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Review

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

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Abstract

The advent of thoracic endovascular aortic repair (TEVAR) heralds a paradigm shift in treating descending aortopathies. TEVAR is viewed as a potential option for ascending aortic dissection (AD) repair. Currently, TEVAR's use in treating ascending aortopathies remains limited. Appropriate animal models are urgently needed to improve our understanding of the endovascular treatment of ascending ADs, also known as Stanford Type-A ADs. This narrative review provides a current literature summary on the subject, including the gross anatomical differences among adult porcine, ovine, and bovine species, compared with those of their human counterparts, as well as specific valvular and coronary vasculature measurement variances. An electronic search of Cochrane Library, PubMed, and Ovid Medline databases from January 1965 to June 2020 was performed. The search was limited to articles published in English. Twenty-three research papers were included in this review. Our findings revealed that whereas macroscopic anatomy remains grossly similar among these species, differences in valvular leaflet shape are present, with porcine and ovine models possessing anatomic characteristics that are comparable to their human counterparts. Inter-species differences concerning the anatomy of the ascending aorta have not been extensively studied, highlighting a literature gap. Conversely, multiple morphological studies have highlighted that porcine coronary vasculature is similar to that of humans. In conclusion, both porcine and ovine species are suitable as appropriate animal models for examining the feasibility of endovascular stent-grafts for ascending ADs. However, given the similarities in coronary and aortic valve anatomy with humans, porcine models are better suited for this purpose.

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

Introduction

The use of non-human tissues in cardiothoracic medical research has markedly increased over the last five decades as a solution to both the ethical dilemmas posed by using human tissues and the lack of readily available human tissues for creating experimental clinical models.[1] One example of research involving such animal models is seen in a 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 based on the 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, managing acute Type-A ADs is touted as a surgical emergency.[5,6] Given the aforementioned high rates of mortality otherwise, there are a few reasons for not following through with operative treatment of Type-A Ads. The main cited reasons are the presence of significant medical comorbidities that affect 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 markedly evolved over the years due to the intertwined combination of technological improvements in equipment and a better understanding of its natural history. Currently, 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 diseases involving the descending aorta. Therefore, TEVAR has been viewed as a potential option for ascending aortic repair, and consequently Type-A AD surgical repair.[9] As a result, selected patients who would otherwise be ineligible for OSR as indicated, 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]

Various types of endovascular therapies, including branched stent-grafts and valve-carrying conduits, are currently viewed as potential therapeutic options for Type-A ADs.[10] However, the use of these novel therapeutic procedures within a clinical setting remains limited, with isolated case reports and case series

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providing the bulk of currently available literature on patient outcomes. Consequently, appropriate animal models are urgently needed to improve our understanding of the endovascular treatment of Type-A ADs.

While there is a wide amount of published research on the variances of cardiothoracic anatomy in non-human species, no literature review synthesizes 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 endovascular treatment of Type-A ADs, relevant to the practicing surgeon. Three broad sections shall be covered, beginning with a discussion on the macroscopic anatomical differences between humans, porcines, ovines, and bovines. The review shall then focus on specific aspects of cardiothoracic anatomy, explicating the valvular, aortic, and coronary vasculature differences. Finally, the suitability of which animal would be best for use as clinical experimental models, from a strictly anatomical standpoint for bettering our understanding of Type-A AD treatment, shall be explored.

Methods

For this review two databases were used: Ovid Medline and PubMed. Within Ovid Medline, since the term 'Type A aortic dissection' is 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 used, and finally, the Boolean operator 'AND' was used to combine all search strings. Twelve results were obtained from Ovid Medline. For this review, search results were limited to the English language. Furthermore, within PubMed, an advanced search was conducted using the search terms 'endovascular', 'aortic dissection', and 'animal model'. The search yielded 26 articles, which were then analyzed in conjunction with previous results obtained through Ovid Medline. A flowchart of our search strategy and study selection is detailed below.

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

Results

Anatomical Considerations for Endovascular Therapy of Type-A Dissections amongst Humans

Despite the advantages of thoracic endovascular aortic repair (TEVAR) use, including the elimination of the need for perioperative cardiopulmonary bypass and the requirement for a major operative incision, such as a sternotomy, there exist certain limitations that prevent its routine use in the current treatment of Type-A ADs.[4,11-13] Given the paucity of large-scale trials documenting its efficacy and 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. The anatomical constraints of this novel therapy have been scrutinized 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 (the aortic arch), which poses a high risk of developing an endoleak. In simplifying landmarks within the complex anatomy of the aortic arch, the Ishimaru classification is commonly used to categorize thoracic aortic 'zones' for stent-grafts.[14]

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

Furthermore, 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 ischemia of the myocardium, resulting in potentially 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 observed in 10–20% of patients.[15] At deployment, the tip of the device must cross the aortic valve, which could lead to 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 in the anatomy of the normal aorta may interfere with a wholly endovascular modality of treatment for Type-A ADs. For instance, in patients who have undergone prior coronary artery bypass surgery, the presence of coronary grafts arising directly from the ascending aorta would present an increased risk of myocardial ischemia during endograft deployment.[15,16]

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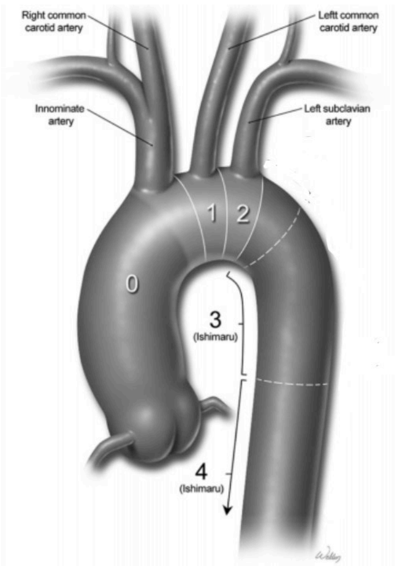
Figure 1. Ishimaru Classification of Various Landing Zones of Proximal Aorta for Endovascular Arch Repair.



Legend: Reference: Zanotti G, Reece TB, Aftab M. Aortic Arch Pathology: Surgical Options for the Aortic Arch Replacement. Cardiol Clin. 2017; 35(3):367-85. *Printed with permission from Baylor College of Medicine.*[14]

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

Legend: Reference: Atlas of Human Cardiac Anatomy, University of Minnesota/© Medtronic. Comparative Anatomy of the Valves. Available from: http://www.vhlab.umn.edu/atlas/comparative-anatomy-tutorial/valves.shtml. Last updated Jan 14,2019; cited Jan 20,2020.[19]

Introduction and General Cardiac Anatomy

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

Concerning the hearts of porcine and ovine species, the distance between the posteroinferior base to apex, left lateral base to apex, and the coronary sinuses' length are significantly greater than their human counterparts. Therefore, in conjunction with its larger size, the average human heart maintains a larger organ-to-body weight ratio than both porcine and ovine species. A similar scenario is visible in that of bovines, which possess a nearly identical organ-to-body weight ratio to the ovine species.[19]

Valvular Anatomy

While the general cardiac anatomy of different hearts remains roughly similar, variations in the four valves exist that distinguish among porcine, ovine, bovine, and human species, despite certain structural similarities. Illustrated in *Table 1*, average aortic valve annulus diameters for humans are identical to those 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 than animal hearts, an indication of their reduced cardiac output.[20] Similarly, the human aortic valve at the annulus level 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 ovine, bovine, and porcine valves from the human aortic valve. Notably, in clinical trials involving sub-coronary transplantation, this increased muscle mass has resulted in aortic-valvular stenosis.[20]

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

Measurement (mm)		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 commis-sure 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]

Differences in aortic valve leaflet shape and structure are also present, with only porcine valve leaflet depths 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 observed in ovine species, may not be structurally strong enough to support heavy pressure loads during clinical use for long periods.

Aortic Anatomy

Unlike the aspects of valvular anatomy, studies into the differences in the ascending aorta between human and non-human species have not been extensively performed, highlighting a current literature gap. However, morphometric studies have been documented to determine the largest artery's structural characteristics in mammals. Primarily, compared to the human heart, the porcine heart has only two head branches originating from the aortic arch.

Dimensionally, the diameter of the proximal aorta among porcine species at its largest part is about 21% lesser than that of their human analogues. Notably, unlike their human counterparts, which exhibit a gradual diameter decrease in a tapering fashion, the porcine aortic diameter decreases sharply from the descending thoracic aorta to the abdominal aorta (*Table 2*). Conversely, while studies on the aortic anatomy of ovine species are inadequate, the ascending aorta, while 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. Its 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, the bovine ascending aortic anatomy is the most reviewed of the three non-human species described in this review article. The 'bovine aortic arch' has been described as the single most common congenital aortic anatomic variant within humans as well. While this term itself is a misnomer, it is used to supposedly refer to the variant within bovine species, which is characterized 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, left common carotid, and left subclavian arteries.[28,29]

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

Coronary Anatomy

The suitability of porcine species as an animal model in coronary arterial disease is well established, with multiple morphological studies highlighting that porcine coronary vasculature is similar to humans.[33] In pigs, both coronary arteries arise from the aortic sinuses below the supravalvular ridge, as is observed in human species, with one study highlighting that all tested porcine models showed right coronary artery (RCA) dominance (humans typically exhibit RCA dominance anywhere between 75 to 85%, depending on the chosen study analyzed).[34] However, as with their human counterparts, certain inter-species variants are present and should be considered in 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 through 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 use 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 conducted to elucidate the differences between ovine and human heart models, highlighting a significant literature gap.[36]

Table 2. Dimensions of the Aorta.

Measurement (mm)	Human	Porcine	Bovine	Ovine
Aortic annulus diameter	23.0 ± 2.5 [21]	20.0 ± 1.2 [21]	48.0 ± 0.92 [24]	Not document-ed in adults
Thoracic aortic diameter at sinotubular junction	27.2 ± 3.0 [21]	20.0 ± 0.9 [21]	Not documented in adults	Not document-ed 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 document-ed in adults

Legend: Standard deviations for abdominal aortic dimensions in pigs were not documented.

Table 3. Dimensions of the Coronary Vasculature.

Measurement (mm)	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

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 observed with their human counterparts.[37] The dimensions of coronary ostia are listed in *Table 3*, but it is important to 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 use as animal models to mimic the human coronary system merits 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 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.

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, given the marked differences from humans, 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 due to the aortic arch anatomy within bovines, further exemplifying their unsuitability as animal models in this context.[40]

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

The aortic valvular anatomy is significant when choosing an appropriate animal model, particularly with AD tears extending proximally into the aortic root.[41] As indicated, variations in leaflet thickness are important, as the heavy pressure loads exerted during clinical use 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. As a result, porcine models are preferred to the other models.

Finally, the coronary vasculature of these animal models also has 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 use as an animal model in better understanding the various treatment options for Type-A ADs is hence not justified, given that these findings would not necessarily accurately represent what we might observe in humans.[38,39]

Between porcine and ovine species, the coronary vasculature is similar to that of humans. However, as indicated, much more research has been conducted on the coronary arterial supply of pigs, with little to no comparative research being conducted 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

Comparing ovine, porcine, and bovine cardiac anatomy and their use as animal models will undoubtedly provide important new insights into new endovascular treatment options for Type-A AD. However, as explored in this review, several limitations exist, with a prominent example being the lack of literature on anatomical differences among these species. First, there is a lack of information on the microscopic anatomical differences in cardiac anatomy among species, such as the anatomical variances in the layers of the aorta among 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 conducted. These tie into our final limitation, which is the nature of this review itself. As a narrative review, while it provides information about the current state of research and addresses future directions and possible clinical applications, it was limited in comprehensive results analysis. Potentially, a systematic review might yield more comprehensive data and identify any biases 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 despite 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 as animal models for proximal aortic endovascular treatment, with the former possessing a slight advantage, given similarities in the 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 for Type-A ADs and consequently needs to be hastened.

Summary - Accelerating Translation

Open heart surgery has seen a marked evolution over the last century, with improving technologies and advancing surgical techniques providing better outcomes to patients worldwide. In particular, the advent of minimally-invasive surgical repair of one's blood vessels, also known as endovascular repair, has heralded a paradigm shift in this field, providing patients with quicker recovery times and offering life-saving surgery to a significantly larger proportion of people who would otherwise be too frail for such a delicate procedure. The usage of endovascular repair has greatly increased for diseases involving the descending aorta, but has currently been used with limited scope for the ascending aorta, given the latter's proximity to the heart. Consequently, appropriate animal models are urgently needed to improve our understanding of endovascular treatment of ascending aortic dissections, also known as Stanford Type-A ADs, a condition with a mortality rate of nearly 100% if left untreated for longer than a fortnight.

This narrative review aims to provide a current literature summary on the subject, including the gross anatomical differences among adult porcine, ovine, and bovine species, compared with those of their human counterparts, as well as specific valvular and coronary vasculature measurement variances. An electronic search of Cochrane Library, PubMed, and Ovid Medline databases from January 1965 to June 2020 was performed, with the search limited to articles published in English. In total, twenty-three research papers were included and synthesized for this review.

Several conclusions were drawn, with our findings revealing that while macroscopic anatomy remains grossly similar among these species, differences in valvular leaflet shape are present, with porcine and ovine models possessing anatomic characteristics that are comparable to their human counterparts. Inter-species differences, concerning the anatomy of the ascending aorta, remain an area of ongoing research, and have not been extensively studied at present, highlighting a literature gap. Conversely, multiple studies have highlighted that porcine coronary vasculature, or the arteries which supply the heart muscle itself, is similar to that of humans.

In summary, both porcine and ovine species are suitable as appropriate animal models for examining the feasibility of endovascular stent-grafts for ascending ADs. However, given the similarities in coronary and aortic valve anatomy with humans, porcine models are better suited for this purpose.

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