Left Ventricular Twist Mechanics in the Context of Normal Physiology and Cardiovascular Disease: A Review of Studies using Speckle Tracking Echocardiography

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Introduction and background

Left ventricular (LV) function is determined by the complex interactions between tissue anatomy, myocardial contractility, and prevailing hemodynamics. Among the four cardiac chambers the LV is unique in having a double-helical myocardial fiber arrangement that surrounds the circumferential fibers in the midwall (18, 80). Sub-endocardially, the spiral holds a left-handed helix while a right-handed helix exists in the epicardium (6, 40, 84, Figures 1A and 1B, 85). Following iso-volumic pre-ejection motion, contraction of circumferential fibers and both helices causes circumferential narrowing and opposite rotation of the LV base and apex, resulting in a twisting motion around the long-axis of the LV. In the healthy heart, when viewed from the LV apex, the apex rotates in an overall counterclockwise direction and the base rotates clockwise. Functionally, LV twist has been suggested to equalize transmural mechanical stress, and contribute to a relatively high ejection fraction despite limited myofiber shortening (1, 12, 13, 96, 108).

During contraction, kinetic energy is stored in cardiac proteins such as titin (39). This stored potential energy is subsequently released during early myocardial relaxation (43), thereby aiding rapid uncoiling of circumferential fibers and untwisting of helices, together producing diastolic ‘suction’ (28, 65, 79). LV twist therefore provides a key mechanistic link between systole and diastole. The relationship between systolic twist and diastolic untwisting (LV twist mechanics), and its relevance in cardiovascular health and disease remains incompletely understood and is an area of active scientific inquiry. Echocardiographic speckle tracking imaging (STI) permits rapid and accurate assessment of LV twist mechanics and has been validated with cardiac magnetic resonance imaging (MRI) techniques (42, 64). The increasing availability of STI due to advances in imaging platforms and analysis software has fueled growing interest in the assessment of LV twist mechanics in normal physiology and cardiovascular disease. However, image acquisition, measurement, and presentation of LV
twist mechanics data require careful attention to ensure accuracy and reproducibility of data. Although elegant reviews have been published previously (69, 117), and the number of articles in the clinical arena have increased substantially, the normal physiological LV twist responses to exercise and aging have received much less attention. This may be due to difficulties in the standardization of image acquisition during physiological interventions such as acute and chronic exercise training, dehydration, hyperthermia and high altitude. However, understanding the LV twist response to normal physiological challenges is essential for the interpretation of its behavior in cardiovascular disease. Therefore, this article provides a contemporary review of LV twist mechanics with specific emphasis on its assessment and role in the normal CV response to changes in cardiac load, exercise, aging and disease. It was not the authors’ intention to perform a meta-analysis or full systematic review, but rather to review LV twist in health and disease in the context of normal CV physiology, drawing upon fundamental or significant papers in the field.

Assessing Left Ventricular Rotation and Twist

Definitions and fundamentals of image acquisition and analysis

The terminology related to LV twist mechanics has suffered from a lack of consistency in the literature. This inconsistency has made the interpretation of results and comparisons between studies a challenging task. Recently, the American Society of Echocardiography (59) has attempted to address this issue by providing standardized definitions of LV twist mechanics parameters in an attempt to encourage clarity and uniformity and an excellent review article by Young & Cohan provides further assistance in the differentiation between different mechanical variables (117). In accordance with these publications, in the present article LV twist refers to the net twist angle, which is the parameter most commonly reported in the contemporary empirical literature. Where appropriate, we specifically refer to LV torsion as
the net LV twist angle normalized to the end-diastolic length and to torsion-to-shortening ratio as proposed by Arts et al. (7). LV untwisting rate is indicated by the most pronounced velocity of untwisting during early diastole.

In addition to the use of consistent terminology, accurate assessment of LV twist mechanics requires precise standardization of LV data acquisition and raw data analysis. A brief overview of the fundamentals of LV twist mechanics assessment is therefore provided here.

**Imaging Modality.** Data collection / analysis for the quantification of LV twist mechanics can be performed with tissue Doppler and speckle tracking echocardiography, vector velocity imaging, MRI, and sonomicrometry. Each method has inherent strengths and limitations. At present, there is no gold standard for the assessment of LV twist mechanics but the above imaging modalities have been compared against one another showing good agreement (42, 64, 66). Owing to the authors’ expertise in echocardiography and its relative accessibility / portability, high frame rate, and wide range of application, we have focused on data acquisition and analysis related to two-dimensional (2D) echocardiographic STI. Data on the use of three-dimensional (3D) speckle tracking echocardiography is emerging (37) but is currently beyond the scope of this review, as it is likely to require further technological advancements (*inter alia* frame rates, computer processing power) prior to its routine implementation.

**Standardization of data acquisition.** 2D echocardiography STI-derived LV twist mechanics are obtained by acquisition of parasternal short-axis images from the LV base and apex. The combination of data derived from these images can be used to construct LV twist mechanics curves characterizing the entire cardiac cycle (Figure1C and 1D). While discrete anatomic landmarks of the LV base (i.e. closed mitral valve during ventricular systole) facilitate standardization of this imaging plane, careful attention is required to ensure that full-thickness myocardium is imaged throughout the cardiac cycle. To account for the normal 12
– 15 mm systolic excursion of the LV base, we define the optimal basal level as the imaging plane with full-thickness myocardium surrounding the mitral valve at end-systole. This distinction is essential to ensure that basal rotation can be tracked with accuracy throughout the entire cardiac cycle. Standardization of the apical imaging plane is more challenging and more important as the level of apical imaging plane acquisition has been shown to significantly impact the measurement of apical rotation (Figure 2, also see reference (106)). There are relatively few distinct anatomic landmarks within the apical LV region, which spans from the distal papillary muscle insertion site to the often densely trabeculated point of apical systolic obliteration. Thus in practice, the “apex” is a sizable ventricular zone with a wide range of rotation angles. This fact has led to the conceptual development of numerous standardization techniques, each with advantages and disadvantages. One technique involves measuring the end-diastolic ratio of the LV cavity diameter to the total LV diameter. Using a constant ratio of 0.5 during all data acquisition facilitates adequate comparison within and between subjects (112, 113). Another method involves the identification of the true apex from an apical 4-chamber imaging window. Once this is located the transducer is tilted into the true short-axis plane and the apical short-axis image is acquired as close to the true apex as possible, keeping the LV cavity as circular as possible. Regardless of the chosen technique, careful description of methodology in scientific publications is essential to ensure within and across subject reproducibility and to facilitate meaningful cross study comparison. Acquisition of short-axis images also requires careful attention and standardization of frame rates as reported previously (32). Paying attention to frame rates is important because low frame rates will result in longer gaps between data points and, potentially, truncation of peak values and subsequently the estimates of twist and untwisting rates; in particular during rapid events in the cardiac cycle such as the iso-volumetric periods. Interpolation of the raw frame-by-frame data (23, 93, 94) can reduce some of the error associated with low frame rates
during acquisition. Averaging of data over multiple cardiac cycles then further reduces the error, although it is not possible to completely eliminate the impact of missing data caused by low frame rates during data acquisition. In addition to paying attention to frame rates, other factors such as imaging depth (87) and optimization of the quality of the gray scale should be respected. Failure to account for any of these factors may result in inaccurate LV rotation and consequently incorrect LV twist data. Given the above factors, we propose the prospective use of an LV twist specific imaging protocol in research investigations aiming to assess LV twist mechanics (59), as the post hoc use of images obtained for other purposes often introduces unacceptable error, particularly in the assessment of apical rotation.

**Standardization of image analysis and data reporting.** Three main factors require attention during post-processing image analysis. First, manual tracing of the endocardium needs to include all myocardial tissue but should exclude papillary muscle and trabeculations. Second, the region of interest must cover the entire myocardium spanning from endo- to epicardium. Layer-specific differences exist (41) and failure to include all of the myocardium may result in over- or underestimation of LV twist mechanics. Third, tracking of the myocardial segments over the course of the cardiac cycle should be visually inspected and verified in an attempt to limit dependence on the “tracking quality” score inherent in most commercially available software packages.

Peak systolic apical/basal rotation, peak systolic twist, and maximal untwisting velocity during early diastole are the most commonly reported LV twist mechanical values reported in the literature. In addition, there is increasing interest in the assessment of time to peak systolic rotation/twist and time to peak systolic and diastolic rotation velocity for the entire myocardium and for individual myocardial segments. Such additional parameters may further enhance our understanding of the role of LV twist mechanics with regards to LV synchronicity and diastolic function.
Many prior studies have reported LV twist parameters produced directly by commercially available software. However, intra- and inter-individual differences in heart rate and subsequent effective frame rates suggest the need to use advanced post-processing procedures such as those outlined by Burns and colleagues (23). A comprehensive presentation of a methodological approach to LV twist mechanics assessment utilizing echocardiographic STI is provided as a supplement to this review (see Figure 3, video 1 and supplemental guide online).

LV Twist Mechanics in Health: Response to Physiologic Challenges and Ageing

Before LV twist mechanics can be meaningfully applied to patients with specific cardiovascular diseases, a comprehensive understanding of normal physiology is required. This includes a thorough understanding of the normal pattern for each key LV twist parameter across the cardiac cycle, at rest and under acute and chronic physiologic perturbation. Recent work addressing this important topic is discussed below.

Acute changes in LV loading, chronotropy and inotropy: Beyond the technical considerations that contribute to the variability in measurements of LV twist mechanics as outlined above, there are several key physiological factors that deserve consideration. Several elegant animal studies have shown that LV twist mechanics are sensitive to changes in LV loading conditions and thus it must be emphasized that LV twist mechanics cannot be considered load-independent indicators of contractility or lusitropy. Gibbons-Kroeker et al. (38) showed that alterations in loading conditions change LV apical rotation in dogs and concluded “LV twist … is primarily a function of volume”. Using a different animal model that allowed for the isolated manipulation and quantification of the effect of load on LV twist, Dong et al. (27) confirmed that changes in preload or afterload impact LV twist mechanics.
Specifically, they showed that increased or reduced preload caused a decline or augmentation of LV twist, respectively. In addition, acutely elevated or reduced afterload resulted in reduced or enhanced LV twist mechanics, respectively (27, 113, 114). Together, these results provide a reference point for the influence of altered hemodynamics on LV twist mechanics. However, it is noteworthy that the original studies were based upon animal experiments with measurements made only at the apex (38), thus not considering whole-chamber twist, or examined torsion of the endocardial surface only (27), which does not account for the different contributions from endocardial and epicardial rotation.

To further explore the influence of hemodynamic loading on LV twist mechanics in humans, recent studies have attempted to isolate the effect of both preload or afterload manipulation using isometric handgrip testing (115), saline infusion (21, 113), and glyceryl trinitrate (GTN) (21) and nitroprusside (74) administration. In agreement with previous findings from animal studies, two studies applying saline infusion (21, 113) showed that enhanced preload increases systolic LV twist mechanics. Similarly, Weiner and colleagues (115) also confirmed the previously shown reduction in LV twist caused by acutely enhanced afterload, by studying the effects of isometric handgrip testing. These findings were recently advanced by Balmain et al. (8), who showed that the increased heart rate during handgrip-induced afterload attenuates an even greater decline in LV twist. These data elegantly reveal the integrative nature of LV twist mechanics. Further, Park et al. (74) provided evidence in humans that LV twist is enhanced when afterload is reduced by infusion of sodium nitroprusside. Taken together, the current findings suggest that relatively isolated changes in preload or afterload impact LV twist mechanics in accordance with the Frank-Starling principle (76) and the afterload-shortening relationship (see Figure 4, 89). Similarly, LV untwisting rate has been associated with early-diastolic load and restoring forces but not LV stiffness (22, 70). Typically, an acute increase in LV twist is linearly associated with an
increase in LV untwisting rate (93), which has been attributed to the release of energy stored during contractions below the equilibrium volume (110).

In contrast to the effects of isolated hemodynamic manipulation, normal physiologic tasks, such as exercise or orthostatic challenge, involve a combination of altered preload, afterload, and possibly contractility. Accordingly, studies that have examined conditions with combined changes in loading and contractility have produced inconsistent results. For example, a marked reduction in preload caused by lower body negative pressure (LBNP), which is also known to increase sympathetic nervous output and thus LV contractility, did not alter systolic LV twist mechanics (31). Furthermore, both administration of GTN (21) and dehydration (92) reduce preload and afterload simultaneously, resulting in enhanced LV twist, yet a similar change in loading conditions during exercise with dehydration did not alter LV twist mechanics. In contrast, enhanced preload during acute exercise with normal hydration seems to cause the most marked increase in LV twist mechanics (29, 90, 93, 94). Overall, the current LV twist data obtained during a variety of physiological perturbations show a marked inter-study heterogeneity, which may tempt some researchers to conclude that measuring LV twist may not be of value in the clinical setting. Indeed, we would agree that the current lack of normative values for LV twist and untwisting rate in relation to the prevailing haemodynamic load prevents these markers to be used routinely as clinical indicators. However, the present data equally present an opportunity to develop a better understanding of the existing concordant responses and inter-individual differences in the acute state of LV twist mechanics, which may be useful in the development of normative reference values in the future.
**Chronic alterations influenced by exercise training and ageing:** Our understanding of LV twist mechanics has also been informed by studies examining chronic hemodynamic stimuli. One such area of investigation is the impact of exercise training on LV twist mechanics. Several cross-sectional studies have reported that individuals with greater aerobic fitness appear to have significantly lower LV twist than normal sedentary controls (68, 94, 121), and it appears that LV twist mechanics may respond to exercise training in the absence of overt changes in cardiac structure, heart rate, or arterial hemodynamics (94). Additionally, a recent longitudinal study reported an initial increase in LV twist in response to 90 days of rowing training (112) which was normalized following three years of continued training in the same individuals (111). These data are in accordance with the phasic exercise training adaptations observed in conduit arteries (100) and provide an important addition to the literature. However, more longitudinal data are required, as another study has shown that six months of exercise training increased LV twist (3). Factors such as the type of sport, participant age, duration and intensity of training, total blood volume status and variability in measurement technique may explain some of the discordant data to date. Future research employing standardized measurement techniques is needed to determine the nature of the LV twist adaptation to exercise training, and how this relates to changes in myocardial structure and function, in an effort to better define this aspect of athlete’s heart.

In contrast to the somewhat discordant data on exercise training, studies examining the relationship between LV twist mechanics and age have produced more consistent results. Despite age related increases in afterload and concomitant reductions in preload (34, 49, 57), which may be expected to reduce LV twist, ageing has actually been shown to result in increased LV twist mechanics (4, 20, 33, 44, 53, 63, 67, 71, 97, 104, 116, 120). Mechanisms other than changes in the loading state or chronotropy outlined previously are therefore likely responsible for the LV twist response to aging. Lumens et al. suggested that LV twist
increases with age because of a reduced influence of the sub-endocardial fibers, thereby increasing net LV twist and even the torsion-to-shortening ratio (53). However, it must be noted that true experimental evidence for this hypothesis is still outstanding, since direct force measurements in the aged sub-endocardium have not yet been performed. Other authors have shown that the age-related increase in LV twist can potentially be offset by the physiological effects of endurance exercise training (56). Whatever the mechanisms responsible for the age-related increase in LV twist are, it is likely that their discovery will improve our knowledge of normal cardiac function and our understanding of cardiac maladaptation in response to pathology. In this context, future studies should include the full lifespan, including pre-pubertal examinations (67).

**LV Twist Mechanics in Cardiovascular Disease**

The clinical utility of measuring LV twist mechanics will be greatest when applied to patients with cardiovascular diseases. Ultimate goals for the analysis of LV twist mechanics in the context of cardiovascular disease include, 1) identification of subclinical myocardial dysfunction, 2) provision of diagnostic and prognostic information, and 3) assessment of response to drug or device therapy. At the present time, LV twist mechanics cannot provide all of this information for any specific cardiovascular disease state and thus the routine clinical use of LV twist mechanics measurement is currently limited. However, high quality studies of LV twist mechanics in common cardiovascular conditions are becoming more numerous and are summarized below and in Table 1.

*Cardiomyopathy / Reduced Ejection Fraction*

*Ischemic cardiomyopathy*
The impact of coronary artery disease (CAD) on LV twist depends on the extent and location of ischemia and/or infarct. With ischemia confined to the subendocardial fiber layer, apical rotation increases (48). This is due to increased dominance of the epicardial lever arm, which produces greater apical rotation and twist, similar to what occurs with aging (as above) and diabetic cardiomyopathy (25). In contrast, transmural ischemia results in decreased apical rotation and twist.

Takeuchi et al. showed that in patients with anterior myocardial infarction (MI) LV apical rotation, twist, and untwisting rate are decreased in those with LV ejection (LVEF) <45% (99). Other studies support the finding that reduction in LV twist is proportional to the size of the infarct and decrease in LVEF (10, 35) A recent study utilized LV twist response to dobutamine stress echocardiography (DSE) to help predict reverse remodeling (decrease in LV systolic volume) 6 months after acute MI (45). This study showed that the LV twist increase during DSE was associated with reverse remodeling and suggests that LV twist may be a novel marker of contractile reserve. The incremental value of LV twist analysis above more conventional functional parameters in the diagnosis, prognostication, and management of CAD remains to be determined.

*Dilated cardiomyopathy (DCM)*

In DCM, similar to ischemic cardiomyopathy, LV apical rotation and overall LV systolic twist are reduced, the extent of which is proportional to the degree of LVEF impairment (46, 72). In severe cases, apical rotation may be so profoundly impaired that the LV base is the primary determinant of overall LV twist and experimental work is now focusing on mechanical augmentation of apical rotation to assist failing hearts.(101) Studies have extended to specific etiologies of non-ischemic cardiomyopathy, including LV
noncompaction (77, 101). The impact of available DCM treatments on LV twist is also under evaluation. Data indicate that LV reduction surgery (i.e. left ventriculectomy) does not improve LV twist, possibly due to disturbed fiber orientation after surgery (86). In contrast, efforts to restore synchronized contraction of the LV with cardiac resynchronization therapy (CRT) may enhance twist. Bertini et al. have reported that immediate increase in LV twist after CRT implantation is a stronger predictor of 6-month response to CRT than conventional measures of LV dyssynchrony (11).

Cardiomyopathy / Preserved Ejection Fraction

Heart Failure with Preserved Ejection Fraction (HFpEF)

Park et al. examined LV twist across the severity spectrum of diastolic dysfunction and showed that LV twist and untwisting rate are increased in early stage (grade I) disease (73). Increased untwisting rate may serve as a compensatory mechanism for reduced longitudinal relaxation of the myocardium in early diastolic dysfunction thereby helping to maintain normal LV filling and left atrial pressure. In patients with more advanced diastolic dysfunction, irrespective of etiology, LV twist and untwisting rate are normalized or reduced (110). This may in part explain why early diastolic filling in advanced disease depends less on LV suction and more on a compensatory increase in left atrial pressure.

Furthermore, prolonged time to peak twist plays a major role in diastolic dysfunction. The underlying problem is prolonged shortening of the right-handed helical arm or descending segment of the myocardial fibers, resulting in a delayed peak LV twist after aortic valve closure, thereby disrupting the normal energetics during iso-volumic relaxation and a subsequent reduction in diastolic function (17, 19). Global reasons for prolonged time to peak twist and reduced peak untwisting rate include LV hypertrophy or altered calcium flux.
Improving calcium flux may become a valuable treatment option to correct the twist/untwisting imbalance. Modifying calcium efficiency with the myofilament calcium sensitizer levosimendan reversed diastolic dysfunction in animals (9). Specific therapies for HFpEF / diastolic dysfunction are clinically needed in humans, as many of the existing medical therapies for heart failure with reduced ejection fraction have not provided benefit in clinical studies of HFpEF (78).

**Hypertrophic cardiomyopathy (HCM)**

LV twist is preserved or increased in HCM (118), particularly in those with LV outflow tract (LVOT) obstruction (102). Although untwisting rate is also typically preserved or increased, the timing of untwisting is delayed in HCM, reflecting ineffective diastolic uncoiling of the hypertrophic myocardium (102, 103). This may in part underlie the clinical syndrome of HFpEF which is common in this patient population. While increased twist among patients with HCM may appear to be adaptive, analysis of the exercise response in HCM patients suggests otherwise. Soullier *et al.* showed that HCM patients fail to augment LV twist and that peak early diastolic untwisting rate is lower and occurs later in diastole during submaximal exercise compared to control subjects (90). Notomi *et al.* report similar findings, indicating that HCM patients lack a “twist reserve” with exercise which may in part explain the exercise intolerance seen in these patients (65). Further support comes from a study of septal reduction therapy in HOCM showing that untwisting occurs earlier after septal reduction and is associated with improvement in LV filling and exercise tolerance.(109) Finally, a recent echocardiographic and MRI study examined the relationship of LV twist and myocardial fibrosis in HCM, and showed that LV twist values were higher in HCM patients with fibrosis than in those without fibrosis (119). As fibrosis is increasingly recognized as a precursor of sudden cardiac death in HCM patients, it is possible that analysis of myocardial
mechanics may aid in future efforts to risk stratify HCM patients and identify those who may benefit from implantable cardiac defibrillator (ICD) placement (109).

Hypertension (HTN)

In patients with essential HTN, preserved LV ejection fraction, and concentric LV hypertrophy LV apical rotation and peak systolic LV twist are increased (2). This likely represents a compensatory mechanism to preserve myocardial function in the setting of the chronic increase in afterload inherent to hypertensive heart disease. Park et al. (73) further demonstrate that LV twist appears to normalize as the severity of hypertensive diastolic dysfunction progresses, perhaps indicating LV twist mechanics as a novel marker of the transition from compensated to decompensated phases of disease. Schiros et al. (82) have utilized cardiac MRI to study LV torsion (additionally normalized to LV radius) and showed this to be increased in hypertensive concentric remodeling, thereby helping to further characterize LV diastolic function in hypertensive heart disease. Similar to studies of HCM and myocardial fibrosis, hypertensive heart studies have investigated the relationship of LV twist to circulating biomarkers of collagen turnover. Maharaj et al. showed an inverse correlation between serum concentrations of matrix metalloproteinases and LV twist, suggesting that integrity of the extracellular matrix may play an important role in maintaining myocardial function in hypertensive heart disease (54). Mizuguchi et al. have attempted to add further clinical relevance by studying the effect of HTN treatment, and have shown that LV twist decreases after 12 months of therapy with an angiotensin receptor blocker (58). However, whether the magnitude of LV twist at the time of initial medication predicts the response to medical therapy, or if twist decreases in parallel reduction of blood pressure, remains unknown.
Diastolic untwisting rate among patients with HTN has also been examined but with inconsistent results. Park et al. (73) showed that the early diastolic dysfunction caused by HTN is characterized by increased early diastolic untwisting velocity. However, Takeuchi et al. found that similar to HCM, early diastolic untwisting rate was delayed and attenuated among patients with HTN (98). This highlights the need for careful phenotypic characterization of disease stage (i.e. hypertension with structurally normal myocardium, hypertension with compensatory LV hypertrophy, hypertension with systolic dysfunction, etc.) in studies designed to examine disease-specific LV twist mechanics profiles. Further, it should be noted that potential differences in assessment techniques such as those highlighted above might also explain some inconsistencies between clinical studies. Similar to the discussion of HFpEF (above) and mitral regurgitation (below), the stage of disease will impact the LV twist properties and ultimately the goal is to utilize LV twist mechanics data to identify disease stage and appropriate timing and/or effect of therapy.

Aortic stenosis (AS)

LV apical rotation and twist are increased in valvular AS (62, 95). This is similar to HTN, and supports the notion that a chronic increase in afterload results in increased twist. Although multiple mechanisms are likely responsible, this may in part result from diminished coronary blood flow to the subendocardium compared to the subepicardium, resulting in a relative increase in the contribution of the epicardial lever arm. This may be a common mechanism whereby various triggers for LVH result in increased LV twist. Similar to HTN, van Dalen et al. have shown that diastolic untwisting rate in AS is not only delayed but also reduced (105). This apparent “uncoupling” of LV twist mechanics (i.e. increased peak systolic twist in conjunction with relative impairment of early diastolic untwisting rate) remains poorly understood and represents an area of important future work. In addition,
future studies are needed to better define LV twist mechanics across the AS severity spectrum (from mild to severe disease) as it is known that alterations in LV twist mechanics change with disease progression in other cardiomyopathic conditions such as non-valvular HFpEF (73).

Several recent studies have begun to examine the impact of aortic valve replacement on LV twist mechanics. Lindqvist et al. studied the impact of conventional surgical aortic valve replacement and report that peak systolic LV twist decreases after this procedure (51). Bloechlinger et al. showed similar findings, and extended follow up to show that after 2.5 years had elapsed since surgical aortic valve replacement there was further decrease in LV twist values (14, 51). Data on LV twist mechanics after transcatheter aortic valve replacement (TAVR) are limited (83) but will become increasingly available as this procedure continues to increase in popularity. Studies comparing LV twist mechanics and patient outcomes before and after both transfemoral and transapical approaches are warranted, although the transapical approach may distort the myocardial architecture and impact apical rotation in an unpredictable fashion.

**Disease Characterized by LV Volume Challenge**

**Mitral regurgitation (MR)**

The impact of chronic MR on LV twist appears complex as changes in twist depend on the stage of the disease, and as noted above changes in LV volume independent of disease also impact twist mechanics. In contrast to prior animal work (30), human studies of chronic compensated MR show normal or increased LV systolic twist that reduces following surgical mitral valve repair (16, 47). Mechanistic work studying chymase inhibition of titin supports the finding of increased LV twist in chronic MR (75). When considering clinical application of LV twist mechanics assessment in patients with MR, it is plausible that LV twist analysis may serve as a novel measure of myocardial function that assists in
determining the appropriate timing of mitral valve intervention. Moustafa et al. have shown that patients with moderate MR have increased LV rotation and twist, and those with severe MR have reduced twist (61). An elegant cardiac MRI study by Reyhan et al. showed that peak LV systolic twist-per-volume slope decreased as the severity of MR progressed to severe. (61, 81). Identification of an inflection point when twist begins to normalize may ultimately be used as an adjunct to accepted echocardiographic parameters to help determine the optimal timing of mitral valve repair / replacement. Furthermore, a study of mitral valve repair versus replacement showed that repair was associated with improved LV rotation and twist, indicating that preserving the mitral apparatus may have favorable impact on myocardial mechanics (24).

Assessing the Development of Cardiotoxicity

A primary goal of the assessment of LV twist mechanics has been to identify abnormalities in systolic and diastolic myocardial function that are not captured by conventional imaging assessment. This may be beneficial in identifying patients with early stages of myocardial toxicity, given that conventional parameters, such as LVEF, may not be present until later stage disease. At the present time, studies defining LV twist mechanics in patients administered anthracyclines or other potentially cardiotoxic chemotherapeutic agents are sparse. One recent study reported a negative correlation between anthracycline dose and peak systolic LV twist (60). It is expected that investigations of LV twist in the growing population of cancer patients exposed to new therapeutic patients will become more numerous and results may inform the cardio-oncologic community about the need for modifications to treatment regimens.
CONCLUSIONS AND AREAS OF FUTURE WORK

Systolic LV twisting and early diastolic LV untwisting are key components of normal ventricular function and appear to play important roles in physiologic ventricular adaptation and in the development of clinically relevant cardiovascular disease. Despite recent advances, considerable additional work is needed to fully define all aspects of LV twist mechanics and to determine its role in the assessment of human health and disease. The relatively recent development of speckle tracking echocardiography enables rapid assessment of LV twist mechanics, which have informed our understanding of both normal ventricular physiology and adaptation, and also decompensated function in key disease states. It is important to note that disease is often accompanied by altered hemodynamics and autonomies and so changes in LV twist mechanics in clinical populations may not necessarily reflect the disease process per se. Additionally, it is essential to consider alternative parameters for clinical decision making, such as the deformation-based variable “longitudinal strain”. Also termed “Global longitudinal strain” (GLS), this parameter has shown to be predictive of outcome in a number of clinical studies (26, 88, 91) and has recently made it into the general guidelines for the assessment of LV structure and function (50). However, in the interest of a balanced review, it is important to note that GLS has not always been shown to provide superior clinical insight (15) and, despite the obvious limitations of ejection fraction, the extremely wide association between longitudinal strain and ejection fraction suggests that GLS – similar to LV twist – requires further scrutinization (5, 52).

Future work will benefit from a combined approach where changes in LV twist mechanics and GLS are considered and interpreted within the context of both altered physiology and disease state and consequently it will be possible to derive normative values. This will best be accomplished by applying careful attention to the key methodological steps...
including image acquisition, post-imaging data analysis, and consideration of relevant physiologic mediators such as ventricular loading, athletic status and age of individuals. Equally, it is important to consider the implications of measuring LV twist (net twist angle) or whether normalization of data is necessary, for example by calculating LV torsion (twist per LV length) or the torsion-to-shortening ratio (7, 107). Finally, the inter-vendor differences that are apparent for some 2D STI derived deformation data need to be resolved (36, 55), in order to further increase the reproducibility of data. It is our hope that this review will represent a foundation for investigators to responsibly and accurately perform such work and for clinicians to appropriately interpret and apply emerging data as they become available. Together with concerted efforts by all vendors and the adoption of a systematic approach resulting in standardized protocols the assessment of LV twist mechanics holds significant potential to advance our understanding of LV function in human health and cardiovascular disease.
References


### Table 1. Left Ventricular Twist in Various Cardiovascular Diseases

<table>
<thead>
<tr>
<th>Cardiovascular Disease State</th>
<th>Left Ventricular Twist*</th>
<th>Main Findings</th>
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<tbody>
<tr>
<td>Ischemic Cardiomyopathy$^{1,2,3}$</td>
<td>↓</td>
<td>Twist decrease depends on the extent and location of ischemia and/or infarct</td>
</tr>
<tr>
<td>Dilated Cardiomyopathy$^4$</td>
<td>↓</td>
<td>Decrease in twist proportional to the degree of LVEF impairment</td>
</tr>
<tr>
<td>Heart Failure with Preserved Ejection Fraction$^{5,6}$</td>
<td>Normal or ↑</td>
<td>Twist increased in early stages as a compensatory mechanism; prolonged time to peak twist and delayed untwisting plays a role in diastolic dysfunction</td>
</tr>
<tr>
<td>Hypertrophic Cardiomyopathy$^{7,8}$</td>
<td>↑</td>
<td>Increased twist particularly if LVOT obstruction present; Lack of a twist ‘reserve’ with exercise</td>
</tr>
<tr>
<td>Aortic Stenosis$^{9,10}$</td>
<td>↑</td>
<td>Increased twist observed in states of chronic increased LV afterload; decreased twist after aortic valve replacement</td>
</tr>
<tr>
<td>Mitral Regurgitation$^{11}$</td>
<td>↑ (can be ↓ in later stage disease)</td>
<td>LV volume overload states resulting in increased twist during compensated stages of disease; potentially use twist as an adjunctive parameter to determine timing of intervention</td>
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*Indicates LV twist value compared to healthy controls.
**Figure legends**

**Figure 1.** Left ventricular (LV) helices and twist. A, LV endocardial and epicardial helix configuration in end-diastole and B, rotational directions of the LV base and apex. C, Typical LV rotation and twist in a healthy individual during resting conditions. D, Typical untwisting velocity in a healthy individual during resting conditions. For the purpose of clarity the underlying base and apex velocities have been omitted.

**Figure 2.** Importance of standardization of image acquisition of LV apical rotation. LV rotation increases the closer short-axis images are taken towards the true apex. Caudal and oblique views must be avoided accordingly. Schematic in accordance with original findings by van Dalen et al. (99).

**Figure 3.** Examples of basal (top) and apical (bottom) rotation curves generated by the software. The process of analyzing speckle tracking LV twist mechanics is shown in the video that can be found online at: [Insert hyperlink here]. An accompanying document with a more detailed description of the analysis and guide on important methodological aspects is presented at: [Insert hyperlink here].

**Figure 4.** The influence of preload, afterload and contractility on LV twist. The top center figure displays the combined effects of alterations in preload, afterload and contractility on LV twist during exercise, highlighting the large change in LV twist during exercise.