CHAPTER 4

Role of Left Ventricular Twist Mechanics in the Assessment of Cardiac Dyssynchrony in Heart Failure

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ABSTRACT

The authors discuss an incremental value of assessing left ventricular (LV) twist mechanics in patients with heart failure (HF) and its potential usefulness in characterizing response to cardiac resynchronization therapy (CRT) and reversal of LV remodeling at 6 months follow-up. They also underscore a critical relationship between LV lead position and changes in LV twist after CRT, and suggest that the reversal of LV remodeling in HF patients following CRT primarily results from restoration of the global sequence of LV twist mechanics.

INTRODUCTION

Heart failure (HF) remains one of the major public health problems in developed countries. In the U.S., nearly 6 million patients have HF symptoms, and 500,000 new patients are diagnosed yearly.[1] Recently, important advances in HF therapy, such as cardiac resynchronization therapy (CRT), have improved the outcome of these patients.[2] However, the prognosis still remains poor with a 5-year mortality of 42.3% after hospitalization for HF.[1] Left ventricular (LV) rotation, twist, and torsion are important aspects of the cardiac mechanics. The term "rotation" refers to the rotation of short-axis sections of LV. Due to the spiral architecture of LV myofibers, the rotation of LV apex and base are counter-clockwise and clockwise, respectively, as viewed from the LV apex. The opposite rotation of LV apex and base leads to an LV systolic wringing motion during systole referred to as twist or torsion. In particular, LV twist is the net difference at isochronal time points between apex and base in the rotation angle along LV longitudinal axis, whereas LV torsion is LV twist indexed to the distance between LV apex and LV base (LV length).[3, 4] This peculiar characteristic of the LV contributes significantly to LV systolic function, in addition to myocardial shortening and thickening. Furthermore, the potential energy stored by LV twist during the systolic phase is rapidly released during LV untwisting and constitutes an important determinant of diastolic suction.[5]

After a brief overview of physiology of LV rotational mechanics, an in-depth discussion is provided on different LV twist patterns in systolic HF and the evolving role of LV twist as a marker of LV dyssynchrony for understanding response to CRT.

NORMAL LV TWIST MECHANICS

In the normal heart, the myofiber geometry of the LV changes gradually from a right-handed helix in the subendocardium to a left-handed helix in the subepicardium. Taber et al.[6] explored the impact of this changing transmural myofiber orientation on LV rotational mechanics in a 1-layer cylindrical model that consisted of obliquely aligned muscle fibers embedded in an isotropic matrix. The contraction of the epicardial fibers rotated the apical end of the model in the counterclockwise direction and the base in the clockwise direction. Conversely, shortening of the subendocardial fibers rotated the apex and base in clockwise and counterclockwise directions, respectively. When both layers are coupled to contract simultaneously, a larger radius of rotation for the outer epicardial layer resulted in the epicardial fibers having a mechanical advantage in dominating the overall direction of rotation. The endocardial layer does provide some opposition to epicardial motion. This opposing action ensures that epicardial and endocardial sarcomere shortening in all directions are equilibrated during ejection, resulting in an optimal distribution of LV stress and strain.[7] Elimination of twist

decreases epicardial shortening at the expense of an increase in endocardial shortening. This, in turn, increases endocardial stress and strain, which increases oxygen demand and reduces the efficiency of LV systolic performance. The model of Taber et al.[6] also provides explanation for the temporal changes in the sequence of LV twist during a cardiac cycle. The initial shortening of subendocardium causes a brief clockwise rotation of LV apex during the isovolumic contraction.[5, 8] Subsequent transmural spread of electrical activation results in simultaneous shortening of subendocardial and subepicardial fibers. Due to the subepicardial fibers having a larger moment arm, the direction of rotation is shifted toward a counterclockwise rotation for the LV apex and a clockwise rotation for the LV base (Fig. 1).

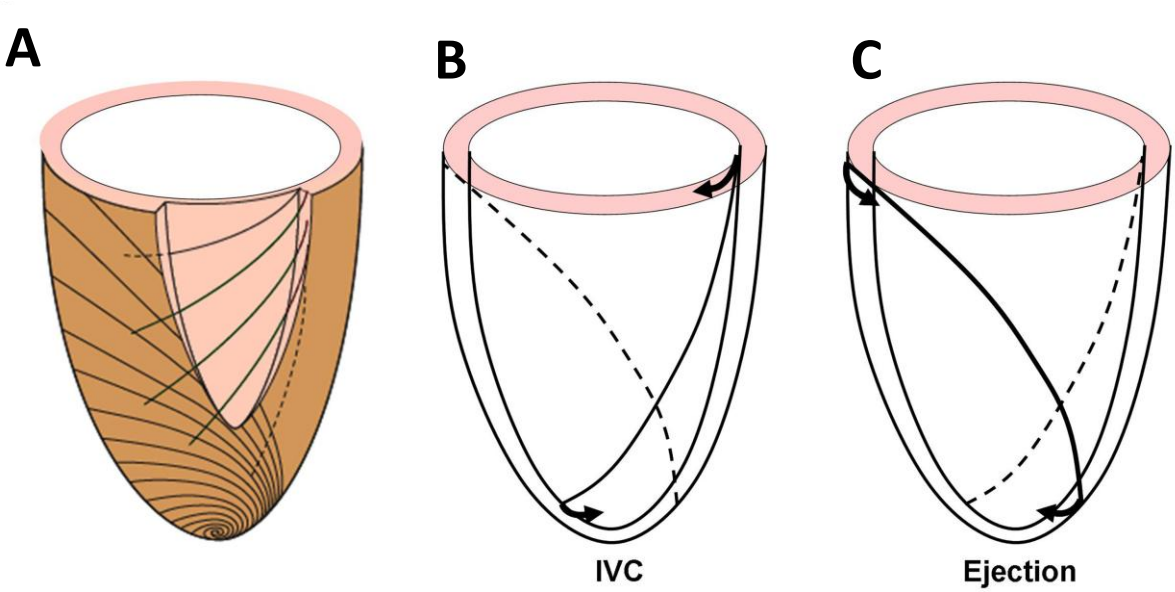

Figure 1. Mechanism of LV Twist. Left ventricular (LV) fiber orientation changes from a right-handed helix in the subendocardium to a left-handed helix in the subepicardium (A). During isovolumic contraction (IVC), circumferential components of force (arrows) are generated by endocardial fiber shortening, which rotates the LV about the long axis clockwise as viewed from the apex (B). During ejection, shortening of subepicardial fibers wrapped in an opposite, lefthanded helix rotates the LV counterclockwise (C). Twisting force by epicardial shortening overcomes the forces of subendocardial shortening because the torque of the epicardial force is larger due to a greater radius of the epicardial fibers from the central LV long axis.

Twist deformation of the LV wall causes fiber rearrangement that maximizes the LV wall thickening. In particular, twisting and shearing of the subendocardial fibers also deforms the matrix and results in storage of potential energy by compression of cardiac proteins such as titin.[5] The potential energy stored in the titin is subsequently unleashed during diastole, aiding myocardial relaxation and diastolic filling. The sequence of untwisting (clockwise rotation) of LV apex coincides with the onset of isovolumic relaxation.[5, 8] About 50% of untwisting is completed during the isovolumic relaxation time without any changes in LV volume.[7, 8] Finally, a large

extent of the remaining untwisting is completed during early diastole with minimal contributions during diastasis and late diastole.

Factors affecting LV twist. Alterations in pre-load, afterload, and contractility have been shown to altercardiac rotation.[7] The directly proportional relationship between torsion and LV end-diastolic volume and the inversely proportional relationship between torsion and end-systolic volume illustrate the volume dependency of LV torsion. Like changes in loading conditions, increasing contractility increases LV twist; for example, positive inotropic interventions such as dobutamine infusion and paired pacing greatly increase LV twist, whereas negative inotropic interventions markedly reduce twist.[7] Moreover, the LV twist increases gradually from infancy to adulthood. Notomi et al.[9] assessed LV torsion and twisting velocities in individuals from 9 months to 49 years and found that with advancing age there was an increase in LV torsion and untwisting velocity. It has been proposed that endocardial function is more likely to reduce with age due to the subendocardium's greater susceptibility to fibrosis and/or subclinical reductions in perfusion.

As per the model of Taber et al.[6] the reduced endocardial function would result in less opposition to the dominant epicardial action causing increase in rotation. The finding of reduced subendocardial function and increased torsion in older individuals results in preservation of global left ventricular ejection fraction (LVEF), suggesting a compensatory mechanism that helps to preserve global LVEF despite the presence of subendocardial dysfunction.

LV TWIST IN THE DYSSYNCHRONOUS, FAILING VENTRICLE

Several investigators have previously reported a significant correlation between LV twist and LVEF, the most commonly used index of LV systolic function in clinical practice.[10] However, there is increasing evidence that LV twist is superior to LVEF in characterizing hemodynamic aberrations in patients with HF. For example, Kim et al.[11], in a recent experimental study, reported a strong correlation between dP/dtmax (an invasive, relatively load-independent, measure of LV contractility) and LV twist ($R2 = 0.747$, $p < 0.001$); however, the correlation between dP/dtmax and LVEF, despite being significant, was weaker ($R2 = 0.408$, $p < 0.001$). This observation is related to specific differences in LV twist and LVEF: LV twist is an index of systolic myocardial deformation, while LVEF simply reflects LV volume reduction during systole. In particular, the LV torsional deformation, related to the spiral architecture of LV myofibers, permits the generation of LVEF $\geq$ 60% from myofibers that can shorten by only 15%; otherwise, simple longitudinal or circumferential shortening would not allow LVEF higher than 30%.[12, 13] Besides being a sensitive indicator of myocardial performance, the LV rotational mechanics appear strongly related to the sequence of LV depolarization as well; the propagation of the electrical cardiac activity is indeed significantly related to the spiral architecture and the

anisotropic properties of cardiac myofibers.[14] The assessment of LV twist, therefore, may provide more in-depth understanding of the pathophysiology of HF, as compared with the traditional parameters of LV systolic function.

The ischemic versus the nonischemic failing ventricle

Significant alterations of LV rotational mechanics have been observed in patients with previous myocardial infarction (MI) and chronic ischemic and nonischemic HF.

Myocardial Infarction

An impairment of LV twist after MI[7, 10, 15, 16] correlates with the reduction of LVEF, the number of dysfunctional myocardial segments, and the infarct mass. The injury caused by the infarction to the LV myofiber architecture may explain these findings. Indeed, Wu et al.[17], using diffusion tensor magnetic resonance imaging, observed an increase of left-handed myofibers and a decrease of right-handed myofibers in the infarct area; the extent of these changes was associated to the infarct size. Interestingly, opposite changes were observed in the remote zone, likely representing an adaptive response to increased wall stress.

Ischemic versus nonischemic HF

As compared with MI patients, HF patients present an even more pronounced impairment of LV rotational mechanics, irrespective of HF etiology as result of reduction of both LV basal and apical rotation (Fig. 2).[10, 18-21] In particular, the typical counterclockwise rotation of the LV apex may be completely abolished, or even reversed in a clockwise rotation. Recently, in a population of advanced HF patients with prolonged QRS duration, Bertini et al.[22] showed a modest but significant correlation between LV twist and LVEF ($r = 0.53$, $p < 0.001$). This finding supports the hypothesis that LVEF and LV twist are not identical parameters, and LV twist may provide incremental information on LV systolic performance.

As demonstrated by Taber et al.[6], LV dilation and thinning, present in dilated cardiomyopathy, equalize the radii of the subepicardial and subendocardial layers; as a result, the mechanical advantage of the subepicardial myofibers (the major determinants of LV twist under physiological conditions) is reduced. Consequently, LV twist decreases with increasing cavity volume. Moreover, the long-lasting processes determining dilated cardiomyopathy and eccentric hypertrophy cause myofiber disarray and alterations in myofiber angle.[20] These phenomena eventually lead to the loss of the physiological spiral architecture of the LV and to the impairment of LV twist.[23] Last but not least, slowed transmural fiber activation, related to fibrosis and remodeling of gap junctions, may delay the activation of the epicardial myofibers, determining an initial clockwise twist (because of the unopposed rotation of the endocardial myofibers) thereby impairing the peak LV twist.[24, 25]

It has been postulated that surgical techniques restoring a more physiological shape of the LV would improve the LV torsional deformation.[21] Indeed, in a preliminary study of 26

patients with ischemic dilated cardiomyopathy, LV reconstruction surgery improved LV twist in the patients with more severely impaired LV twist at baseline[21]; these patients showed also significantly greater improvement of LVEF after surgery as compared with the patients with relatively more preserved LV twist at baseline.[21]

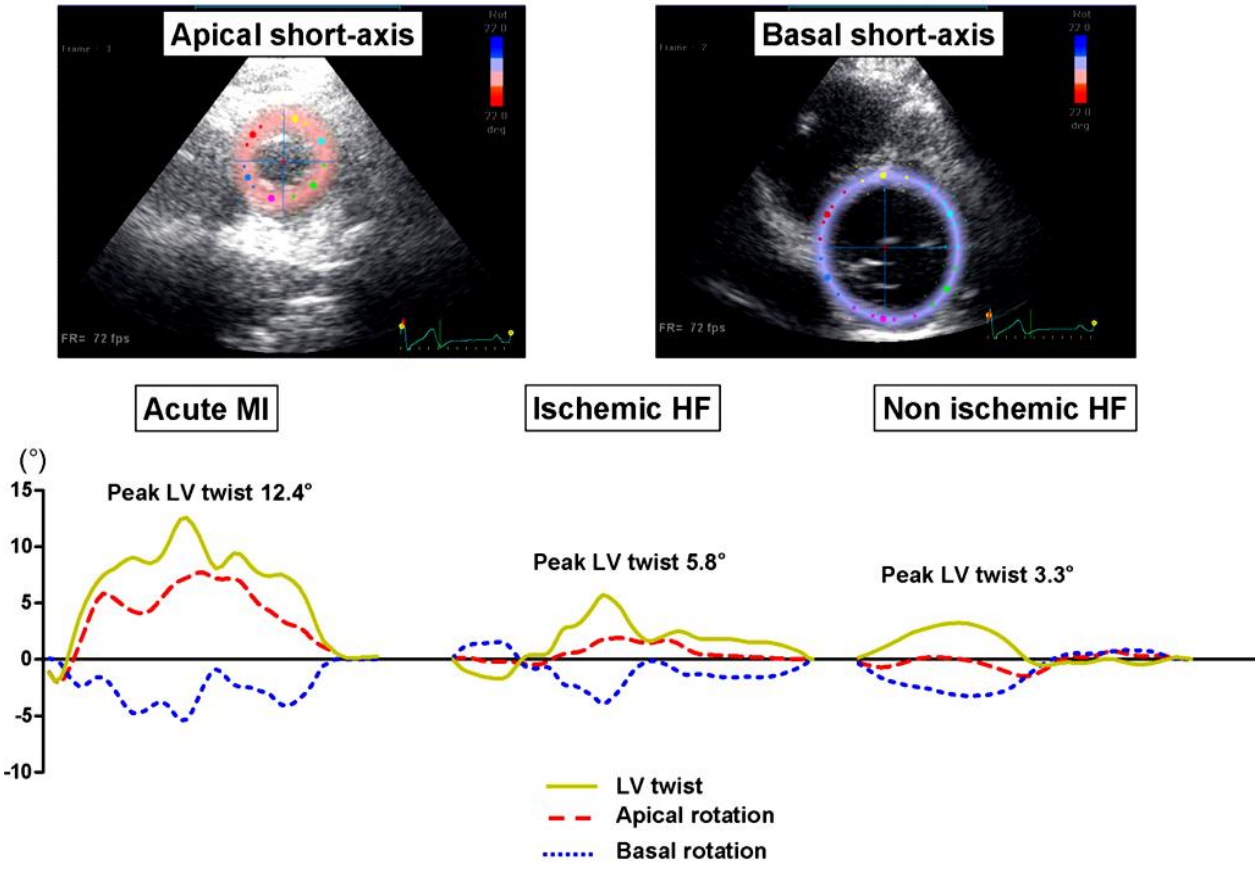

Figure 2. LV Twist in Acute MI and Ischemic Versus Nonischemic HF. Examples of left ventricular (LV) twist assessed with speckle tracking echocardiography in acute myocardial infarction (MI), and chronic ischemic versus nonischemic heart failure (HF). Of note, LV twist is markedly reduced in the patients with HF as compared with the patient with acute MI. In HF patients, LV twist impairment likely results from a long-standing process, with a rearrangement of LV myofibers and a consequent loss of the specific LV architecture that is responsible for the wringing motion. Conversely, in the setting of acute MI, the reduction in LV twist may result from an acute impairment in rotation of the LV region that is involved in the infarction.

Relation LV twist-LV dyssynchrony

The presence of an abnormal activation sequence of the ventricles (e.g., right ventricular [RV] apical pacing, right or left bundle branch block) results in a slower spread of the electrical breakthrough across the myocardium and in a dyssynchronous mechanical activation of the ventricles.[26] In addition, the anisotropy of the LV myocardium determines the propagation of

the electrical wavefront. As previously described[14, 27], activation of the LV includes the development of a potential over the lateral-apical region, which reflects endocardial-toepicardial propagation of the LV free-wall activation front. Subsequently, this epicardial potential is seen to migrate from the lateral LV apex toward the posterolateral base. The propagation is faster in the longitudinal direction of the myofibers rather than across in the circumferential cross-fiber direction due to the higher density of gap junctions concentrated in the intercalated disks along the longitudinal axis, as compared with the cross-fiber densities.[14] In the remodeled, failing LV, this particular architectural pattern may be distorted, with loss of anisotropy and gap junctions, resulting in a slower conduction of the electrical excitation.

Several experimental studies have demonstrated the deleterious effects of asynchronous ventricular activation on LV performance and the relation between the LV activation pattern and LV twist.[28-32] Prinzen et al.[30] showed the differences in temporal sequence of electrical and mechanical activation during spontaneous and ectopic beats. Ectopic activation induced asynchronous electrical activation and, subsequently, asynchronous cardiac motion (mechanical asynchrony). Interestingly, mechanical asynchrony was larger than electrical asynchrony because the time interval between the electrical activation and the onset of fiber shortening was more prolonged at the most delayed mechanical activated segments. Furthermore, myocardial work within the LV wall was evaluated during RV and LV pacing in normal hearts of dogs. Both pacing modes determined a pronounced redistribution of midwall fiber shortening and work, with a 50% decrease in myofiber work at the paced regions (hypofunctioning regions) and 150% increase at the remote areas (hyperfunctioning regions). These regional changes resulted in significant reductions in LV pump function.[31] Recently, Delgado et al.[33] compared the effects of RV apical pacing on LV twist in 25 patients without structural heart disease. With the use of 2-dimensional speckle tracking imaging, the authors demonstrated that RV apical pacing induced a dyssynchronous mechanical activation of the LV, as measured by radial strain and a subsequent significant decrease in LV global longitudinal shortening and LV twist (Fig. 3). Finally, 2 recent studies pointed out the relationship between LV dyssynchrony and LV twist in advanced HF patients with prolonged QRS duration.[22, 34]. A first study showed that the extent of LV dyssynchrony was inversely related to LV twist.[34] Subsequently, these results were extended in another study demonstrating that LVEF and LV dyssynchrony were both independently correlated to LV twist.[22] This observation further underscores that LV twist is not only a parameter of LV function, but also reflects the extent of LV (dys) synchrony.

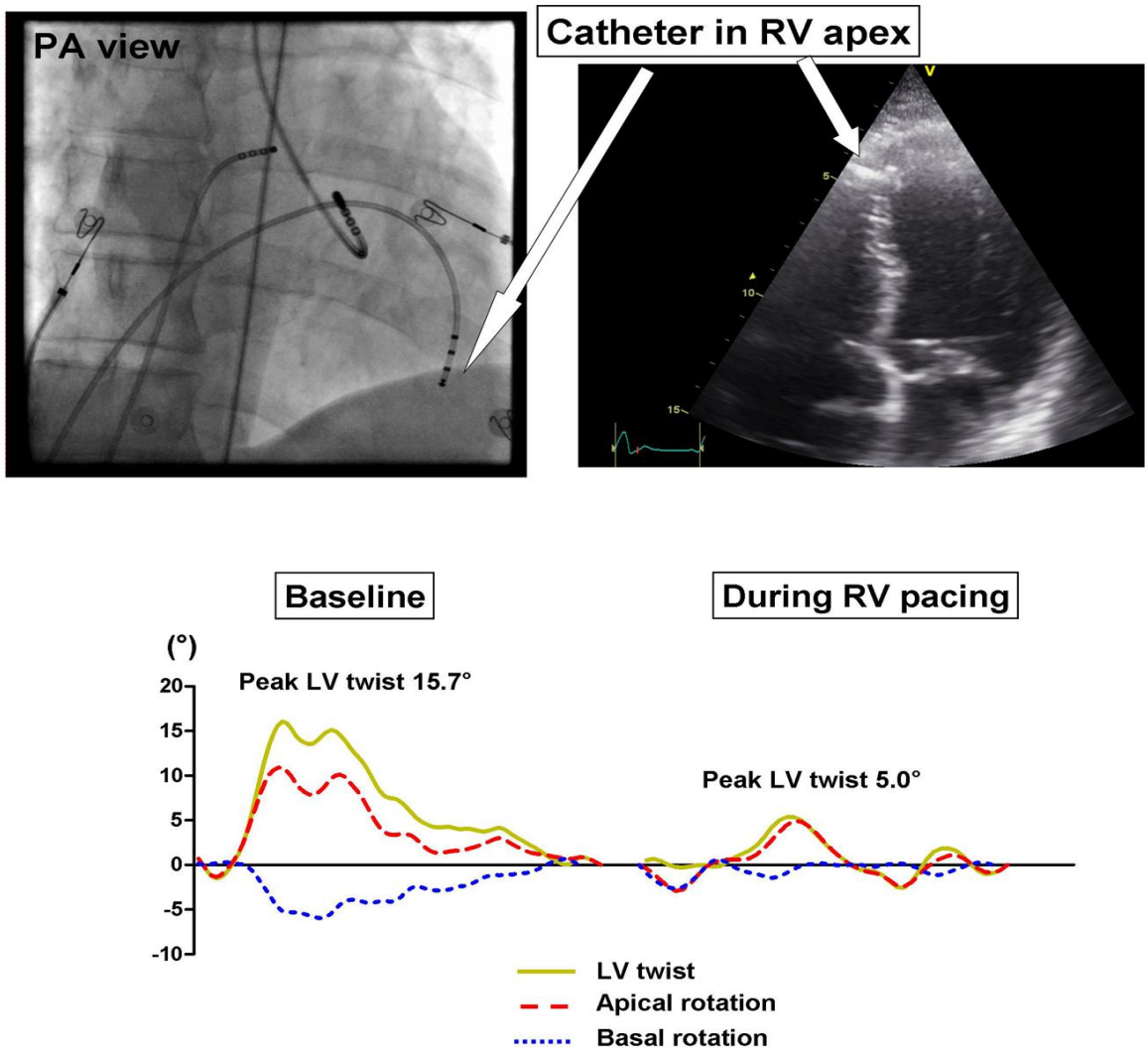

Figure 3. LV Twist During RV Pacing. Example of left ventricular (LV) twist during sinus rhythm (baseline) and during right ventricular (RV) pacing in a patient without structural heart disease. A standard diagnostic catheter was positioned in the RV apex as illustrated in the posteroanterior (PA) view at fluoroscopy (upper left) and the 4-chamber apical view at standard 2-dimensional echocardiography (upper right). The curves of LV rotational parameters at baseline (lower left panel) and during RV pacing (lower right panel) are shown. RV pacing induced a severe impairment in LV twist by decreasing both LV apical and basal rotation.

LV TWIST IN CRT

LV mechanics and particularly LV twist are strictly dependent on electromechanical activation and are influenced by different pacing modalities.[28, 29, 35] However, thus far, data on the effects of CRT on LV twist are limited.[22, 34, 36] Previous studies showed that LV twist is significantly altered in advanced HF patients with prolonged QRS duration.[10, 18] Particularly, abnormal rotational mechanics may result from 2 different conditions that can also coexist: 1) absolute

reduction of LV apical and basal rotation (and consequently of LV twist), due to an impaired myocardial contractility; and 2) dyssynchronous contraction of LV apical and basal regions, due to an altered pattern of LV electromechanical activation (Fig. 4). Consequently, CRT, leading to a more physiological electrical depolarization and mechanical contraction of the myofibers, has the potential to improve rotational mechanics in these patients.

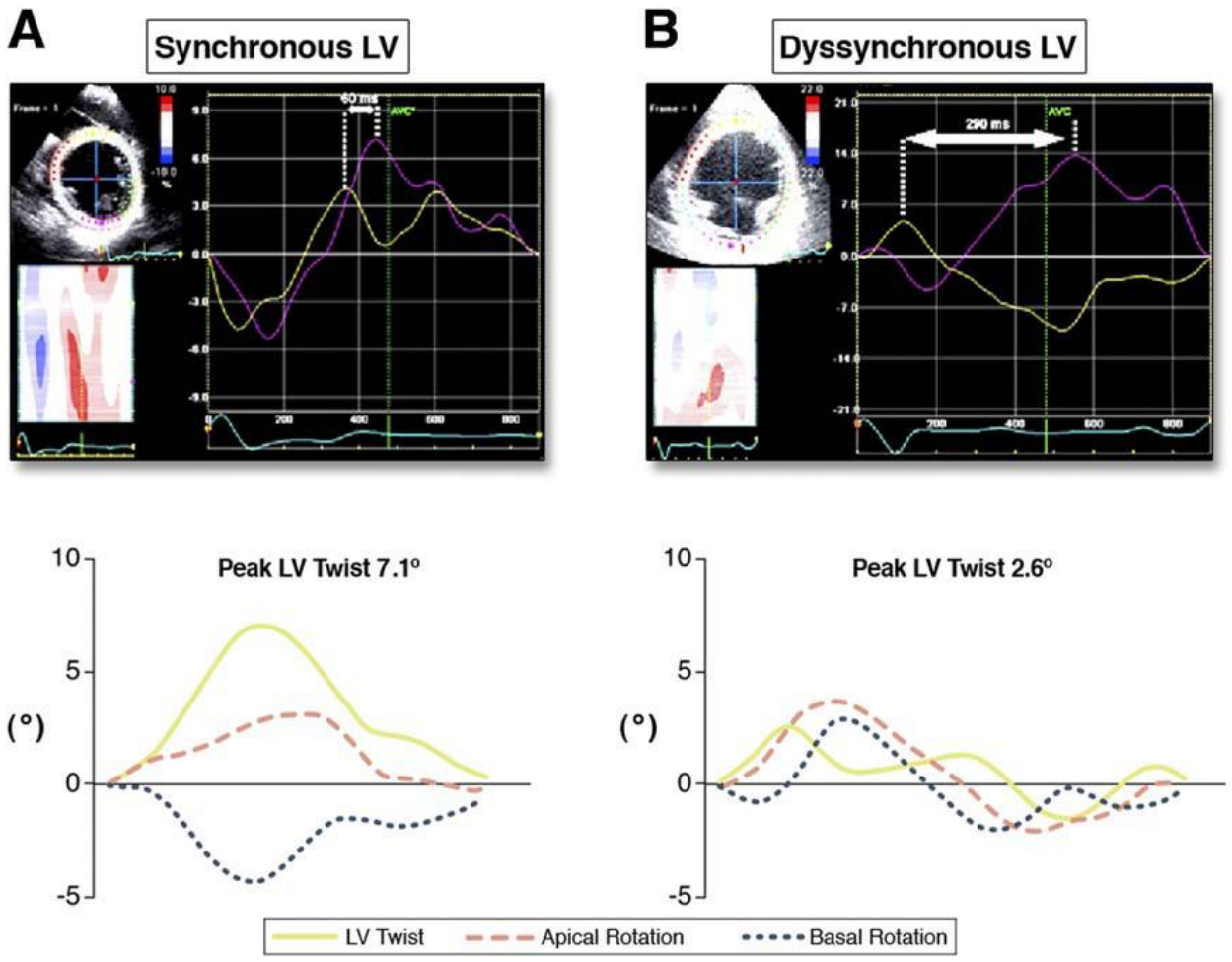

Figure 4. LV Twist in the Synchronous and Dyssynchronous Failing LV. Example of left ventricular (LV) twist in 2 patients with dilated cardiomyopathy and severe LV dysfunction (LV ejection fraction < 30%). Example of patients with synchronous (A) and with dyssynchronous LV contraction (B). In both the synchronous (A) and the dyssynchronous LV (B), the curves of the LV rotational parameters reveal reduced LV twist. Of note, the peaks of apical and basal rotation occur almost at the same time interval in the synchronous LV (A), whereas they occur at different time intervals in the dyssynchronous LV (B). In particular, in the dyssynchronous LV (B), apical rotation is markedly earlier as compared with the basal rotation, which may result in further worsening of LV twist.

Global changes in LV twist after CRT

All the available studies are based on 2-dimensional speckle tracking echocardiography that, unlike tagged magnetic resonance imaging, allows the analysis of rotational parameters also after device implantation.

Recently, Zhang et al.[36] studied 39 patients scheduled for CRT, measuring LV twist at baseline and 3 months after implantation. At baseline, peak LV twist was significantly reduced in the HF patients as compared with normal control subjects. The authors also noted that in some patients, the presence of apical and/or basal segments showed a paradoxical rotation (clockwise for the apex and counterclockwise for the base). However, at shortterm follow-up, the authors could not detect any improvement of LV twist after CRT, although a significant increase of LVEF was observed. Different findings were reported by Sade et al.[34], who studied the acute effect of CRT on 33 patients. At baseline, LV twist was significantly reduced as compared with that of normal control subjects either for ischemic and nonischemic HF patients and correlated well with LVEF and radial dyssynchrony. A significant improvement of LV rotational mechanics was observed immediately after CRT. This may be related to the potential role of the LV lead position in determining LV twist pattern. However, no data about LV lead position were reported in these studies. A more recent study[22] reported the short- and long-term effects of CRT on LV twist exploring also the influence of LV lead position. Specifically, in a group of 80 HF patients who were candidates for CRT, a significant and progressive improvement of LV twist was observed immediately after implantation and at 6 months follow-up (Fig. 5).

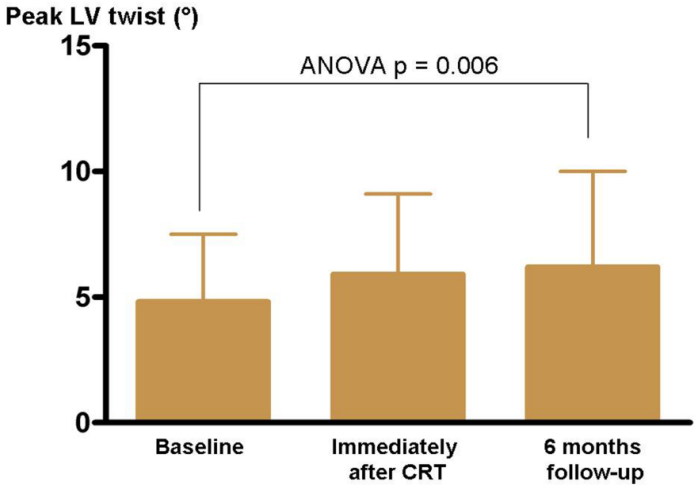

Figure 5. Progressive Improvement of LV Twist Induced by CRT. A significant and progressive improvement of left ventricular (LV) twist was observed immediately after cardiac resynchronization therapy (CRT) and at 6 months' follow-up.[22] ANOVA = analysis of variance.

Responders versus nonresponders

The effect of CRT on rotational mechanics is more evident if the evaluation is performed according to the presence of LV reverse remodeling. Sade et al.[34] evaluated the changes in LV twist in 33 HF patients treated with CRT. Responder patients (with a reduction in LV end-systolic volume > 10%) had an improved LV twist. Conversely, in nonresponders LV twist did not change or tended to worsen. Similarly, in a more recent study[22], a significant improvement in LV rotational mechanics was noted only in patients who showed LV reverse remodeling (responders), both at the short- and long-term followup. In particular, peak LV twist progressively improved in responders during follow-up (analysis of variance [ANOVA] $p < 0.001$), whereas in nonresponders a gradual deterioration of peak LV twist was observed (ANOVA $p < 0.001$) (Fig. 6). The changes of peak LV twist immediately after CRT showed a good correlation with the changes in LVEF ($r = 0.83$, $p < 0.001$). Furthermore, at the multivariable logistic regression analysis, in which LV dyssynchrony and function parameters were included, absolute difference in LV twist was the strongest predictor of response to CRT at 6 months follow-up (odds ratio: 1.837, 95% confidence interval: 1.378 to 2.449, $p < 0.001$). These findings suggest that CRT may (partially) restore LV twist, possibly by providing a more physiological electrical depolarization and mechanical contraction of the myofibers.

LV twist and LV lead position.

In clinical scenarios, the optimal site for LV pacing in patients receiving CRT remains controversial. Previous studies indicated that patients with a (postero) lateral LV lead position and patients with an LV lead located close to the region with the latest mechanical activation not only derive more benefit in restoring systolic LV function, but also tend to have superior long-term survival after CRT.[37-40] Thus, in CRT patients, the magnitude of LV twist may be related to the LV pacing site. However, there is currently minimal data addressing this issue. Previously, experimental studies showed that LV twist was influenced by the pacing mode (atrial, right, and biventricular pacing).[28, 29, 35] For example, Sorger et al.[29] evaluated the changes in LV twist during pacing from 3 different locations: right atrium, RV apex, and base of the LV free wall. Biventricular pacing with LV lead placed at the basal level of the lateral wall, similar to apical RV pacing, worsened LV twist as compared with a more physiological electrical stimulation (i.e., right atrial pacing).

A recent study[22] explored the change in LV twist after CRT in relation to different LV lead positions in the (postero) lateral veins. Interestingly, the authors observed that patients with LV leads positioned in midventricular and apical regions exhibited a larger increase in systolic function with a significant increase in LV twist as compared with patients with LV leads positioned in the basal regions of the LV free wall (Fig. 7). Possibly, LV pacing sites that yield the largest improvement in LV twist may likely determine a more efficient cardiac contraction and subsequent improvement of LV energetic.[41] Similar results were obtained in an experimental study in a canine HF model, reporting that the midapical part of the LV free wall was the

optimal stimulation site.[42] These findings could be explained by the direction of cardiac depolarization, traveling from the apex towards the base in the normal heart.[14, 43] Therefore, pacing close to the LV apex may replicate a more physiological pattern of LV depolarization and subsequent mechanical activation.[22, 29] Furthermore, as the myocardial wall is thinner in the LV apex compared with the LV base[44, 45], pacing leads positioned near the apex are closer to the Purkinje network. This results in a faster electrical propagation of the cardiac pulse and, subsequently, a more synchronous LV contraction. These are early data derived from small experimental and clinical studies; therefore larger multicenter studies are needed to confirm these findings.

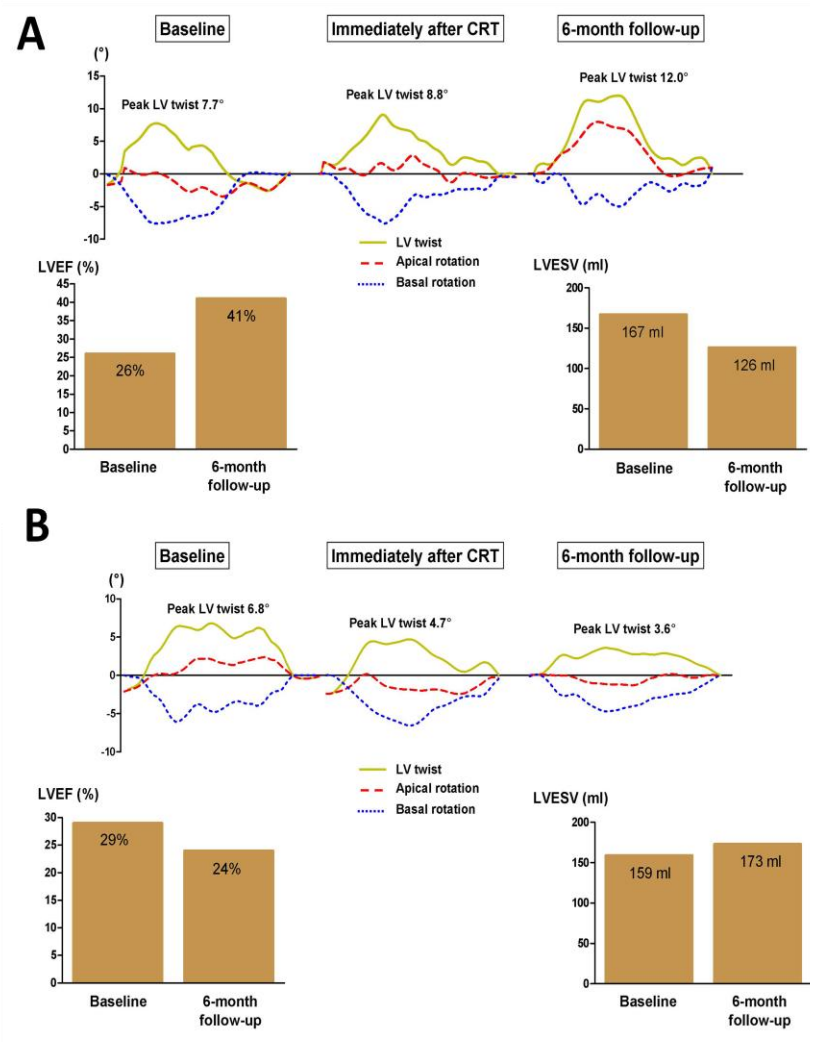

Figure 6. LV Twist Changing in CRT Responders and Nonresponders. (A) Example of responder to CRT. Peak LV twist increases progressively from baseline to 6-month follow-up. Immediately after CRT, LV twist increases secondary to an improved electromechanical activation of the LV. Further improvement is observed at 6-month follow-up when LV reverse remodeling has also occurred. The lower panels show the improvement in left ventricular ejection fraction (LVEF) and reduction in left ventricular end-systolic volume (LVESV) after 6-month follow-up. (B) Example of nonresponder to CRT. Peak LV twist declines progressively from baseline to 6 months' follow-up. The direction of LV apical rotation is reversed (negative pink dashed curve) immediately after CRT and at 6 months follow-up. At 6 months' follow-up, a reduction in LV basal rotation is also observed, which contributes to a further deterioration of LV twist. The lower panels show the parallel worsening in LVEF and LVESV after 6 months followup. Abbreviations as in Figure 5.

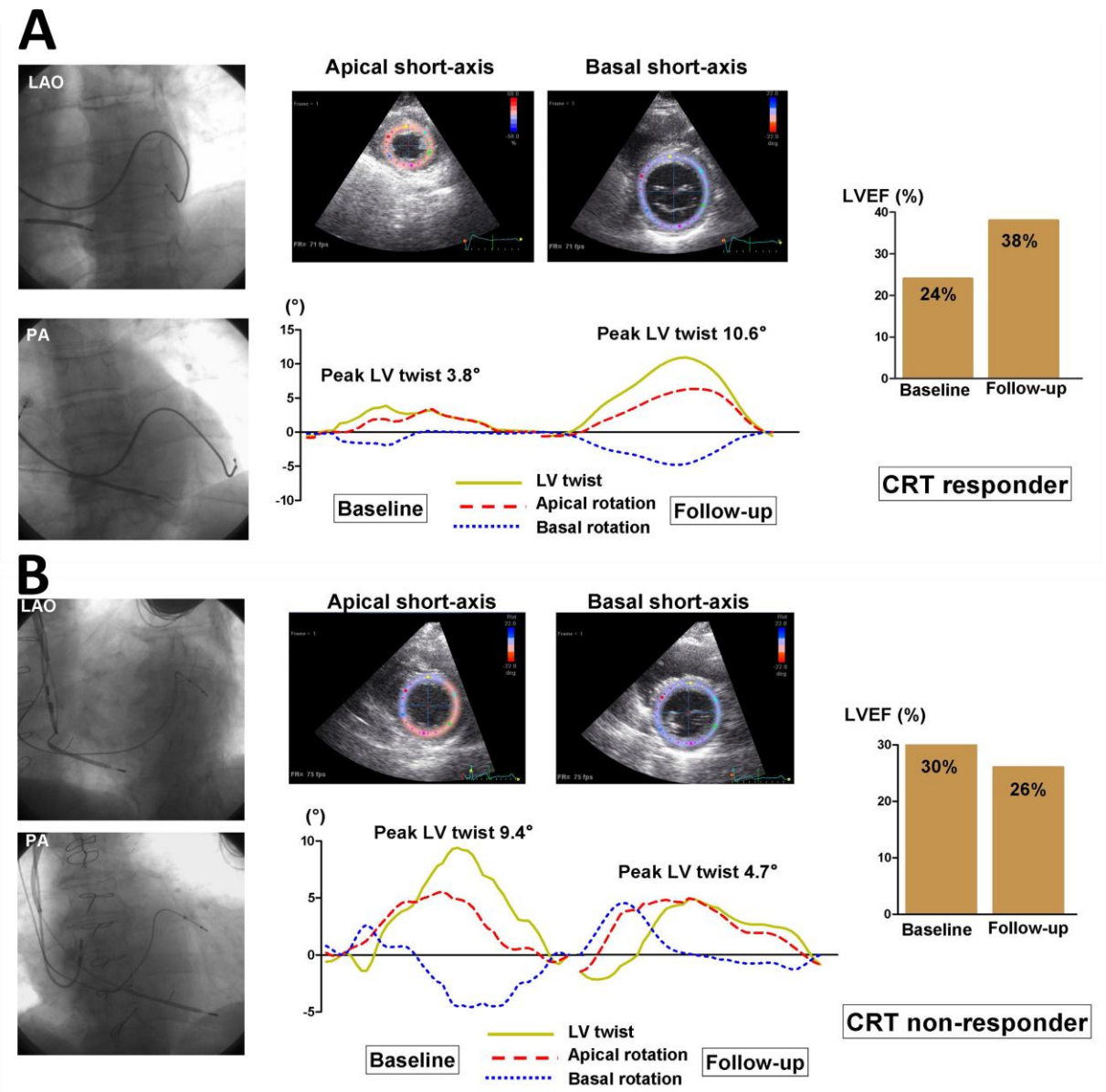

Figure 7. LV Twist Versus LV Lead Position. (A) Example of responder to cardiac resynchronization therapy (CRT) with the LV lead placed in a (postero)lateral vein with an apical position. Biplane fluoroscopy (left) displays the LV lead position. Particularly, the left anterior oblique (LAO) view shows the LV lead in the (postero)lateral vein whereas the PA view shows the LV lead in an apical position. Peak LV twist increased from 3.8° at baseline to 10.6° at 6-month follow-up. Left ventricular ejection fraction (LVEF) improved from 24% at baseline to 38% at 6-month follow-up. In this patient, pacing close to the LV apical region may produce a more physiological pattern of electromechanical activation, resulting in a significant improvement in LV twist. (B) Example of nonresponder with the LV lead placed in a lateral vein (LAO view) with a basal position (PA view). Peak LV twist decreased from 9.4° at baseline to 4.7° at 6-month follow-up. LVEF decreased from 30% at baseline to 26% at 6-month follow-up. In this patient, pacing close to the LV basal region may induce a further worsening of the electromechanical activation with a significant worsening of LV twist. Abbreviations as in Figure 3.

FUTURE DIRECTIONS

Thus far, several indexes of mechanical dyssynchrony have been proposed to select candidates for CRT. However, the response to CRT is also determined by other pathophysiological issues such as LV lead position and myocardial scar.[46] The analysis of LV twist may provide a more comprehensive evaluation of LV mechanics and may help to understand the effects of CRT in HF patients. Moreover, at present, CRT response relies on changes in clinical status, LV reverse remodeling, and improvement in LVEF. In this regard, LV twist analysis may be incremental to changes in LV volumes and LVEF to characterize and define CRT response.

Future studies are warranted to elucidate whether the magnitude and/or the specific pattern of baseline LV twist and immediate changes in LV twist after CRT may be used as a more sensitive index for the identification of CRT responders. Currently, 2-dimensional speckle tracking echocardiography permits reliable assessment of LV twist mechanics.[47] Furthermore, different authors reported a good reproducibility of the assessment of LV twist with 2-dimensional speckle tracking.[22, 48, 49] However, 2-dimensional speckle tracking echocardiography has some limitations for the assessment of LV twist mainly related to the acquisition of LV apical short-axis images and presence of through-plane motion, particularly at the basal level, which may affect the accuracy of the measurement of LV rotational parameters. Recently developed 3-dimensional speckle tracking analysis may partially overcome these limitations and may provide even more global characterization of LV twist mechanics.[50]

CONCLUSIONS

LV twist mechanics is a promising tool for characterizing the pathophysiology of HF. In advanced systolic HF, the rotational parameters are severely deteriorated and may be improved by restoring electro-mechanical activation through CRT. An immediate improvement in LV twist after CRT may be a good surrogate of a more physiological LV depolarization, and is independently related to reversal of remodeling after CRT. Finally, LV lead position is important for modifying the extent of LV twist after CRT; in particular, pacing sites that provide the greatest improvement of LV twist likely determine the largest reversal of LV remodeling after CRT.

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