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EDITORIAL COMMENT

Ventricles Under Stress

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The left ventricle (LV) can be an innocent bystander in valvular heart disease, or, in the case of mitral functional regurgitation, it can be part of the cause. Whether the ventricle is innocent or guilty of causing valvular dysfunction, it adapts to the subsequent hemodynamics at hand. Much of that adaptation is mediated by the changes in LV wall stress caused by valvular dysfunction.

WALL STRESS IS COMPLEX, BUT THE PRINCIPLES ARE SIMPLE

The forces acting on the ventricle during systole and diastole are complex. Increased ventricular cavity pressure leads to both tensile force on the long axis of the myocytes but also compressive forces on the cells. In addition, the muscle is composed of myocytes and connective tissue, each with different viscoelastic properties. Moreover, the LV has a complex geometry, which means that these forces acting on the muscle during the cardiac cycle vary regionally and through the thickness of the myocardium.[1]

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Many equations have been developed to model the forces acting on the ventricle. The Law of Laplace calculates an average wall stress in the middle of the myocardium and is the simplest. That equation is most frequently used in medicine to assess ventricular wall stress and was used by Papapostolou et al[2] in this issue of *JACC*. The LaPlace Law, however, does not consider the heterogeneous viscoelastic properties or complex geometry of the myocardium.

Other models to calculate wall stress, such as those developed by Falsetti,[3] Regen,[4] and McHale and Greenfield,[5] try to match experimental findings in animal models by adding in the elastic properties of the muscle and the time delay in the spread of stress with a change in pressure (hysteresis). These are more precise than the LaPlace Law, but one dominant theme always comes through: the larger the ventricular volume, the more wall stress is required to generate a given pressure. This concept can be easily derived from energy principles as well: it takes more energy to pressurize a larger volume of blood in the ventricle (pressure $\times$ volume $=$ energy).

APPLICATION OF WALL STRESS MEASUREMENTS TO VALVULAR HEART DISEASE

Wall stress during systole is generated primarily by the contracting myocyte. In the case of aortic stenosis, the restricted ventricular outflow leads to increased systolic wall stress as the ventricle contracts against a high resistive load. The myocytes "feel" tensile force associated with the wall stress rather than the pressure; wall stress is what the cells are contracting against. In response to the increased tensile load, the myocytes grow by increasing in diameter, leading to concentric hypertrophy (much like skeletal muscle of weightlifters). The high tensile load produces a very high energy consumption and with time, the ventricle develops more inter-myocyte collagen, replacement fibrosis, loss of systolic function, and dilation.[6] As the ventricular chamber dilates, the wall stress that the contracting myocytes must develop to maintain the same systolic pressure increases further (with the LV diameter). Hence, ventricular dilation leads to a marked increase in wall stress, which in turn leads to higher myocyte strain and oxygen consumption, leading to further deterioration. It is the increase in wall stress that mediates hypertrophy and eventual ventricular failure at end-stage aortic stenosis.

In patients with mitral regurgitation, the story is the same but different. The volume overload induced by mitral regurgitation leads to rapid and sometimes

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massive diastolic LV filling, causing increased diastolic wall stress. The tensile load on the relaxed myocyte during diastole increases, leading to longitudinal growth and ventricular enlargement. This is the same mechanism that produces the Starling effect, in which increases in preload (diastolic myocyte tensile lengthening) cause an increase in contractility *and* increased energy consumption. The enlargement of the ventricular cavity with chronic mitral regurgitation then markedly increases the *systolic* wall stress. Eventually, the ventricle is no longer able to compensate to this increased systolic wall stress and its high energy demands, developing increased intermyocyte matrix and fibrosis, and eventually loss of systolic function.[7]

The increase in diastolic wall stress with mitral regurgitation is moderated by a number of factors that influence the rate and volume of diastolic LV filling: the extent of the regurgitant volume, the compliance and size of the left atrium, and the presence (or absence) of atrial contraction. Systemic factors that affect intravascular volume (eg, renal failure) further modulate diastolic wall stress. Hence for a given regurgitant volume, the change in diastolic wall stress will vary from patient to patient and time to time.

EFFECTS OF VALVULAR CORRECTION ON WALL STRESS

The concentric myocyte hypertrophy of pure systolic pressure overload regresses when the resistive load and systolic tensile force on the myocytes is greatly reduced by aortic valve replacement. Papapostolou et al[2] found that transcatheter aortic valve replacement resulted in an immediate fall in LV wall stress. Subsequent regression of concentric cellular hypertrophy in response to the reduced wall stress, however, takes time. An interesting follow-up to these studies would be late assessment of the regression of hypertrophy and LV dimensions compared with the initial change in LV wall stress.

The long-term effects of the myocyte lengthening associated with regurgitant valves are more complicated. Clinical studies suggest the ventricular changes regress much less after longstanding valvular regurgitation is repaired.[8] Papapostolou et al[2] found that mitral repair indeed reduced diastolic wall stress but had no immediate effect on the elevated systolic wall stress.

Curing the stimulus of diastolic wall stress overload with mitral repair leaves a ventricle that largely remains enlarged and in many cases with fibrosis.[9] Systolic wall stress is persistently elevated because, in systole, the ventricle still must pressurize a greater amount of blood in the enlarged ventricle, which requires increased energy in parallel to the increased ventricular volume. The persistent myocyte elongation and elevated systolic workload to develop systolic pressure reduces the extent of the benefit of removing the valvular regurgitation, often leading to improved but persistent symptoms after mitral repair. Early valve repair, before these changes take place, appears to improve long-term outcome.

Nature designs energy-efficient systems. The volume of a normal ventricle is matched precisely to the stroke volume needs of the organism. If it is too small, the organism will fail. If it is too large, precious energy is wasted as more blood is pressurized with each systole than is needed for ejection. In response to changing conditions, the ventricle modulates its dimensions to meet the new demand. Athletes who require higher cardiac output grow their ventricular chamber size and mass, but not the wall thickness. Increases in ventricular wall stress induced by valvular disease result in hypertrophy to meet systolic loads and enlargement to meet regurgitant loads. Nature seems less able to regress adaptive changes once the abnormal wall stress load is reversed. Although we do not fully understand the long-term effects of these adaptive responses, they are important because they can influence clinical outcomes. The use of wall stress and other assessments of ventricular adaption to valvular disease may allow us to intervene before the onset of irreversible changes in ventricular mechanics.

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