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EDITORIAL COMMENT

A New Twist on Mitral Regurgitation*



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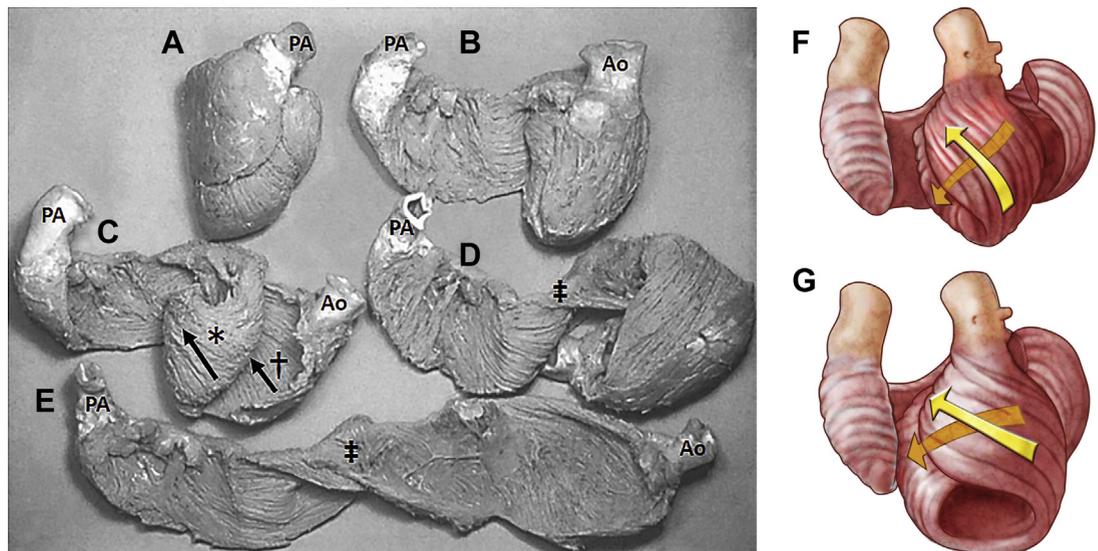
Theories concerning the organization of myocardial fibers in normal mammalian hearts and its relationship to function have been the topic of research for centuries (1). Recently, one relatively easy to understand, clinically relevant theory has emerged based on the work of Francisco Torrent-Guasp which has been brought to the forefront largely through the efforts of Gerald Buckberg (1-3). Torrent-Guasp developed a simple method of blunt, hand dissection of hearts after softening connective tissues by boiling them in water. He showed that the normal ventricular myocardium consists of a single, muscular band that extends from the pulmonary artery to the aorta, with the chambers formed by a well-defined wrapping of this band around the heart's axis. This is best appreciated when the band is unwrapped during the dissection process via naturally occurring dissection planes as shown in sequence of images in **Figures 1A to 1E**. It is demonstrated that the left ventricular (LV) free wall consists of 2 main layers resulting from the overlap of the so-called "descending segment" (see the * in **Figure 1C**) and "ascending segment" (see the † in **Figure 1C**) of the muscular band. Relative to the LV axis, these fiber bundles in these layers are predominantly oriented at ~60° so that when the layers are folded on top of each other to form the LV free wall, the muscle bundles of the inner layer are oriented at +60° while those of the outer layer are oriented at predominantly -60° (**Figure 1F**). Within the muscle bundles identified by Torrent-Guasp, there is a complex secondary

structure of muscle fibers which he likened to the fibers of a multistranded rope. Accordingly, some anatomists have arrived at more complex (e.g., up to 7 muscular layer) models of the myocardial wall. Nevertheless, the dominant angles identified by Torrent-Guasp correlate very well with those identified by Streeter et al. (4) who measured fiber orientations at various depths across the myocardial wall in fixed histological samples.

It is this complex, although highly conserved architecture of the mammalian myocardial wall that underlies its ability to achieve ejection fractions in excess of 60% in the face of only 15% to 20% linear fiber shortening under normal conditions (5), since contraction results in thickening of the wall with simultaneous decreases in length and radius of the chamber. These planes of opposing fiber orientations also result in the normal "wringing" motion of the heart during contraction which, in turn, results in differential rotation of the base and apex. When viewed from the apex, the base of the heart rotates clockwise during contraction while the apex rotates counterclockwise. The net difference in rotation between the base and the apex (quantified in angular degrees) is referred to as twist or torsion. Although ventricular torsion is the result of the distribution of fiber angles across the wall, the degree of torsion is strongly influenced by myocardial contractility and loading conditions (6,7). Torsion can also be influenced by differences in inner and outer muscle bundle layer properties. For example, twist is increased in patients with severe aortic stenosis which has been hypothesized to be due to preferential impairment of endocardial fiber shortening (8). Finally, torsion is also strongly influenced by myocardial activation sequence. Torsion is largely lost in patients with left bundle branch block (9), likely due to the dyssynchronous contractions within and between the inner and outer muscle bundles; accordingly, torsion can be improved by cardiac resynchronization therapy (CRT).

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

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FIGURE 1 Illustration of the Ventricular Myocardial Band

Torrent Guasp et al. (2) identified that the heart is composed of a single myocardial band wrapped on itself to form the ventricular chambers. (A) The band in its normal position in the intact heart. (B) The root of the pulmonary artery (PA) and anterior interventricular groove have been dissected free and the right ventricular free wall is folded back. (C) The aortic root (Ao) and contiguous epicardial, ascending segment of the myocardial bundle (†) is separated and folded off from the descending segment of the myocardial bundle (*) that comprises the endocardial layer of the free wall. The arrows indicate myocardial fiber direction. (D) The left ventricular (LV) chamber is further unfolded towards the right to reveal the “myocardial fold” (‡). (E) The endocardial portion of the band is unfolded to reveal the entire band extending from the PA to the Ao. (F) Schematic representation of normal relative fiber orientations of the epicardial and endocardial fibers (+60° and -60°). (G) In heart failure, with LV dilation, the angle between fiber angles in the 2 layers is reduced, which contributes to LV dysfunction reflected by a reduction of torsion during contraction. Reproduced with permission Torrent-Guasp et al. (2).

Under normal conditions, the heart exhibits a net torsion of ~15°. It is observed clinically that as ejection fraction decreases and the heart remodels, torsion also decreases. Dissections of hearts from patients with heart failure and reduced ejection fraction provide insights into the mechanism (3). Specifically, ventricular dilation is associated with stretching and reorientation of the muscle bundles in such a manner that the relative angle between the main fiber bundles is markedly reduced, with the fibers in both layers coursing more circumferentially (Figure 1G). This reorientation results in a reduction in chamber contractility, independent of changes in chamber size, load, or intrinsic myocardial contractility. This reorientation also results in reduced torsion. Accordingly, a reduction in torsion may be a sensitive, though not a specific marker of remodeling of ventricular wall architecture.

In this issue of *JACC: Basic to Translational Science*, Notomi et al. (10) set out to test whether preservation of ventricular torsion is a prognostic indicator of outcome in symptomatic (New York Heart Association functional classes III and IV) patients with dilated

(nonischemic) cardiomyopathy undergoing surgery for severe mitral regurgitation. This was a retrospective analysis correlating ventricular torsion at baseline to clinical outcomes and LV reverse remodeling in 50 such patients. Nine patients underwent mitral valve replacement and the rest underwent mitral valve repair with preservation of the sub valvular apparatus. There was no post-operative mortality; this is significant in that it suggests that mortality results identified in the study predominantly reflect the underlying disease and treatment of mitral regurgitation.

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Among patients with a normal electrical activation sequence (n = 32), torsion measured prior to surgery was significantly higher in patients who survived over a 2-year follow-up period compared to those who died. This was despite the fact that the groups had similar ejection fractions and Society of Thoracic Surgeons (STS) scores. In addition, patients in whom torsion was reasonably well preserved exhibited more reverse remodeling as indexed by reductions in

end-diastolic and end-systolic volumes and, in the long run, increases in ejection fraction. Patients whose hearts lost torsion at baseline were also more likely to be hospitalized for heart failure during the follow-up period.

Patients with abnormal electrical action (QRS >120 ms with left bundle branch electrocardiogram morphology) were divided into 2 groups: those with pre-existing CRT (n = 6) and those who received CRT as a new therapy in combination with mitral surgery (n = 12). Torsion in these 2 subgroups were similar to each other, but appeared to be less than in the subgroup with normal QRS and preserved torsion. Yet, mortality was extremely high in the group with pre-existent CRT compared to those receiving CRT as a new, additional therapy. Neither of these subgroups exhibited significant reverse remodeling during the follow-up period.

Management of patients with idiopathic cardiomyopathy with severe mitral regurgitation is challenging, with guideline recommendations mainly based on expert opinion rather than evidence. In particular, the role of mitral surgery, the type of mitral surgery, and patient baseline characteristics associated with clinical benefit remain unclear (11). Based on their findings, Notomi et al. (10) propose that loss of torsion and pre-existing CRT (independent of torsion) are factors that predict poor outcome in these patients. As acknowledged by the authors, the small number of patients limits the degree to which the findings can be extrapolated to general practice. In addition, differences in other baseline characteristics between survivors and nonsurvivors such as larger ventricular size and trends towards greater degrees of mitral regurgitation and larger left atrial sizes in nonsurvivors further limit the conclusions regarding the prognostic power of torsion alone in this population.

Despite its limitations, the study highlights the potential utility of torsion in prognostication. This parameter, along with other parameters, such as regional and global measurements of strain, have become more readily available through the use of 2- and 3-dimensional ultrasound speckle tracking (8). Torsion and longitudinal strain have been touted as measures of myocardial dysfunction that may be more sensitive to the presence of pathology than ejection fraction. Although they may be sensitive, it should be appreciated that because they are influenced by many factors, they lack specificity as diagnostic tools. Insights into such matters are borne out by computational approaches, such as finite element methods, where the relative roles of factors, such as fiber orientation, contractility,

hemodynamic load, and nonhomogenous distribution of muscle properties, can be investigated (e.g., see reference [7] for a recent analysis of torsion). The fact that torsion increases with severe aortic stenosis (rather than decreases) (8) highlights potential complexities inherent in the interpretation of this parameter. Thus, such parameters may be most useful for detecting the presence of some pathology, and potentially for tracking natural history of disease progression or responses to therapy (e.g., as noted above for the case of restored torsion following CRT [9]).

It is also of interest to consider certain mechanistic implications of the present findings. As suggested by Notomi et al. (10), it can be hypothesized that a loss of torsion in the context of end-stage dilated cardiomyopathy might reflect an irreversible structural change of fiber orientations that would prevent reverse remodeling after the volume load of mitral regurgitation is eliminated (or lessened) by surgery. In contrast, a heart with retained torsion might reflect a state in which such fiber disorientation has not yet occurred or is only minimally present, allowing for better recovery of function following treatment of the mitral regurgitation. Such a hypothesis has broad implications for predicting the likelihood of reverse remodeling following any treatment for heart failure, not just mitral surgery.

As new, less-invasive interventional methods become available for treating mitral regurgitation (12), there will be the opportunity to treat a larger number of patients, particularly those who are more symptomatic and less likely to be treated surgically. Efforts to identify patients most likely to benefit from such procedures is of prime importance. Such efforts will assuredly be aimed at noninvasive approaches such as offered by ultrasound speckle tracing. In this regard, the correlations between pre-operative torsion and clinical outcomes observed by Notomi et al. (10) deserve further investigation in larger studies. Also, in view of the nonspecific nature of ventricular torsion, it should be noted that newer techniques such as second-order motion-compensated spin echo diffusion tensor imaging that allow for high spatial- and temporal-resolution quantification of fiber angles within the wall of the human heart in vivo may permit such questions concerning changes in myocardial architecture to be addressed through direct measurements (13).

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KEY WORDS contractility, fiber angle, heart failure, LV mechanics, torsion