Abnormal Ventricular and Aortic Wall Properties Can Cause Inconsistencies in Grading Aortic Regurgitation Severity: A Computer Simulation Study

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Background: Assessment of aortic regurgitation (AR) severity is often based on Doppler echocardiographic imaging. Hemodynamic responses to AR are influenced by the interplay among cardiovascular properties, including left ventricular (LV) and aortic tissue properties, that cannot be measured directly. The aim of this study was to investigate how both echocardiographic measures of AR severity and the hemodynamic consequences of AR are influenced by LV and aortic stiffness.

Methods: AR was simulated using the CircAdapt computational model of the human cardiovascular system. Simulations were performed with normal LV and aortic stiffness, high LV stiffness, high aortic stiffness, and high LV and aortic stiffness. For each configuration of levels of stiffness, four AR severity grades were simulated by setting the effective regurgitant orifice area (ROA) of the aortic valve at 0, 0.05, 0.25, and 0.6 cm^2, representing no, mild, moderate, and severe AR, respectively. The regurgitant volume, regurgitant fraction (RF), and pressure half-time (PHT) were computed for each simulation giving an AR severity score (mild, moderate, or severe). Mean left atrial pressure was also calculated.

Results: Increasing ROA resulted in faster decay of diastolic flow velocity and larger regurgitant blood flow across the aortic valve. This caused shorter PHT and larger regurgitant volume and RF, all indicating higher AR severity. Increasing aortic stiffness resulted in a larger decline in diastolic aortic pressure, whereas increasing LV stiffness resulted in a larger rise in diastolic LV pressure. Hence, increasing LV and/or aortic stiffness led to faster decay of the transvalvular pressure gradient and, therefore, to faster decay of diastolic flow velocity across the aortic valve compared with normal stiffness with the same ROA. This faster decay led, on one hand, to a shorter PHT, indicating higher severity scores, and, on the other hand, to a lower RF, as less regurgitant blood volume traveled into the left ventricle, indicating lower severity scores. AR severity scores reflected mean left atrial pressure poorly when variations in tissue properties were present.

Conclusions: Simulating altered AR hemodynamics caused by variations in cardiovascular tissue properties led to inconsistent severity scores when evaluating the severity using RF, regurgitant volume, and PHT. In this situation, pulmonary congestion is poorly reflected by AR severity as quantified by ROA, RF, and PHT. Cardiac and aortic tissue properties should therefore be taken into account to improve clinical assessment of AR severity. (J Am Soc Echocardiogr 2016;■:■-■.)

Keywords: Compliance, Aortic insufficiency, Model simulations, Heart failure, CircAdapt

Aortic regurgitation (AR) is a valvular disease characterized by improper aortic valve (AoV) closure, causing diastolic blood flow from the aorta into the left ventricle.[1,2] When the onset of AR is acute, the sudden increase in diastolic left ventricular (LV) pressure can cause pulmonary edema.[3] Gradual development of AR is accompanied by LV enlargement and remodeling, together with high aortic pulse pressure.[4] Severe AR has been associated with LV failure and increased cardiovascular mortality.[5] In both cases, accurate assessment of the severity of both the valvular lesion and its hemodynamic consequences is crucial for timing operative intervention.[6,7]

Current guideline recommendations for AR assessment provide follow-up and management strategies that include quantification of AR severity.[4,8] Evaluation of AR severity consists of integrating a set

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Abbreviations

AoV = Aortic valve
AR = Aortic regurgitation
CO = Cardiac output
LV = Left ventricular
mLAP = Mean left atrial pressure
PHT = Pressure half-time
RF = Regurgitant fraction
ROA = Regurgitant orifice area
RVol = Regurgitant volume
SV = Stroke volume

of imaging-based, mostly echocardiographic, indices providing information about the anatomy and hemodynamics of the AoV.[2,9] The interpretation of these clinical indices remains challenging because of the complex interactions among multiple patient-specific cardiovascular factors that can influence the hemodynamic signals acquired for diagnostic purposes.[10] Previous clinical studies have hypothesized that AR severity indices are influenced not only by the effective regurgitant orifice area (ROA) of the AoV but also by structural properties of the heart and aorta, such as aortic wall stiffness and LV diastolic stiffness.[11-13] The effect of these tissue properties on the hemodynamic consequences of AR is difficult to determine in clinical studies because most noninvasive measures of LV and aortic stiffness are indirect and likely confounded by the presence of AR.[14,15] Computational models of the cardiovascular system allow controlled variation of LV and aortic wall tissue properties and, hence, mechanistic understanding of the relation between the altered flow across the AoV and hemodynamics and tissue mechanics throughout the cardiovascular system.[13,16]

In this study, we used a computational model to (1) investigate how hemodynamic responses to AR are influenced by LV and aortic stiffness, (2) evaluate how clinical indices in the current guidelines for assessing AR severity could be influenced by interpatient differences in LV and aortic stiffness, and (3) investigate how these echocardiographic AR severity indices relate to clinical consequences in terms of pulmonary congestion.

METHODS

We used the CircAdapt[17,18] computational model of the cardiovascular system to simulate cardiovascular mechanics and hemodynamics in the presence of AR (www.circadapt.org). CircAdapt enables fast beat-to-beat simulation of cardiovascular hemodynamic signals in both healthy and pathologic conditions. The model consists of a network of different modules representing the main elements of the closed-loop cardiovascular system, including the atrial and ventricular cavities, the atrioventricular and ventriculoarterial valves, the aorta, and the pulmonary and peripheral vascular circulation (Figure 1A). The mechanics and hemodynamics of all the elements are governed by nonlinear physics and physiologic principles forming a system of differential equations.

AoV, Left Ventricle, and Aorta

The AoV, left ventricle, and aorta were modeled as previously described.[17,18] A detailed description and corresponding mathematical implementation can be found in the Supplemental Methods. Briefly, the AoV consists of a narrow orifice whose area varies over time and whose proximal and distal structures are the left ventricle and the aorta, respectively (Figure 1A). The flow across the AoV in our model is derived by assuming unsteady, incompressible, and nonviscous plug flow traveling from the left ventricle into the aorta through the AoV. The effective opening orifice area of the AoV is 5 cm^2. In AR, the AoV does not close completely, giving rise to backward flow. Hence, in our implementation, effective ROA is 0 cm^2 in the healthy situation, whereas a nonzero ROA allows regurgitant flow (AR) to occur.

The left ventricle is modeled as a cavity surrounded by the LV free wall and septal wall. According to Laplace's law, LV pressure is determined by LV volume and wall tension, which depends on active and passive stress in the myofibers.[18] Diastolic LV stiffness is varied by modifying the passive stress component, as explained in more detail in the Supplemental Methods. Normal diastolic LV stiffness is evident at an LV volume of 132 mL and an LV pressure of 15 mm Hg at mitral valve closure.

The aorta is treated as a compliant large blood vessel, whose distal structure is the peripheral vascular circulation modeled as a systemic vascular resistance. Hemodynamics in the aorta are governed by a pressure–cross-sectional area relationship arising from stress and strain in the vessel walls.[19] This relationship depends on the exponent k as described in the Supplemental Methods, which represents the nonlinearity in the stiffness of the aortic wall. When aortic stiffness is normal ($k = 8$), the corresponding systemic arterial compliance is 1.51 mL · mm Hg^{-1}, as shown in Supplemental Figure S3.[15]

Simulation Protocols

Our reference simulation, representing the healthy situation, corresponded to both normal LV and aortic stiffness and no AR (ROA = 0 cm^2). From this reference simulation with normal levels of stiffness, increases in ROA to 0.05, 0.25, and 0.6 cm^2 were simulated, representing mild, moderate, and severe AR, respectively, following current clinical guidelines.[2] For all four ROAs, simulations were performed with high LV stiffness, with high aortic stiffness, and with high LV and aortic stiffness (Figure 1B). Simulations of AR with high LV or aortic stiffness represent patients with AR with coexisting clinical conditions that increase vascular or ventricular stiffness, summarized in Table 1.[20-22] Global LV stiffness was increased up to 125% above normal LV stiffness, resulting in LV pressure and volume at mitral valve closure of 19 mm Hg and 131 mL, respectively, with normal aortic stiffness. Aortic stiffness was increased by increasing k from 8 to 15,[23,24] resulting in a systemic arterial compliance of 0.82 mL · mm Hg^{-1},[15] with normal LV stiffness, as shown in Supplemental Figure S3. In total, 192 simulations were performed (Figure 1B). All other model parameters were kept constant in all simulations. Simulations were performed at a heart rate of 71 beats/min[25] and with cardiac output (CO) and mean arterial pressure maintained at 5 L/min and 91 mm Hg, respectively, to represent homeostatic pressure-flow regulation through adaptation of systemic vascular resistance and circulating blood volume.[17]

Indices of AR Severity

Four indices that are commonly used in echocardiographic assessment of AR severity in patients were calculated for all simulations: ROA, regurgitant volume (RVol), regurgitant fraction (RF), and pressure half-time (PHT).[10] RVol was the total blood volume flowing backward across the AoV during diastole, in milliliters per beat (Figure 2A).[10] RF was the ratio of RVol over stroke volume (SV), expressed as a percentage (Figure 2A).[10] SV was defined as the total forward volume ejected by the left ventricle during one cardiac cycle.