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The porcine model for human cardiovascular diseases

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Abstract
Cardiovascular diseases are a group of public health disorders involving pathology of heart and blood vessels, Development of animal models for such diseases to accurately imitate the illness and respond to infection in the same way that humans do is essential to explore better therapeutic modalities for clinical use. This idea could be supported by specific facts or concluded from similarities between the animal model and humans. Pigs, dogs, and lambs are frequently employed in translational experimental studies of cardiovascular disease. Pigs were chosen as a viable animal model for the human cardiovascular system because human research presents substantial scientific and ethical challenges. Although the pig and human hearts have similar coronary circulation and hemodynamics, human healthcare practices and instruments can be used on the pig to fully grasp the structure, function, and an excellent model for studying cardiovascular disorders. Pigs and humans share many characteristics, making them a suitable model for examining cardiovascular conditions.

Keywords: Stent, atherothrombotic disease, trapezoidal silhouette, chronic total occlusion, *in vivo*, xenotransplantation

1. Introduction
Animal models have been utilized in exploratory examinations to superior human understanding and help within the determination of biological and biomedical issues. Animal species must meet specific necessities that are reliable with the in general reason of the investigate in order to be utilized as a model [1]. Since their cardiovascular anatomy, coronary supply route dispersion, ventricular execution, cardiac metabolism, electrophysiology and collateralization after intense myocardial infarction are physiologically very comparative to humans, pigs are regularly utilized as a cardiac preclinical demonstration, especially for testing surgical and mechanical mediations for heart disease. The pig genome is additionally indistinguishable in size and composition to that of humans. Distinctive pig breeds offer diverse benefits and challenges for investigating tries [2].
Pig anatomy, hereditary qualities, and physiology are greatly comparable to human anatomy, genetics, and physiology. Pig breeds change in measure from small to large. Catheterization, valve control, endoscopy and broncho-alveolar lavages, heart surgery are common surgical and non-surgical strategies in human medicine. Humans and pigs have strikingly comparative physiologies. Since they are both omnivores, their organs are usually practically comparable. Taking after primates and mice's resistant frameworks, the pig resistant framework is most likely the leading understood, with a wide extend of tried-and-true techniques and innovation. Pigs-safe frameworks are more comparative to humans [3].
Sus scrofa domesticus is a species of pig with a broad variety of breeds, ranging in size and appearance. Farm pigs (Yorkshire, Landrace, Durocs and their hybrids), as well as minipigs (which include Yucatan pigs, Hanford pigs, Gutttingen pigs, and Sinclair pigs) are divided into two distinct categories. Minipigs possess a higher level of development than farm pigs for the same weight, while their tissues are more tolerant of experimental techniques, which is a major advantage over farm breeds. Minipigs may be a useful feature for some researchers due to the difficulties associated with intubation of farm pigs, such as the presence of a deep larynx and expanded soft palate, as well as the sensitivity of the trachea. Additionally, agricultural breeds tend to have a tendency towards Ventricular Fibrillation and certain genetic lines are prone to malignant Hyperthermia. Additionally, the large size and rapid growth of farm pigs may make husbandry difficult for conventional laboratory facilities. As a result, many scientists prioritize the use of minipigs, especially in long term survival studies [4].

2. Pig heart comparisons with normal human cardiac structure

The ratio of heart to body weight in pigs weighing between 20 and 30 kg, which are frequently used in cardiovascular research, is equivalent to that of adult humans (5 grams per kilogram). In addition, the ratio is significantly higher in such young pigs (between 2.5 and 2.9 grams per kilogram) than in adult pigs [4].

The anatomy of pigs and humans was compared through gross inspection and cardiac examination. Human hearts, on average, weigh approximately 266.5g, while pig hearts weigh approximately 302.8g. The adult human heart measures approximately 9.8 cm (9.2 cm - 12 cm) in length from the base to the apex, 8.6 cm (7.4 cm - 10.8 cm) in length transversely and approximately 7.1cm (5 cm - 8.4 cm) in length anteroposteriorly. The typical pig heart measures approximately 10.2 cm (8.5 cm - 11 cm) in length base to apex, 8.9 cm (6.5 cm - 11 cm) transversely and 6.6 cm (5cm - 8cm) to the anteroposteriorl length [5].

The shape of the pig heart is the classic “Valentine heart” due to the position of the heart in its thorax and the body orientation. On the other hand, if we look at the human heart from the front, we can see that the human heart has a trapezoidal shape. However, the pig heart has an apex as well as a base with slightly smaller upper and smaller lower limits, just like the human heart [6].

In the human heart, left atrial appendage is usually tubular. The free part of right atrial appendage is mostly triangular. The atrial appendage on right or left may be bigger than the other side. Unlike in the case of four-toed mammals, the ventricles of the human heart vena cava enter the right atrium straight, one superiorly and one inferiorly. Generally, four or five pulmonary veins return blood to the left atrium. In the pig heart, the left atrial appendage is normally triangular and bigger, whereas the right atrial appendage is half-moon shaped. The vena cava enters the right atrium perpendicular to the human heart. The left azygous vein is a coronary sinus tributary that delivers blood from the body to the heart. In the pig heart, two pulmonary veins usually come back into the left atrium. This is because the Thebesian valve encases some of the corneal sinus ostium in the right atria, which means the functional diameter of the cornea is much smaller than in pig [6-7].

The pig heart contains fewer and coarser trabeculations than the human heart's right and left ventricles, which have more and finer trabeculations [8]. The right ventricular moderator band in the human heart is typically depicted as a free arc, however, it can also take the form of a ridge and emerge more apically from the septal walls, which are inserted from the anterior papillary muscles. The left ventricular band is also common in the human heart. The anterior papillary muscle is the most prominent muscle in the human heart, while the posterior papillary muscle, septal muscle, and septal muscle are also present. The anterior papillary muscle of the left ventricle is composed of one to three anterior muscles and one or two posterior muscles, with the moderator band forming a free-arching section of the anterior papillary muscle. This muscle is attached to the septum papillary muscle of the pig heart and originates from the on or near septal papillary muscle. The right ventricle, on the other hand, is composed of three septal papillary muscles, one anterior papillary muscle and one or three posterior papillary muscles. The left ventricle of the pig heart is composed of an anterior and a posterior papillary muscle only [6].

Blood is supplied to the myocardium of the heart via two arteries that branch from the aorta right beyond the aortic valve cusps. The right coronary artery or both the right and left coronary arteries may supply a majority of the myocardium in the pig heart. Pig heart vascular collateralization is limited. Blood is transported from the body to the right atrium through the left azygous vein of the pig heart [6]. Similar to the swine heart, the human heart's myocardium receives the majority of its blood from the right coronary artery and exhibits minimal collateralization across arteries [9].

Although the septal (posterior) to lateral (anterior) and anterior (superior) to posterior (inferior) diameters are broadly equivalent between humans and these model animals, the anterior to posterior diameter in humans is substantially bigger than in swine. The two-cusped mitral valve, which separates the left atrium and left ventricle, contains two main cusps. In addition to the two major cusps that are always present, big animals also have a variable number of lesser commissural cusps, often called scallops, that give the impression of extra leaflets. Humans and pigs have a comparable anterior (superior) to posterior (inferior) diameter of the mitral valve in terms of size. When the parameters are the same in both humans and animal models, the human septal (posterior) to lateral (anterior) diameter is bigger. The mitral and aortic valves are connected to the left fibrous trigone by the fibrous intervalvular septum [10]. Aortic valves in humans are frequently wider than those in pigs [8].

The human heart's AV node is situated close to the base of the atrial septum, prior to the coronary sinus, and just above the tricuspid valve in conduction systems. It is unknown exactly where the AV node and the bundle of His meet, however they are both situated on the crest of the interventricular septum, directly below the membranous septum. The unbranched segment of the His bundle is 2-3 mm long and enters the main fibrous body at a distance of 0.25-0.75 mm. When the bundle leaves the major fibrous body, it divides in half [11]. The AV node is situated more inferiorly on the ventricular septum, on the right side of the crest, in the pig heart than it is in the human heart. After leaving the bundle of His, the conduction channel ascends to the crest of the ventricular septum on the right and then enter the central fibrous body. Compared to the human conduction system, the bundle of His bifurcates across the conduction channel more quickly [12].

3. Various pig models of cardiovascular disease

3.1 Models of stent application in swine

In some cardiovascular research applications, an animal's natural, unmodified anatomy might be adequate for simulating particular study scenarios, eliminating the need for the creation of a disease model. This is valid, for instance, when examining the biological responses to implanted prostheses or judging how well medical equipment are used in practice. For research reasons, such as toxicity studies that examine the effects of drug-eluting stents, one such cardiovascular model involves the implantation of stents into healthy arteries. New anti-restenosis medications have also been tested using this stent placement model [13]. In order to investigate the outcomes of stenting *in vivo*, imaging techniques like optical coherence tomography are used [14].

The breed of pigs that will be used in the study must be carefully chosen by the researchers based on its idea. The normocholesterolemic domestic crossbred pig is frequently utilized for short-term tests due to its low cost and wide

availability, while the adult mini-pig is more appropriate for longer-term studies in which researchers assess stents over time. Researchers need to keep a careful eye on the relationship between stents and vascular diameters. Stents need to be 1.0–1.1 times wider than the artery they are being inserted into. A too large stent might strain the artery wall, resulting in mechanical harm and falsifying any safety and efficacy statistics. On the other hand, a stent that is too tiny could move away from its intended position. If the model is supposed to mimic a real-life scenario, any stents used in it should be dimensionally similar to those employed in clinical treatment. In this model, researchers often provide vascular access via a carotid or femoral artery before implanting a stent. Through a surgical incision or percutaneously, with or without the use of ultrasound during the puncture, the Seldinger procedure can be utilized to accomplish this. The swine must receive antithrombotic medication similar to those used in clinical settings during stent implantation investigations [2].

3.2 Swine model of aneurysmal diseases

By artificially inducing a carotid aneurysm using autologous tissue, researchers may examine the effects of aneurysm therapies and recreate carotid aneurysms. This method involves first removing jugular vein tissue before closing one side to create a pouch. The carotid artery was then given an elliptical arch, and the pouch was then sewn shut over the arch. The pouch develops into an aneurysm once the artery's blood flow has been repaired; at this time, the carotid artery should be examined to make sure that blood is flowing normally and is not leaking from the suture. Angiograms taken after the incision has been stitched up allow researchers to see the aneurysm. Researchers can examine and evaluate stented arteries after stent placement utilizing a variety of clinical imaging modalities, including as optical coherence tomography, transcutaneous ultrasound, intravascular ultrasound, angiography, and others [2].

3.3 Swine model for atherothrombotic disease

Due to rising atherosclerosis, which commonly results in thrombosis, ischemic heart disease and stroke are the major causes of mortality and disability in the world. In ischemic heart disease, the heart suffers from ischemia, or a reduction in blood flow. The main cause of cardiac ischemia is a blockage of the coronary arteries, which provide blood to the heart [15]. The most frequent form of the issue is atherosclerosis with or without superimposed thrombosis. Coronary artery disease is by far the most common cause of coronary blood flow limitation. Atherothrombosis is a term used to describe atherosclerosis with thrombosis superimposed [16].

Contrary to small animal models, pig atherosclerosis frequently develops gradually and may be produced either intentionally (by eating a high atherogenic diet) or naturally (by giving regular food). In addition, small atherosclerotic lesions manifest initially in the coronary arteries if atherosclerosis is left untreated and the distribution and composition of atherosclerotic plaque (lipid, fibrinogen, smooth muscle cells, and macrophage concentration) mirror human atherosclerosis [17]. Three treatments for pigs that are "atherothrombotic-like" have been identified in the literature; they are sometimes combined. Extracorporeal arteriovenous shunts, high-fat diets for animals and treatments for intravascular injury (balloon, grafting, etc.) are all employed [18].

Pigs on a high-cholesterol diet may experience hypercholesterolemia and atherosclerotic lesions, leading to plasma cholesterol levels similar to those in humans. After 50 days on a high-cholesterol diet, artificially produced pigs developed initial atherosclerosis lesions (fatty streaks) in the abdominal aorta and to some extent in the coronary arteries. In other cases, the lesion composition was exactly like early-stage human atherosclerosis [17].

Regarding regulated research into the function of blood components and rheology, as well as atherosclerotic vascular components, in thrombus development, the *ex vivo* porcine thrombus formation model (e.g., flow chambers coupled to extracorporeal shunts), has become essential. Indeed, it has made it possible for researchers to evaluate the thrombogenic effects of different atherosclerotic plaque elements, including collagen, fatty streaks, smooth muscle cells, and others, as well as the antiplatelet effects of novel antithrombotic medications [18-19]. Due to the damage response being similar to that of human arteries, porcine coronary stenting is a particularly useful model. Animals fed a hypercholesterolemic diet show a more prominent adaptive response [20].

3.4 Chronic total occlusion (CTO) model of swine

Interventional cardiology recently placed more of an emphasis on CTO treatment than restenosis prevention as a result of recent advancements in DES technology. Despite the prevalence of CTOs, not much is understood about their pathophysiology and the reasons why certain CTOs can be crossed but not others. In order to direct treatment experiments, researchers recently created CTO models. Atheroclerotic plaque rupture spontaneously and ensuing artery occlusion are not natural occurrences, not even in animal models genetically modified to create more atheroma. The first complete blockage was produced via an external ligature or Ameroid constriction [21]. Because coronary vessels are less suitable to direct surgical approaches, it can be difficult to simulate luminal and medial pathology as well as micro-calcification and an inflammatory component must be present to mimic human CTO lesions, the development of an accurate and reliable human-like coronary CTO model has been challenging [22].

The creation of long-lasting heart occlusions has also been done using polymers. Because they produced considerable inflammatory responses and arterial obstruction, early polymeric implants were abandoned as stent platforms [23]. After 28 days, the polymer had been absorbed, causing a micro-channelled occlusion that histologically resembled a CTO in individuals. In pig coronary arteries, similar techniques have been tested to produce considerable calcified CTO [24]. These animal models may help researchers better understand the biology of human CTOs and create innovative technical and pharmacological approaches to boost the effectiveness of recanalization in these challenging lesions.

3.5 Swine models of infarction and heart failure

One of the areas of cardiovascular science that has seen the greatest investigation is myocardial ischemia, including studies into the causes, prospective treatments, and pertinent pharmacological interventions in both acute and chronic myocardial infarction. Preclinical research is still necessary for the healing of damaged ischemic myocardium despite major advances in pharmacological, surgical, device, and

interventional treatment. The ideal LAD site and length of blockage for the development of a pig reperfused myocardial infarction model were investigated using left ventricular function, infarct size, and the incidence of ventricular fibrillation [24]. They revealed that in pigs, catheter-based coronary artery occlusion created an infarct of a constant size and blocked a particular coronary artery at a repeatable, suitable site. Additionally, the in-situ double-staining method distinguished unmistakably between the AAR and the necrotic (infarcted) myocardium. For ongoing research on myocardial ischemia and infarction, including cell therapy, gene therapy, and molecular therapies for angiogenesis, large animal models are still required.

A myocardial infarction experimental model must satisfy the following requirements in order to be reliable: The following criteria must be met: (1) the ability to precisely choose the site of coronary artery occlusion (2) the ability to regulate the length of ischemia (3) the use of a minimally invasive procedure to prevent interference with the experiments (4) low additional morbidity and mortality caused by the experimental model itself and (5) a reproducible and consistent progression of myocardial infarction [24].

3.6 Heart failure and chronic myocardial ischemia in pigs

The pig has been the most often used big animal model for the creation of cutting-edge heart failure and myocardial ischemia therapy regimens. However, for a number of reasons, it is difficult to induce severe infarction and persistent myocardial ischemia in pigs. Due to a deficiency in endogenous collateral anastomoses, pigs in particular are susceptible to transmural myocardial infarction [25-26].

With a reasonable chance of death, bottleneck stenting of the proximal LAD or LCX and removal of DAPT led to ischemic cardiomyopathy with a drop in LVEF to 41-44% 4 weeks after stenting and an infarction area of 12–21%. Given that the majority of fatalities occurred in the first week, it is most likely best to administer prospective experimental medications 1-2 weeks following the surgery in the one-vessel model. The researchers developed the first percutaneous two-vessel coronary artery stenosis model by placing bottleneck stents in the proximal LCX and mid-LAD one week later. The infarction area was less in the LAD-alone group compared in the LAD or LCX (DAPT) groups because the second bottleneck stent was positioned in the mid LAD segment as opposed to the proximal LAD segment. This is probably because the DAPT therapy was ongoing and kept the stents from prematurely occluding. Closing both branches of the LCA may not be optimal for therapeutic trials in pigs because to the severely lower LV function (LVEF of 44% in animals that survived) and much greater mortality rate (71%) caused by the two-vessel model [27].

The viability of the catheter-mediated treatment for ischemic heart failure and prolonged myocardial ischemia brought on by the placement of a bottleneck stent in the proximal LAD or LCX is ultimately tested in domestic pigs. A special pig model of reversible myocardial ischemia is provided by the proximal LAD or LCX bottleneck stent, and when the stent is later closed, ischemic heart failure and collateral arterial hypertrophy result. Using this strategy, new treatment modalities can be created. This work gives important insight into the temporal and geographical patterns of coronary collateral growth and justifies the use of PET imaging for evaluating coronary collateral expansion [27].

3.7 Porcine model of progressive cardiac hypertrophy and fibrosis

For the creation of new and enhanced treatment options for cardiac hypertrophy and fibrosis, reliable and pertinent translational animal models are needed. A percutaneous technique for gradually increasing pressure overload in the left ventricle (LV), leading to pre-stenotic systolic hypertension, myocardial hypertrophy with LV diastolic dysfunction, and secondary pulmonary hypertension, has been expressed for the first time in a relevant large animal translational model. The in-grown, internally located stent in the aortic wall prevented the aorta from expanding properly throughout typical body growth. The slow development of the heart's hypertrophy and fibrosis may be precisely monitored thanks to cardiovascular MRI and CT scans, as well as repeated invasive hemodynamic assessments using serial TTE and ILE imaging. The early phases of the minimally invasive percutaneous intervention technique were modelled, demonstrating the delayed development of aortic stenosis in the context of considerable LV hypertrophy, diastolic dysfunction, and secondary (postcapillary) pulmonary hypertension. The prolonged follow-up (5 months) and postponed progression of the hemodynamic anomalies brought on by artificial aortic stenosis are more in accordance with real-world conditions than prior studies that used shorter monitoring intervals post-aortic banding [28]. The Slow-developing artificial aorta isthmus stenosis caused by percutaneous BMS implantation in the descending aorta of young pigs effectively mimics cardiac hypertrophy and fibrosis and is congruent with molecular and physiological pathophysiologic theories of human illness. As a result, it may be used to investigate the molecular reasons of hypertrophy and evaluate potential therapies.

Pigs are now often utilized as preclinical models in the research and development of new medications that may one day be used to treat diseases in humans. Greater care must be made to separate *de novo* cardiomyocyte synthesis from pleiotropic beneficial effects that result in post-injury heart functional recovery in order to accurately interpret cardiac regeneration procedures in pigs for clinical application to human illness. Due to their form and function, pig hearts continue to make an excellent preclinical model for surgical and interventional operations. Due to developments in gene targeting and xenotransplantation, the use of the pig system for heart regeneration and repair research is anticipated to grow in the upcoming years [29].

Early in 2022, a genetically modified pig's heart was used as a source for cardiac xenotransplantation in human clinical study due to its immunosuppressive and growth hormone pathway ablation [30]. The human recipient passed away two months after surgery, despite early results that seemed promising and the underlying processes are still being researched [31]. It is therefore unknown whether such surgical procedures using genetically modified adolescent pig hearts will be able to function as a key therapeutic alternative for the failing human heart in the next 10 years.

Although there have been reports of drugs, tissue-engineered patches, AAV-mediated gene therapies and cell-based therapies encouraging cardiac repair after injury, none of these approaches have been successfully and safely translated into the clinic for treating the human heart. Recent developments in xenotransplantation and gene targeting are expected to lead to a surge in the use of the pig system for research on heart regeneration and repair in the upcoming

years [29].

Conclusion

The success of the creation of large animal models that enable preclinical testing will eventually determine the clinical acceptance of novel diagnostic and therapeutic advancements for cardiovascular diseases. Domestic pigs are a good choice for studying cardiovascular disorders because of their anatomical characteristics. But each animal model has advantages and disadvantages. In comparison to other big animal models, swine models are simpler and less difficult to construct. Heart disease xenotransplantation devices may be abundant in the swine sector. Surgical procedures using genetically engineered cardiovascular components and xenotransplantation may have a significant impact on human health in coming decades.

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