadeden öngörücüsü olarak gösterilmiştir. Bu derlemenin konusu, KRT adaylarını seçmede kullanılan majör ekokardiyografik yöntemler, bu konuda KMR tarafından saptanan kardiyak fibrozisin potansiyel rolü ve kardiyak fibrozisin intraventriküler dissenkroni varlığıyla muhtemel ilişkisidir. *(Anadolu Kardiyol Derg 2011; 11: 263-8)*

Anahtar kelimeler: Miyokardiyal fibrozis, dissenkroni, kardiyak manyetik rezonans

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Introduction

Cardiac resynchronization therapy (CRT) has been approved as an adjunct treatment to patients with systolic heart failure, bundle-branch block and severe symptoms (1). The aim of this treatment is to reverse the adverse hemodynamic consequences of a regional delay in ventricular activation by the early stimulation of a late activated region. The left ventricular lead implanted by the coronary sinus is usually combined with a conventional right ventricular pacing electrode to achieve biventricular stimulation. Heart failure symptoms (NYHA III-IV) refractory to optimal medical therapy, left ventricular (LV) enlargement with reduced ejection fraction below 30% and the presence of a prolonged QRS complex (>130ms) are currently accepted criteria for patient selection (2). Studies have demonstrated the effectiveness of this approach in terms of hemodynamic improvement and have shown a favorable effect on both symptoms and morbidity. However, up to 30% of patients do not respond to CRT and it has become clear that QRS width and ventricular enlargement alone are not sufficient to identify responders to this highly individualized therapeutic modality. Despite intraventricular dyssynchrony detected by numerous echocardiographic methods have emerged for selection, not all patients with dyssynchrony also improve following CRT.

Patients with heart failure often show varying patterns of scarring and myocardial fibrosis. These regions of myocardial fibrosis have been visualized by cardiac magnetic resonance (CMR), appearing as areas of late gadolinium enhancement (LGE) (3). The potential reason for nonresponse to CRT may be the presence of extensive scar tissue in the region of the tip of the LV pacing lead. Pacing the left ventricle in nonviable or scarred myocardium may result in a less effective or even ineffective LV pacing and, as a consequence, no response to CRT. Characterization of scar distribution may therefore aid in the identification of responders to CRT. Accordingly, the main focus of this review is the major echocardiographic modalities to select CRT candidates, the potential role of cardiac fibrosis detected by CMR in this respect, and the possible relation of it with the presence of intraventricular dyssynchrony.

Left ventricular mechanical dyssynchrony

Delayed electrical activation of one of the myocardial walls results in a mechanical dyssynchrony. In a normal left ventricle, all segments are activated and are thus contracting at the same time. While the septum starts contracting, it contributes to increase in LV pressure and ejection, but at the same time, it also pulls the lateral wall towards it. Likewise, lateral wall pulls the septum towards it with an equal strength. However if the lateral wall activation occurs later, there is a time period where the septum is actively contracting while opposing lateral wall is not. Septum contracts against a decreased pressure, therefore it moves faster than the one in a normal ventricle (also known as septal flash). Additionally, this causes an early stretching of the lateral wall. After the lateral wall is activated, it starts on its own to influence the septum. The pulling effect of delayed contraction in lateral wall (with probably even increased contractility due to the pre stretch [Frank-Starling]) leads to an early relaxation of the septum. The combination of early septal contraction stretching the lateral wall and the late lateral wall contraction stretching the septum results in a reduced systolic function, and causes a dissipation of contractile forces in the LV. In carefully selected patients, CRT normalizes abnormal contraction pattern and also dissipates the presence of septal flash.

Major echocardiographic tools for the assessment of intraventricular dyssynchrony

M-mode echocardiography

Parasternal long-axis and short-axis views of the LV can be used for the assessment of dyssynchrony. The septal-posterior wall motion delay can be calculated by the difference in the time to peak inward movement of the ventricular septum and posterior walls. A septal-posterior wall motion delay of 130 ms or more has been shown to predict reduction in LV end-systolic volume index >15% with a sensitivity of 100% and a specificity of 63% in 20 patients at 1 month (4) and to predict improvement in LV ejection fraction (LVEF) >5% and better prognosis at 6 months after CRT (5). Although this method is simple and easily applicable, one potential limitation is that it assesses only the mechanical timing delay between two segments of the ventricle (Fig. 1). Another limitation

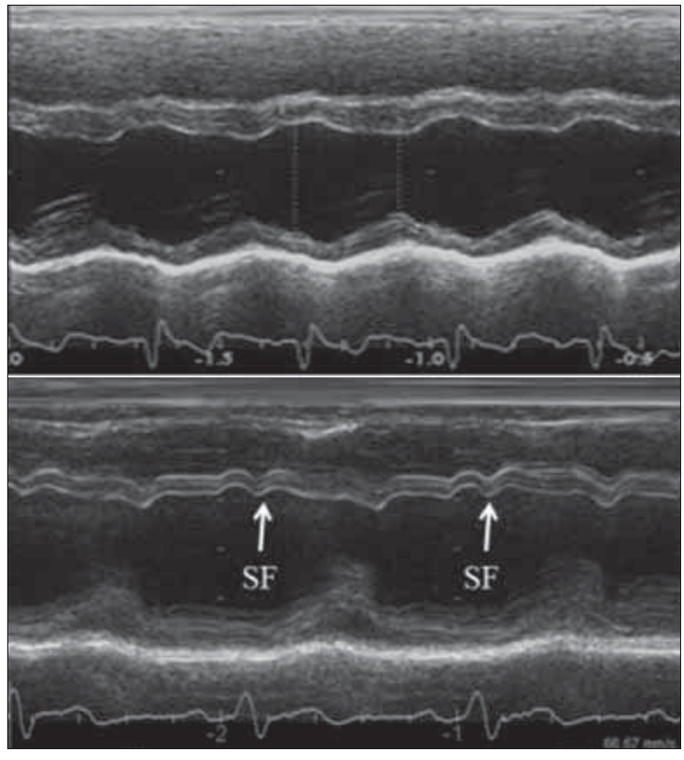

Figure 1. Parasternal long-axis view M-mode images of normal (above) and dyssynchronous (below) left ventricle. Using M-mode echocardiography, it is difficult to calculate septal-posterior wall motion delay, because of the presence of more than one septal motion (septal flash-SF)

is that if patients have an akinetic septum there is no peak to measure for septal inward motion. M-mode of color tissue Doppler imaging enhances timing measurements but is still limited to assess septum and posterior wall. On the other hand, in some reports, it has been shown that septal-posterior wall motion delay did not predict outcome after CRT (6, 7).

Tissue velocity imaging

Tissue Doppler imaging (TDI) allowing measurement of either longitudinal tissue velocity or strain of myocardium or both of them, have been used to measure mechanical dyssynchrony. Most publications have employed tissue velocity based dyssynchrony parameters. However these parameters still have not been standardized to one ideal method and have differed in several aspects.

The advantage of pulsed-wave TDI is that it does not require specific software or equipment and its disadvantage is that it requires sampling of multiple regions from different cardiac cycle which is time consuming and renders tissue velocity peaks more difficult to identify. Measurements can be done real time only. However, previously, no significant difference in septal- lateral delay in time to onset of systolic velocity using pulsed-wave TDI was found between responders and nonresponders (8).

Most published data on mechanical dyssynchrony have used color-coded TDI, which allows simultaneous processing of multiple sample points on the same image for a more comprehensive assessment of dyssynchrony. It is more reliable and feasible than pulsed-wave Doppler method. Bax et al. (9) reported that basal septal-lateral delay > 60ms in time to peak systolic velocity predicted a short term improvement in EF, and as another dyssynchrony index they reported, maximum difference in opposing basal segments (apical 2-chamber, 4-chamber) >65ms predicted reverse remodeling at 6 months after CRT (10). Yu and colleagues proposed a dyssynchrony index of standard deviation in time to peak systolic velocity among 12 basal and mid segments (Ts-SD). Ts-SD >32,6ms predicted reverse remodeling 3 months after CRT (11, 12). They also showed that correlation with reverse remodeling after CRT was the best with Ts-SD among the velocity based tissue Doppler parameters including 2-segment delay, 6-basal segment delay and maximum difference in 12 segments.

Although tissue velocity peak-based parameters are commonly used, several reasons arise, making these parameters suboptimal for analysing LV dyssynchrony. Firstly, defining which velocity peak to measure may be a part of the problem. Two distinct peak of velocity are not uncommon. Besides, patients with conduction delay and reduced EF often show more prominent positive velocities during isovolumic contraction or in the postsystolic period and sometimes do not show any peak during the ejection period. This may cause considerable variations in measurements. Secondly, regional myocardial velocity does not always reflect regional myocardial contraction. In patients with conduction delay and impaired systolic function, one region of the LV myocardium pulls the other and passive motion is a common finding. Thirdly, peak velocities depend on afterload and their timing does not show the true timing of mechanical activation. Lastly, in hearts with left bundle branch block (LBBB), especially in 'rocking' hearts, overall rotational heart motion may be greater than any local velocity, and thus the regional long-axis velocity curves may no longer reflect the timing and magnitude of regional contraction.

Recently, Voigt et al. (13) proposed apical transverse motion (ATM) of the LV, to quantify 'apical rocking', as a new and simple parameter for assessing regional myocardial function inhomogeneities (Fig. 2). They reported that ATM correlates well with the septal-lateral difference in myocardial wall strain as marker of function inhomogeneities, while conventional tissue Doppler parameters do not, and that ATM showed different typical apical motion patterns in different conduction delays. It, furthermore, distinguished between normal hearts and LBBBs with and without scars. As a consequence, ATM, providing information on both regional and temporal function inhomogeneities of the LV, may be used to assess LV dyssynchrony in the clinical context and is a promising parameter in predicting response to CRT.

Strain imaging

Strain can be calculated by TDI or 2-dimensional speckle tracking method (Fig. 3). It is less effected by tethering or translation induced by rotational rocking motion and would theoretically be a more reliable measure of regional myocardial contrac-

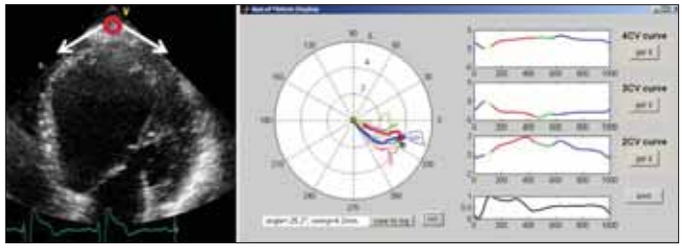

Figure 2. Apical transverse motion (ATM) defined by Voigt and colleagues (13) is a new and reliable predictor of LV dyssynchrony. They calculated ATM, by dedicated software, using displacement curves of three apical scan plans, and provided quantitative assessment of 'apical rocking'. In this figure, dilated left ventricle shows prominent ATM (4.2 mm) (Generated with permission using software developed by Dr. Voigt)

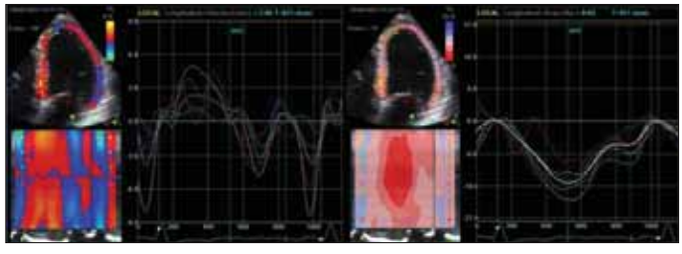

Figure 3. Longitudinal velocity and strain curves of 6 myocardial segments determined by speckle tracking. Speckle tracking is more reliable and feasible than pulsed-wave and color coded TDI as it allows simultaneous processing of multiple sample points on the same image, with angle independency

tion. Tissue Doppler derived strain is highly angle dependent and may be difficult to measure especially in patients with a spherical dilated hearts. However 2-dimensional speckle tracking is superior as it is angle independent, allowing assessment of radial, circumferential, and longitudinal strain in all segments. The disadvantage of speckle tracking is its temporal resolution, which is lower than in tissue Doppler derived strain, especially in dilated hearts requiring large sector angle for imaging.

Using TDI, a delay of 130ms or more in time to peak radial strain in the anteroseptal and inferolateral walls predicted a short term increase in stroke volume (14), and standard deviation in time to peak longitudinal strain among 12 basal and mid segments predicted reverse remodeling 6 months after CRT (15). Using 2-dimensional speckle tracking, a delay >130ms in time to peak systolic radial strain among 6 mid segments in parasternal short axis view predicted increase in EF >15% at 8 months after CRT (16). However, Yu and colleagues (17) reported that standard deviation in time to peak systolic TDI-derived strain in 12 segments did not predict the response to CRT.

Interventricular dysynchrony

Interventricular dyssynchrony (IVDys), represented by the preejection period difference between pulsed wave Doppler flow in the aorta and pulmonary artery, correlates with QRS duration and typically exceed 40ms in patients with wide QRS (18). Although 2 multicenter trials showed that the values >44ms (by SCART group) and 49.2ms (by CARE-HF group) are predictor of echocardiographic response and event free curves after CRT (19, 20), in large prospective studies using pulsed wave Doppler, IVDys was not predictive for the effect of CRT (10, 12).

Cardiac magnetic resonance imaging

Cardiovascular magnetic resonance (CMR) is a rapidly evolving technology that offers a comprehensive assessment of heart failure patients and is now the gold standard imaging technique to assess myocardial anatomy, regional and global function, and viability. Rather than a single technique, CMR consists of several techniques that can be performed separately or in combinations during a patient examination. Cine-CMR can provide assessment of cardiac morphology and function, first-pass contrast-enhanced perfusion CMR with and without vasodilators can provide assessment of myocardial perfusion reserve and late gadolinium enhanced CMR can be used in visualizing cardiac fibrosis and microscars that cannot be detected by other imaging techniques (21).

Myocardial necrosis and myocardial fibrosis are common finding in patients with cardiomyopathies. For imaging those areas of fibrosis / infarct, intravenous gadolinium chelated contrast agents, such as gadolinium diethylenetriamine penta-acetic acid are needed. This CMR technique has been named late gadolinium enhanced CMR (LGE-CMR) and demonstrates nonviable tissue as 'hyperenhanced' or bright (Fig. 4). The physiological basis of late gadolinium enhancement (LGE) is an increase in its volume of distribution within areas of scarring or fibrosis and an abnormally prolonged washout related to decreased functional capillary density in the irreversible injured myocardium (22). In normal myocardium, gadolinium chelates are extracellular contrast agents that are inert and cannot cross myocyte cell membranes, therefore their volume of distribution is hypothetically small. In the setting of acute infarction, there is acute myocyte membrane rupture, which allows additional gadolinium to diffuse into intracellular space. This results in increased gadolinium concentration and hyperenhancement. In the setting of chronic infarction, myocytes have been replaced with collagenous scar. In this situation, the interstitial space is expanded, which again leads to increased gadolinium concentration and therefore hyperenhancement (23). Because of its high sensitivity to detect even small subendocardial infarcts and its very high spatial definition, LGE-CMR has become the reference standard for the assessment of myocardial viability.

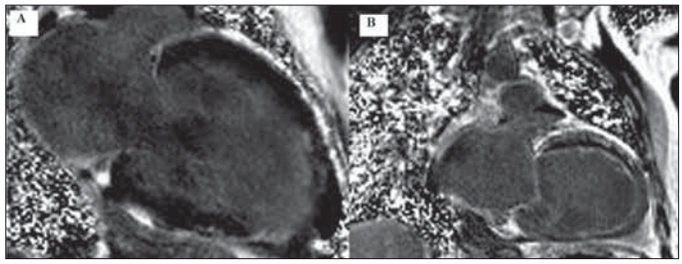

Figure 4. Apical (A) and extensive (B) subendocardial late gadolinium enhancement demonstrating cardiac fibrosis (Reproduced from ref. 32 with permission of authors)

One of the questions that arise in patients with LV dysfunction is whether the dysfunction is ischemic or non-ischemic in aetiology. This differentiation is clinically important as ischemic cardiomyopathy (CM) is associated with shorter mean survival. Additionally patients with ischemic heart disease may benefit from revascularization, aneurysmectomy and secondary preventive pharmacotherapy (24).

Previously, McCrohon et al. (25) performed LGE-CMR in 90 patients with ischemic and non-ischemic dilated CM (DCM) on the basis of coronary angiography. Although all patients with ischemic CM had myocardial hyperenhancement, 41% of idiopathic DCM also had hyperenhancement. Hyperenhancement can be classified as 'ischemic type' and 'non-ischemic type'. The first type is either subendocardial or transmural, and is located in a region, which is consisted with the perfusion territory of an epicardial coronary artery. Following coronary occlusion, myocardial function falls immediately, however little or no cellular necrosis is found until 15 min. From this point, a necrosis begins in the subendocardium and grows towards the epicardium over the next few hours. During this period, the infarcted region within the ischemic zone increases continuously towards a transmural infarction. The second type (non-ischemic), defined by McCrohon et al. (25), is patchy or linear striate of enhancement limited to the mid-myocardium of the ventricular wall. Linear mid-wall hyperenhancement is usually found in the interventricular septum. It is observed more frequently in patients

with possible prior history of myocarditis. On the other hand, they also found that 13% of patients with idiopathic DCM had ischemic type hyperenhancement. The clinical interpretation of this situation is unclear. But the occurrence of recanalization after an occlusive coronary event or embolization from minimally stenotic but unstable plaque may be possible causes.

LGE-CMR in predicting response to CRT

Myocardial viability is important in determining the response to CRT. Especially the clinical response is critically dependent on the presence of viable myocardium (26). There are limited published data, on the prediction of response to CRT through the assessment of myocardial viability. Sciagra et al. (27), showed that large resting perfusion defect on computed tomography perfusion imaging predicted a lack of ventricular remodeling with CRT. Left ventricular pacing from anatomically different sites has been shown to yield varying changes in systolic performance (28). A study using electromechanical endocardial mapping to assess regional viability in patients with DCM showed that pacing from sites with reduced local viability yielded less improvement in maximal LV dp/dt, a measure of LV performance (29). In elegant study using LGE-CMR, Bleeker et al. (30) have recently shown that in patients with a transmural posterolateral LV scar, CRT did not lead to reductions in left ventricular dyssynchrony or LV size, nor to an improvement in LV ejection fraction. Moreover they failed to improve clinically, in terms of NYHA class, exercise capacity, and quality of life. Similarly, Chalil et al. (31) showed that pacing scarred LV myocardium carries greater risk of mortality and morbidity than pacing nonscarred myocardium, detected by LGE-CMR. Consequently, all these findings suggest a substantial influence of regional viability and LV pacing site on clinical response to CRT.

On the other hand, recently Tigen et al. (32) have clearly emerged the relationship between intraventricular dyssynchrony and the presence of cardiac fibrosis. They examined 33 patients with non-ischemic DCM and assessed the presence of cardiac fibrosis with LGE-CMR using 17-segment model. They graded each segment on a 2 point scale and calculated 'cardiac fibrosis index' as 17 / (17-sum of fibrotic segments). After the analysis a cardiac fibrosis index ≥1.4 predicted intraventricular dyssynchrony with 92% sensitivity and 60% sensitivity, furthermore cardiac fibrosis index ≥1.4 was an independent predictor of dyssynchrony. Accordingly, they suggest that a cardiac fibrosis index ≥ 1.4 (in other words, ≥5 cardiac segments with fibrosis) is a useful tool to identify intraventricular dyssynchrony in patients with non-ischemic DCM, to classify patients for therapeutic trials and is a promising parameter to predict response to CRT.

Conclusion

Despite huge output of publication in this field, we currently cannot advise ideal parameters for the selection of candidates and for the prediction of response to CRT. Echocardiography has an ongoing role in helping us to understand how CRT actually works. However it is not the only tool influencing the success of CRT in an individual patient. It is possible that response or non-response to CRT involves multiple interrelated mechanisms (myocardial viability within the paced area, underlying myocardial conditions such as fibrosis and hypertrophy, and location of the pacing lead) rather than a single mechanism of LV dyssynchrony. Cardiac fibrosis defined by LGE-CMR is an important factor either in guiding for the optimal lead placement or in predicting the response. Future research is needed to have a clinically reliable and practical parameter for the effectiveness of this specific therapeutic modality.

Conflict of interest: None declared.

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