

## Comparative Analysis of Porcine and Human Thoracic Aortic Stiffness

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### WHAT THIS PAPER ADDS

This study uses a method to compare published data on porcine and human thoracic aortic stiffness from different studies consistently. The results of this analysis show that the stiffness of young porcine aortas is similar to that of human tissue aged under 60 years and less stiff than human tissue aged 60 years or more. This has implications for using the porcine aorta as a model for human aorta in research.

**Objectives:** To compare porcine and human thoracic aortic stiffness using the available literature.

**Methods:** The available literature was searched for studies reporting data on porcine or human thoracic aortic mechanical behaviour. A four fibre constitutive model was used to transform the data from included studies. Thus, equi-biaxial stress stretch curves were generated to calculate circumferential and longitudinal aortic stiffness. Analysis was performed separately for the ascending and descending thoracic aorta. Data on human aortic stiffness were divided by age <60 or ≥60 years. Porcine and human aortic stiffness were compared.

**Results:** Eleven studies were included, six reported on young porcine aortas, four on human aortas of various ages, and one reported on both. In the ascending aorta, circumferential and longitudinal stiffness were  $0.42 \pm 0.08$  MPa and  $0.37 \pm 0.06$  MPa for porcine aortas (4–9 months) versus  $0.55 \pm 0.15$  MPa and  $0.45 \pm 0.08$  MPa for humans <60 years, and  $1.02 \pm 0.59$  MPa and  $1.03 \pm 0.54$  MPa for humans ≥60 years. In the descending aorta, circumferential and longitudinal stiffness were  $0.46 \pm 0.03$  MPa and  $0.44 \pm 0.01$  MPa for porcine aortas (4–10 months) versus  $1.04 \pm 0.70$  MPa and  $1.24 \pm 0.76$  MPa for humans <60 years, and  $3.15 \pm 3.31$  MPa and  $1.17 \pm 0.31$  MPa for humans ≥60 years.

**Conclusions:** The stiffness of young porcine aortic tissue shows good correspondence with human tissue aged <60 years, especially in the ascending aorta. Young porcine aortic tissue is less stiff than human aortic tissue aged ≥60 years.

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### INTRODUCTION

The porcine aorta is used as a model for the human aorta in various fields of cardiovascular research.<sup>1–4</sup> Differences and similarities between pigs and humans in terms of anatomy and physiology have been investigated to define the translational value of porcine models.<sup>1</sup> Part of the translational value of porcine models depends on the agreement

between human and porcine aortic mechanical behaviour, specifically stiffness.

Aortic stiffness is determined by its structural constituents in the tunica media and adventitia. Elastin and collagen fibres, and the degree of activation of vascular smooth muscle cells together determine the active mechanical behaviour of the aortic wall.<sup>5</sup> The passive mechanical behaviour is determined mainly by the elastin and collagen fibres; the extent of the contribution of smooth muscle on passive mechanical behaviour is not yet known.<sup>5</sup> The presence and orientation of collagen fibre endows the aortic wall with an anisotropic (directionally dependent) material response. In the media, the diagonal orientation of collagen fibres is closer to circumferential alignment, while in the adventitia it is closer to axial alignment.<sup>6</sup> Histological evaluation of the thoracic aorta shows that elastin and

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collagen fibres are organised in the same functional unit in different mammals, and that the difference in size between the thoracic aorta of smaller and larger mammals is directly proportional to the number of these functional units.<sup>7</sup>

Numerous experimental protocols have been used to characterise the mechanical properties of human aortas.<sup>8–13</sup> The results of these experiments have been used to formulate mathematical models that describe aortic mechanical behaviour, specifically the relationship between stress and strain over a wide range of strains. In general, these mathematical formulations are called constitutive models, and their main goal is to be general enough to reproduce the measured experimental data and in doing so, to provide a description of the tissue stiffness. Ferruzzi et al. proposed a complex four fibre constitutive model for aortic mechanical behaviour based on the histological structure of the aortic wall.<sup>14</sup> This model was used by Roccabianca et al. to calculate regional human aortic stiffness for different age groups based on data from the available literature.<sup>12</sup> Such a comparison has limitations, because the included datasets originate from studies with different testing protocols, and cannot fully account for these differences. Nevertheless, it can be used to evaluate the available literature in a consistent manner. Even though it is not straightforward to compare porcine and human aortic stiffness based on literature, the current study uses the same analysis for available data on porcine aortic tissue.

## MATERIALS AND METHODS

### Selection of data on human and porcine aortas

A search was performed of Medline, EMBASE, and Cochrane databases to obtain data on porcine aortic tissue, using the following search terms: “aorta,” “endovascular repair,” “pig,” “porcine,” “ex vivo,” “in vitro,” “experimental,” “isolated,” “biomechanics,” “haemodynamics,” and synonyms. The search was last updated on June 29, 2016. Studies were included if they performed assessment of the stiffness of a specified region of the porcine aorta, and reported the results using either a plot or a non-linear constitutive model with associated best fit values of the material parameters. Studies reporting data only on purified elastic tissue, after other tissue engineering processes or after *in vivo* medical or surgical treatment of the pigs were excluded. The reference lists of the studies that remained after applying in- and exclusion criteria were checked for additional relevant articles. For data on human aortas, data were included from the article by Roccabianca et al., who included four studies after a comprehensive literature search for studies on mechanical testing of human aortic tissue without aneurysm or dissection.<sup>8–12</sup> Although a comparison between porcine tissue and diseased human tissue would be of interest, it was considered beyond the scope of the current study.

### Data analysis

The procedure for creating consistent sets of data with associated stress strain curves for the included studies was the

same in the present analysis as the one previously adopted by Roccabianca et al.<sup>12</sup> Such a procedure represents a consistent means for comparing results from different studies, regardless of the original testing protocols or constitutive relations used in each individual study. In particular, it was aimed to compare equi-biaxial stress strain curves for each individual article that was included in the study. However, the data as reported in the considered articles were not immediately comparable. Therefore, it was necessary to perform additional computations to homogenise these data.

In short, either the strain energy function with the corresponding material coefficients or the stress stretch curves as reported in the corresponding paper were used as input data to simulate five loading protocols (i.e. biaxial tests with stress ratio  $\sigma_{11} : \sigma_{22} = 0.5:1, 0.75:1, 1:1, 1:0.75,$  and  $1:0.5$ , where  $\sigma_{11}$  and  $\sigma_{22}$  are the circumferential and longitudinal stresses, respectively).

Then, the obtained stress stretch curves were fitted using the four fibre constitutive model as reported in Roccabianca et al.

$$W = \frac{c}{2} (I_1 - 3) + \sum_{k=1}^4 \frac{c_1^k}{4c_2^k} (\exp [c_2^k ((\lambda^k)^2 - 1)^2] - 1) \quad (1)$$

where  $c$ ,  $c_1^k$ , and  $c_2^k$  are positive material parameters,  $I_1$  is the first invariant of the right Cauchy-Green tensor  $C$ , and  $\lambda^k$  is the stretch in the direction of the  $k$ -th collagen fibre family and defined in the reference configuration by the unit vector  $M^k = [0, \sin \alpha_0^k, \cos \alpha_0^k]$ , with  $\alpha_0^k$  the angle between the  $k$ -th fibre family (arranged in symmetrical spirals) and the axial direction of the arterial wall (blood flow direction). In particular,  $\alpha_0^1 = 0^\circ$  denotes the axially arranged fibre family,  $\alpha_0^2 = 90^\circ$  the circumferentially arranged fibre family, and  $\alpha_0^3 = -\alpha_0^4 = \alpha$  the two -fibre families symmetrically oriented.

The Cauchy stresses in the circumferential and axial direction,  $\sigma_{11}$  and  $\sigma_{22}$ , are given by:

$$\sigma_{ii} = \lambda_i \frac{\partial W}{\partial \lambda_i} - p, \quad i = 1, 2 \quad (2)$$

with  $p$  a Lagrange multiplier to enforce the incompressibility constraint and computed through the known zero stress in the radial direction,  $\sigma_{33} = 0$ .

To generate the best fit values of material parameters for the four fibre constitutive model, the following objective function was minimised:

$$\chi = \sum_{i=1}^N (\sigma_{11}^{exp} - \sigma_{11}^{mod}) + (\sigma_{22}^{exp} - \sigma_{22}^{mod}) \quad (3)$$

with  $N$  the total number of data points,  $\sigma^{exp}$  the experimental stress data, and  $\sigma^{mod}$  the corresponding model prediction values computed in Eq. (2).

The minimisation was performed with a non-linear trust region reflective algorithm implemented in MATLAB, and multiple, randomly generated starting points were considered to find the global best fit solution.

Finally, circumferential and longitudinal aortic stiffness were calculated for each dataset from the equi-biaxial stress stretch curves ( $\sigma_{11} : \sigma_{22} = 1:1$ ) as the slope of the curve at the stress stretch point corresponding to the physiological pressure of 13.33 kPa (100 mmHg). To determine the stress corresponding to physiological pressure, Laplace's law was used:

$$\sigma = \frac{P_{phys} \cdot r}{h} \quad (4)$$

Sample specific values of radius and thickness were not available, so an average value was assumed based on previous experiments by the present study group.<sup>18</sup> The reported results include a general overview of all included datasets, including those obtained through uniaxial tensile testing, but only the datasets considered to offer the most reliable data on physiological stiffness (because these studies reported on biaxial or inflation tests) were used to calculate a mean value of stiffness. This analysis summarised above was made separately for the ascending aorta and the descending aorta. Additionally, any description of microstructural data, potentially motivating the reported stiffness values, was included.

### Ethics statement

The research for this article was performed by re-analysing published data; no animals or humans were engaged for this research.

### RESULTS

Limiting search results to full length, English language papers yielded a total of 465 articles. A flow chart of the study selection procedure can be seen in Fig. 1. Eleven studies were included, six reported on young porcine aortas,<sup>15–20</sup> four on human aortas of various ages,<sup>8–11</sup> and one reported on both.<sup>13</sup>

### Cauchy stress stretch curve analysis

The best fit material parameters are listed in Table 1. Fig. 2 shows the generated stress stretch curves of porcine and human ascending thoracic aortas. The curves based on the data reported by Jia et al.<sup>16</sup> and Vorp et al.<sup>8</sup> are based on uniaxial tensile testing and clearly differ from the other included studies. Moreover, the curve based on the data reported by Jia et al.<sup>16</sup> shows linear elastic behaviour with a very low stiffness, which did not intersect the 100 mmHg stress point required to calculate circumferential or

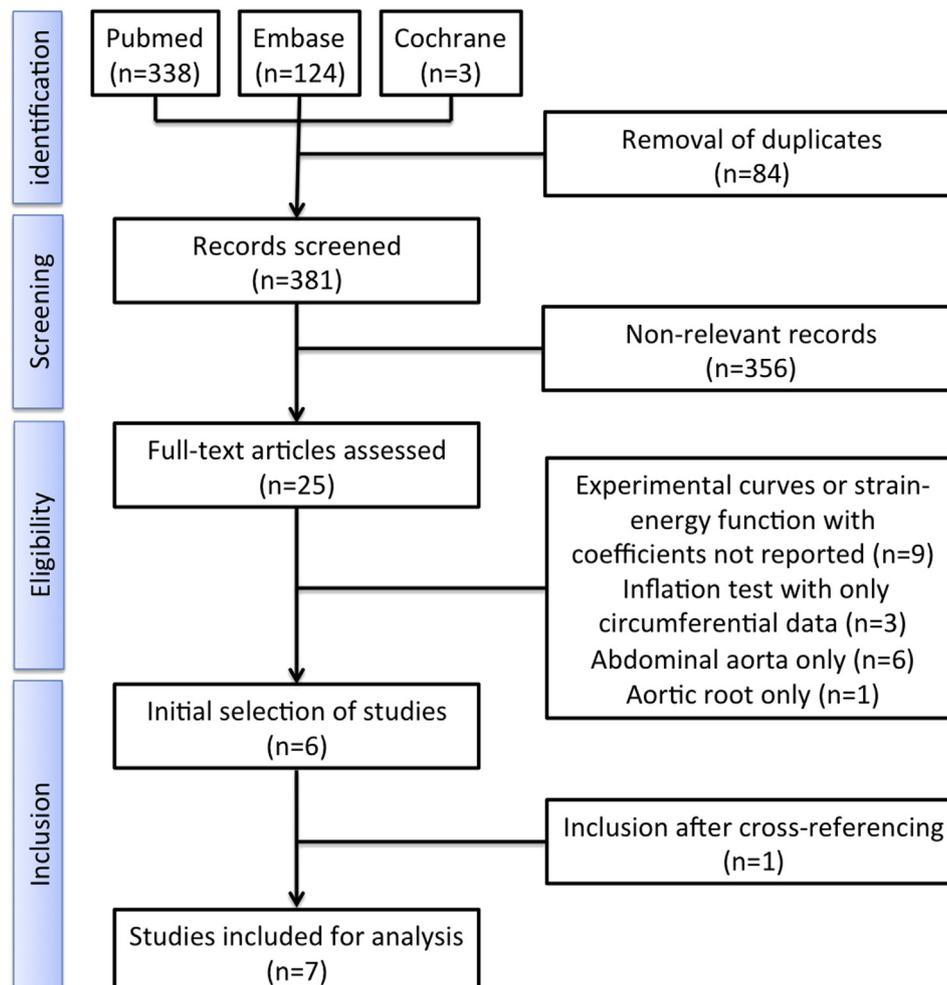
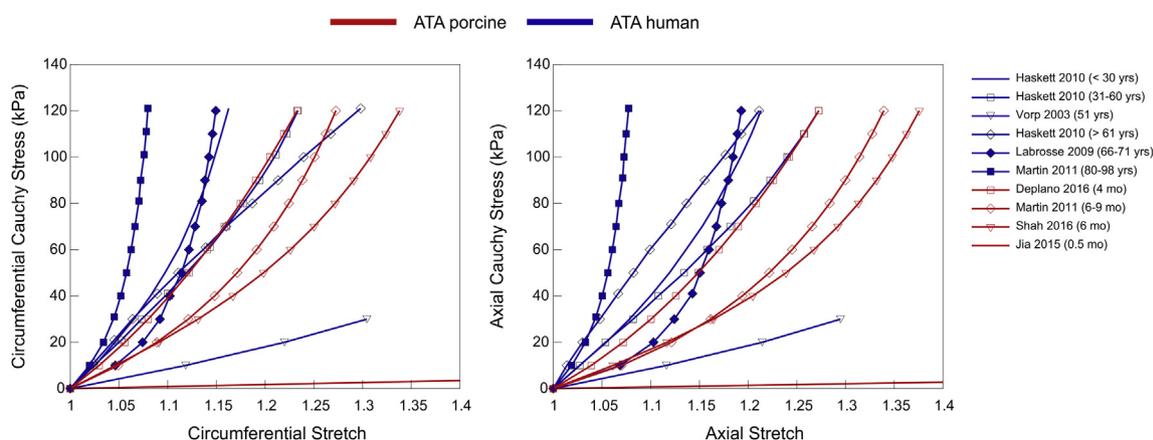


Figure 1. Flow chart of study selection.

**Table 1.** Best fit values of the eight model parameters for the four fibre family constitutive model.

	Tissue	Age	C (kPa)	$c_1^1$ (kPa)	$c_2^1$	$c_1^2$ (kPa)	$c_2^2$	$c_1^{3,4}$ (kPa)	$c_2^{3,4}$	$\alpha_0$ (deg)
<i>Ascending aorta</i>										
Deplano et al. <sup>15</sup>	Porcine	4 mo	0.054	63.260	0.001	45.203	0.001	80.811	0.001	38.424
Martin et al. <sup>13</sup>	Porcine	6–9 mo	0.000	33.614	0.209	45.418	0.280	33.735	1.057	42.716
Shah et al. <sup>20</sup>	Porcine	6 mo	17.828	27.639	0.730	2.850	0.003	23.259	0.590	16.230
Jia et al. <sup>16</sup>	Porcine	0.5 mo	1.540	0.000	0.000	$5.4 \times 10^{-5}$	0.009	0.233	0.001	58.520
Haskett et al. <sup>10</sup>	Human	0–30 y	22.410	58.370	0.600	60.160	3.240	59.850	2.990	48.100
Haskett et al. <sup>10</sup>	Human	31–60 y	47.430	35.230	0.000	40.840	0.100	15.210	2.580	48.980
Vorp et al. <sup>8</sup>	Human	51 y	8.300	16.220	0.070	15.740	0.000	0.000	0.070	2.540
Haskett et al. <sup>10</sup>	Human	≥61 y	88.820	28.380	0.000	0.150	0.000	7.310	0.000	45.000
Labrosse et al. <sup>9</sup>	Human	66–71 y	0.000	10.270	6.310	8.290	11.060	58.170	9.410	47.180
Martin et al. <sup>13</sup>	Human	80–98 y	0.000	113.180	17.380	110.270	16.860	121.580	50.170	44.820
<i>Descending aorta</i>										
Jia et al. <sup>16</sup>	Porcine	0.5 mo	2.002	0.000	0.002	0.147	0.001	0.005	0.000	84.980
Marra et al. <sup>19</sup>	Porcine	4–5 mo	1.800	0.000	0.000	0.000	0.000	74.000	0.930	45.300
Polzer et al. <sup>17</sup>	Porcine	10 mo	4.682	15.593	2.242	16.352	4.670	44.629	0.733	36.824
Nauta et al. <sup>18</sup>	Porcine	10–12 mo	13.672	105.245	0.342	189.944	0.479	141.805	26.312	30.134
Garcia-Herrera et al. <sup>11</sup>	Human	20–35 y	37.200	0.000	0.000	0.000	0.000	28.160	3.480	43.880
Haskett et al. <sup>10</sup>	Human	0–30 y	26.770	43.330	1.520	26.730	1.530	743.350	4.970	44.870
Garcia-Herrera et al. <sup>11</sup>	Human	45–60 y	24.660	0.000	0.000	0.000	0.000	90.100	5.330	42.190
Haskett et al. <sup>10</sup>	Human	31–60 y	0.000	74.500	2.210	67.820	1.680	487.270	15.950	44.710
Haskett et al. <sup>10</sup>	Human	≥61 y	0.000	98.340	0.000	162.730	13.720	803.360	35.640	48.120
Labrosse et al. <sup>9</sup>	Human	57–71 y	0.000	3.870	10.720	6.610	5.020	61.180	6.830	42.470

**Figure 2.** Circumferential (left) and longitudinal (right) equi-biaxial Cauchy stress stretch curves of human and porcine aortic tissue for ascending aorta. The curved shape of these stress stretch relationships (except in the data from Jia et al.<sup>16</sup> and Vorp et al.<sup>8</sup>) shows that porcine and human aortas are non-linearly elastic.

longitudinal stiffness. The curves of the eight remaining datasets (three porcine, five human), which show non-linear elastic behaviour, were considered most reliable, and were used to calculate mean values of aortic stiffness.

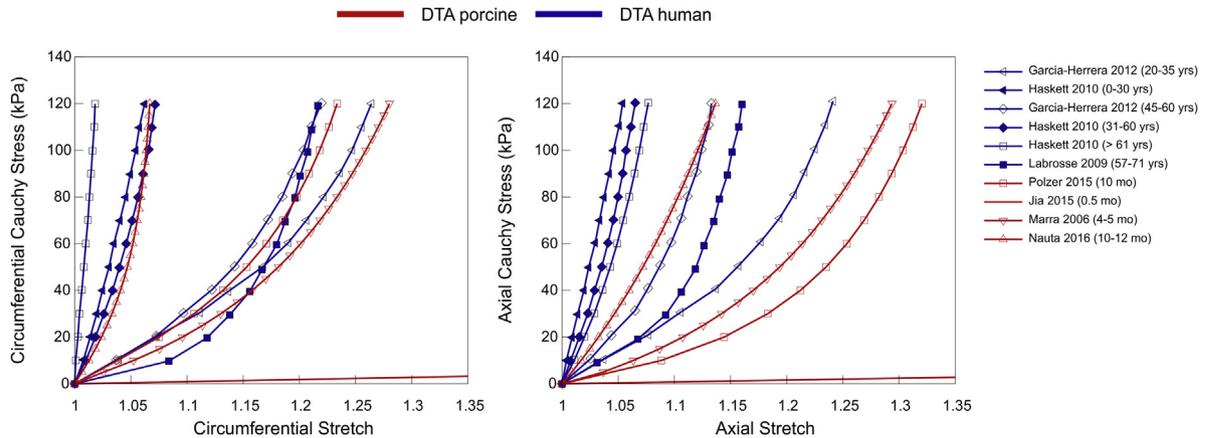
Fig. 3 shows the generated stress stretch curves for descending thoracic aortas. The curves based on the data reported by Jia et al.<sup>16</sup> and Nauta et al.<sup>18</sup> are based on uniaxial tensile testing. The curve based on the data from Nauta et al.<sup>18</sup> shows considerably stiffer behaviour than the curves based on the data from Marra et al.<sup>19</sup> and Polzer et al.,<sup>17</sup> which is most likely because of differences in storage of the tissue. Stiffness values could not be calculated for the data from the study by Jia et al.<sup>16</sup> as the equi-biaxial curves did not intersect the 100 mmHg stress point. The curves of the eight remaining datasets (two porcine, six human), which show non-linear elastic

behaviour, were considered most reliable, and were used to calculate mean values of aortic stiffness.

### Human versus porcine aortic stiffness

Fig. 4 shows the calculated stiffness values for each of the studied datasets for the ascending aorta separately, and combined into groups (porcine samples, human samples <60 years, and human samples ≥60 years). Circumferential and longitudinal stiffness were  $0.42 \pm 0.08$  MPa and  $0.37 \pm 0.06$  MPa for porcine aortas (4–9 months);  $0.55 \pm 0.15$  MPa and  $0.45 \pm 0.08$  MPa for humans <60 years; and  $1.02 \pm 0.59$  MPa and  $1.03 \pm 0.54$  MPa for humans ≥60 years.

Fig. 5 shows the calculated stiffness values for the descending aorta. Circumferential and longitudinal stiffness

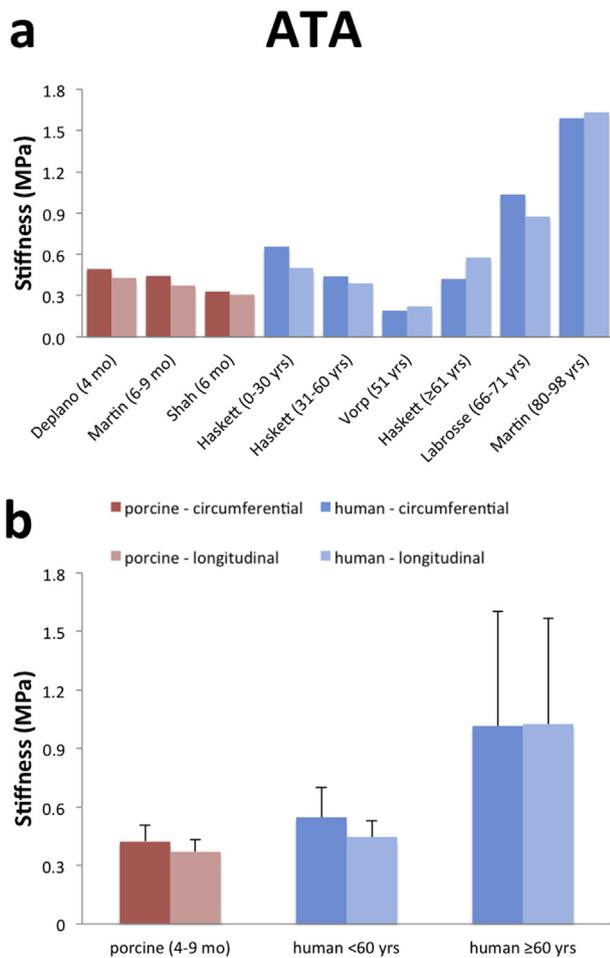


**Figure 3.** Circumferential (left) and longitudinal (right) equi-biaxial Cauchy stress stretch curves of human and porcine descending thoracic aortic tissue. The curved shape of these stress stretch relationships (except in the data from Jia et al.<sup>16</sup>) shows that porcine and human aortas are non-linearly elastic.

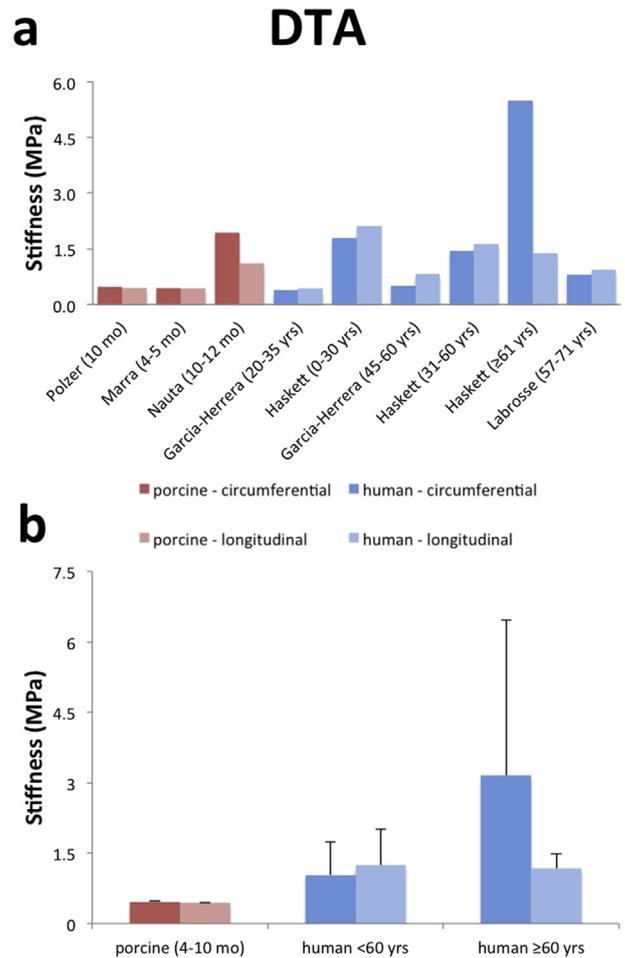
were  $0.46 \pm 0.03$  MPa and  $0.44 \pm 0.01$  MPa for porcine aortas (4–10 months);  $1.04 \pm 0.70$  MPa and  $1.24 \pm 0.76$  MPa for humans <60 years and  $3.15 \pm 3.31$  MPa and  $1.17 \pm 0.31$  MPa for humans  $\geq 60$  years.

**Microstructural analysis**

Martin et al. reported microstructural data on both human and porcine ascending aortic tissue, and noted a higher proportion of collagen fibres in their human tissue samples



**Figure 4.** Calculated stiffness values of porcine and human ascending aortic tissue (a) for each individual study and (b) when combined into groups. Tissue anisotropy is evidenced by the difference in circumferential and longitudinal aortic stiffness.



**Figure 5.** Calculated stiffness values of porcine and human descending thoracic aortic tissue (a) for each individual study and (b) when combined into groups. Tissue anisotropy is evidenced by the difference in circumferential and longitudinal aortic stiffness.

(80–98 years), whereas their porcine tissue samples (6–9 months) showed a higher proportion of elastin fibres.<sup>13</sup> Moreover, the elastin fibres were thinner and straighter in the human tissue samples compared with the more undulated elastin fibres in porcine tissue. This consideration is in line with the higher stiffness values that they found for human tissue compared with porcine tissue. Haskett et al. studied human ascending and descending aortic tissue in different age groups (0–30, 31–60, and >60 years) and found that, for all age groups, the majority of (collagen and elastin) fibres were preferentially oriented in the circumferential direction.<sup>10</sup> The proportion of circumferentially aligned fibres had a negative correlation with peak strain.<sup>10</sup> Finally, the distribution of fibre orientations changed gradually across the thickness of the aortic wall.<sup>10</sup> Polzer et al. found the same pattern for porcine descending aortic tissue (aged 6–9 months), namely that the amount of collagen fibres with circumferential alignment was relatively low at the luminal side of the aortic wall, increased toward the middle of the thickness of the wall, then decreased towards the peripheral wall.<sup>17</sup>

## DISCUSSION

A comparison was made between porcine and human tissue by fitting published data of porcine and human aortas to a well established four fibre constitutive model. This model is motivated by microscopic data on the histological organisation of arterial collagen, and matches the data from humans <60 years well, but also captures the mechanical behaviour of more aged and diseased aortas.<sup>12,14</sup> The results of the current analysis show that porcine ascending and descending thoracic aortic stiffness, which was calculated using data originating from very young (0.5–12 months) tissue, shows more similarity to human tissue of the <60 year age group than the ≥60 year age group. The observations of microstructural data support that aortic stiffness increases with greater collagen content and a more circumferential alignment of collagen and elastin fibres, both of which seem to increase with age in the study by Haskett et al.<sup>10</sup>

The present results suggest that *ex vivo* porcine aortic models, which have been used to investigate biomechanical changes in relation to bicuspid aortic valve,<sup>2</sup> type B dissection,<sup>3,21</sup> and thoracic endovascular aortic repair,<sup>4,18,21</sup> can have good translational value. The stiffness of the young porcine aortic tissue, which was used for these experiments, is relatively similar to that of human tissue up to 60 years of age, compared with older human tissue. This corresponds to the age range of patients with type B aortic dissections, although the presence of the disease may influence aortic stiffness, potentially reducing the similarities with porcine tissue. Porcine aortic tissue may be especially suitable as a model for patients with traumatic aortic injury, in whom the long-term effects of endovascular treatment are still largely unknown. Thoracic aortic aneurysm typically occurs at a later age and the disease affects aortic stiffness, so porcine models may be less suitable to study aneurysmal disease.

The current analysis was based on available literature of aortic biomechanics. By using the same constitutive model for all included studies, values of aortic stiffness were generated equal for different datasets. However, there was considerable heterogeneity in *ex vivo* aortic tissue test protocols, which is a limitation of the present study. The age of porcine tissue, originating from pigs of different races, ranged from 2 weeks to 12 months; biaxial tests,<sup>13,15,17,22</sup> and inflation tests<sup>19,20</sup> were included; and there were differences in test conditions such as the harvest and storage method of the tissue, hydration during testing, ambient temperature, displacement rate, assessment of tissue thickness, and number and range of preconditioning cycles, all of which are known to have an impact on the measured stiffness.<sup>23</sup> Moreover, average values of aortic radius and wall thickness were used for aortic stiffness calculations, because sample specific values were not available, thereby introducing an additional source of bias. Nevertheless, despite differences in testing protocols and in tissue, most porcine curves were qualitatively similar to each other, showing acceptable variability of the model.

Variability in *ex vivo* aortic testing protocols has also been observed for human tissue tests,<sup>12,24</sup> and highlights the need for more standardised biaxial testing of the aorta. Some general recommendations would include testing the aortic tissue <24 h after excision or after cryopreservation at –80 °C,<sup>22</sup> performing the experiments at 37 °C, performing preconditioning at an appropriate strain rate until effects of tissue hysteresis are reduced,<sup>15</sup> performing the actual test up to a maximum strain of 30%,<sup>15</sup> and an axial stretch of 1.25–1.35,<sup>25,26</sup> and using Cauchy stress or 2nd Piola-Kirchhoff as a definition of stress and true strain or Green-St.-Venant strain as a definition of strain.<sup>24</sup> Finally, it may be most informative to calculate stiffness at pressure levels that correspond to physiological, *in vivo* conditions, which it was chosen to do based on the equi-biaxial curves, as others have done.<sup>12</sup> Ideally, it might be calculated at a physiological ratio between circumferential and longitudinal stretch.

In conclusion, biomechanical factors are important when considering the suitability of porcine aortic models. There seem to be few structural differences between human and porcine thoracic aortic tissue; and the stiffness of porcine tissue may be accurately described using the same model as human tissue. Literature data were available for young porcine thoracic aortic tissue only, and for human tissue of different ages. The stiffness of young porcine aortic tissue shows good correspondence with human tissue aged <60 years, especially in the ascending aorta, whereas young porcine aortic tissue is less stiff than human aortic tissue aged ≥60 years. The young porcine thoracic aorta may be useful especially as a model of human aortas aged <60 years.

## CONFLICTS OF INTEREST

None.

## FUNDING

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