The hemodynamic effects of acute aortic regurgitation into a stiffened left ventricle resulting from chronic aortic stenosis

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Abstract

Acute aortic regurgitation (AR) post chronic aortic stenosis is a prevalent phenomenon occurring in patients who undergo transcatheter aortic valve replacement (TAVR) surgery. The objective of this work was to characterize the effects of left ventricular diastolic stiffness (LVDS) and AR severity on LV performance. Three LVDS models were inserted into a physiological left heart simulator. AR severity was parametrically varied through 4 levels (ranging from trace to moderate) and compared to a competent aortic valve. Hemodynamic metrics such as average diastolic pressures (DP) and reduction in trans-mitral flow were measured. AR index was calculated as a function of AR severity and LVDS, and the work required to make up for lost volume due to AR was estimated. In the presence of trace AR, higher LVDS had up to a threefold reduction in trans-mitral flow (13% compared to 3.5%) and a significant increase in DP (two-fold). The AR index ranged from 42 to 16 (no AR to moderate AR), with stiffer LVs having lower values. To compensate for lost volume due to AR, the low, medium, and high LVDS models were found to require 5.1, 5.5, and 6.6 times more work, respectively. This work shows that the LVDS has a significant effect on the LV performance in the presence of AR. Therefore, the LVDS of potential TAVR patients should be assessed to gain an initial indication of their ability to tolerate post-procedural AR.

New and Noteworthy

This study has demonstrated the hemodynamic effects of acute aortic regurgitation (AR) on a left ventricle (LV) which has experienced chronic aortic stenosis (AS). The LV diastolic stiffness resulting from chronic AS dramatically alters the LV's ability to compensate for the lost volume due to AR.

Keywords: aortic regurgitation, left ventricle diastolic stiffness, AR index, left heart simulator, transcatheter aortic valve replacement

1. Introduction

The purpose of the aortic valve (AV) is to prevent the backflow of blood into the left ventricle (LV) from the aorta. Impairment of this function results in retrograde flow from a high-pressure aorta into a lower pressure LV. This complication can result from a multitude of pathological events that can affect the valve primarily e.g. endocarditis, rheumatic disease or affect the ascending aorta primarily e.g. ankylosing spondylitis, idiopathic dilation of the aorta, Marfan syndrome, etc. (1, 2, 3). However, a new mechanism for aortic regurgitation (AR), commonly known as paravalvular leak, stems from a relatively recent AV replacement technique - transcatheter aortic valve replacement (TAVR). Though this minimally invasive surgical technique has many advantages for the treatment of high-risk and inoperable aortic stenosis (AS) patients, it usually results in trace to mild, and in some cases moderate, paravalvular AR (4, 5, 6, 7). This complication (paravalvular AR) has significant correlation to increased patient mortality (4, 5, 6, 7, 8).

When compared to patients who have isolated AR, the 1-year mortality rate of mild AR patients with pre-existing AS is about 3 to 4 times higher (5, 8). The pre-existing isolated AS in TAVR patients has most likely resulted in an increase in the transvalvular pressure gradient across the AV, eventually leading to myocardial hypertrophy. Myocardial stiffening impairs LV relaxation during the diastolic phase of the cardiac cycle (9, 10). Compounding the pathological changes due to isolated chronic AS with the effects of AR compromises the LV's ability to increase its end diastolic volume (EDV) effectively, hence the total stroke volume (SV) and forward SV decrease (11, 12, 9). It is therefore suspected that this sudden change from pressure overload due to AS, to volume overload resulting from acute AR, affects patient survival.

To gain deeper insight on the severity of AR post-chronic AS, Sinning et al. proposed a new metric to supplement what is clinically used for AR classification, the AR index (13). This novel metric utilizes the ratio of the pressure gradient across the AV during diastole to the peak systolic aortic pressure. Sin-

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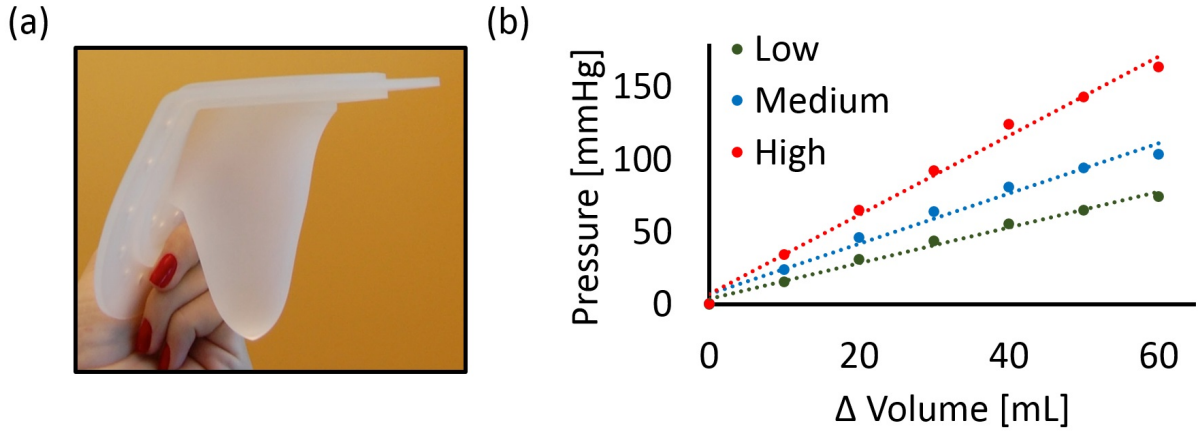

Figure 1: (a) Left ventricle (LV) model and (b) Increase in LV pressure as a function of LV volume from peak systolic state. The y-axis is a change in volume from the end systolic volume of the LV models. The diastolic stiffness values for the low, medium, and high LV models were 1.24, 1.72, and 2.72 mmHg/mL, respectively.

ning demonstrated that this new index is correlated to 1-year mortality risk. Nevertheless, the AR index only provides information regarding the severity of acute AR post-chronic AS, and offers insight to the chances of survival of an individual. It is also necessary to understand the hemodynamic and survival consequences of inducing AR in an individual who has already experienced LV remodeling due to chronic AS. In other words, how well can a LV, which has undergone remodeling resulting from chronic AS, tolerate acute AR?

We hypothesize that the increased LV diastolic stiffness (LVDS) resulting from chronic AS decreases the efficiency of the LV while concurrently increasing the stroke work (SW) required to maintain a healthy forward SV. Decoupling AR and LV function could generate a more cohesive understanding of AR in the presence of AS and could lead to better patient specific therapeutic strategies.

In this current study, the isolated effects of LVDS and AR on LV performance were evaluated. We demonstrated that the LVDS of a patient should be taken into consideration in order to gain insight on the patient's ability to tolerate AR post-TAVR. In this study, AR severity and LVDS were varied in an extensively validated, physiological left heart simulator (14, 15). The use of this fully controllable experimental environment allowed for the study to be performed in the absence of other confounding factors that exist in vivo.

2. Methods

2.1. Left Ventricle

The LV model geometry (Figure 1a) was designed based on the end systolic cardiac phase of a healthy human subject (please see our previous work for more details (14)). A 1 mm thick, isotropic, silicone polymer was used to model the LV wall. The LVDS was increased by varying the composition of the polymer, thereby modifying its ability to stretch under an applied pressure.

To measure the LVDS of each of the models, the inner LV chamber was filled with fluid (to the end systolic volume - non-stretched state of the LV model) and then sealed. Fluid was then incrementally added, stretching the LV models (please see Figure 1b). At each volume increment, the absolute pressure within the LV was measured. The stiffness of each of the LV models was then approximated as the slope of a linear fit to its corresponding measurements. For this study, 3 LVDS values (1.24, 1.72, and 2.72 mmHg/mL) were chosen such that they varied within the range of patients with chronic AS (16, 10). For the purpose of this work, we refer to the above LVDS values as low, medium, and high stiffness, respectively. The LV models were custom manufactured by Venair, Inc. (Terrassa, Spain) via a casting process.

2.2. Aortic Valve

The AV used in this work was constructed from an excised 23 mm porcine aortic valve. The commissures of the valve leaflets were sutured to the posts of a 3-pillared stent (Figure 2a). The sutured aortic valve was then lightly fixed with 0.1% glutaraldehyde solution for 6 hours. AR was induced via a second stent (AR stent) which was inserted into the coaptation zone of the AV such that the leaflets coapted along the walls of a central, hollow AR channel (Figure 2b and c). The walls of the AR channel were 0.2 mm thick - too thin to significantly affect the pressure drop across the AV (Figure 2d and Table I). The geometry of the AR stent regurgitant orifice area (ROA) was taken from computed tomographic images of patients with central AR as reported by Calleja et al. (17). To induce multiple levels of AR, the extracted ROA was scaled by a constant. In this work, five levels of AR conditions (four plus control) were investigated, with ROAs ranging from 0 to 0.16 cm^2 (Table I). This ROA range led to AR fractions of up to 45% (mild to moderate according to AHA guidelines (11)).

Table 1: Hemodynamic Parameters and Classification of AR according to AHA (6). The term "mean" refers to an average across all LV models tested.

AR Stent	**ROA,** cm^2	**Mean TVPG,** $mmHg$	**Mean AR Fraction, %**	**AHA Classifcation**
Control	0	8.13±0.35	2.20±1.64	None (closing volume)
1	0.0121	9.98±0.56	9.20±1.77	Trace
2	0.0331	10.48±0.49	15.7±0.25	Mild
3	0.0866	11.71±0.12	32.0±1.24	Mild/Moderate
4	0.1598	12.45±1.22	43.7±4.58	Moderate

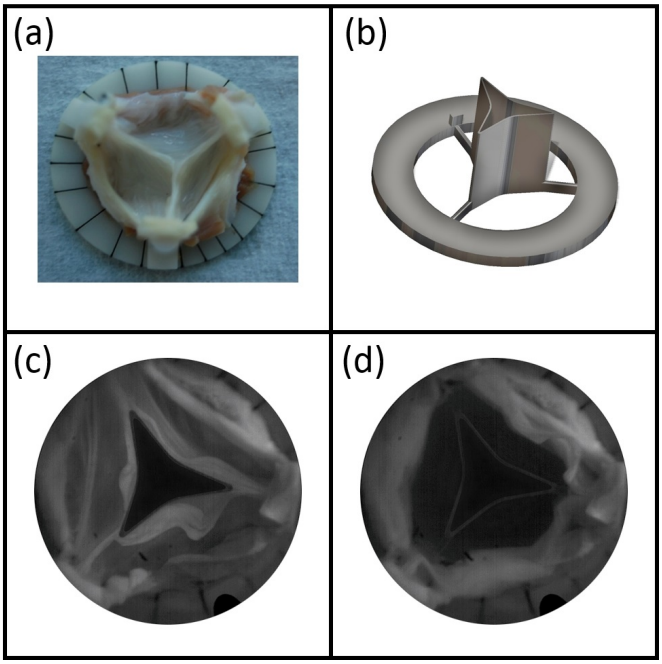

Figure 2: (a) Excised porcine aortic valve sutured to the 3-pillared stent (b) AR stent model (c) Aortic valve leaflets coapting along the sides of the AR stent model walls (d) Open aortic valve during systolic flow with AR stent present.

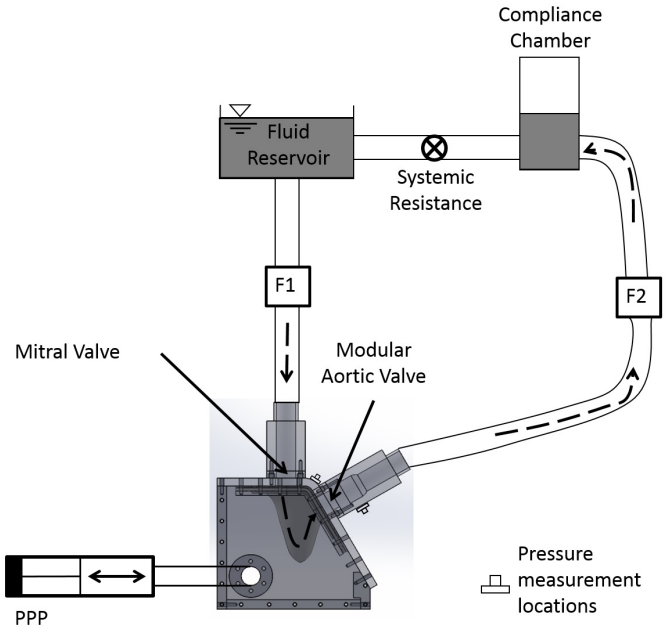

Figure 3: Schematic of left heart simulator. The dashed arrows indicate the direction of flow. PPP stands for programmable piston pump. F1 and F2 are flow probes.

2.3. Left Heart Simulator

The LV models and AV were integrated into a validated physiologic left heart simulator (LHS) (14, 15). In summary the LHS consists of a rigid atrium, a compliant LV, and a rigid aorta. The LHS was designed to be modular such that the valves and the LV could be easily exchanged. A programmable linear piston pump controlled the motion of the LV (Figure 3). The blood analogue used was a mixture of 36 v/v% glycerin-water solution, which mimicked the viscosity of blood. A 33mm Hancock II valve was used at the mitral valve position.

Lumped systemic resistance and compliance elements were used to tune the simulator to physiologic conditions. Flow rates into and out of the LV were measured using ultrasonic flow probes (TS 410, Transonic Systems Inc., Ithaca, NY). Pressures were measured in the LV and aorta using strain-gage pressure transducers (Model 6199, Utah Medical Products Inc., Midvale, UT). An in-house LabVIEW (National Instruments Corporation, Austin, Texas) program was used to record 200 cardiac cycles of hemodynamic data at a frequency of 2 kHz. Due to the robustness and high repeatability of the system, the cycle-to-cycle variations were insignificant. The standard deviations in the global hemodynamic parameters collected were found to be less than 1% of their respective mean values.

2.4. Hemodynamic Conditions

Five levels (including a competent AV - Control) of ROAs were parametrically varied along with three levels of LVDS. For each of the LV models, baseline hemodynamic conditions were initially established in the LHS utilizing a competent AV, after which the AR stents were sequentially introduced to the system. The baseline hemodynamic conditions were as follows: ~125/80 mmHg aortic pressure, heart rate of 70 beats/minute, cardiac output of ~5.0 L/min, diastolic duration of ~67% of the cardiac cycle, peak aortic flow rate of ~28 L/min, and peak mitral E and A-wave flow rates of ~18 and ~16 L/min (E/A ratio of ~1.13), respectively. Within each of the LV models, the work input to the simulator via the linear piston pump was held constant. This was done by monitoring the pressure in the outer LV chamber and keeping the linear pistons' displacement constant across each LV model condition.

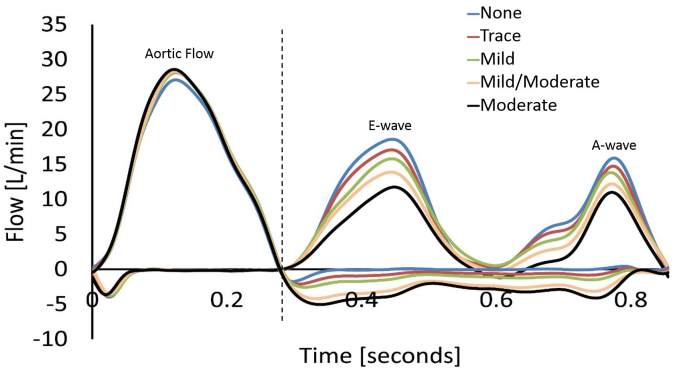

Figure 4: Representative mitral and aortic flow curves for all AR levels - Low LVDS model.

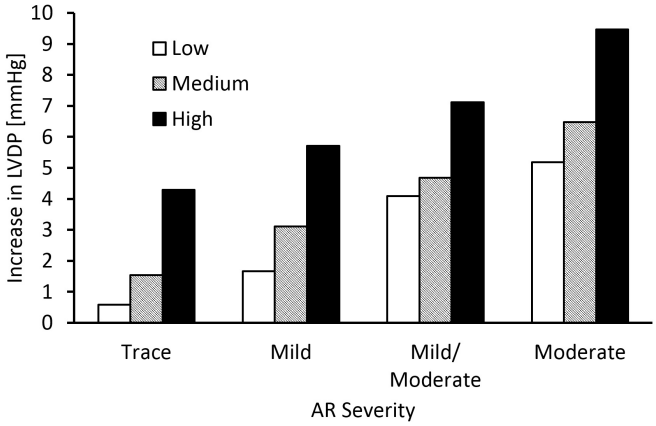

Figure 6: Increase in LVDP as a functions of AR severity and LVDS. The legend represents the severity of LV stiffness.

3. Results

3.1. Changes in LV Hemodynamics

For all LV models tested, AR severity increased with increasing ROA (ranging from none to moderate AR - Table I), leading to a decrease in the effective CO. Figure 4 shows that the peak aortic flow rate for all ROAs studied remained relatively constant at approximately 28 L/min. The LV filling rate via the mitral valve (MV) was found to decrease during the E and A-waves as ROA increased. This decrease in LV filling rate was more pronounced as LV diastolic stiffness increased. Figure 5 shows a difference in the temporal integration of LV filling curves via the MV of each experimental condition from its respective control case (no AR). It indicates the changes that occur in LV filling volume as LVDS increased. As the LVDS increased by a factor of ~2, the corresponding reductions in LV filling volumes as AR was induced increased. This increase in the reduction of LV filling was more apparent for lower AR fractions.

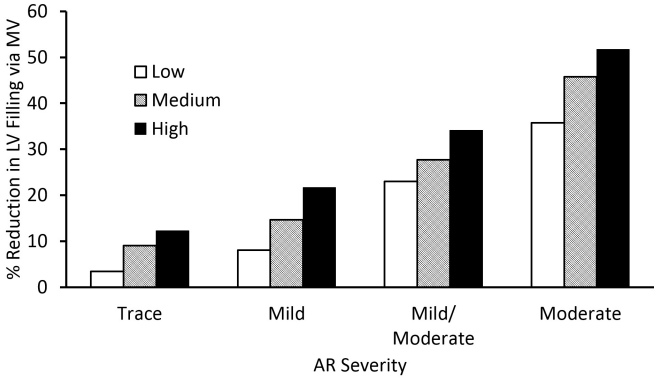

Figure 5: Percent reduction in trans-mitral filling as a function of AR severity and LVDS. The legend represents LVDS.

Due to an increase in the back pressure from the aorta, the DP within the LV increased as ROA increased. The LVDP was also observed to increase as LVDS was increased as depicted in Figure 6. This rate of increase in LVDP as ROA increased was found to be similar across LV models.

3.2. AR Index

The AR index was calculated using Equation 1 below (13)

$$\text{AR INDEX} = 100 \times \frac{DBP - LVEDP}{SBP} \tag{1}$$

where DBP is diastolic blood pressure in the aorta, LVEDP is the left ventricular end diastolic pressure, and SBP is the systolic blood pressure in the aorta. Figure 7 shows the change in the AR index as a function of AR severity and LVDS. The values of AR index measured in the study ranged from approximately 42 to 16. As ROA increased, the AR index decreased. In the same fashion, it was observed that as LVDS increased, the AR index decreased. The reduction in AR index as a function of ROA was quantitatively similar when comparing all LV models studied.

3.3. Additional Stroke Work Requirement

To determine how much more work the LV would have to generate to make up for the lost volume during AR, for each ROA, the SV was increased such that the effective cardiac output was increased back to the original 5.0 L/min. For each of those cases, the SW was calculated using Equation 2 below:

$$SW = \oint_C PdV \tag{2}$$

where P and V are the pressure and volume in the LV model, respectively, and C indicates that the integration was performed over the closed pressure-volume loop.

Figure 8 illustrates the percent additional SW required by the LV to maintain a CO of 5.0 L/min as a function of ROA for each of the LV models. Each individual plot is the percentage difference from its respective baseline (with no ROA). Hence, an additional SW requirement of 10% indicates a 110% energy requirement was necessary, for that specific LV model, to maintain an effective cardiac output of 5.0 L/min. A linear regression analysis was performed with a goodness of fit, R^2. The slope of the regression describes the fold change in work needed per cm2 of ROA. It was found that as LVDS increased,

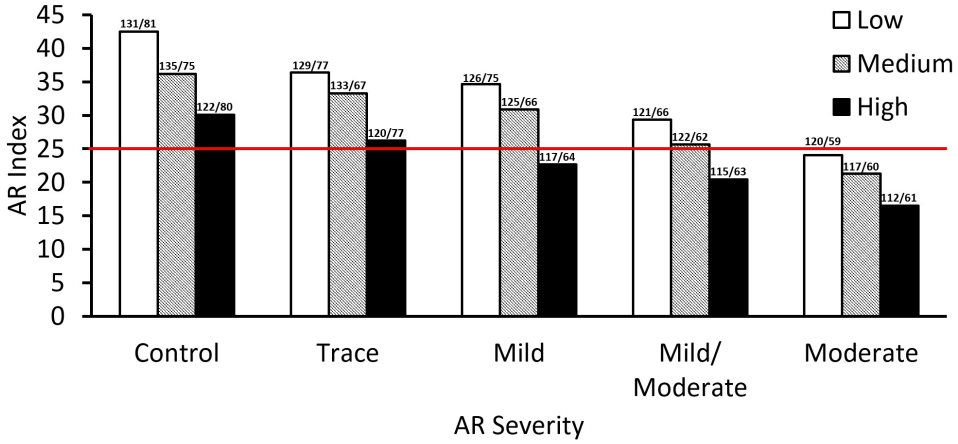

Figure 7: AR index as a function of AR severity and LVDS. The horizontal line represents the cutoff value for survival at 1 year as determined by Sinning et al. (13). The legend represents the severity of LVDS. The numbers above each individual bar are the aortic systolic/diastolic pressures in mmHg.

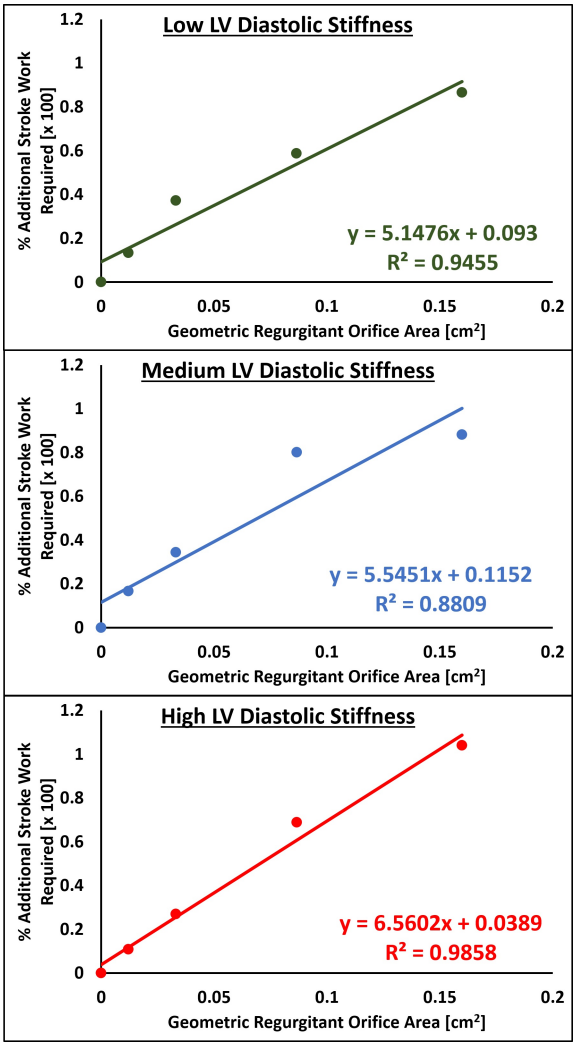

Figure 8: Percent additional SW required to increase the cardiac output back to 5.0 L/min as a function of AR severity.

the slope of the linear regression increased. The slopes from Figure 8 revealed that for the low, medium, and high diastolic stiffness models, the LV would need to work 5.1, 5.5, and 6.6 times harder, respectively, per square-centimeter of ROA.

4. Discussion

In this study, we quantitatively evaluated the effects of LVDS on LV performance in the presence of AR. For each of the different levels of LVDS, AR was parametrically varied from none to moderate AR. The AR index was used as a metric to estimate AR tolerance by the LV as it has previously been shown to correlate strongly to high mortality (13).

Before the TAVR procedure is carried out, improved pre-procedural data have the potential to determine a patient's ability to tolerate different levels of AR. This becomes increasingly important as TAVR indications expand towards lower risk patients (18). From previous studies, we understand that for patients to tolerate AR, the LV must be able to compensate for the extra volume returning from the aorta (19, 20, 21, 22, 9). In the case of patients with preexisting chronic AS, this compensatory mechanism is diminished (9). It is, therefore, important to estimate the LVDS pre-surgery, to gain an indication of how much AR the LV may tolerate. Furthermore, there is a need to understand the physiology of the LV performance as a function of AR severity and LVDS.

In this study, we observed a decrease in trans-mitral flow as AR increased and this effect was exacerbated as the LVDS increased. Furthermore, the rate of filling of the LV also decreased with increasing LVDS. This observed phenomenon was due to the rate of equalization of pressures between the left atrium and LV as a function of cardiac cycle diastolic time (23, 24). The increase in the rate of pressure equalization is affected by the LVs myocardium's ability to stretch during both passive and active filling (24, 25). As the regurgitant flow from the aorta is forced into the LV, the lack of myocardial diastolic compliance prevents the LV from stretching to accommodate the extra volume, hence raising the LVDP (Figures 5

and 6) (26). This increase in LVDP is an increase in the preload which the atrial pressure must then overcome in order for adequate LV filling via the mitral valve to occur.

The values of AR index measured in the study ranged from approximately 42 to 16. Figure 6 shows an increase in the LVDP as LVDS was increased. In Figure 7, we clearly observe that higher LVDS decreased the AR index. Sinning et al. correlated this index to survival of TAVR patients with AR and showed statistical evidence that a cutoff value of 25 was optimal for survival one year post-surgery (13). Based on this value, Figure 7 shows that for the highest LVDS, even trace AR was sufficient to push the AR index close to the threshold. Every other AR severity case for this LV model fell below this cutoff value. For the low LVDS case, the AR index was above the cutoff until the AR severity was at a moderate level, where it fell just below the threshold. These results emphasize the effectiveness of LVDS as a metric to evaluate the AR tolerance of patients prior to aortic valve replacement. They indicate that patients with low LVDS could have a higher tolerance to post-intervention AR.

From the definition of the AR index (Equation 1), either a large numerator (DBP - LVEDP) or a small denominator (SBP) is preferred - both would lead to higher AR index values (13). The reduction of the difference between DBP in the aorta and the LVEDP results from AR, as the pressures in the aorta decreases due to blood leaking into the LV (9). Simultaneously, the LVDP increases as the LV chamber is no longer sealed off from the much greater systemic pressures. This increase in LVDP is further intensified as LVDS increases (27). On the other hand, a lower SBP can be obtained by reducing the systemic resistance (or pressure). However, unlike acute AR, during chronic AR, the LV attempts to remodel such that it is able to push out the lost volume resulting from the backflow of blood. This inherently raises the SBP, and hence, lowers the AR index. It is therefore, important to note that the AR index is only a complementary parameter to be used to assess AR severity.

Finally, to gain an idea of the extra workload imposed on the LV as a result of AR severity, Figure 8 depicts the percent additional SW required as a function of ROA for each of the LV models studied. In basic terms, the LV SW is a multiplication of pressure and volume. Again, as the change in volumes across all the LV models were similar, the only parameter which affected the calculated SW was the difference in pressures. The results show that the LV model with the highest LVDS has to work approximately 30% harder than the lowest stiffness model in the presence of AR. We speculate that this difference is too great for the LV to compensate for, which could be the reason why mild/moderate AR post-TAVR results in high mortality (28, 29, 18, 30, 7).

5. Limitations

While the results of this study have important clinical implications, a few limitations need to be noted. Firstly, the LV models used in this work were isotropic in nature, meaning they were idealized and uniform in terms of LVDS and geometry. Secondly, this study was conducted using an idealized in vitro simulator, which does not contain the multiple disease confounders, which exist in patients undergoing the TAVR procedure. However, an in vitro model such as this allows for fully controlled parametric studies to be performed, ensuring that the differences being observed are only a result of the altered parameter. Thirdly, central AR (not paravalvular) was modeled in this study; however, the metrics analyzed resulted from bulk hemodynamic parameters. Therefore, the results observed in this study should hold true for paravalvular AR as well. Finally, although this work focuses on the effect of LVDS and AR on LV performance, it should be noted that other factors, such as residual prosthesis stenosis, cardiac output, LV size, etc., influence how well the patient might tolerate AR post AS.

6. Conclusions

This work has provided, in an in vitro model, evidence that LVDS affects the hemodynamic severity of AR. It was shown that increased LVDS substantially increases the SW requirement to maintain a forward SV of 70 mL/beat in the presence of AR. The results presented suggest that a TAVR patient's LVDS significantly impacts their ability to compensate for post-procedural AR, and has potential to predict TAVR patient outcomes. Within the limitations of this study, these findings suggest that pre-operative measurement of LVDS could potentially be used to augment patient-specific assessment of TAVR risk. An investigation of this work using animal models would lend more insight to its generalization towards humans.

7. Acknowledgments

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References

[1] Raffi Bekeredjian and Paul A Grayburn. Valvular heart disease: aortic regurgitation. *Circulation*, 112(1):125–34, jul 2005.

[2] R O Bonow, E Lakatos, B J Maron, and S E Epstein. Serial long-term assessment of the natural history of asymptomatic patients with chronic aortic regurgitation and normal left ventricular systolic function. *Circulation*, 84(4):1625–1635, 1991.

[3] Maurice Enriquez-Sarano and A Jamil Tajik. Aortic regurgitation. *New England Journal of Medicine*, 351(15):1539–1546, 2004.

[4] Philippe Généreux, John G Webb, Lars G Svensson, Susheel K Kodali, Lowell F Satler, William F Fearon, Charles J Davidson, Andrew C Eisenhauer, Raj R Makkar, Geoffrey W Bergman, Vasilis Babaliaros, Joseph E Bavaria, Omaida C Velazquez, Mathew R Williams, Irene Hueter, Ke Xu, and Martin B Leon. Vascular Complications After Transcatheter Aortic Valve Replacement: Insights From the PARTNER (Placement of AoRTic TraNscathetER Valve) Trial. *Journal of the American College of Cardiology*, 60(12):1043–1052, 2012.

[5] Susheel K Kodali, Mathew R Williams, Craig R Smith, Lars G Svensson, John G Webb, Raj R Makkar, Gregory P Fontana, Todd M Dewey, Vinod H Thourani, Augusto D Pichard, Michael Fischbein, Wilson Y Szeto, Scott Lim, Kevin L Greason, Paul S Teirstein, S Chris Malaisrie, Pamela S Douglas, Rebecca T Hahn, Brian Whisenant, Alan Zajarias, Duolao Wang, Jodi J Akin, William N Anderson, and Martin B Leon. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *The New England journal of medicine*, 366(18):1686–95, may 2012.

[6] Stamatios Lerakis, Salim S Hayek, and Pamela S Douglas. Paravalvular aortic leak after transcatheter aortic valve replacement: current knowledge. *Circulation*, 127(3):397–407, jan 2013.

[7] Jan-Malte Sinning, Mariuca Vasa-Nicotera, Derek Chin, Christoph Hammerstingl, Alexander Ghanem, Johan Bence, Jan Kovac, Eberhard Grube, Georg Nickenig, and Nikos Werner. Evaluation and management of paravalvular aortic regurgitation after transcatheter aortic valve replacement. *Journal of the American College of Cardiology*, 62(1):11–20, jul 2013.

[8] Corrado Tamburino, Davide Capodanno, Angelo Ramondo, Anna Sonia Petronio, Federica Ettori, Gennaro Santoro, Silvio Klugmann, Francesco Bedogni, Francesco Maisano, Antonio Marzocchi, Arnaldo Poli, David Antoniucci, Massimo Napodano, Marco De Carlo, Claudia Fiorina, and Gian Paolo Ussia. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. *Circulation*, 123(3):299–308, jan 2011.

[9] Michael Gotzmann, Michael Lindstaedt, and Andreas Mügge. From pressure overload to volume overload: aortic regurgitation after transcatheter aortic valve implantation. *American heart journal*, 163(6):903–11, jun 2012.

[10] W. Grossman, M. a. Stefadouros, L. P. Mclaurin, E. L. Rolett, and D. T. Young. Quantitative Assessment of Left Ventricular Diastolic Stiffness in Man. *Circulation*, 47(3):567–574, mar 1973.

[11] Robert O Bonow, Blase a Carabello, Kanu Chatterjee, Antonio C de Leon, David P Faxon, Michael D Freed, William H Gaasch, Bruce Whitney Lytle, Rick A. Nishimura, Patrick T. O'Gara, Robert A. O'Rourke, Catherine M Otto, Pravin M Shah, Jack S Shanewise, Sidney C Smith, Alice K Jacobs, Cynthia D Adams, Jeffrey L Anderson, Elliott M Antman, David P Faxon, Valentin Fuster, Jonathan L Halperin, Loren F Hiratzka, Sharon a Hunt, Bruce W Lytle, Rick Nishimura, Richard L Page, and Barbara Riegel. ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease. *Journal of the American College of Cardiology*, 48(3):e1–e148, aug 2006.

[12] Blase A Carabello and Walter J Paulus. Aortic stenosis. *The Lancet*, 373(9667):956–966, mar 2009.

[13] Jan Malte Sinning, Christoph Hammerstingl, Mariuca Vasa-Nicotera, Viktoria Adenauer, Sisa Josefina Lema Cachiguango, Anne Cathérine Scheer, Sven Hausen, Alexander Sedaghat, Alexander Ghanem, Cornelius Mller, Eberhard Grube, Georg Nickenig, and Nikos Werner. Aortic regurgitation index defines severity of peri-prosthetic regurgitation and predicts outcome in patients after transcatheter aortic valve implantation. *Journal of the American College of Cardiology*, 59(13):1134–1141, 2012.

[14] Ikechukwu U. Okafor, Arvind Santhanakrishnan, Brandon D. Chaffins, Lucia Mirabella, John N. Oshinski, and Ajit P. Yoganathan. Cardiovascular magnetic resonance compatible physical model of the left ventricle for multi-modality characterization of wall motion and hemodynamics. *Journal of Cardiovascular Magnetic Resonance*, 17(1):51, dec 2015.

[15] Ikechukwu U. Okafor, Arvind Santhanakrishnan, Vrishank S. Raghav, and Ajit P. Yoganathan. Role of Mitral Annulus Diastolic Geometry on Intraventricular Filling Dynamics. *Journal of Biomechanical Engineering*, 137(12):121007, nov 2015.

[16] W. H. Gaasch, W. E. Battle, a. a. Oboler, J. S. Banas, and H. J. Levine. Left Ventricular Stress and Compliance in Man: With Special Reference to Normalized Ventricular Function Curves. *Circulation*, 45(4):746–762, apr 1972.

[17] Anna Calleja, Paaladinesh Thavendiranathan, Razvan Ioan Ionasec, Helene Houle, Shizhen Liu, Ingmar Voigt, Chittoor Sai Sudhakar, Juan Crestanello, Thomas Ryan, and Mani A Vannan. Automated quantitative 3-dimensional modeling of the aortic valve and root by 3-dimensional transesophageal echocardiography in normals, aortic regurgitation, and aortic stenosis: comparison to computed tomography in normals and clinical implications. *Circulation. Cardiovascular imaging*, 6(1):99–108, jan 2013.

[18] R Lange, S Bleiziffer, D Mazzitelli, Y Elhmidi, A Opitz, M Krane, M A Deutsch, H Ruge, G Brockmann, B Voss, C Schreiber, P Tassani, and N Piazza. Improvements in Transcatheter Aortic Valve Implantation Outcomes in Lower Surgical Risk Patients. *Jac*, 59(3):280–287, 2012.

[19] Israel Belenkie and A Rademaker. Acute and chronic changes after aortic valve damage in the intact dog. *The American journal of physiology*, 241(1):H95–103, jul 1981.

[20] J. L. Bolen and E. L. Alderman. Hemodynamic consequences of afterload reduction in patients with chronic aortic regurgitation. *Circulation*, 53(5):879–883, may 1976.

[21] R O Bonow, D R Rosing, K M Kent, and S E Epstein. Timing of operation for chronic aortic regurgitation. *The American journal of cardiology*, 50(2):325–336, 1982.

[22] W H Gaasch, C W Andrias, and H J Levine. Chronic aortic regurgitation: the effect of aortic valve replacement on left ventricular volume, mass and function. *Circulation*, 58(5):825–836, 1978.

[23] C P Appleton, J M Galloway, M S Gonzalez, M Gaballa, and M a Basnight. Estimation of left ventricular filling pressures using two-dimensional and Doppler echocardiography in adult patients with cardiac disease. Additional value of analyzing left atrial size, left atrial ejection fraction and the difference in duration of pul. *Journal of the American College of Cardiology*, 22(7):1972–1982, 1993.

[24] Y Ishida, J S Meisner, K Tsujioka, J I Gallo, C Yoran, R W Frater, and E L Yellin. Left ventricular filling dynamics: influence of left ventricular relaxation and left atrial pressure. *Circulation*, 74(1):187–196, 1986.

[25] N M Magid, Donald C Wallerson, J S Borer, Ashis Mukherjee, Mason S Young, R B Devereux, and John N Carter. Left ventricular diastolic and systolic performance during chronic experimental aortic regurgitation. *The American journal of physiology*, 263(1 Pt 2):H226–33, jul 1992.

[26] W. Gerald Austen, Harvey W. Bender, Benson R. Wilcox, and Andrew G. Morrow. Experimental aortic regurgitation. *Journal of Surgical Research*, 3(10):466–470, dec 1963.

[27] O. M. Hess, M. Ritter, J. Schneider, J. Grimm, M. Turina, and H. P. Krayenbuehl. Diastolic stiffness and myocardial structure in aortic valve disease before and after valve replacement. *Circulation*, 69(5):855–865, may 1984.

[28] Paul T L Chiam and Carlos E Ruiz. Percutaneous transcatheter aortic valve implantation: Evolution of the technology. *American heart journal*, 157(2):229–42, feb 2009.

[29] FERNANDO Florenzano and STANTON A Glantz. Left ventricular mechanical adaptation to chronic aortic regurgitation in intact dogs. *American Journal of Physiology-Heart and Circulatory Physiology*, 252(5):H969–H984, 1987.

[30] N M Magid, George Opio, D C Wallerson, Mason S Young, and Jeffrey S Borer. Heart failure due to chronic experimental aortic regurgitation. *The American journal of physiology*, 267(2 Pt 2):H556–62, aug 1994.