Comparative anatomy and angiography of the cardiac coronary venous system in four species: Human, Ovine, Porcine and Canine

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ABSTRACT:

Introduction: The coronary arterial system has been the subject of greater investigation than its venous system due to the importance of human coronary artery disease. With the advent of new percutaneous treatments, the anatomy of the coronary venous system has increasing relevancy. We compared the organization of the coronary venous circulation in three species commonly used in research and compared these to normal humans using both macroscopic anatomic and angiographic studies.

Animals: The anatomy of five explanted hearts from healthy dogs, pigs, and sheep were studied macroscopically, and ten explanted hearts per animal species and 10 clinically normal human were examined by angiography.

Methods: Animal hearts were injected with latex and dissected macroscopically. The coronary venous system of humans was evaluated from clinical angiographic studies. In the animal hearts a retrograde angiographic study was performed via a Foley catheter in the coronary sinus.

Results: The general organization of the coronary venous circulation was similar among humans, dogs, sheep and pigs. Despite overall similarities to humans, animal hearts demonstrated absence of the OV and differences in position and organization of venous valves; venous diameters; number of tributary veins; and presence of an anastomosis between the left and right (human anterior and posterior) venous tree. The left azygos of the pig and sheep joined the coronary sinus [1, 2].

Conclusions: Anatomical differences must be considered when planning biomedical and veterinary studies incorporating cardiac veins. This study provides baseline data regarding structure and organization of the cardiac venous system.

Key words: Heart, Veins, Translational, Animal Model

Abbreviations table:

AIV	**Anterior interventricular vein**
CS	**Coronary sinus**
GCV	**Great cardiac vein**
IMMR	**Institut Mutualiste Montsouris Recherche**
LMV	**Left marginal vein**
LPV	**Left posterior vein**
MB	**Myocardial bridge**
OV	**Oblique vein of the left atrium (Marshall)**
PIV	**Posterior interventricular vein**

INTRODUCTION

Studies of cardiac vascularization have focused largely on the arterial system as coronary artery pathology is responsible for the majority of cardiovascular related mortality and morbidity in humans, especially in developed countries [3-6]. However, with the advent of new treatment options for various cardiovascular diseases, such as biventricular pacing, ablation procedures, and implantation of medical devices (as with percutaneous mitral annuloplasty), the coronary sinus (CS) is increasingly used to access the coronary venous system [5, 7-13]. Knowledge of coronary venous anatomy has therefore become important, and pre-clinical research focusing on the CS has increased dramatically [5, 14-22]. Choosing the appropriate animal model in translational, pre-clinical studies is essential to the success of subsequent human studies [23, 24]. Additionally, laboratory animal experience might provide a baseline for therapies in veterinary medicine. A few studies published studies have presented anatomical details of mammalian coronary veins [25], though most describe the systems of the mouse and guinea pig [26-29].

The cardiac veins can be grouped into three categories according to the regions drained: the CS and its tributaries, the anterior cardiac veins, and the Thebesian veins. The normal organization of the CS and its tributaries has been described in humans both anatomically and through imaging studies. The CS ostium is located in the right atrium and constitutes the terminal portion of the coronary venous system. The CS is typically connected to the great cardiac vein (GCV), then to the anterior interventricular vein (AIV), followed by the posterior interventricular vein (PIV) which begins close to the apex of the heart and goes into the posterior interventricular groove and enters the CS close to the CS ostium [30]. The normal cardiac venous drainage has been described in the literature for pigs [31-33] and dogs [34-36], and to a lesser extent in the sheep[37]. These references seem to describe a similar general organization similar to that found in humans but detailed comparative descriptions are lacking.

The present study investigated the structure of the coronary venous system of three species commonly used in cardiovascular research (ovine, porcine and canine) and compared the findings to human subjects using angiographic and dissection studies. Our hypothesis was that the general anatomy of the coronary venous system was similar among these four species, but with some crucial differences that might influence animal model choice as well as interventional approaches.

ANIMALS & SUBJECTS, MATERIALS AND METHODS:

Anatomical and angiographic studies were performed on each species. This study was approved by the ethics committee of Institut Mutualiste Montsouris Research (IMMR). Explanted hearts of clinically healthy human, canine, ovine and porcine subjects were used. All animals were determined healthy by relevant institutions before harvesting of the organ according to the regulatory meat inspections, however no antemortem diagnostics were performed to rule out subclinical disease of any body system. The porcine and ovine hearts were obtained from two slaughterhouses (Etablissements Guy Harang, 78550 Houdan, France and Etablissement SAROVI, Jossigny, France respectively). Canine hearts were obtained from animals used in other non-cardiovascular studies at IMMR at the end of their protocol and also from a breeding center where dogs were scheduled to be euthanized (Centre d’Elevage des Souches 89130, Mezilles, France). All hearts were explanted within their pericardial sac and with their main vessels, in order to preserve the coronary vasculature. The human hearts were obtained through the Centre du Don des Corps, Université Paris Descartes, France. After explantation, all hearts were kept in a -20° C freezer until studied. All hearts were studied within 1-2 months of being frozen.

Terminology used for this study (figure 1)

General orientation terminology: in animals ventral/dorsal directions correspond to anterior/posterior in humans. Likewise, cranial/caudal corresponds to superior/inferior. Distal refers to the side of the vessel that is closest to the right atrium, to match the direction of blood flow.

The following terminology was used to describe the coronary veins as shown in Figure 1. This terminology originates from the accepted human terminology.

The CS opens directly into the right atrium and courses along the posterior wall of the left atrioventricular groove. The proximal portion of the CS was delineated by the valve of Vieussens in human hearts (Figure III available in Supplementary Material online). In the animal species, where the valve of Vieussens was absent, the proximal limit was determined as the area of abrupt and distinct tapering of the CS as it joined with the GCV (figure I available in Supplemental Material online). The GCV is the continuation of the AIV and joins the CS at the level of the atrioventricular sulcus. The proximal limit is where there is an abrupt 90° change in direction of the vessel into the AIV. This vessel runs parallel to the left circumflex coronary artery. The AIV courses anteriorly between the left and right ventricle, parallel to the anterior interventricular artery. It begins either at the apical level of the distal third or distal half of the anterior interventricular sulcus and ends where it forms an abrupt angle entering the GCV [7]. The PIV, also known as inferior interventricular vein or middle cardiac vein, courses between the left and right ventricles on the posterior/inferior aspect of the human heart, parallel to the posterior descending coronary artery, within the caudal/posterior interventricular sulcus [3]. The distal limit is at the confluence into the CS. The left marginal vein (LMV) or left lateral vein, arises from and courses over the free wall of the left ventricle, adjacent to the obtuse marginal artery.

The posterior vein of the left ventricle (LPV) is an inconsistent branch which arises from the proximal third of the left ventricle wall and ends either in the great cardiac vein or the CS. The oblique vein of the left atrium, or Vein of Marshall (OV) [38] is present in humans, and this small vessel descends obliquely from the left atrium and ending in the CS, continuous with the ligament of the left vena cava. It is a remnant of the embryonic left superior cardinal vein.

Anatomical study:

The CS of five explanted hearts from each species was injected with latex [a] until the latex had filled all vessels and was filling the PIV [39]. The injected heart was refrigerated for 24-48 hours before dissection. Myocardial bridges (MBs) over the studied vessels, were noted. These are defined as macroscopically visible bridges of myocardial tissue overlying arteries and veins. Figure II (data available in Supplemental Material online) illustrates MBs. The length and diameter of each vessel was recorded as described below. The diameter of the orifice of each vessel was measured at the most proximal point of each vessel i.e. furthest from the CS side. The diameter of the latex cast of each vessel was also evaluated and as they were comparable to the measurements taken on the formalin fixed hearts, then these measurements were recorded. Five freshly explanted hearts of each species were kept in 4% formalin for a minimum of one week and dissected. The presence of valves and their structure was also recorded.

Angiographic studies:

In vivo coronary venous angiographic examinations of 7 male and 3 female human subjects **(**certified to be normal by a cardiologist – FA) were obtained from the Faculté de Médecine de Rouen, CHU CH Nicolle, Rouen.

The CS of ten explanted animal hearts per species and one human heart were injected with a mixture of injectable[b] and oral[c] contrast material. The mixture was injected in the coronary venous system through a Foley catheter snared by a purse string suture at the exit of the CS in the right atrium until all veins were filled and slightly bulging. The mixture consisted of approximately 70% of the oral solution and 30% of the injectable solution to optimize ease of filling of the small vessels with backflow into the ventricles. The injection was stopped when the contrast had reached the PIV and started to overflow through the purse-string. In the human heart, due to the difficulty of obtaining completely fresh samples, the contrast medium leaked out of the vessels. Hence clinical angiographic data was used instead for comparison during this study instead of the data from injected human hearts.

The right ventricle of each heart was then filled with moistened 5x5 cm gauze squares to obtain the closest natural anatomical shape. In most hearts, the left ventricle was left empty as the myocardium maintained the original shape adequately. The hearts were then placed in an consistent anatomical position for imaging, with the left side of the heart depicted on the left of the image screen in all species (Figure 2). One lateral view, one dorsoventral view and one 3D-rotational view were obtained for each heart. Image optimization was performed with adequate zooming and field of view choices tailored individually. The images were obtained with a fluoroscopy system[d] at 30 images per second for the lateral and dorsoventral views, and in a single 8 second rotation at 30 images per second for the 3D views. The images were then reconstructed using the Allura's 3D-CA 3D reconstruction system which minimizes foreshortening.

Sample analysis:

For each heart, the overall distribution and tributaries of each vessel were studied on the angiographic images. Their course, location and relationship to each other and the number of afferent vessels to each of the main veins was recorded. The angiographic studies allowed 3D visualization of small vessels coursing within the deeper myocardium. Visualization of Thebesian veins and their patterns were noted. Accurate calibration on explanted heart angiographic studies was difficult to obtain as the explanted heart was not fixed in its anatomical and physiological state. For this reason, the measurements were performed on the formalin fixed hearts.

The presence/absence of valves and number of leaflets was noted after dissection of the vessels. Systematic macroscopic measurements of the CS and tributaries were performed using a flexible stainless ruler[e] graduated in mm and a dial caliper[f] graduated every 0.02 mm. For each vein, the length, diameter, presence or absence of MBs, location, course and relationship to other vessels, were recorded. The number of afferent tributary veins was recorded, as well. However, the angiographic studies offered better visualization of the afferent veins, especially the smaller ones, so the results of these studies were recorded.

RESULTS

Ten animals of each species were used. The pigs were of Normande breed, weighed a mean (SD) of 95 ± 6.2 kg at the time of slaughter and were a mixture of males and females. The dogs were male beagles with a mean weight of 20 ±3.4 kg, and a mean age of 4.3 years. The sheep were females of Lacône breed weighing a mean of 68 ±5.3 kg. For the human specimens, there was one male and four female subjects, with a mean weight of 70 kg and mean age of 93 years.

The results found in these anatomical and angiographic studies are presented below vessel by vessel. Published human data are also presented as a comparison when available.

Coronary sinus:

The CS is located in the caudal portion of the coronary sulcus. It is a continuum of the GCV and empties into the right atrium directly. It is seen as an orifice adjacent to the opening of the caudal vena cava on the caudo-medial aspect of the right atrium. It is the largest cardiac venous structure and drains most of the venous territory corresponding to that of the left coronary system, including veins from the left atrium and left ventricle. The right side of the heart is primarily drained by the anterior cardiac veins, which empty in the right atrium, although some drainage of the right side also occurs via the CS [40].

The average CS length in humans varies from 45 to 63 mm [8, 30], and the diameter of the ostium varies from 4 mm to 9 mm [14, 30, 41]. The results of our anatomical study are presented in Table 1.

The CS appears in all species as a fairly wide tubular structure which courses in the coronary sulcus just ventral to the left atrium and forms a partial circle around the heart, between the left atrium and the left ventricle

The imaging study demonstrated that in pigs and sheep, the left azygos vein joins the CS at the distal third of its length from the ostium in the right atrium. In humans and in dogs, the right azygos vein drains into the superior (cranial) vena cava and no left azygos vein is seen. This was also seen on our anatomical studies. Aside from the major veins presented in this study (GCV and LMV), no smaller vessels were seen to enter directly into the CS in any of the specimens.

Anterior interventricular vein

The AIV is the largest and most constant of all cardiac veins [7]. It travels in the anterior interventricular sulcus, more or less parallel to the left anterior interventricular descending artery or paraconal coronary artery in animals), being confluent with the GCV. In humans, a certain degree of variability between the AIV and the left anterior interventricular descending artery has been described. It originates either at the apical level of the distal third or distal half of the anterior interventricular sulcus and ends where it forms an abrupt angle as it enters the GCV.

The results of the anatomical study are presented in Table 2.

On the anatomical specimens, MBs were found to be coursing over the AIV in 3/5 pigs, 1/5 dogs, 0/5 sheep and 1/5 human subjects. Myocardial bridges coursed over both coronary veins and arteries and were not compressing the underlying vessels. In animals, these were found to be coursing over the tributaries of the AIV of 2/5 dogs, and none in the other species. In humans, MB have been reported to be seen over the tributaries of the AIV of 5% of people[14]. Only one person out of 21 had MBs over the AIV in that study.

The angiographic studies showed that all human, pig and sheep hearts had one AIV, whereas in 6/10 canine hearts, multiple AIVs were found (2 in 5 dogs and 3 in one dog). The number of afferent veins entering the AIV varied depending on the species. Human hearts had an average of 3.9 +/-1.6 afferent veins (min 2, max 6), sheep had an average of 8.8 +/- 2.9 (min 5, max 14), pigs had an average of 4.5 +/-1.35 (min 3, max 7), and dogs had an average of 4.7 +/- 1.5 (min 3, max 7). In dogs, the afferents ran parallel to the main vein, whereas in other species, the afferents were joining the main vein more at a 60-90° angle.

Great cardiac vein

The GCV is the continuation of the AIV. It runs along the left atrioventricular groove parallel to the left circumflex artery in all species, although variation of the relationship of the GCV and the left circumflex artery has been observed in human patients[42]. The GCV is confluent with the CS. In humans, the OV marks the end of the GCV externally, and the valve of Vieussens plays that role internally. The OV was absent in all of the animal species studied in this study.

In humans, the mean diameter of the GCV has been reported to be 3.55 +/- 1.24 mm[18] and 3.9 +/- 1.1 mm[14]. The length of the cardiac vein was not reported in human literature. It was possible to measure the length and diameter in only three human hearts in this study due to poor preservation of two samples. Mean length was

38 +/- 9 mm, mean diameter 3.2 +/- 1.53 mm. Table 3 presents the results of the anatomical study.

On angiography, the number of afferent veins entering the GCV was species dependent. In humans an average (SD) of 0.6 ± 1.07 (range 0 - 3) afferent veins were seen; in sheep the average was 2.5 ± 0.97 (range 1 - 4); pigs had an average of 1.6 ± 1.17 (range 0 - 3); and dogs had an average of 1.9 ± 1.52 (range 0 - 5).

Oblique vein of the left atrium

The OV courses along the left-posterior aspect of the human left atrium. It is located within a vestigial fold: the ligament of Marshall. This is a remnant of the left superior vena cava that progressively involutes during embryogenesis. The OV was observed in all human specimens but was not observed in any of the animal hearts. This may indicate a difference in embryogenesis between humans and other mammalian species.

Left marginal vein and left posterior vein

The LMV courses along the lateral aspect of the left ventricle and drains into the GCV or directly into the CS. The posterior vein of the left ventricle either consisted of one vessel or multiple small vessels draining into the CS or GCV. The imaging examinations identified the LMV in all human and animal hearts. The LPV was present in 1/10 human, 2/10 sheep, 3/10 pigs and 6/10 dogs hearts. In all hearts where a single prominent LPV was not present, two to five, with a mean of 3, small afferents to the GCV drained the right ventricle in all species.

Venous Anastomoses

The existence of intra-myocardial anastomoses between the AIV and PIV has been described. Habib et al. [7] report an incidence of around 30% of human hearts in which the apical branch of the AIV is thought to be continuous with the PIV. Similarly, Ortale et al. [14] described the existence of anastomoses between the anterior and posterior cardiac venous system.

In the present study, the average length (SD) of the anastomosis between the AIV and PIV on macroscopic examination was 32.8 ± 8.8 mm in pigs; 29.1 ± 5.4 mm in dogs; 36.2 ± 7.7 mm in sheep; and 2.56 ± 3.2 mm in humans. This length was measured from the point where the AIV started coursing deeper in the myocardium to the point where it resurfaced at the level of the PIV. This anastomosis occurred near the apex, in the apical third of the left ventricle.

The imaging studies showed an anastomosis between the AIV and the PIV in all hearts. Angiographic examination of human hearts identified the anastomosis as consisting of two veins in 4/10 hearts, and of a single vein in 6/10 hearts. In sheep, only 1/10 specimens had two veins, the rest had one. In pigs, 2/10 had two veins and 8/10 had one. Finally, in dogs, 3/10 had two veins and 7/10 had only had one. Another anastomosis between the AIV and the LMV was found on angiography in 7/10 sheep, 3/10 pigs, and in one dog. These were not found in the human angiographic studies.

Posterior interventricular vein (inferior interventricular vein)

The PIV courses in the posterior (subsinuosal) interventricular sulcus, parallel to the posterior interventricular descending (subsinuosal) artery. It drains just proximal to the termination of the CS through a distinct entry into the right atrium.

Anatomically, MBs were found over the PIV in 3/5 pigs and 4/5 dogs but were absent in sheep. Data on human hearts concerning the MB over the PIV has not been found in the literature. Measurements of the PIV are presented in table 4.

On imaging the number of PIVs varied depending on the species. Most had only one PIV, but 1/10 human, 0/10 sheep, 2/10 pigs and 4/10 dog hearts had two PIVs, and one dog had 3 PIVs. The afferent veins of the PIVs in the dog appeared longer than in the other species, and often joined the PIV distally and followed the path of the main PIV in a parallel fashion. This often gave the impression that multiple main veins were seen instead of one main vein surrounded by multiple parallel affluent veins. On angiography, the average number (SD) of afferent veins in humans was 2.6 ± 2 (range 0 - 6), in sheep 2.4 ± 1.83 (range 0 - 5), in pigs 2 ± 0.94 (range 1 - 4), and in dogs the average number of afferents was 2.1 ±1.45 (range 0 - 4).

Thebesian veins

The Thebesian veins are a number of small veins draining the subendocardium. These are composed of endothelial cells and are continuous with the endothelial lining of the cardiac chambers [30]. These veins are of much smaller diameter, they are present in large numbers but are only visible on angiography and individual veins can be difficult to identify. Their course is highly variable, and most of them then divide into smaller vessels.

In all species studied, the AIV drained the largest number of Thebesian veins. The Thebesian veins were graded as having a marked, moderate, mild or no identified pattern in our study, by using a subjective visual scale based on their number and the resulting level of opacification seen on the post contrast study (Figure 3). In the one explanted human angiographic study performed, both AIV and PIV drained a conspicuous number of Thebesian veins.

Pig hearts were noted to have the most marked Thebesian vein pattern. Table 5 indicates the results.

The Thebesian veins were not visible on the clinical angiographic examinations of human hearts provided for our study. However, this could be due to the difference in injection pressure between cadaver studies and clinical studies as revealed in the angiographic explanted human heart study performed.

Valvules of the cardiac veins

According to human literature, the CS ostium is guarded by the Thebesian valve in 63 to 84 % of cases [5, 8, 41]. The morphology of this valve is variable, ranging from a totally absent valve to a valve which occludes the CS ostium completely. The average dimensions of the ostium in hearts containing Thebesian valves is smaller than their counterparts[5]. The presence of valves or an unusual morphology of these valves (e.g. Chiari network[43]) can lead to a challenging or impossible catheterization of the CS in some patients. These valves were absent in all animal species in this study, but were present in 4/5 human patients with 1 leaflet in 3 out of 4 patients and two leaflets in 1 out of 4 patients.

In humans, the valve of Vieussens is present between the CS and the GCV and was present as a uni- or bi-leafleted valves in all human hearts examined in this study. This valve was present in 3/5 pigs, 2/5 sheep and 5/5 dogs in our study and appeared as a uni-leaflet structure in all animal species. Beside these commonly described valves, 3/5 pigs had one or two valves in the basal AIV. These valves were uni-leaflet and appeared to be non-return valves (preventing backflow).

Left atrial veins

In our angiographic studies, it was noted that the left atrium was drained by either none, one or multiple very fine veins which, when single, entered the larger coronary venous system at the level of the most proximal afferent of the AIV. These veins have not been described in the veterinary literature previously but have been reported in one human study [44]. In humans from our study one such vein was seen in 7/10 hearts. In the remaining 3/10 hearts, no vein was seen. Four sheep had one vein, two sheep 2 veins, three sheep 6 veins and one sheep had 7 veins. In pigs 7 animals had a single vein, to had two veins and one had 3 veins. Finally, 8/10 dogs showed one left atrial vein and the other two animals had multiple fine veins.

DISCUSSION

This study has shown that organization of the CS and its tributaries, which has been extensively described in humans, can also be applied generally to sheep, pigs and dogs. This opens the possibility of the transfer of human therapeutics to veterinary patients and makes these animals potentially good models for research involving the cardiac venous system depending on the size of the devices and diseases treated. However, the present study also identified key a number of differences between the animal species and humans, including the lack of an oblique vein of Marshall, the different distribution of valvules and varying numbers of vessels running along the main vessels.

Some of the main obstacles to successful catheterization of human venous structures include the presence and distribution of valves; the diameter, length, territory of drainage; the presence of varicosities or venous aneurysms; and the tortuosity of the vessels; and angle of confluence with the CS. [45, 46] The length of the CS approaches that of the human in all species studied, with the pig being the species in which the length was the closest to humans. The weights of the animals differed between the species studied. The difference in sizes of the animals might account for some discrepancies between species. The porcine and ovine hearts were the closest in size and weight when compared to the human hearts in our study.

Dogs are also used for research but weigh less than adult humans, and all specimens in this study were adult hearts. The relative thickness of the right versus left ventricular walls is similar in dogs and humans, with a 3:1 ratio. The diameter at the CS ostium was closest to human size in the sheep, with a larger CS diameter in the pig and smaller diameter in the dog. For all the other segments, the mean vessel diameter was usually smaller in the dogs than in the other two species, and sheep had the longest general mean length of vessels. Animal species also had a large number of afferent veins, which was higher than the human patients in all segments. Contrary to results found in other studies, no small vessels were seen entering directly into the CS of any of the subjects in this study. Certainly, the difference in sizes of the animals might account for some discrepancies between species. The porcine and ovine hearts had the closest size and weight when compared to the human hearts in our study. Myocardial bridges appeared to be more common in the animal species, although located in similar areas as in the humans.

Some valves were found in the pig in the AIV, but not in any other species studied. The pig was the species with the most valves. Compared to human hearts, there was no valve guarding the entrance of the CS in the animal species, along with no OV. This represents one less obstacle to successful catheterization in animals compared to humans. However, catheterization can sometimes be technically difficult in animals, particularly in pigs, owing to the presence of other valves as identified in our study. A valve which could be described as the valve of Vieussens was found in all dogs, but was not consistently seen in the other species. Therefore, in a study focusing developing catheters based on the ease of passage of a device through the vessels, dogs would seem to be a better model as an additional obstacle would be anatomically present.

In sheep and pigs, the left azygos vein enters the CS at a similar level to where the OV has been described to enter in humans. In dogs, the azygos vein enters the venous circulation at the level of cranial vena cava, which is closer to the anatomy found in humans. The azygos vein in pigs and sheep can make catheterization of the CS challenging. Indeed, as the ostium of this vessel is wider than that of the GCV, guide-wires tend to enter the azygos vein more easily than the GCV.

The dog was often found to have two afferent veins leading to the main vessels, whereas other species had one. These non-tortuous afferent veins ran parallel to the main vein, sometimes giving the impression on angiographic studies that multiple main veins were present. This characteristic can be used for multiple catheterizations or can be a seen as a hindrance in some pre-clinical studies by making catheterization more challenging, although it depends on the caliber of the veins, the tortuosity, the angle of entrance in the main channel, and other factors.

The Thebesian were the most marked in the pig, but were identified in all animal species. In studies focusing on Thebesian veins and ischemia of the ventricular myocardium, the pig could represent a better model than the other two species. This study also showed the existence of anastomoses between the anterior and posterior segments of the heart. These anastomoses had already been alluded to in the literature [18, 30, 34]. This is a very important feature as this may represent a new access route to the posterior segment of the heart in both humans and animals.

This study also has some limitations. Anatomical measurements were performed on non-injected, cadaveric, formalin-fixed heart specimens. This might affect measurements by underestimating the size due to venous collapse. Furthermore, dimensions can change based on the phase of the cardiac cycle and pressures in the beating heart [42]. However, all data was compared to similar cadaveric formalin studies done with the same technique in human models. The same measurements had been performed on fresh latex injected hearts and similar measurements were obtained from the formalin study. Another limitation is that angiographic studies from clinical patients were taken as the human reference, as human cadaveric specimens are difficult to obtain. This might induce a potential bias in some obtained results as retrograde injections on cadaveric specimens might highlight vessels that vivo angiographic studies cannot reach due to reduced injection pressure. This was likely relevant for the Thebesian veins. However, the angiographic studies were performed in a similar way as our cadaveric study by retrograde injection with balloon occlusion. Some of the human measurements used as references were mean values obtained from the literature.

However these measurements were taken from large scale published human studies which have been widely cited. Finally, the small number of cases included in this study may constitute a limitation to this work and contribute to wider standard deviations in the estimates.

CONCLUSIONS

This study is the first to highlight the comparative anatomy of the coronary venous system in humans, pigs, sheep and dogs, including both macroscopic dissection and angiographic finding. The general organization of the CS and its venous tributaries are similar across the species; however, the studied animals do not contain a vein of Marshall, pigs and sheep have an azygos vein that enters the CS, and the number and position of venous valves was different in animals and humans. The veins were the most often paired in dogs. In all species, two types of anastomoses between the anterior (cranioventral) and posterior (dorsocaudal) sides of the heart were found which potentially opens new gateways for catheterization. This study provides baseline data for the study of the coronary venous system of dog, pig, and sheep.

Conflicts of interest: The authors declare that they have no conflict of interest.

Informed consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinky Declaration of 1975, as revised in 2005. Informed consent was obtained from all patients included in the study.

All institutional and national guidelines for the care and use of laboratory animals were followed and approved by the appropriate institutional committees.

Footnotes:

Line 130: [a]Latex pré-vulcanisé, Esprit Composite, 75014, Paris

Line 147 : [b] Visipaque® 320 mg/ml iodine injectable solution, GE healthcare

Line 147:[c] Micropaque® 100 mg/ml barium sulfate oral solution, Guerbet

Line 164: [d] Philips AlluraXper FD20

Line 179:[e] Covidien, Devon Industries, 6” x ½”

Line 179 : [f] IHM, France, 79110, Chef Boutonne

REFERENCES

1. Crick SJ, Sheppard MN, Ho SY, Gebstein L, Anderson RH. Anatomy of the pig heart: comparisons with normal human cardiac structure. J Anat. 1998 Jul;193 (Pt 1):105-19.

2. DiVincenti L, Westcott R, Lee C. Sheep (Ovis aries) as a Model for Cardiovascular Surgery and Management before, during, and after Cardiopulmonary Bypass. Journal of the American Association for Laboratory Animal Science : JAALAS. 2014;53(5):439-48.

3. Saremi F, Muresian H, Sanchez-Quintana D. Coronary veins: comprehensive CT-anatomic classification and review of variants and clinical implications. Radiographics. 2012 Jan-Feb;32(1):E1-32.

4. Mehra L, Raheja S, Agarwal S, Rani Y, Kaur K, Tuli A. Anatomical Consideration and Potential Complications of Coronary Sinus Catheterisation. J Clin Diagn Res. 2016 Feb;10(2):AC12-5.

5. Mak GS, Hill AJ, Moisiuc F, Krishnan SC. Variations in Thebesian valve anatomy and coronary sinus ostium: implications for invasive electrophysiology procedures. Europace. 2009 Sep;11(9):1188-92.

6. Mueller RL, Sanborn TA. The history of interventional cardiology: cardiac catheterization, angioplasty, and related interventions. Am Heart J. 1995 Jan;129(1):146-72.

7. Habib A, Lachman N, Christensen KN, Asirvatham SJ. The anatomy of the coronary sinus venous system for the cardiac electrophysiologist. Europace. 2009 Nov;11 Suppl 5:v15-21.

8. Silver MA, Rowley NE. The functional anatomy of the human coronary sinus. Am Heart J. 1988 May;115(5):1080-4.

9. Duckett SG, Ginks MR, Knowles BR, Ma Y, Shetty A, Bostock J, et al. Advanced image fusion to overlay coronary sinus anatomy with real-time fluoroscopy to facilitate left ventricular lead implantation in CRT. Pacing Clin Electrophysiol. 2011 Feb;34(2):226-34.

10. Jongbloed MR, Lamb HJ, Bax JJ, Schuijf JD, de Roos A, van der Wall EE, et al. Noninvasive visualization of the cardiac venous system using multislice computed tomography. J Am Coll Cardiol. 2005 Mar 1;45(5):749-53.

11. Plass A, Valenta I, Gaemperli O, Kaufmann P, Alkadhi H, Zund G, et al. Assessment of coronary sinus anatomy between normal and insufficient mitral valves by multi-slice computertomography for mitral annuloplasty device implantation. Eur J Cardiothorac Surg. 2008 Apr;33(4):583-9.

12. Spencer JH, Sundaram CC, Iaizzo PA. The relative anatomy of the coronary arterial and venous systems: Implications for coronary interventions. Clin Anat. 2014 May 26.

13. Tops LF, Van de Veire NR, Schuijf JD, de Roos A, van der Wall EE, Schalij MJ, et al. Noninvasive evaluation of coronary sinus anatomy and its relation to the mitral valve annulus: implications for percutaneous mitral annuloplasty. Circulation. 2007 Mar 20;115(11):1426-32.

14. Ortale JR, Gabriel EA, Iost C, Marquez CQ. The anatomy of the coronary sinus and its tributaries. Surg Radiol Anat. 2001;23(1):15-21.

15. D'Cruz IA, Shala MB, Johns C. Echocardiography of the coronary sinus in adults. Clin Cardiol. 2000 Mar;23(3):149-54.

16. Malago R, Pezzato A, Barbiani C, Sala G, Zamboni GA, Tavella D, et al. Non invasive cardiac vein mapping: role of multislice CT coronary angiography. Eur J Radiol. 2012 Nov;81(11):3262-9.

17. Chiribiri A, Kelle S, Gotze S, Kriatselis C, Thouet T, Tangcharoen T, et al. Visualization of the cardiac venous system using cardiac magnetic resonance. Am J Cardiol. 2008 Feb 1;101(3):407-12.

18. Gilard M, Mansourati J, Etienne Y, Larlet JM, Truong B, Boschat J, et al. Angiographic anatomy of the coronary sinus and its tributaries. Pacing Clin Electrophysiol. 1998 Nov;21(11 Pt 2):2280-4.

19. Alikhani Z, Li J, Merchan JA, Nijhof N, Mendel J, Orlov MV. Coronary sinus anatomy by computerized tomography, overlaid on live fluoroscopy can be successfully used to guide left ventricular lead implantation: a feasibility study. J Interv Card Electrophysiol. 2013 Apr;36(3):217-22.

20. Auricchio A, Sorgente A, Soubelet E, Regoli F, Spinucci G, Vaillant R, et al. Accuracy and usefulness of fusion imaging between three-dimensional coronary sinus and coronary veins computed tomographic images with projection images obtained using fluoroscopy. Europace. 2009 Nov;11(11):1483-90.

21. Christiaens L, Ardilouze P, Ragot S, Mergy J, Allal J. Prospective evaluation of the anatomy of the coronary venous system using multidetector row computed tomography. Int J Cardiol. 2008 May 23;126(2):204-8.

22. Mao S, Shinbane JS, Girsky MJ, Child J, Carson S, Oudiz RJ, et al. Coronary venous imaging with electron beam computed tomographic angiography: three-dimensional mapping and relationship with coronary arteries. Am Heart J. 2005 Aug;150(2):315-22.

23. Hasenfuss G. Animal models of human cardiovascular disease, heart failure and hypertrophy. Cardiovasc Res. 1998 Jul;39(1):60-76.

24. Suzuki Y, Yeung AC, Ikeno F. The pre-clinical animal model in the translational research of interventional cardiology. JACC Cardiovasc Interv. 2009 May;2(5):373-83.

25. Knackstedt C, Muhlenbruch G, Mischke K, Bruners P, Schimpf T, Frechen D, et al. Imaging of the coronary venous system: validation of three-dimensional rotational venous angiography against dual-source computed tomography. Cardiovasc Intervent Radiol. 2008 Nov-Dec;31(6):1150-8.

26. Ahmed SH, Rakhawy MT, Abdalla A, Assaad EI. The comparative anatomy of the blood supply of cardiac ventricles in the albino rat and guinea-pig. J Anat. 1978 May;126(Pt 1):51-7.

27. Ciszek B, Skubiszewska D, Ratajska A. The anatomy of the cardiac veins in mice. J Anat. 2007 Jul;211(1):53-63.

28. Halpern MH. The dual blood supply of the rat heart. Am J Anat. 1957 Jul;101(1):1-16.

29. Khan H KA, Faruqi A. Comparative histology of coronary arteries in mammals. Journal anatomical society of India. 2006 2006;55(1):27-30.

30. Shah SS, Teague SD, Lu JC, Dorfman AL, Kazerooni EA, Agarwal PP. Imaging of the coronary sinus: normal anatomy and congenital abnormalities. Radiographics. 2012 Jul-Aug;32(4):991-1008.

31. Alejandro Gomez F, Ballesteros LE, Stella Cortes L. Morphological description of great cardiac vein in pigs compared to human hearts. Rev Bras Cir Cardiovasc. 2015 Jan-Mar;30(1):63-9.

32. Gomez Fabian A. BLE, Cortes Luz S. Morphological expression of the pig coronary sinus and its tributaries: a comparative analysis with the human heart. Eur J Anat. 2015;19:139-44.

33. Kaimovitz B, Lanir Y, Kassab GS. A full 3-D reconstruction of the entire porcine coronary vasculature. Am J Physiol Heart Circ Physiol. 2010 Oct;299(4):H1064-76.

34. Di Guglielmo L, Baldrighi V, Montemartini C, Schifino A. Roentgen investigation of the coronary veins in the dog. Acta radiol. 1960 Mar;53:191-200.

35. Piffer CR, Piffer MI, Santi FP, Dayoub MC. Anatomic observations of the coronary sinus in the dog (Canis familiaris). Anat Histol Embryol. 1994 Dec;23(4):301-8.

36. Esperanca Pina JA, Correia M, O'Neill JG, Rendas AB. Morphology of the veins draining the coronary sinus of the dog. Acta Anat (Basel). 1981;109(2):122-8.

37. Besoluk K, Tipirdamaz S. Comparative macroanatomic investigations of the venous drainage of the heart in Akkaraman sheep and Angora goats. Anat Histol Embryol. 2001 Aug;30(4):249-52.

38. Harikrishnan S, Nair K, Tharakan J. Oblique vein of Marshall. Heart. 2005 Feb;91(2):e16.

39. Hood WB, Jr. Regional venous drainage of the human heart. Br Heart J. 1968 Jan;30(1):105-9.

40. Singh JP, Houser S, Heist EK, Ruskin JN. The coronary venous anatomy: a segmental approach to aid cardiac resynchronization therapy. J Am Coll Cardiol. 2005 Jul 05;46(1):68-74.

41. Noheria A, DeSimone CV, Lachman N, Edwards WD, Gami AS, Maleszewski JJ, et al. Anatomy of the coronary sinus and epicardial coronary venous system in 620 hearts: an electrophysiology perspective. J Cardiovasc Electrophysiol. 2013 Jan;24(1):1-6.

42. Bales GS. Great cardiac vein variations. Clin Anat. 2004 Jul;17(5):436-43.

43. Islam AK, Sayami LA, Zaman S. Chiari network: A case report and brief overview. J Saudi Heart Assoc. 2013 Jul;25(3):225-9.

44. von Ludinghausen M, Ohmachi N, Besch S, Mettenleiter A. Atrial veins of the human heart. Clin Anat. 1995;8(3):169-89.

45. von Ludinghausen M. Clinical anatomy of cardiac veins, Vv. cardiacae. Surg Radiol Anat. 1987;9(2):159-68.

46. Karaca M, Bilge O, Dinckal MH, Ucerler H. The anatomic barriers in the coronary sinus: implications for clinical procedures. J Interv Card Electrophysiol. 2005 Nov;14(2):89-94.

Tables:

	Coronary sinus ostium diameter (mm)		Coronary sinus length (mm)	
Species (weight)	Mean	SD	Mean	SD
Sheep (68 kg)	7.4	1	35.1	6.3
Pig (95 kg)	9.7	2.5	42	6.9
Dog (20kg)	5.5	1.3	32.1	5.7
Human (70 kg)	7.9	1.0	57.5	21.9

Table 1. *Macroscopic anatomical measurements for the coronary sinus. (mean and SD: standard deviation)*

	AIV diameter (mm)		AIV length (mm)	
Species (weights)	Mean	SD	Mean	SD
Sheep (68 kg)	2.65	0.7	105.8	9.3
Pig (95 kg)	2.3	0.5	88.6	7.7
Dog (20 kg)	1.5	0.9	69.8	0.7
Human (70 kg)	1.8	0.4	103.9	17

Table 2.*Macroscopic anatomical measurements for the anterior interventricular vein. (mean and SD: standard deviation)*

	GCV diameter (mm)		GCV length (mm)	
Species (animal weights)	Mean	SD	Mean	SD
Sheep (68 kg)	3.75	0.9	47.3	7.3
Pig (95kg)	3.4	0.6	56.5	10.7
Dog (20 kg)	2.39	1.2	30.7	10.8

Table 3: *Macroscopic anatomical measurements for the great cardiac vein. (mean and SD: standard deviation)*

	PIV diameter (mm)		PIV length (mm)	
Species (animal weight)	Mean	SD	Mean	SD
Sheep (68 kg)	2	1.1	70.3	8.7
Pig (95 kg)	1.2	0.4	57.7	22.6
Dog (20 kg)	1.09	0.7	53.8	6.6
Human (70 kg)	3.1	1.1	87.3	23

Table 4. *Macroscopic anatomical measurements for the posterior interventricular vein (mean and SD: standard deviation)*

Anterior interventricular vein	Not identified	Mild	Moderate	Marked
Dog	2 (20 %)	5 (50%)	2 (20 %)	1 (10 %)
Sheep	2 (20%)	6 (60 %)	2 (20%)	0 (0%)
Pig	0 (0%)	5 (50%)	4 (40%)	1 (10%)

Posterior interventricular vein	Not identified	Mild	Moderate	Marked
Dog	7 (70%)	3 (30%)	0 (0 %)	0 (0 %)
Sheep	6 (60 %)	4 (40 %)	0 (0 %)	0 (0 %)
Pig	6 (60%)	4 (40%)	0 (0%)	0 (0%)

Table 5.*Number of afferent veins visualized on angiographic studies.*

Figure captions:

Figure 1. General arrangement of the venous system. Left: viewed dorsally from the base of the canine heart. Right: ventrodorsal (anterior-posterior) view. Legends for both: CS: Coronary sinus, AIV: anterior interventricular vein, PIV: posterior interventricular vein, GCV: great cardiac vein, LMV: left marginal vein, C: catheter. Anterior posterior view shows PIV not seen confluent with the CS because the catheter balloon is obstructing the entrance of the CS.

Figure 2. Positioning for angiographic studies. Porcine heart.

Figure 3**:** Thebesian vein patterns of the AIV (porcine). Latero-medial views of the heart. From left to right: mild, moderate, marked subjective visual scale. Legend: CS: coronary sinus, AIV: anterior interventricular vein, PIV: posterior interventricular vein, GCV: great cardiac vein, C: catheter.

Supplementary Figure captions:

Figure I: Abrupt tapering between the Coronary sinus and Great Cardiac Vein (Porcine).

Figure II: Myocardial bridge on a porcine heart.

Figure III: Vieussens valve (porcine heart).