Stent-Graft Deployment Increases Aortic Stiffness in an Ex Vivo Porcine Model

Hector W.L. de Beaufort,1 Michele Conti,2 Arnoud V. Kamman,1 Foeke J.H. Nauta,1 Ettore Lanzarone,3 Frans L. Moll,4 Joost A. van Herwaarden,4 Ferdinando Auricchio,2 and Santi Trimarchi,1 Milan and Pavia, Italy, and Utrecht, The Netherlands

Background: Aortic stiffness is an independent predictor of cardiovascular mortality. In this study, the effect of thoracic endovascular aortic repair (TEVAR) on aortic stiffness is investigated by measuring aortic pulse wave velocity (PWV) in an ex vivo porcine model.

Methods: Fifteen fresh porcine thoracic aortas were connected to a benchtop pulsatile system. Intraluminal pressures were recorded in the ascending aorta and at the celiac trunk using a needle connected to a pressure sensor. The distance between the needles was divided by the time difference between the base of the pressure peaks to calculate aortic PWV at baseline and after stent-graft deployment and distal stent-graft extension.

Results: Mean aortic PWV was 5.0 m/s at baseline. PWV increased by 4% after proximal stent-graft deployment ($P = 0.09$) and by 18% after stent-graft extension ($P < 0.001$). Pulse pressure in the nonstented ascending aorta increased by 11.0 ± 1.2 mm Hg after proximal stent-graft deployment ($P < 0.001$) and by 17.3 ± 1.5 mm Hg after stent-graft extension ($P < 0.001$). The increases in PWV and pulse pressure showed a positive linear correlation with the percentage of stent-graft coverage ($P < 0.001$ and $P < 0.001$).

Conclusions: In this experimental setup, aortic stiffness increased after stent-graft deployment, dependent on the percentage of the aorta that was covered by stent graft. These results show that TEVAR leads to significant changes in aortic hemodynamics, which merits evaluation in the clinical setting.

INTRODUCTION
Thoracic endovascular aortic repair (TEVAR) has shown to be a safe treatment option for patients with thoracic aortic disease, in particular in those with severe comorbidities.1,2 Current stent grafts offer high degrees of conformability to the native aorta. Nonetheless, computer-simulated models show that they are characterized by a certain degree of stiffness, dependent on the type of graft material.3 Aortic stiffness is an important hemodynamic parameter that has become recognized as an independent predictor of cardiovascular death.4 Understanding the effects of TEVAR on aortic hemodynamics may play a role in successfully maintaining the delicate circulatory balance of TEVAR patients, but many of these effects remain unknown. Since the velocity of a pulse wave along an artery is positively related to the stiffness of this artery, aortic stiffness can be adequately quantified by measuring aortic pulse wave velocity (PWV).5,6
In the present article, we report the results of experimental measurements of aortic PWV before and after TEVAR, to test the hypothesis that aortic stiffness increases after TEVAR.

**MATERIAL AND METHODS**

**Preparation of Porcine Aortic Specimens**

Fifteen thoracic aortas of healthy pigs of a hybrid breed (10- to 12-month-old, 160–180 kgs) were used. No pigs were sacrificed specifically for the purpose of this study; therefore, ethical approval by the local ethics committee was waived. The aortas were collected within 30 min after slaughter and transported at 4°C in isotonic saline solution and used for experiments on the same day. Each specimen was surgically prepared from the aortic root to the celiac trunk by removing excess connective tissue and ligating side branches. The aorta was then connected to a continuous flow system and pressurized to 100 mm Hg. A marker was added at the proximal connection site to the system (i.e. ascending aorta), at 5 cm more distally (i.e. aortic arch), and at the distal connection site (i.e. celiac trunk). Two independent observers measured the centerline aortic length between the most proximal and distal marker with a centimeter and the diameter of the proximal and distal descending thoracic aorta with a digital caliper.

**Pulsatile Mock Loop System**

Subsequently, the aorta was connected to a custom-made pulsatile mock loop system, which is a replica of a system previously described. A schematic representation of the experimental setup can be seen in Figure 1. It consists of 2 main elements: a controlled volumetric pump and a hydraulic afterload. The pump replicates the left ventricle and supplies the flow. The waveform of this flow was generated according to the Swanson and Clark formula. The afterload consists of a lumped parameter simulator of the input impedance of the human circulation. This provides linear resistances, which generates a pressure waveform in response to the flow waveform that accurately simulates vascular function, as opposed to quadratic resistances used in other pulsatile flow models.

**Measurement of Pulse Wave Velocity before and after TEVAR**

The aorta was inserted between the volumetric pump and the afterload of the pulsatile mock loop system using connecting tubes inserted 1 cm into the aorta. Plastic straps were tied around the connection sites to prevent leaking. The system was fixed at a heart rate of 60 bpm and a cardiac output of 5 L/min. Water at a temperature of 37°C was used for perfusion of the system to allow optimal nitinol performance. A flow meter (SonoTT Clamp-On transducer, em-tec GmbH, Finning, Germany) was positioned at the connecting tubes at the proximal and distal ends to measure inflow and outflow of the system. The downstream mean pressure could be fine tuned by changing the height of the water reservoir. This allowed for recording of all data at the same mean pressure. A 25-gauge needle was inserted at the location of the proximal and distal markers and connected to a 5-mm-long fluid-filled catheter and pressure sensor (Micro Switch Pressure Sensor 40PC Series, Honeywell, Freeport, Illinois). Data on pressure and flow were acquired and digitalized at a frequency of 1 kHz with the NI DAQ USB-6210 (National Instruments, Austin, Texas). These data were recorded for 5 subsequent cardiac cycles for each test.

A thoracic stent graft with interrupted stent design (Valiant, Medtronic, Santa Rosa, California)
Fig. 2. Typically generated pressure waveforms. Five recorded cardiac cycles (above) are averaged into 1 curve (below). The difference in time between the base (arrows) of the pressure peaks in the ascending aorta (red) and at the celiac trunk (blue) is used to calculate PWV.
was then deployed, using a custom-made delivery system. A 15-cm-long stent graft was deployed in each aorta, with the proximal landing zone 1–2 cm distal to the left subclavian artery. Stent grafts of different diameters were used to reach an intended oversizing of 10%. While maintaining the same flow and pulse rate, and pressure conditions as before TEVAR, PWV measurement was repeated after TEVAR. Subsequently, total stent-graft length was extended on the distal end with a 10-cm-long stent graft, also at 10% oversizing, with an intended overlap of 1–2 cm with the proximal stent graft. Total stent-graft length was then determined from the outside with a centimeter. A third measurement of PWV was performed after extension, under the same conditions.

The acquired pressure waveform data were analyzed with Matlab R2104a software (The Mathworks Inc, Natick, Massachusetts). An example of typical flow and pressure curves that were generated can be seen in Figure 2. An average pressure waveform of the 5 acquired cycles was created. Intraluminal pressures in the ascending aorta and at the celiac trunk were recorded simultaneously. The difference in time between the base of the pressure peak in the ascending aorta and the base of the pressure peak at the celiac trunk (Fig. 2) was extracted. Based on the formula that the average velocity over a certain distance can be calculated by this distance (x) divided by the difference in time (t), that is, \(\text{PWV} = \frac{\Delta x}{\Delta t}\), centerline aortic length was divided by the difference in time between the bases of the pressure peaks in the ascending aorta and at the celiac trunk to obtain PWV.6,7 Systolic, diastolic, mean, and pulse pressures were noted.

### Statistical Analysis

Statistical analysis was performed with IBM SPSS Statistics, version 22 (SPSS Inc., Chicago, Illinois). A repeated measures analysis of variance was used to compare PWV before stent-graft deployment to PWV after stent-graft deployment and PWV after stent-graft extension. Pearson’s rank correlation test was used to assess correlation between change in PWV and pulse pressure and the percentage of total aortic length covered by stent graft. Statistical significance was assumed at \(P\) values less than 0.05.

### RESULTS

Baseline characteristics of the 15 aortas can be seen in Table I. A 26-mm proximal diameter stent graft was deployed in 13 cases, and for the remaining 2 cases a 24-mm stent graft was used. For the distal extension, a 22-mm diameter stent graft was used in 14 cases and a 26-mm stent graft in one case. Main results can be seen in Table II. Mean aortic PWV was 5.0 m/s at baseline. Proximal stent-graft deployment caused a 4.0% increase in PWV to 5.2 m/s (\(P = 0.09\)), and stent-graft extension resulted in an 18.0% increase compared with baseline (\(P < 0.001\)) to 5.8 m/s. The increase in PWV as a percentage of baseline PWV and the percentage of total aortic length covered by stent graft showed a positive linear correlation with a correlation coefficient of 0.65 (\(P < 0.001\)).

Changes in intraluminal pressure in the ascending aorta and at the celiac trunk can be seen in Figure 3. In general, mean pressure per cardiac cycle and diastolic pressure remained stable after stent-graft deployment, but systolic pressure increased, causing a significant increase in pulse pressure. Pulse pressure increased after stent-graft deployment by a mean of 11.0 mm Hg (± 1.2 mm Hg) in the ascending aorta (\(P < 0.001\)) and 6.5 mm Hg (± 0.8 mm Hg) at the celiac trunk (\(P < 0.001\)). After stent-graft extension, the pulse pressure was elevated further by 17.3 mm Hg (± 1.5 mm Hg) in the ascending aorta (\(P < 0.001\)) and by 9.4 mm Hg (± 0.7 mm Hg) at the celiac trunk (\(P < 0.001\)). The absolute increase in pulse pressure in the ascending aorta and the percentage of total aortic length covered by stent graft showed a positive linear correlation with a correlation coefficient of 0.62 (\(P < 0.001\)); at the celiac trunk, the correlation coefficient was 0.47 (\(P = 0.01\)).

### DISCUSSION

The present study was conducted to assess aortic stiffness before and after stent-graft deployment by measuring PWV in fresh porcine aortas. A moderate change in PWV was seen after stent-graft deployment with a stent-graft length of 15 cm, but a
marked increase was seen when stent-graft length was extended. The increase in PWV may be limited when a shorter part of the aorta is stented, possibly because nonstented aortic segments are able to compensate for the stiffer stented part. When the majority of aortic length is covered by stent graft, PWV increase is more evident.

In humans, a large meta-analysis showed that each 1 m/s increase in PWV was associated with a 15% risk increase of cardiovascular mortality. Arterial stiffening leading to increased PWV often develops in parallel with cardiovascular disease, and an increased PWV is often seen as a marker of atherosclerotic burden. However, it may also lead to independent pathophysiological changes that cause an increased mortality. A supposed pathophysiological mechanism is the increase of pulse wave reflections. Because the aorta is stiffer, its storage capacity is reduced, and the pulse wave reaches the more resistant peripheral arteries at a higher velocity. This leads to a greater part of the pulse wave being reflected instead of being transferred to the peripheral circulation, which increases left ventricular afterload and myocardial oxygen demand, ultimately leading to diastolic dysfunction. Moreover, increased arterial stiffness is involved in the pathogenesis of hypertension. It causes an increased pulse pressure, leading to endothelial dysfunction and hypertension, which in turn may cause further increases in arterial stiffness. TEVAR-induced aortic stiffness has been associated with onset of hypertension in young trauma patients. This illustrates that the potential clinical consequences of increased PWV after TEVAR are considerable and also that the artificially induced stiffening after TEVAR offers an opportunity to investigate the isolated effects of increased aortic stiffness on cardiovascular remodeling.

Central (i.e. aortic) PWV is influenced by many factors, including the method used to measure it. The most commonly used method to measure central PWV is with echo Doppler signals of the carotid and femoral artery. When heart rate, Doppler signal transmission time, and the distance between carotid and femoral artery are known, the PWV can be calculated. This noninvasive method is considered the gold standard of measuring aortic stiffness, and reference values have been established for different age groups. Carotid-femoral PWV of healthy individuals up to 30 years of age is usually between 5.3 and 7.1 m/s. It gradually increases with age and normally ranges between 8.0 and 14.6 m/s for older subjects. In the presence of hypertension, end-stage renal disease or other cardiovascular disease, these values can increase markedly. The reliability of carotid-femoral PWV measurements is affected by different factors, most notably those that influence a patient’s blood pressure, such as vasoactive medication, physical activity, and patient position. Moreover, it is not possible to determine the exact distance between carotid and femoral artery from the outside. Differences in path length can lead to differences in carotid-femoral PWV values of up to 30%. Our model allows for elimination of many of the aforementioned clinical confounders, including, in particular, arterial blood pressure modifications and the distance between the 2 points of measurement.

The available clinical evidence of aortic stiffening after TEVAR is limited. Tzilalis et al. measured carotid-femoral PWV in 11 young patients treated with TEVAR for traumatic aortic injury, 13 to 60 months after the procedure, and compared this

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>After proximal stent-graft deployment</th>
<th>After stent-graft extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal pressure, mm Hg</td>
<td>97.3 ± 1.3</td>
<td>97.2 ± 1.2</td>
<td>97.0 ± 1.3</td>
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<tr>
<td>Stent-graft coverage, %</td>
<td>40.0 ± 3.9</td>
<td>63.8 ± 6.3</td>
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<tr>
<td>Pulse wave velocity, m/s</td>
<td>5.0 ± 0.3 m/s</td>
<td>5.2 ± 0.4</td>
<td>5.8 ± 0.4</td>
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</table>
to a group of age-matched controls. They noted a mean PWV of 7.45 m/s in their control group and reported a PWV of 10.41 m/s in the TEVAR group, despite some patients receiving antihypertensive medication. Preclinical studies of the relation between TEVAR and aortic stiffness found an acute reduction in compliance directly after TEVAR in an in vivo porcine model, and a large increase in PWV of > 3 m/s in an in vivo canine model. Similarly, in our ex vivo model, we observed a significantly increased PWV after TEVAR, even more evident after TEVAR extension.

Using ex vivo porcine aortas to study hemodynamics has several limitations. Although the elastic properties of porcine aortic tissue are within the range of human arterial tissue properties, young porcine aortic tissue is less stiff than aged human tissue. Second, water was used as a test fluid, for reasons of leaking and to prevent clogging of the pulsatile pump, like in other ex vivo porcine aortic studies. Although we acknowledge this as a limitation since the viscosity of water is lower than blood, the influence of using fluid with a different viscosity than blood can be expected to be small for the purpose of this study, because of the high velocity of blood in the aorta. Also, although no live cells were used in the experiments, Krebs-Ringer or isotonic saline for perfusion might still leave the cells of the aortic wall in better condition than water. Although some deterioration of the aortic wall tissue undoubtedly must have taken place, we believe the duration of the each test was sufficiently short (± 2 hr) to justify the use of water. Furthermore, we usually opted to deploy a distal extension with a smaller diameter than the proximal component, because porcine aortas show considerable tapering over a relatively short distance. This is unusual in clinical practice; however, aortic stent size was always congruent with the aortic model size, and the potential presence of type III endoleak was considered of limited importance for the analysis. Another limitation is the fact that only 1 type of stent graft was used, while differences in stent graft design can lead to differences in aortic compliance.

CONCLUSIONS

Stent-graft deployment increased aortic stiffness and pulse pressure in this ex vivo pulsatile porcine model, especially with greater stent lengths. These observations might have important consequences for clinical practice. Therefore, aortic stiffness after TEVAR merits further investigation.

REFERENCES


