Endovascular Repair of Blunt Thoracic Aortic Trauma is Associated With Increased Left Ventricular Mass, Hypertension, and Off-target Aortic Remodeling

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Background: Aortic elasticity creates a cushion that protects the heart from pressure injury, and a recoil that helps perfuse the coronary arteries. TEVAR has become first-line therapy for many aortic pathologies including trauma, but stent-grafts stiffen the aorta and likely increase LV afterload.

Objective: Test the hypothesis that trauma TEVAR is associated with LV mass increase and adverse off-target aortic remodeling.

Methods: Computed Tomography Angiography (CTA) scans of 20 trauma TEVAR patients (17 M/3 F) at baseline [age 34.9 ± 18.5 (11.4–71.5) years] and 5.1 ± 3.1 (1.1–12.3) years after repair were used to measure changes in LV mass, LV mass index, and diameters and lengths of the ascending thoracic aorta (ATA). Measurements were compared with similarly-aged control patients without aortic repair (21 M/21 F) evaluated at similar follow-ups.

Results: LV mass and LV mass index of TEVAR patients increased from 138.5 ± 39.6 g and 72.35 ± 15.17 g/m^2 to 173.5 ± 50.1 g and 85.48 ± 18.34 g/m^2 at the rate of 10.03 ± 12.79 g/yr and 6.25 ± 10.28 g/m^2/yr, whereas in control patients LV characteristics did not change. ATA diameters of TEVAR patients increased at a rate of 0.60 ± 0.80 mm/yr, which was 2.4-fold faster than in controls. ATA length in both TEVAR and control patients increased at 0.58 mm/yr. Half of TEVAR patients had hypertension at follow-up compared to only 5% at baseline.

Conclusions: TEVAR is associated with LV mass increase, development of hypertension, and accelerated expansile remodeling of the ascending aorta. Although younger trauma patients may adapt to these effects, these changes may be even more important in older patients with other aortic pathologies and diminished baseline cardiac function.

Keywords: blunt aortic trauma, hypertension, left ventricular mass, remodeling, stent-graft, ventricular-arterial coupling, Windkessel

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Traditional open surgical intervention for thoracic aortic disease or injury requires large chest incisions, clamping of the aorta, and other adjunctive maneuvers, such as cardiopulmonary bypass, which are associated with substantial short-term morbidity and mortality. Minimally invasive endovascular aortic repair using stent-grafts has revolutionized aortic surgery primarily because it does not require aortic clamping and can be performed through small incisions via peripheral arteries remote from the area of aortic disease. The textile components of aortic stent-grafts [usually polytetrafluoroethylene (ePTFE) or polyethylene terephthalate (PET)] are similar to traditional tubular textile surgical bypass grafts. In stent-grafts however, the material is attached to a metallic stent skeleton that creates an outward radial force to expand the diameter of the device within the vessel to secure it in place while creating a hemostatic seal in aorta proximal and distal to the treated lesion. Because endovascular surgery produces significantly improved short-term outcomes compared to open surgery, thoracic endovascular aortic repair (TEVAR) is currently recommended as first-line therapy for many patients requiring intervention for degenerative and traumatic aortic pathologies.[1–5]

The native healthy aorta acts as an elastic buffering chamber for the heart and stores approximately 50% of the left ventricular (LV) stroke volume during systole.[6,7] During diastole, the aortic wall recoils and propels some of this blood volume to the peripheral circulation, thereby helping to create nearly continuous blood flow at the capillary level. This is particularly important for coronary artery flow which occurs primarily during diastole. This aspect of ventricular-arterial coupling is often referred to as the Windkessel effect, and its primary roles are to reduce LV afterload during systole; and during diastole, to promote coronary blood flow, facilitate LV relaxation, and maintain normal flows and pressures to distal organs and tissues.[6,8]

Although the effects of natural aortic stiffening due to aging and risk factors have been intensively studied, the effects of artificial segmental aortic stiffening by ePTFE or PET stent-grafts are significantly less understood.[9] As the aorta stiffens with age,[10–12] higher ventricular forces are required to distend the aortic wall and this may contribute to increases in systolic blood pressure,[13–15] pulse wave velocity, and LV afterload,[16–20] that may lead to LV hypertrophy and fibrosis, eventually culminating in contractile dysfunction and cardiomyopathy.[21–23] Because both ePTFE and PET materials used in conventional stent-grafts are substantially stiffer than aortic wall,[24] their implantation stiffens[17,25–27] and effectively ages the aorta. Standard metrics used to assess stent-graft performance typically include shorter-term morbidity, mortality, and local complications requiring re-intervention,[28] but rarely have data been reported on the cardiac and off-target aortic effects of TEVAR. Although most patients receiving stent-grafts have rather short life expectancies and multiple comorbidities that may mask or trump more subtle device effects, expansion of aortic stent-grafting to younger and healthier trauma patients with significantly longer life expectancies and better endurance to accumulating complications before experiencing severe events, demand a more comprehensive approach to the investigation of additional metrics to evaluate device performance.

The goal of our study was to test the hypothesis that mechanical stiffening of the descending thoracic aorta (DTA) with stent-grafts is associated with LV and off-target aortic remodeling. To test this hypothesis, we compared trauma patients with blunt thoracic

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aortic injury requiring TEVAR to similarly-aged control subjects of both sexs without any vascular repair or cardiac or aortic abnormalities.

METHODS

Tevar Patients

The study was approved by the Institutional Review Board of the University of Nebraska Medical Center, and a waiver of informed consent was obtained due to retrospective nature of the analysis. The University of Nebraska Medical Center patient database was searched for patients treated with TEVAR for blunt thoracic aortic injury. Subjects that had at least 1 baseline (usually done within a month of stent-graft placement) and 1 follow-up scan separated by $\geq$1 year were included, whereas patients with aortic aneurysmal disease, dissection, and aortic coarctation were excluded. The search resulted in 20 patients (17 male/3 female) with 103 CTA scans (average of 5 per patient) with an average slice thickness of 1.29 ± 0.35 mm. A total 63% of TEVAR scans were electrocardiography (ECG)-gated, all scans were contrast-enhanced and obtained with a 64-channel CTA scanner at 512 $\times$ 512 pixel resolution. Patients were treated with a variety of stent-graft devices between the years of 2005 and 2017. The average age of TEVAR patients at baseline was 34.9 ± 18.5 years with a range of 11.4–71.5 years. Follow-up duration was 5.1 ± 3.1 years, with the shortest follow-up of 1.1 and the longest of 12.3 years.

Control Subjects

Control subjects were selected from the same database, set to match TEVAR patients in terms of age and follow-up duration. Patients with at least 2 CTA scans of the chest separated by $\geq$1 year were included, and patients with baseline LV hypertrophy, congestive heart failure, aortic aneurysm, dissection, congenital cardiac abnormalities, and prior vascular intervention or reconstruction were excluded. This resulted in 42 control subjects (21 male/21 female) with 158 CTA scans (77 male, 81 female) with an average slice thickness of 1.74 ± 0.87 mm. Indications for CTA included shortness of breath/chest pain (50%), all-cause trauma (26%), cancer (10%), pulmonary embolism (10%), and hemoptysis (4%). A total 43% of scans were ECG-gated, all were contrast-enhanced and obtained with a 64-channel CTA scanner at 512 $\times$ 512 pixel resolution. The average age of control subjects at baseline was 37.1 ± 16.1 years, with an age range of 13.7–82.5 years. Follow-up duration was 4.6 ± 2.7 years, 4.1 ± 2.0 years for male and 5.2 ± 3.2 years for female subjects.

Reconstructions of the LV and the Aorta

Three-dimensional (3D) reconstructions of the LV from CTA scans were completed in 3 steps. First, the epicardial surface of the LV from the apex to the aortic valve and the pulmonary trunk was segmented manually using a multi-slice edit tool in Mimics v21 (Materialize Co, Leuven, Belgium). Second, the endocardial surface was segmented by thresholding and overlapping the resulting mask with the epicardial surface mask. Third, the endocardial mask was subtracted from the epicardial mask, which resulted in the 3D geometry of the LV wall. The LV wall was transected immediately below the aortic valve (Fig. 1) and this geometry was then analyzed in 3D. To ensure consistency and assess variability, all TEVAR scans were reconstructed twice, in random order by the same operator. Because CTAs could be gated to different parts of the cardiac cycle,

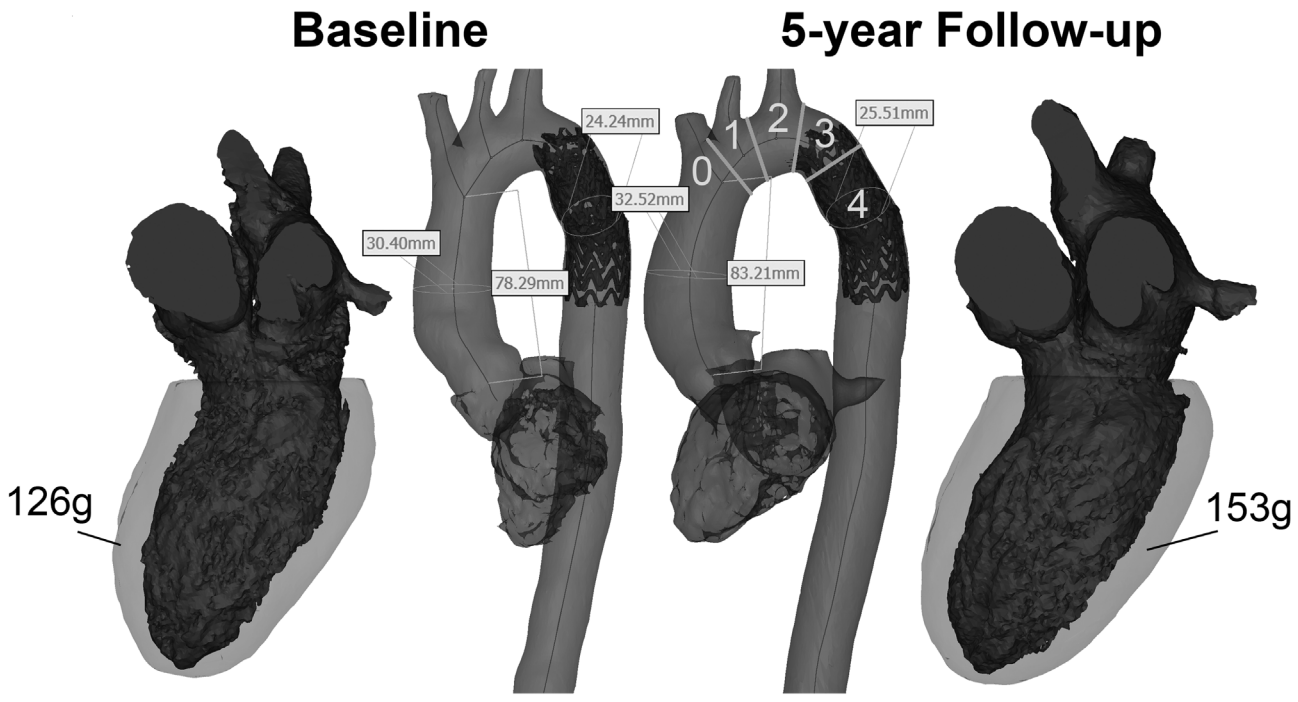

FIGURE 1. Assessment of left ventricular (LV) mass, length of the ascending thoracic aorta (ATA), and diameters of the ascending and descending thoracic aorta in the middle of the stent-grafted segment in a representative patient after thoracic endovascular aortic repair (TEVAR) at baseline (32 yr) and at the 5-yr follow-up (37 yr). Note larger LV mass, longer ATA length, and wider aortic diameters at follow-up compared with baseline. Yellow lines and numbers delineate aortic attachment zones as defined by Fillinger et al.[30]

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we assessed the effect of ECG-gating on LV mass characteristics by analyzing gated 4D CT images of 5 patients 66.8 ± 6.2 years old. Each patient had 11 phases (0%–95%) which were analyzed independently and compared.

3D geometry of the thoracic aorta was also reconstructed in Mimics v21 software using a combination of semi-automatic segmentation, region growing, mask separation, and 3D editing tools.[29] After segmentation, a centerline was fit into the aortic geometry which allowed measurement of the ascending thoracic aortic (ATA) length between the aortic valve and the brachiocephalic artery, the length of the DTA between the left subclavian and the celiac artery, and the diameter of the ATA half-way between the aortic valve and the brachiocephalic artery (Fig. 1). In TEVAR patients, the aortic diameter was additionally measured in the middle of the stent-grafted segment, and within 1 cm from each end to assess how quickly the aorta remodeled to the nominal size of the device. All aortic reconstructions were performed by the same operator to ensure consistency and assess variability in aortic segmentation, which was evaluated by reconstructing a random set of 50 control scans twice and measuring differences in ATA diameters.

Statistical Analysis

Group comparisons were performed using 2-tailed independent sample *t*-tests and nonparametric 2 sample Mann-Whitney *U* (MWU) tests, Chi-square tests (CSQ), or Fisher exact tests (FET). Comparisons within the groups at baseline and follow-up were performed using paired *t*-tests and McNemar (McN) tests. Correlations between continuous variables were assessed using Pearson correlation coefficients *r*, and correlations between pairs of continuous and dichotomous variables were assessed using point biserial correlation coefficients r_{pb}. Values of *r* and r_{pb} closer to ±1 indicated stronger relation. Statistical significance of correlation was assessed by testing the hypothesis of no correlation against the alternative that there was a nonzero correlation assuming statistical significance at $P \leq 0.05$. The analysis was performed in SPSS v22 (IBM, Armonk, NY).

RESULTS

Patient Characteristics at Baseline and Follow-up

Demographics and risk factors for TEVAR patients and control subjects are summarized in Tables 1 and 2. Half of TEVAR patients were treated with GORE Excluder devices (W.L. Gore, Flagstaff, AZ), 30% were treated with Conformable GORE TAG Thoracic Endoprostheses (C-TAG, W.L. Gore), 15% with GORE TAG Thoracic Endoprostheses (TAG, W.L. Gore), and 5% with the Medtronic Talent (Medtronic Vascular, Santa Rosa, CA) device. Of the 10 patients treated with GORE Excluder devices, only 3 received 1 stent-graft, 4 patients were treated with 2 devices, and 3 were treated with 3 stent-grafts. The patient with the Medtronic Talent device was treated with 2 stent-grafts, and the rest of the TEVAR cohort were treated with 1 stent-graft each. On average, stent-grafts covered 32.2% ± 11.3% (range 13.0%–53.1%) of the DTA. In 70% of patients the most proximal treated aorta was Zone 3 within 2 cm distal to the left subclavian artery, whereas in 15% it involved Zone 2, in 10% Zone 1, and in 5% Zone 4.[30] No stent-grafts were placed in aortic Zone 0.

There were no differences between control and TEVAR patients in terms of age at baseline ($P = 0.64$), follow-up duration ($P = 0.56$), baseline or follow-up weight ($P = 0.39$, $P = 0.83$), body

TABLE 1. Characteristics of TEVAR Patients

Characteristic	Baseline	Follow-up	*P*
No. of subjects		20	
No. of scans		103	
Patient characteristics			
Follow-up, yr		5.1 ± 3.1 (1.1–12.3)	
Sex		17 (85%) Male / 3 (15%) Female	
Race/ethnicity		85% Caucasian, 10% Hispanic, 5% African American	
Age, yr	34.9 ± 18.5 (11.4–71.5)	40.0 ± 19.8 (18.7–83.9)	
*Weight, kg**	77.6 ± 16.9	85.4 ± 19.0	*0.02*
*Body mass index**	26.3 ± 5.4	28.5 ± 5.7	*0.03*
Body surface area,[31,*] *m^2*	1.92 ± 0.26	2.01 ± 0.28	*0.03*
Risk factors			
Tobacco use, %	50	55	
*Smoking, pack-yr**	8.8 ± 13.0	10.1 ± 13.9	*0.01*
Alcohol abuse, %	30	35	
Drug abuse, %	10	10	
Coronary artery Disease, %	5	15	
Hypertension,† %	5	50	*<0.01*
Hyperlipidemia, %	10	20	
Diabetes mellitus, %	5	5	
Chronic kidney disease, %	0	0	
LV mass			
LV mass,† *g*	138.5 ± 39.6	173.5 ± 50.1	*<0.01*
LV mass growth,† *g/yr*	10.03 ± 12.79		*<0.01*
LV mass index,† *g/m^2*	72.35 ± 15.17	85.48 ± 18.34	*<0.01*
LV mass index growth,† *$g/m^2/yr$*	6.25 ± 10.28		*<0.01*
ATA diameter			
ATA diameter,† *mm*	27.6 ± 3.4	30.3 ± 3.8	*<0.01*
ATA diameter growth,† *mm/yr*	0.60 ± 0.80		*<0.01*
ATA length			
ATA length,† *mm*	75.5 ± 13.7	79.6 ± 10.5	*<0.01*
*ATA length growth,** *mm/yr*	0.58 ± 1.43		*0.04*

P-values indicate statistically significant differences between baseline and follow-up or difference from 0 (in case of growth) at *$P \leq 0.05$ and †$P < 0.01$ levels.

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TABLE 2. Characteristics of Control Subjects

Characteristic	Baseline			Follow-up			*P*-value
	All			All			
	Male	Female		Male	Female		
No. of subjects	42 (21 Male, 21 Female)						
No. of scans	160						
Patient characteristics							
Follow-up, yr	4.6 ± 2.7 (1–12.1) Male: 4.1 ± 2.0, Female: 5.2 ± 3.2						
Race/ethnicity	79% Caucasian, 2% Hispanic, 19% African American						
Age, yr	37.1 ± 16.1 (13.7–82.5)			41.8 ± 16.6 (18.0–89.5)			
	37.1 ± 15.7	37.1 ± 16.9		41.2 ± 16.3	42.4 ± 17.3		
Weight, kg*	81.8 ± 18.3			84.3 ± 20.7			*0.05*
	83.5 ± 18.9	80.1 ± 17.9		88.5 ± 20.0	80.0 ± 20.9		*0.01* 0.98
*Body mass index**	28.1 ± 5.6			28.8 ± 5.9			0.16
	26.3 ± 5.0	29.9 ± 5.6		27.7 ± 5.1	29.9 ± 6.6		*0.02* 0.95
Body surface area,[31,*] *m^2*	2.0 ± 0.3			2.0 ± 0.3			*0.05*
	2.0 ± 0.3	1.9 ± 0.2		2.1 ± 0.3	1.89 ± 0.3		*0.01* 0.85
Risk factors							
Tobacco use, %	43			52			
	48	38		52	52		
Smoking, pack-yr†	10.3 ± 20.3			11.9 ± 20.7			*<0.01*
	14.3 ± 26.1	6.3 ± 11.5		15.9 ± 26.6	7.9 ± 11.9		*<0.01 0.03*
Alcohol abuse, %	19			21			
	33	5		33	10		
Drug abuse, %	14			19			
	24	5		24	14		
Coronary Artery Disease, %	5			5			
	5	5		5	5		
Hypertension, %	24			29			
	19	29		19	38		
Hyperlipidemia, %	10			12			
	5	14		5	19		
Diabetes mellitus, %	10			12			
	5	14		10	14		
Chronic kidney disease, %	0			5			
	0	0		0	10		
LV Mass							
LV mass, g	113.8 ± 27.6			116.3 ± 30.3			
	128.3 ± 24.5	99.4 ± 22.9		133.4 ± 28.7	99.3 ± 21.2		
LV mass growth, g/yr	−0.01 ± 3.75						
	Male: 0.84 ± 4.27, Female: −0.87 ± 3.02						
LV mass index, g/m^2	58.29 ± 11.64			58.44 ± 11.74			
	64.04 ± 11.65	52.53 ± 8.52		64.09 ± 10.83	52.79 ± 9.89		
LV mass index growth, g/m^2/yr	−0.25 ± 1.90						
	Male: -0.35 ± 2.15, Female: -0.15 ± 1.66						
ATA diameter							
ATA diameter,† *mm*	28.9 ± 4.7			30.1 ± 5.0			*<0.01*
	29.7 ± 4.7	28.0 ± 4.6		30.9 ± 4.8	29.3 ± 5.1		
ATA diameter growth,† *mm/yr*	0.25 ± 0.44						*<0.01*
	Male: 0.27 ± 0.50, Female: 0.22 ± 0.37						
ATA length							
ATA length, mm*	73.9 ± 11.6			76.2 ± 12.5			*0.02*
	76.3 ± 11.9	71.5 ± 11.1		79.3 ± 14.1	73.1 ± 10.1		*0.02* 0.28
ATA length growth, mm/yr*	0.58 ± 1.96						*0.03*
	Male: 0.78 ± 1.78, Female: 0.38 ± 2.16						*0.03* 0.22

P-values indicate statistically significant differences between baseline and follow-up or difference from 0 (in case of growth) at $^{*}P \leq 0.05$ and $^{\dagger}P < 0.01$ levels.

mass index (BMI, $P = 0.95$, $P = 0.62$), or body surface area (BSA, $P = 0.56$, $P = 0.78$). Predominantly male TEVAR patients and male control subjects gained weight ($P = 0.02$, $P = 0.01$), and had increased BMI ($P = 0.03$, $P = 0.02$), and BSA ($P = 0.03$, $P = 0.01$) at the time of the longest follow-up compared with baseline (Tables 1 and 2). Weight, BMI, and BSA of female control subjects was not different between baseline and follow-up ($P = 0.98$, $P = 0.95$, $P = 0.85$).

TEVAR patients and control subjects were not different at either baseline or follow-up in terms of smoking pack-year history ($P = 0.73$, $P = 0.69$), alcohol abuse [$P = 0.33$ (MWU), $P = 0.26$ (MWU)], or drug abuse ($P = 0.64$ (MWU), $P = 0.37$ (MWU)]. The percentage of TEVAR patients and control subjects that used tobacco, or abused alcohol or drugs did not change significantly over the course of the follow-up, although the number of pack-years increased in both TEVAR and control groups as expected ($P < 0.01$).

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The prevalence of hyperlipidemia [$P = 0.95$ (MWU), $P = 0.40$ (MWU)], diabetes mellitus [$P = 0.54$ (MWU), $P = 0.39$ (MWU)], or chronic kidney disease [$P = 1$ (MWU), $P = 0.33$ (MWU)] was not different between TEVAR and control subjects at either baseline or follow-up.

The prevalence of coronary artery disease (CAD) in TEVAR patients and control subjects was not different at either baseline [$P = 0.97$ (MWU)] or follow-up [$P = 0.17$ (MWU)], but whereas in control subjects CAD prevalence remained at 5%, in TEVAR patients it increased from 5% to 15%, with 2 TEVAR patients developing CAD at the ages of 29.5 (treated with coronary artery stents) and 37.5 years (wall hypokinesis and LV hypertrophy), both within 4.5 years of stent-graft placement.

At baseline more control subjects had hypertension (HTN, peak systolic blood pressure >140 mm Hg) than TEVAR patients [24% vs 5%, $P = 0.07$ (MWU), $P = 0.09$ (FET)], but at the time of the longest follow-up HTN was more prevalent in TEVAR patients [50% vs 29%, $P = 0.10$ (MWU), $P = 0.16$ (CSQ)]. At baseline, only 1 (5%) TEVAR patient was diagnosed with HTN, whereas at the time of the follow-up (5.1 ± 3.1 years), 8 (40%) TEVAR patients were diagnosed and receiving medical treatment for HTN, usually in the form of ACE inhibitors, beta blockers, and hydrochlorothiazide. Two additional patients (10%) had peak systolic blood pressure of >140 mm Hg on at least 2 consecutive clinical visits, bringing the total number of TEVAR patients with HTN at the time of their longest follow-up to 10 (50%), which was significantly larger than at baseline [$P < 0.01$ (McN)]. Importantly, none of the TEVAR patients had high blood pressure on their first follow-up visit after stent-graft placement, suggesting that the incidence of HTN at baseline was not underestimated. TEVAR patients that developed HTN after their stent-graft placement did so 3.6 ± 3.5 years after their endovascular repair at the median age of 33.8 years (average 41.4 ± 18.1, range 20.1–65.6 years). Unlike the TEVAR patients, HTN status of control subjects was not different between baseline and follow-up [$P = 0.63$ (McN)]. None of the trauma control subjects developed HTN during follow-up.

Effects of ECG-gating on LV Characteristics

Fig. 2 demonstrates differences in LV mass, inner LV cavitary volume, and LV wall thickness over the cardiac cycle relative to the time-averaged mass, inner volume, and myocardium thickness. LV mass was calculated from the measurements of LV myocardium volume assuming constant tissue density of 1 g/cm^3. Average absolute difference in LV mass over the entire cardiac cycle was $1.3\% \pm 0.5\%$ (max 2.4%), supporting the assumption of LV incompressibility. Conversely, measurements of LV inner cavitary volume and LV wall thickness over the cardiac cycle differed by an absolute average of $27.3\% \pm 12.1\%$ (max 46.5%) and $13.8\% \pm 7.6\%$ (max 32.7%), respectively, demonstrating the importance of proper ECG-gating for their correct assessment. Because CTAs analyzed in this study could have been obtained at different parts of the cardiac cycle, LV mass and LV mass index (LVMi) defined as the ratio of LV mass to BSA[31] were the primary LV characteristics extracted and calculated from the CTA scans and patient records. As BMI may fluctuate over time, the LVMi metric was particularly informative as it accounted for changes in BSA and BMI over time.

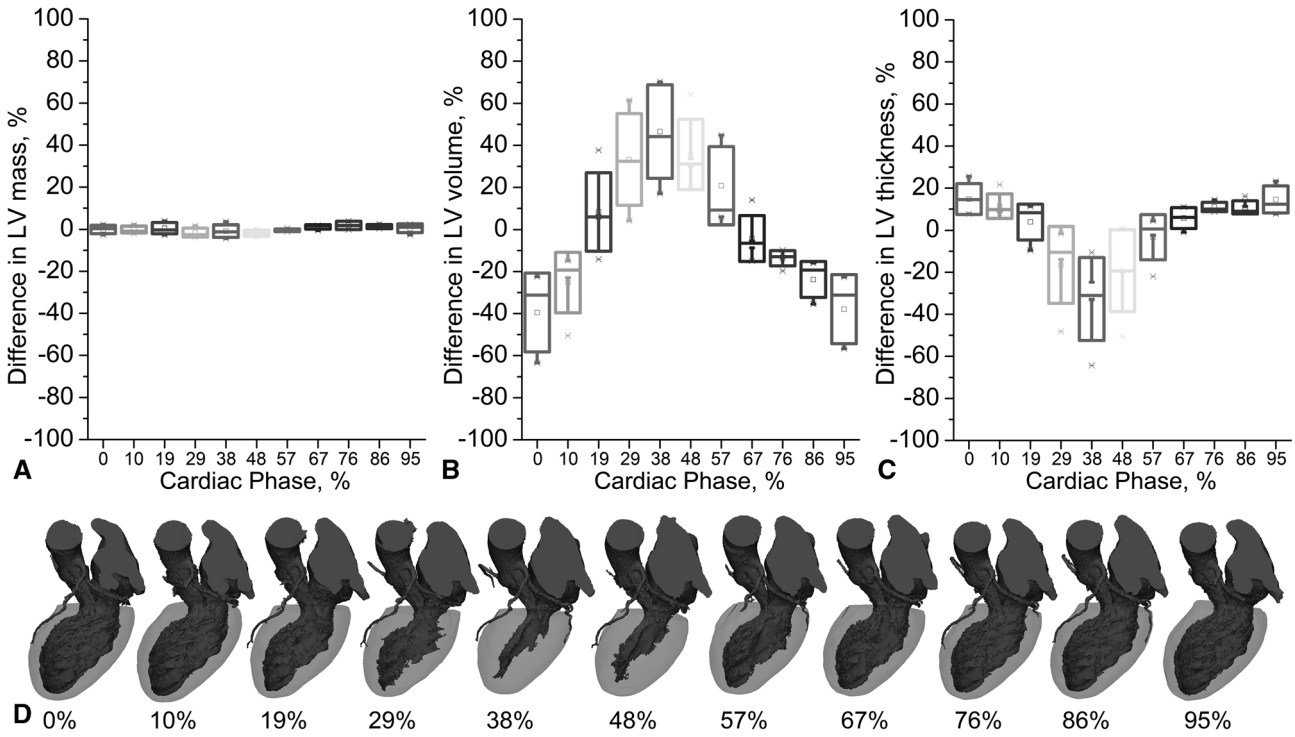

FIGURE 2. Changes in (A) left ventricular (LV) mass, (B) LV inner cavitary volume, and (C) LV thickness (%) during the cardiac cycle. Boxes bound 25th and 75th percentiles, whiskers extend to 5th and 95th percentiles, and 99th percentile is marked with a cross (×). Additionally, mean values are marked with a hollow square, and median is represented by a horizontal line within each box. D, Illustrates LV of a representative patient at each cardiac phase (0-95%). Note that despite significant changes in LV inner cavitary volume and thickness, LV mass remains relatively constant throughout the cardiac cycle.

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LV Mass and LVMi

Changes in LV mass and LVMi in TEVAR patients and in control male and female subjects are presented in Fig. 3, Table 1, and Table 2. At baseline, LV mass and LVMi of predominantly male TEVAR patients were 138.5 ± 39.6 g and 72.35 ± 15.17 g/m^2, which were not significantly different from those of control male subjects at baseline (128.3 ± 24.5, $P = 0.33$, and 64.04 ± 11.65 g/m^2, $P = 0.06$). At the time of the longest follow-up, LV mass and LVMi of TEVAR patients increased to 173.5 ± 50.1 g and 85.48 ± 18.34 g/m^2, which were significantly larger than 133.4 ± 28.7 g and 64.09 ± 10.83 g/m^2 of control male subjects at the time of their longest follow-up ($P < 0.01$). On the contrary, LV mass and LVMi of control subjects did not change significantly between baseline and follow-up ($P = 0.24$, $P = 0.98$ for male, and $P = 0.95$, $P = 0.85$ for female). Because LV mass and LVMi of control male subjects were larger than those of female subjects at both baseline and follow-up ($P < 0.01$) by ~30% and ~20%, respectively, differences in LV characteristics between TEVAR patients and control female subjects at follow-up were even more pronounced.

LV mass and LVMi of TEVAR patients grew on average 10.03 ± 12.79 g/yr and 6.25 ± 10.28 g/m^2/yr ($P < 0.01$), whereas LV mass and LVMi of control subjects did not grow with age ($P = 0.98$ and $P = 0.40$) neither in male ($P = 0.38$, $P = 0.47$), nor in female ($P = 0.20$, $P = 0.68$) subjects. Within the first year after implantation of the stent-graft, in 25% of TEVAR patients LV mass decreased, perhaps due to the initial cardiac edema associated with trauma and thoracic injury that resolved within the first year. This decrease; however, was not statistically significant for the entire TEVAR cohort ($P = 0.20$). There was no significant correlation between the type of stent-graft and LV growth rates (LV mass $r_{pb} = -0.13$, $P = 0.61$; LVMi $r_{pb} = 0.17$, $P = 0.50$). Average variability in LV mass measurement was $6.8\% \pm 5.5\%$, and this variability was not different between ECG-gated and non-gated scans ($P = 0.98$).

ATA Diameter

Changes in ATA diameters in TEVAR patients and control subjects are presented in Fig. 4A, B, Table 1, and Table 2. At baseline, ATA diameters of TEVAR patients were on average

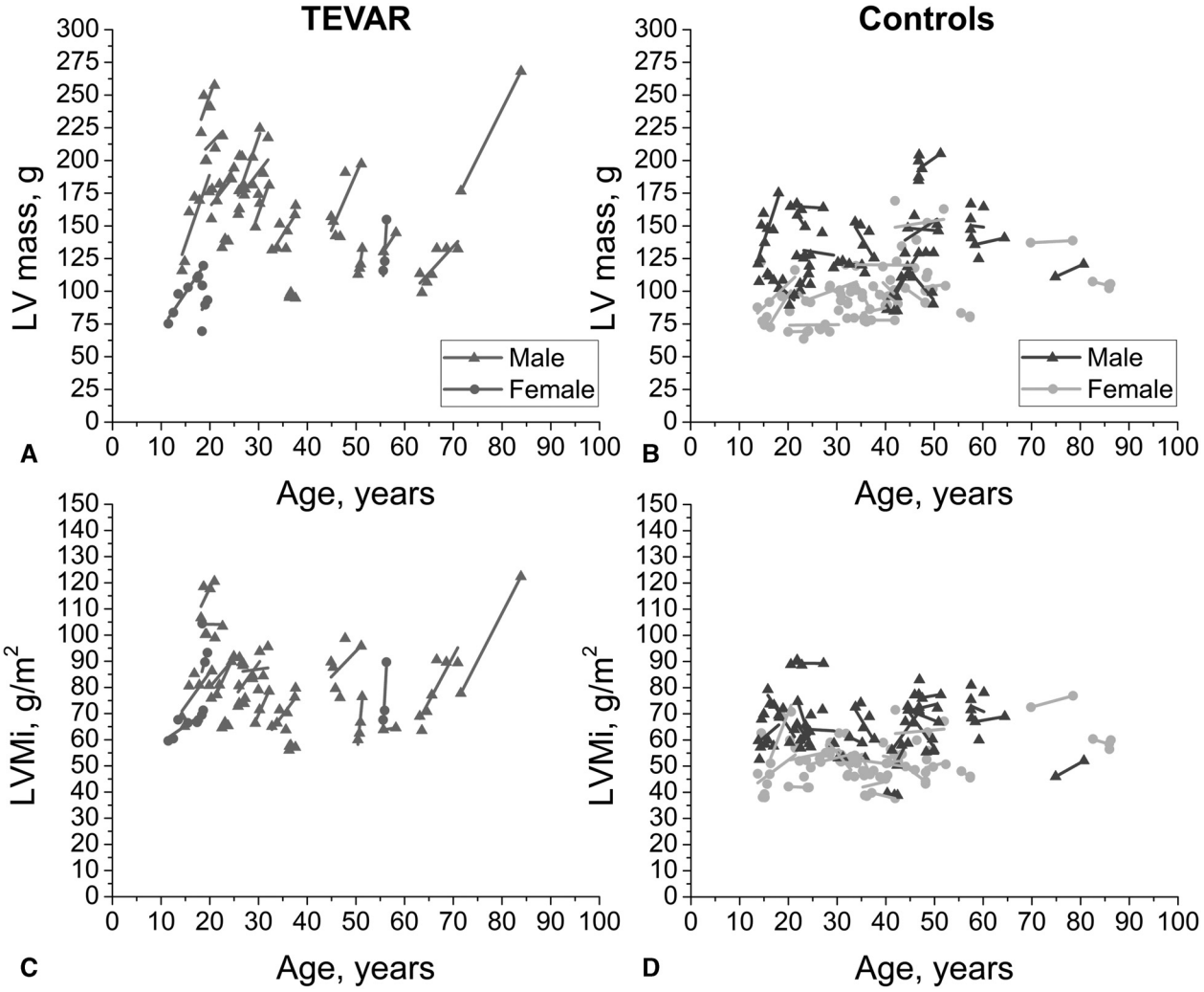

FIGURE 3. Change in left ventricular (LV) mass (A, B) and LV mass index (LVMi) (C, D) with age in patients after thoracic endovascular aortic repair (TEVAR) and control subjects. Red and blue color represent male, whereas magenta and cyan colors represent female subjects. Note significant increases in LV mass and LVMi in TEVAR patients but not in control subjects.

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27.6 ± 3.4 mm, which was not statistically different from 28.9 ± 4.7 mm in control subjects ($P = 0.29$). At the time of the follow-up, ATA diameters in TEVAR patients increased to 30.3 ± 3.8 mm ($P < 0.01$), and in control subjects to 30.1 ± 5.0 mm ($P < 0.01$). ATA diameters in male and female control subjects were not statistically different neither at baseline ($P = 0.25$), nor at follow-up ($P = 0.30$). In both TEVAR patients and control subjects ATA diameters grew with age ($P < 0.01$), but in TEVAR patients the growth was 2.4-fold more rapid at 0.60 ± 0.80 mm/yr compared with only 0.25 ± 0.44 mm/yr rate in control subjects ($P = 0.04$). Fig. 4A, B illustrates this effect by sharper rising growth curves, with some of the younger <20 year-old TEVAR patients reaching >30 mm aortic diameters at the time of their last follow-up – an effect that can be observed in control patients at the age of 50 years. In control patients, ATA diameter growth rates were not different in male and female subjects ($P = 0.68$). The diameter of the DTA in TEVAR patients approached the size of the stent-graft usually within the first 6 months of repair and remained stable thereafter. The type of stent-graft did not affect ATA diameter growth rates ($r_{pb} = 0.20$, $P = 0.41$). Variability in ATA diameter measurement was $1.7\% \pm 1.9\%$.

ATA Length

Changes in ATA length in TEVAR patients and control subjects are presented in Fig. 4C, D, Table 1, and Table 2. At baseline, ATA length in TEVAR patients was 75.5 ± 13.7 mm which was not different from 73.9 ± 11.6 mm measured in control subjects ($P = 0.65$). At the time of the follow-up, ATA length increased to 79.6 ± 10.5 mm in TEVAR patients ($P < 0.01$), and to 76.2 ± 12.5 mm in control subjects ($P = 0.02$), although the increase in control subjects was only significant for males ($P = 0.02$), but not for females ($P = 0.28$). Despite the trend for longer ATA lengths in male control subjects, differences in ATA lengths between male and female control subjects did not reach statistical significance neither at baseline ($P = 0.18$) nor at follow-up ($P = 0.11$). In TEVAR patients, ATA length increased at 0.58 ± 1.43 mm/yr ($P = 0.04$), and the same growth rate was observed in control subjects (0.58 ± 1.96 mm/yr, $P = 0.03$). ATA length growth rate was not

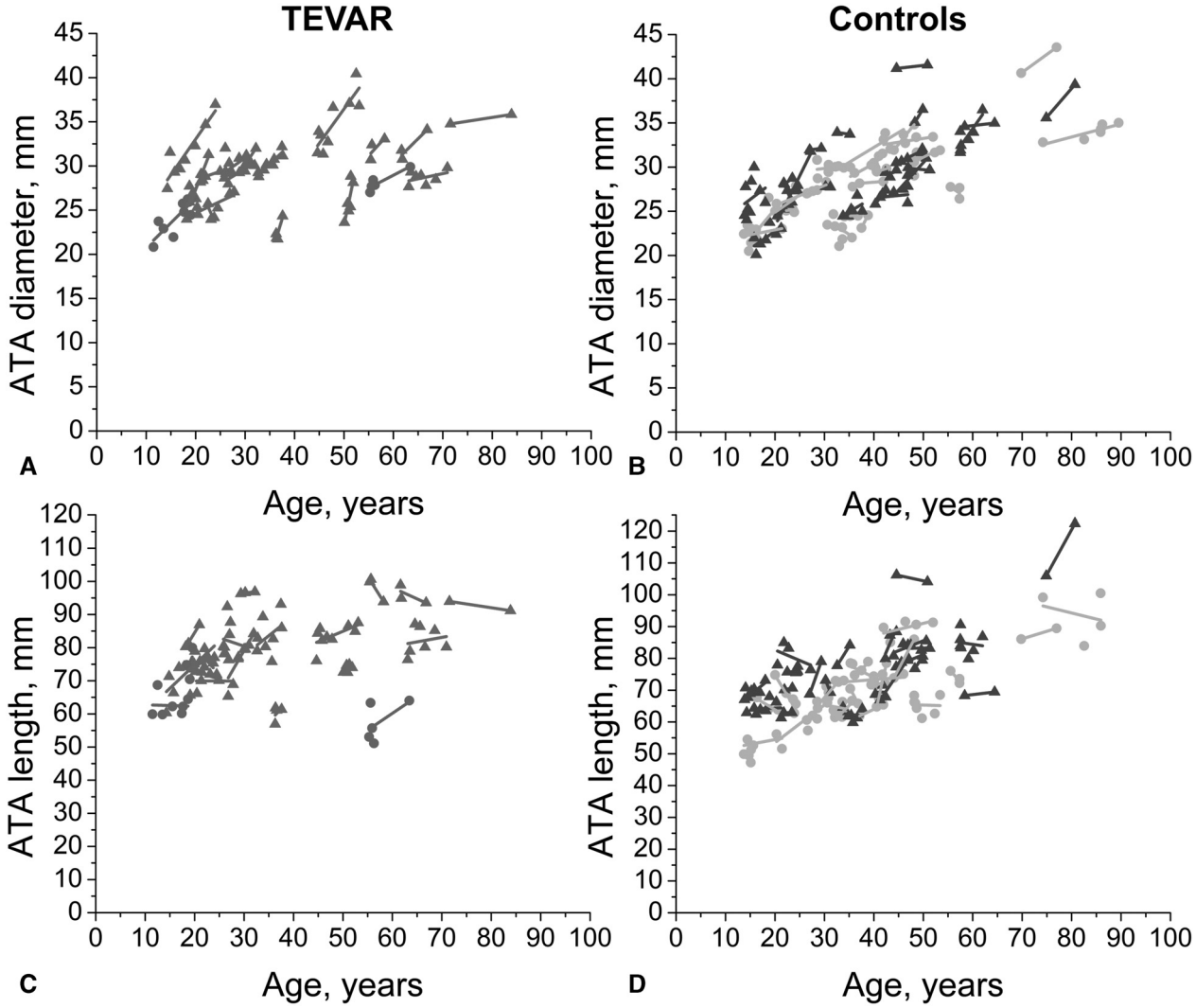

FIGURE 4. Change in the ascending thoracic aortic (ATA) diameter (A, B) and length (C, D) with age in patients after thoracic endovascular aortic repair (TEVAR) and control subjects. Red and blue color represent male, whereas magenta and cyan colors represent female subjects. Note faster growth of ATA diameters in TEVAR patients compared with control subjects.

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different between control male and female subjects ($P = 0.52$), and the type of stent-graft did not affect ATA length growth ($r_{pb} = 0.09$, $P = 0.71$).

DISCUSSION

Our data and analysis suggest that thoracic aortic stent-grafts are associated with LV hypertrophy, the development of hypertension, and accelerated expansile ATA remodeling. We hypothesize that adverse hemodynamics, influenced by segmental aortic stiffening is likely an underlying mechanism. The Windkessel feature of ventricular-arterial coupling blunts peak blood pressure and flow waves providing a cushioning effect that protects the heart, aorta, and downstream organs from pressure injury. Although stiff stent-grafts are generally thought to work well in the aorta, the subtle long-term effects associated with artificial aortic stiffening may not be detected or reported in the stent-graft literature. Indeed, traditional metrics used to assess stent-graft performance (ie, shorter-term morbidity, mortality, and local complications requiring re-intervention) rarely evaluate increases in LV mass or off-target aortic remodeling, because most patients receiving stent-grafts have rather short life expectancies and multiple comorbidities. In addition, patient follow-up after stent-graft placement for trauma is notoriously poor.[32] With recent expansion of stent-graft use to younger and healthier trauma victims, and because these patients are capable of enduring the accumulation of these effects for longer periods of time before experiencing symptomatic complications, a more detailed and refined assessment of device performance is warranted.

Emerging clinical evidence demonstrates increased vascular stiffness and LV mass, along with decreased exercise tolerance in patients with stiff aortic grafts and stent-grafts.[9,17,26,27,33–35] Our current analysis supports these concerns demonstrating a substantial increase in LV mass and LVMi in TEVAR patients at the rate of 10.03 g/yr and 6.25 g/m^2/yr, compared to no change in the LV characteristics in similarly-aged control subjects. Normal LV mass in adults determined using gradient-recalled echo and magnetic resonance imaging is 146.8 ± 25.2 g based on 6 studies summarized in Sandstede et al.[36] Assuming that hypertrophied LVs are at least 2 standard deviations larger than normal, the lower limit of hypertrophied LV mass is 197 g, which agrees with the 185 g result reported earlier by Fulton et al[37] using autopsied hearts. Because the average LV mass of TEVAR patients at baseline was 138.5 ± 39.6 g, at a growth rate of 10 g/yr it may take 7–8 years for an average TEVAR patient to reach an increase of 40%–50% and cross the threshold to LV hypertrophy. Average follow-up in our study was 5.1 ± 3.1 years, which produced a 25% increase in LV mass in TEVAR patients, but 35% of patients had LV mass larger than 190 g at the time of their last follow-up.

Large animal data also align with our findings. In swine, wrapping of the aortic arch to reduce compliance resulted in significantly increased systolic and pulse pressures, with a 40% increase in LV mass after only 60 days.[18] Implantation of stents into the DTA of swine resulted in altered coronary artery flow,[38] whereas in dogs, cardiac ejection into a stiff conduit worsened cardiac dysfunction as demonstrated by LV pressure-volume loops and aortic pressure and flow measurements.[39,40]

In addition to LV growth, TEVAR patients also demonstrated off-target aortic remodeling similar to accelerated vascular aging. Specifically, ATA diameters of TEVAR patients increased at 0.60 mm/yr which was 2.4-fold faster than controls, resulting in some of the <20-yr-old TEVAR patients having ATA diameters >30 mm which are more characteristic of 50-year-old control subjects. Although none of the ATA diameters in our TEVAR patients reached the threshold of 55 mm that would classify them as aneurysms requiring treatment,[41] several patients that had normal aortas at baseline were >35 mm in diameter during their last follow-up. Assuming a constant rate of ATA diameter increase, these young patients may require repair in 3–4 decades at the age of 50–60 years. Although the mechanism of rapid ATA diameter increase requires further investigation, several possible explanations could include Windkessel compensation to accommodate blood volume in the setting of diminished DTA elasticity after stent-graft implantation; and a mechano-biological loop triggered by mechanical aortic stiffening, leading to inflammation and proteolytic destruction of elastic lamellae and fibers, resulting in biological stiffening and widening of the aorta. Surprisingly; however, TEVAR was not associated with an accelerated increase in ATA length, as both TEVAR and control groups demonstrated the same growth rate of 0.58 mm/yr. This finding demonstrates the importance of using controls, as ATA length increases in TEVAR patients were recently associated with stent-graft placement.[42,43]

Morphological changes to the LV and the aorta in TEVAR patients were accompanied by changes in patient risk factors. Most importantly, 50% of TEVAR patients had HTN only 5 years after their repair – a significant increase from 5% at baseline. Associations between hypertension, aortic stiffening, and LV hypertrophy have long been demonstrated,[11–15] and our results suggest that artificial stiffening of the aorta with stent-grafts may produce similar effects. A higher incidence of CAD in young TEVAR trauma patients also suggests that this artificial stiffening and LV remodeling may affect coronary artery perfusion, perhaps leading to abnormal hemodynamics, and possibly contributing to cardiac events that are typically associated with older age and risk factors in more traditional TEVAR patients treated for aortic aneurysms.

Although the aortic Windkessel effect is strongest in young healthy aortas,[44] and may be particularly important during vigorous exercise,[33,35] emerging clinical data demonstrate that even in aortas stiffened by aneurysmal disease, implantation of stiff stent-grafts alters cardiac structure and function, resulting in LV mass increase and decreased exercise tolerance.[26,35,49] In the long-term, patients treated with stent-grafts and conventional stiff surgical interposition grafts demonstrate excessive cardiovascular morbidity and mortality.[45,46] Though this is often attributed to preexisting cardiovascular disease, traditional clinical risk factors, and lack of stent-graft durability, our current data suggest that the effect of aortic stiffening due to the reconstruction might be a major contributor that has thus far been overlooked. Hearts of older patients with degenerative aneurysmal disease may be even more susceptible to the loss of any remaining aortic compliance,[47] and might benefit more from devices that would preserve the aortic Windkessel effect.

Our results point to the need for further detailed investigations of LV and off-target aortic characteristics after TEVAR, and may guide several aspects of these future studies. First, because some trauma TEVAR patients are children whose LV is expected to grow, it is important to consider not only the LV mass, but also the LVMi characteristic that minimizes differences across pediatric and adult populations[48] as it accounts for the BSA and BMI. Our data demonstrate growth in both LV mass and LVMi in almost all TEVAR patients as opposed to controls, which points to the independence of the observed phenomena from the effects of puberty. Second, our data stress the importance of longer (>2-year) follow-up studies with multiple scans to account for LV mass and segmentation variability. Ideally, follow-up duration should extend 7–10 years to allow sufficient time to manifest LV hypertrophy. Third, it is important to use age and sex-matched control subjects in studies of LV and aortic remodeling. Although in the current study we have used control patients without aortic pathology or previous repair, our results demonstrate that severe trauma may cause cardiac edema that subsequently resolves, which may overestimate the LV mass in

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trauma patients at baseline compared with non-trauma control subjects. We; therefore, speculate that for trauma TEVAR patients, the best controls should be similarly-injured patients with low-grade aortic injuries that were not treated with stent-grafts. Because long-term follow-up studies of trauma patients are challenging due to poor patient compliance with surveillance,[32] this calls for prospective cohort analyses.

Other possible reasons for the increase in LV mass, LVMi, and HTN in trauma TEVAR patients observed here could be baroreceptor-related effects, post-cardiac contusion remodeling, or other as of now unknown causes not necessarily related to stent-grafts. Further study using larger sample sizes is necessary to confirm our findings and better understand the underlying mechanisms. In addition, most commercial grafts and stent-grafts are made of similar materials that are significantly stiffer than the aortic wall, which likely explains the lack of correlation between the type of stent-graft device and the rate of LV or aortic remodeling observed here. We would not advocate a resurgence of open aortic surgery to avoid stent-graft associated adverse LV and aortic remodeling consequences as traditional bypass grafts have previously demonstrated similar results.[33,40] Instead, our data point to the need for developing better aortic graft materials and stent-grafts capable of preserving optimal ventricular-arterial coupling, particularly as endovascular aortic repair moves into the ATA closer to the heart.

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