Title: Comparative Review of Large Animal Models for Suitability of Proximal Aortic Endovascular Repair

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Data Curation	Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later reuse.			
Formal Analysis	Application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data.	X		
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Investigation	Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection.	X		
Methodology	Development or design of methodology; creation of models	X		
Project Administration	Management and coordination responsibility for the research activity planning and execution.	X	X	X

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Resources	Provision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools.	x		
Software	Programming, software development; designing computer programs; implementation of the computer code and supporting algorithms; testing of existing code components.			
Supervision	Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team.	x	x	x
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2. Can ascending aortic surgery occur without the presence of cardiopulmonary bypass?

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ABSTRACT.

The advent of thoracic endovascular aortic repair (TEVAR) heralds a paradigm shift in treating descending aortopathies and is viewed as a potential option for ascending aortic dissection (AD) repair too. Currently, TEVAR's usage for ascending aortopathies remains limited. An urgent requirement exists to choose appropriate animal models to better contemporary understanding of endovascularly treating ascending ADs, also known as Stanford Type-A ADs. This narrative review provides a current literature summary on this topic, including the gross anatomical differences between adult porcine, ovine and bovine species versus that of their human counterparts, as well as specific valvular and coronary vasculature measurement variances. To achieve this, an electronic search of Cochrane Library, PubMed and Ovid Medline databases from January 1965 to June 2020 was performed, limited to articles published in English. A total of twenty-three research papers were included in constructing this review. Our findings showed that whilst macroscopic anatomy remains grossly similar, differences in valvular leaflet shape are present, with porcine and ovine models possessing anatomic characteristics that are comparable to their human counterparts. Research into inter-species ascending aortic anatomy has not been extensively performed, highlighting a literature gap. Conversely, multiple morphological studies have highlighted that porcine coronary vasculature is closely resemblant to that of humans. In conclusion, both porcine and ovine species are suitable as appropriate animal models in examining the feasibility of endovascular stent-grafts for ascending ADs. However, given the similarities in coronary and aortic valve anatomy to their human analogues, porcine models are better suited for this purpose.

Key Words: Aortic dissection; Endovascular; Ascending aorta; Animal models (Source: MeSH-NLM).

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INTRODUCTION.

The usage of non-human tissue in cardiothoracic medical research has markedly risen over the last half a century, as a solution to both the ethical dilemmas posed by using, as well as the lack of readily available human tissue for creating experimental clinical models.[1] One example of research involving such animal models is seen in better understanding treatment outcomes for acute aortic dissections (AD), a life-threatening pathology that carries significant mortality rates of over 70% within one week of onset when left untreated.[2,3] Several classifications of ADs currently exist, but arguably perhaps, one of the most commonly used is the Stanford classification system. This system categorizes dissections on the basis of site of intimomedial tear as either Type-A, defined as any AD involving the ascending aorta or Type-B, which are ADs not involving the ascending aorta (NB. This review focuses primarily on Type-A ADs).[4]

With few exceptions, the management of acute Type-A ADs is touted as a surgical emergency.[5,6] Given the aforementioned high rates of mortality otherwise, there are few reasons for not following through with operative treatment of Type-A ADs, with the main cited reasons being presence of significant medical comorbidities that impact survival to one year or less, as with very advanced age and frailty, advanced malignancies or patient/family wishes.[7] The surgical intervention for Type-A ADs has seen a marked evolution over the years, due to the intertwined combination of technological improvements in equipment, as well as a better understanding of its natural history. At present, open surgical repair (OSR) remains the gold standard of care for this otherwise catastrophic condition.[4,8] However, the advent of thoracic endovascular aortic repair (TEVAR) has heralded a paradigm shift in treatment options for aortic disease involving the descending aorta, and as such has been viewed as a potential option for ascending aortic repair, and consequently Type-A AD surgical repair as well.[9] As a result, selected patients who would otherwise be ineligible for OSR as aforementioned, which typically comprise up to 20% of all individuals, would benefit from having the opportunity of still receiving life-saving treatment in the form of minimally invasive endovascular techniques.[10]

There are various types of endovascular therapies currently viewed as a potential solution in treating Type-A ADs, including branched stent-grafts and valve-carrying conduits.[10] However, the employment of these novel therapeutic procedures within a clinical setting remains limited, with isolated case-reports and case-series providing the bulk of currently available literature on patient outcomes. Consequently, there exists an urgent requirement to choose appropriate animal models in order to better our understanding of endovascularly treating Type-A ADs.

While there is a widespread amount of published research on the variances of cardiothoracic anatomy in non-human species, there exists no literature review synthesizing this information, highlighting the accelerated need for one to be formulated. Consequently, this review article aims to combat this issue by providing a summary of currently available information on this topic, with a particular focus on determining which animal model amongst those of adult porcine, ovine or bovine species would be ideal for research pertaining to endovascularly treating Type-A ADs, relevant to the practising surgeon. Three broad sections shall be covered, beginning with a discussion of the macroscopic anatomical differences amongst humans, porcines, ovines and bovines. The review shall then focus on specific aspects of cardiothoracic anatomy, explicating in particular the valvular, aortic and coronary vasculature differences. Finally, the suitability of which animal

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would be best for being used as clinical experimental models, from a strictly anatomical standpoint for bettering our understanding of Type-A AD treatment shall then be explored.

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METHODS

To appropriately answer the aforementioned questions on this topic, two main databases were utilized. These included:

a) Ovid Medline
b) PubMed

Within Ovid Medline, since the term 'Type A aortic dissection' is quite well known within medical literature (as opposed to its verbatim analogue 'Stanford Type A aortic dissection'), the search string was commenced by initially mapping the keyword 'Endovascular' with the MeSH term 'Type A aortic dissection'. This was followed by using the Boolean operator 'AND'. The keyword 'models' was them utilized, and finally, the Boolean operator 'AND' was employed to combine all search strings. A total of 12 results were obtained from Ovid Medline. For the sake of this review, search results were limited to the English language. Secondly, within PubMed, an advanced search was conducted using the search terms 'endovascular', 'aortic dissection' and 'animal model'. This result in a total of 26 results, which were then analyzed in conjunction with previous results obtained through Ovid Medline. A flow-chart of our search strategy and study selection is detailed below.

Finally, to obtain a better pictorial representation of the cardiothoracic anatomical variations between porcine, ovine and bovine models, images from the University of Minnesota Atlas of Human Cardiac Anatomy were used with permission.

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RESULTS

Anatomical considerations for endovascular therapy of Type-A dissections amongst humans

In spite of the advantages the utilisation of thoracic endovascular aortic repair (TEVAR) affords, including eliminating the needed for perioperative cardiopulmonary bypass and the requirement for a major operative incision such as a sternotomy, there exist certain limitations that prevent its routine employment in currently treating Type-A ADs.[4,11-13] Given the paucity of large-scale trials documenting its efficacy however, as well as long-term follow-up of patients who receive this modality of treatment, there exists a literature gap in describing the specific limitations of endovascular therapy for ascending aortic pathologies. That being said, the anatomical constraints of this novel therapy have received particular scrutinization, and shall now be explored further.

One of the major challenges in successfully treating Type-A ADs with currently available stent-grafts lies in the need to insert a straight device into a curved structure i.e. the aortic arch, which poses a high risk of developing an endoleak. In an attempt to simplify landmarks within the complex anatomy of the aortic arch, the Ishimaru classification is commonly used to categorize thoracic aortic 'zones' for stent-grafts.[14]

Utilising Ishimaru's zone classifications, it is essential to ensure a 'safe' distance between the proximal and distal landing zones, to facilitate successful deployment of the stent-graft, as well as to avoid catastrophic aortic rupture.[3,15,16] However, this measurement remains dependent on both the characteristics of the chosen stent-graft, as well as the technical expertise of the operating doctor. Consequently, although there exists some variation in what constitutes a 'safe' distance, a proposed criterion has been a length of at least 20 millimetres between the two landing zones, to avoid aortic rupture during graft deployment.[16]

Secondly, problems are also created by the entry dissection tear occurring proximally within Zone 0 as illustrated in ***Figure 1***, specifically proximal to the sinotubular junction. A tear occurring within this region would fail to allow endograft deployment in a manner that would allow coronary blood flow to be maintained.[15] Occlusion of the coronary ostia by closed ends of the stent-graft would cause ischaemia of the myocardium, resulting in potential irreversible damage.[17,18] Additionally, those with Type-A ADs extending into the aortic valve would not be suitable for endovascular treatment with conventional stent-grafts, a situation typically seen in between 10-20% of patients.[15] This is because at deployment the tip of the device must cross the aortic valve, which could eventuate in possible ventricular perforation. Although this would pose a barrier to treatment with currently available stent-grafts, given that they possess a distal cone that prevents their deployment too close to the aortic valve, a proposed method to combat this has been suggested in the form of novel 'valve-carrying conduits'.

Thirdly, variations with the anatomy of the normal aorta may interfere with a wholly endovascular modality of treatment for Type-A ADs. For instance, in those who have received prior coronary artery bypass surgery, the presence of coronary grafts arising directly from the ascending aorta would present an increased risk of myocardial ischaemia during endograft deployment.[15,16]

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Based on these caveats, it is evident that the anatomy of the ascending aorta, aortic valve and coronary vasculature are of particular significance in determining an appropriate animal model for Type-A dissection research, which shall be addressed in the following sub-section.

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Introduction and general cardiac anatomy

Similar to those of humans, the holistic cardiac anatomy of large mammals is analogous; four cardiac valves are present with similar structures comparable to most quadruped mammals. Whilst human hearts can appear in a variety of shapes, including elliptical, trapezoidal, and 'valentine', porcine species tend to be valentine shaped, whilst the ovine heart varies from valentine to conical in shape, as illustrated in ***Figure 2***.[19]

With respect to the hearts of porcine and ovine species, the distance between the posteroinferior base to apex, left lateral base to apex and the length of coronary sinuses are all significantly greater in their human counterparts. As expected therefore, in conjunction with its comparatively larger size, the average human heart maintains a larger organ to body weight ratio to that of both porcine and ovine species. A similar scenario is visible in that of bovines, which possesses a nearly identical organ to body weight ratio of the ovine species.[19]

Valvular anatomy

Whilst the general cardiac anatomy of different hearts remains roughly similar, variations in the four valves exist that distinguish porcine, ovine, bovine and human species, in spite of certain structural similarities. Illustrated in table 1, average aortic valve annulus diameters for humans are identical to that of their porcine counterparts, with the ovine species possessing a slightly narrower annulus on average. Conversely, bovine diameters are nearly 40% greater than their human counterparts, possibly accounted for due to the increased cardiac output within this species.[20]

Additionally, humans have much less muscular attachment surrounding the aortic valve compared to animal hearts, an indication of their reduced cardiac output.[20] On a similar note, the human aortic valve at the level of the annulus possesses muscular attachment along 43% of its circumference, compared to respective figures of 56%, 60%, and 57% in porcine, bovine, and ovine valves.[20,21] Additionally, a greater amount of myocardial tissue support is also present at the aortic valve's right and left coronary cusp bases, distinguishing all three of ovine, bovine, and porcine valves from the human aortic valve. It should be noted that in clinical trials involving sub-coronary transplantation, this increased muscle mass has been shown to result in aortic valvular stenosis.[20]

Differences in aortic valve leaflet shape and structure are also present, with only porcine valve leaflet depths being comparable to their human analogues, although specimen analysis visualized more inter-species variation between individual leaflets in the former.[20] Variations in leaflet thickness are particularly important to make note of, as thin and fragile leaflets such as those seen in ovine species may not be structurally strong enough to support heavy pressure loads during clinical usage for long periods of time.

Aortic anatomy

Unlike the aforementioned aspects of valvular anatomy, research into specifically the ascending aortic differences between human and non-human species has not been extensively performed, highlighting a current literature gap within this area. However, morphometric studies to determine the structural

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characteristics of the largest artery in mammals have been documented. Primarily, compared to the human heart, the porcine species has only 2 head branches that originate from the aortic arch.

Dimensionally, the diameter of the proximal aorta amongst porcine species at its largest part is about 21% lesser than that of their human analogues. What is noteworthy is that unlike their human counterparts, which exhibit a gradual diameter decrease in tapering fashion, there is a sharp decrease in aortic diameter from the descending thoracic aorta to the abdominal aorta within porcine, with exact values having been documented in Table 2. Conversely, whilst research on the aortic anatomy of ovine species is scarce, it is known that the ascending aorta itself, whilst maintaining a similar aortic diameter to that of their human counterparts after accounting for the changes in organ to body weight ratio, is relatively short, of which the implications shall be discussed in the next section.[27] There is also a marked decrease in the number of elastic lamellae within ovine aorta, greatly reducing its mobility as well.[27]

Finally, of the three non-human species described in this paper, perhaps the most review has been done on bovine ascending aortic anatomy, with the 'bovine aortic arch' having been described as the single most common congenital aortic anatomic variant within humans as well. Whilst this term itself is a misnomer, it is used to supposedly refer to the variant within bovine species, which is characterised by a common single brachiocephalic trunk trifurcating into bilateral subclavian vessels and a single bicarotid trunk, as opposed to the more common human aortic arch which splits into a single brachiocephalic trunk, the left common carotid and the left subclavian arteries.[28,29]

Similar to their ovine counterparts, little to no research has been done explicating the dimensional differences in aortic root diameter between bovines and humans, elucidating the need for further research in this area.

Coronary anatomy

The suitability of porcine species usage as an animal model in coronary arterial disease is well established, with multiple morphological studies highlighting that porcine coronary vasculature is closely resemblant to that of man.[33] In pigs, both coronary arteries arise from the aortic sinuses below the supravalvular ridge, as is seen in human species, with one study highlighting that all tested porcine models showed right coronary artery (RCA) dominance (humans typically exhibit RCA dominance of anywhere between 75 to 85%, depending on the chosen study analysed).[34] As with their human counterparts however, certain inter-species variants are present, and should be kept in mind whilst choosing a porcine animal model.[34,35]

With regards to the coronary arterial system, in contrast to their porcine and human analogues, ovine species primarily have a left coronary type circulation; ergo, the majority of the myocardium receives its blood supply via branches of the left coronary artery.[36] However, given that ovines do not possess an extensive coronary collateral network, it may be still suitable to utilise their models for research. More specifically, although there exists considerable literature that is descriptive of specific aspects of ovine cardiac anatomy, little to no comparative research has been performed to elucidate the differences between ovine and human heart models, highlighting a significant literature gap in this area.[36]

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The coronary vasculature of bovine species has also been studied and documented. In all examined animals, the coronary ostia were located beneath the sinotubular junction, as seen within their human counterparts.[37] The dimensions of coronary ostia are listed in Table 3, but it is important note that ovines are one of the most common veterinary species to exhibit coronary artery anomalies, with examples of such abnormalities including coronary-to-pulmonary artery fistulae and anomalous origin of the left coronary artery from the pulmonary trunk. Consequently, their usage as animal models to mimic the human coronary system merits careful scrutiny before findings can be extrapolated.[38,39]

Suitability for use as animal clinical models in Type-A aortic dissection research

Having explored the anatomical differences between ovine, bovine and the porcine species, the anatomic feasibility of using these as animal models to better our understanding of Type-A AD treatment options shall now be explored.

As aforementioned, Type-A ADs involve the ascending aorta, making this aspect of the model's anatomy significantly important. Bovine aortic anatomy is particularly unhelpful for this pathology therefore, given the marked differences compared to their human counterparts, as elucidated previously.[28] Indeed, the 'bovine aortic arch effect' is an epidemiological term used to highlight the linkage between ascending and thoracic aortic dilatation as a result of the aortic arch anatomy within bovines, further exemplifying their unsuitability as an animal model in this context.[40]

Between the ovine and porcine species, it appears that each share some features with that of humans, whilst also exhibiting some differences that impact their usage as animal models. For instance, whilst ovines maintain a uniform aortic diameter similar to their human counterparts, their short immobile aorta could pose a challenge to graft repair within animal models.[27] Conversely, in spite of the larger aorta within pigs, the aortic diameter being nearly a fifth lesser than that of their human counterparts could also affect reproducibility of findings to the latter. Consequently, it is difficult to assess which of ovine or porcine models is better for modelling Type-A ADs, at least from the ascending aortic anatomy point-of-view.

The aortic valvular anatomy also holds certain significance when choosing an appropriate animal model, particularly with AD tears extending proximally into the aortic root.[41] As aforementioned, variations in leaflet thickness are of importance, as the heavy pressure loads exerted during clinical usage with can affect the structural stability of the animal model. Consequently, species with relatively thinner valvular commissures, such as in ovines, must be handled with due care, and it is for this reason that porcine models are preferred to their counterparts.

Finally, the coronary vasculature of the aforementioned animal models also has particular relevance to the pathology of Type-A ADs, especially with tears arising in the aortic root, or even with any more distal tears causing dissections in the proximal sinotubular junction, both of which would affect the coronary supplies, and thus consequently cause ischemia of the cardiac musculature. Given that bovine species exhibit the most coronary artery anomalies, their usage as an animal model in better understanding the various treatment

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options for Type-A ADs is hence not justified, given that these findings would not necessarily accurately represent what we might see within humans.[38,39]

Between porcine and ovine species however, the coronary vasculature is similar to that of humans. However, as aforementioned, much more research has been performed on the coronary arterial supply of pigs, with little to no comparative research being performed on their ovine counterparts, and as such, the former takes current precedence when selecting an animal model for Type-A AD research.

Limitations of this review & insights on future research

The comparison of ovine, porcine and bovine cardiac anatomy, and their usage as animal models will undoubtedly provide important new insights in new endovascular treatment options within the Type-A AD paradigm. However, as explored in this paper, several limitations exist, with a prominent example being the lack of literature in anatomical differences amongst each of these three species. Firstly, there is a lack of information in the microscopic anatomical differences between species' cardiac anatomy, such as the anatomical variances in the layers of the aorta amongst porcine, ovine and bovine species. Additionally, although considerable literature describes either very general or very specific aspects of mammalian cardiac anatomy, little quantitative, truly comparative research has been done. These ties in to our final limitation, which is the nature of this review itself. As a narrative review, whilst it provides information about the current stage of research and addresses future directions and possible clinical applications, it has a limited comprehensive results analysis. Potentially, a systematic review might yield more comprehensive data as well as identify any bias or random errors. In the long term, the authors encourage researchers currently using animal models of cardiovascular disease to publish their findings and add to the literature to allow such translation to human interventions.

Conclusion

The introduction of intravascular stent-grafts as a surgical treatment option for Type-A ADs represents one of the most successful innovations in cardiothoracic surgery within the last few decades. However, lingering high numbers of patient mortality rates in spite of surgical intervention highlights the accelerated need for our better understanding of novel treatment options for this disease, explicating the necessity of developing an appropriate animal clinical model. From a strictly anatomical standpoint, bovine species do not meet this need, given the significant variations in aortic arch anatomy, the lack of literature on aortic valvular anatomy and finally the significant variation in coronary artery anatomy. However, both porcine and ovine species appear to be suitable options to be used as animal models for proximal aortic endovascular treatment, with the former possessing a slight advantage given similarities in coronary artery and aortic valve anatomy to their human analogues. The identification of appropriate animal models will provide knowledge for further insight into the available endovascular treatment options into Type-A ADs, and consequently needs to be hastened.

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FIGURES AND TABLES.

Figure 1. Ishimaru Classification of Various Landing Zones of Proximal Aorta for Endovascular Arch Repair

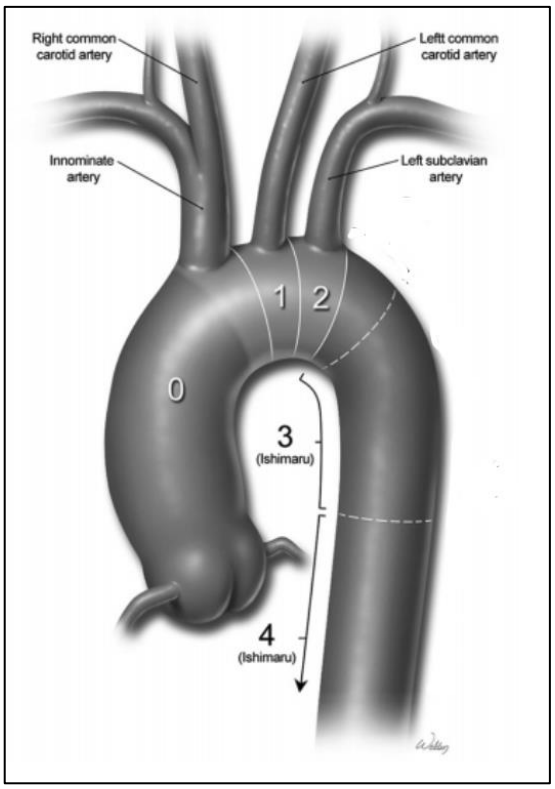

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Figure 2. Plastinated Human (upper left), Ovine (upper right) and Porcine (bottom) Hearts

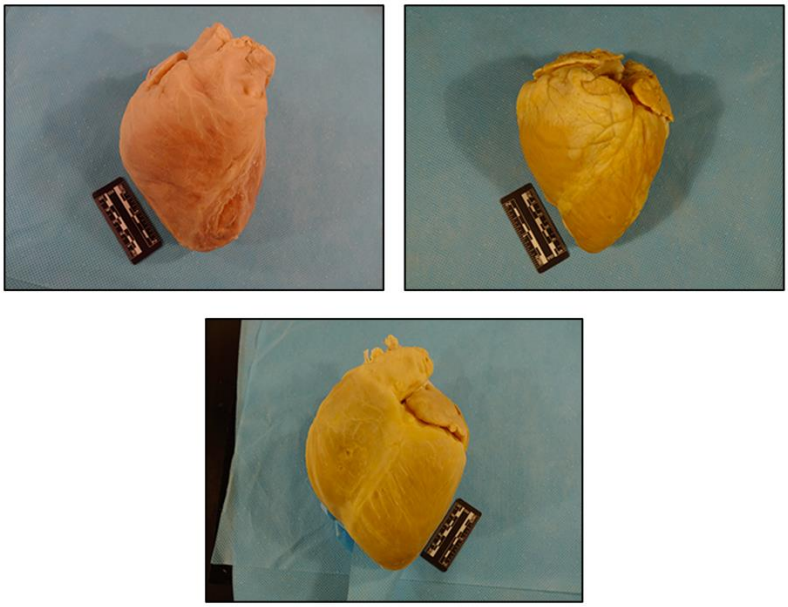

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Table 1. Mean Dimensions and Standard Deviations of Aortic Valve Measurement

Measurement		Human	Porcine	Bovine	Ovine
Annulus diameter of aortic valve (obturator diameter)		26.4 ± 3.15 [20]	26.6 ± 1.84 [20]	33.7 ± 2.74 [20]	25.8 ± 1.29 [20]
Leaflet depth	Non-coronary cusp	9.1 ± 1.66 [20]	8.9 ± 1.46 [20]	9.2 ± 1.58 [20]	7.4 ± 1.36 [20]
	Right coronary cusp	9.8 ± 2.21 [20]	10.2 ± 1.45 [20]	9.9 ± 1.21 [20]	7.6 ± 1.26 [20]
	Left coronary cusp	9.3 ± 1.24 [20]	8.6 ± 1.56 [20]	9.9 ± 0.96 [20]	7.8 ± 1.77 [20]
Valvular commissure height	Non-coronary cusp	18.5 ± 1.96 [20]	14.9 ± 1.84 [20]	19.5 ± 1.92 [20]	13.7 ± 1.52 [20]
	Right coronary cusp	17.5 ± 2.95 [20]	17.3 ± 2.28 [20]	19.4 ± 1.57 [20]	13.4 ± 1.75 [20]
	Left coronary cusp	17.3 ± 2.61 [20]	16.3 ± 2.00 [20]	19.1 ± 2.53 [20]	13.9 ± 1.30 [20]

NB. All measurements in the table above are in millimetres.

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Table 2. Dimensions of the Aorta

Measurement	Human	Porcine	Bovine	Ovine
Aortic annulus diameter	23.0 ± 2.5 [21]	20.0 ± 1.2 [21]	48.0 ± 0.92 [24]	Not documented in adults
Thoracic aortic diameter at sinotubular junction	27.2 ± 3.0 [21]	20.0 ± 0.9 [21]	Not documented in adults	Not documented in adults
Abdominal aorta diameter (measured at level of superior mesenteric artery)	22.0 ± 0.3 [25]	10.4 [21]	Not documented in adults	Not documented in adults

NB. All measurements in the table above are in millimetres. Standard deviations for abdominal aortic dimensions in pigs were not documented.

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Table 3. Dimensions of the Coronary Vasculature

Measurement	Human	Porcine	Bovine	Ovine
Left coronary ostia diameter	4.8 ± 0.5 [21]	5 ± 0.5 [21]	7.1 ± 1.7 [38]	5.38 ± 1.59 [39]
Right coronary ostia diameter	3.7 ± 0.9 [21]	4.7 ± 0.5 [21]	5.3 ± 1.4 [38]	1.75 ± 0.44 [39]
Coronary collateralization	Limited	Limited	Anomalous	Limited

NB. All measurements in the table above are in millimetres

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