Journal of the American Association for Laboratory Animal Science
Vol 54, No 1
January 2015
Pages 10–16

Variability in the Cardiac Venous System of Wistar Rats

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Rats are often used as animal models in experimental cardiology for studying myocardial infarctions and various cardiologic procedures. Currently the cardiac venous system is a target for the delivery of drugs, gene vectors, angiogenetic growth factors, stem cells, and cardioprotective reagents. The purpose of this study was to describe the anatomic configuration and variability of the cardiac venous system in Wistar rats, by using the corrosion cast method and perfusion of colored latex. The distribution of veins in the rat heart disagrees with prior descriptions for other mammals, except mice, which have a similar pattern. Coronary venous drainage in the 36 rats examined consistently involved the left cardiac, left conal, major caudal, right cardiac, and right conal veins. Other veins involved inconsistently included the cranial cardiac vein (58.3% of cases), minor caudal veins (16.7%), conoanastomotic vein (66.7%), and left atrial vein (75%). In 4 cases (11.1%), the collateral veins were located between the left conal and left cardiac veins. In this study, high morphologic variability between cases was manifested by differences in the arrangement, size, mode of opening, and formation of the common root and affected all regions of the heart but primarily the right ventricle.

Cardiac venous circulation has become the subject of considerable interest in recent years. The venous system of the heart has been the focus of cardiac electrophysiology, radiofrequency catheter ablation, arrhythmia mapping, and defibrillation.[15] In the area of electrophysiology, the coronary venous system has long served as a conduit for the insertion of leads for left ventricular pacing in cardiac resynchronization therapy.[15] The implanting electrophysiologist frequently is challenged by high variability in the cardiac venous anatomy, and transvenous lead placement is dependent on vein accessibility.[29] In addition, the coronary venous system has a key importance in the application of new technologies and techniques designed for the treatment of cardiovascular disease.[15]

Rat models that mimic human cardiac diseases, such as myocardial infarction and ischemia–reperfusion injury, are standard, popular, and useful models to study cardiovascular disease.[35,36] A rat model of retrograde intracoronary infusion would be useful for investigating the effectiveness of the retrograde intracoronary route for delivering stem cells to infarcted myocardium and for conveying vehicles for gene transfection, angiogenetic growth factors, or cardioprotective reagents into the heart.[28,30] Data from rat studies suggest that the transplantation of myoblasts into the postinfarcted area may improve ventricular function and prevent negative remodeling.[18] Although gaining a detailed knowledge and understanding of the complexity and variability of the coronary venous system anatomy is important before initiating many cardiologic procedures, less attention has been paid to the coronary venous system compared with the coronary arterial system. In addition, the cardiac veins likely demonstrate more interindividual variations than do the coronary arteries.[12]

The morphology of the cardiac veins has been documented for some domestic animals,[1,5,22] mice,[8,16] porcupines,[2] rabbits,[3,33,34] and the North American beaver.[6] So far, only a few studies regarding the cardiac veins of rats have been published,[4,10,13,14,25,26] and none address anatomic variations of the coronary venous system in this species.

The number and distribution of veins are highly variable during development.[13] Therefore the aim of the present study was to describe the anatomic conformation, field of drainage, and mode of opening with regard to the anatomic variants of the cardiac veins in rats, by using corrosion cast methods and latex injection.

Materials and Methods

We studied the anatomy of the cardiac venous system in 36 adult, healthy Wistar rats of both sexes (mean weight, 320 g; Laboratory of Research Biomodels, University of PJ Safarik, Košice, Slovak Republic). Rats were anesthetized by intraperitoneal injection of sodium pentobarbital (50 mg/kg; Thiopental, Valeant Czech Pharma, Prague, Czech Republic). Under anesthesia and after heparin administration (50,000 IU/kg; Heparin Léčiva, Zentiva, Czech Republic), rats were exsanguinated from the jugular vein before they could regain consciousness. The application of an anticoagulant is a key requirement for high-quality vascular casting.[32] After lateral thoracotomy, the caudal vena cava was cannulated, and the heart was perfused manually with 0.9% physiologic saline.[19] Saline was perfused continually until casting, to remove the fixative and increase the permeability of the resin. The cranial caval veins, pulmonary trunk, and aorta were ligated. Colored latex and the corrosion cast method were used to visualize the coronary venous system. Colored latex (Het, Ohníč u Teplic, Czech Republic) was injected into the caudal vena cava; after perfusion, the heart was removed and cleaned of connective tissue. Cardiac vein

Received: 24 Mar 2014. Revision requested: 30 Apr 2014. Accepted: 02 Jul 2014.
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courses were analyzed macroscopically and under an operating microscope (model M 320, Leica).

Corrosion casts were prepared by using a self-curing adhesive resin (Spofacryl, SpofaDental, Jičín, Czech Republic). The product is a 2-component methacrylate resin, containing a copolymer (methyl methacrylate-comethyl acrylate) and a liquid mixture of 3 monomers (methyl methacrylate, methacryl acid, ethylene glycol dimethacrylate), which together provide a crosslinked, mechanically and corrosion-resistant substance. A plastic cannula was inserted and fixed in the caudal vena cava, and the casting medium was injected. After vascular casting with the resin was complete, rats were left undisturbed for 30 min, after which they were submersed in water at 40 to 60 °C for 30 min to 24 h to achieve full polymerization of the resin.[17,31] Soft tissues were macerated by immersion in KOH solution (2% to 4%) at 60 to 70 °C for 3 to 6 d.[20] Detergents (0.5%) were used to facilitate tissue removal by KOH.[32] After polymerization, corroded specimens were submersed in water[23] and dried at room temperature. The cardiac veins were evaluated macroscopically and by using an operating microscope (model M 320, Leica). Coronary veins were named in accordance with Nomina Anatomica Veterinaria[9] and previous reports.[3,13,34]

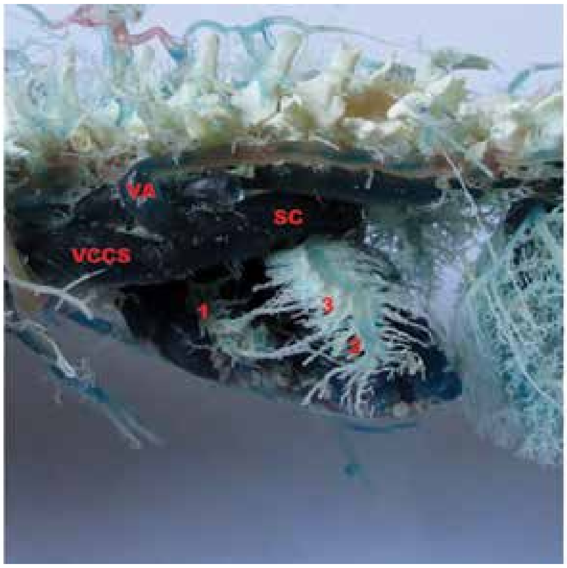

Figure 1. Collateral veins on the left surface of the rat heart, corrosion cast. VCCS, vena cava cranialis sinistra; SC, sinus coronarius; VA, vena azygos; 1, vena coni arteriosi sinistra; 2, vena cordis sinistra; 3, collateral veins.

Results

For the coronary sinus (sinus coronarius), the left cranial vena cava (vena cava cranialis sinistra) ran ventrally to the arcus aortae to achieve the caudal aspect of the right atrium (atrium dextrum), which it entered together with the caudal vena cava (vena cava caudalis). Before it merged with the caudal vena cava, the left cranial vena cava received the azygos vein; from this point, this structure is referred to as the coronary sinus. The coronary sinus was the most consistent feature of the coronary venous system, and it comprised the left cardiac, major caudal, and left atrial veins.

The left conal vein (vena coni arteriosi sinistra) usually originated at the lower part of the proximal third of the heart as 3 veins that integrated into a single vein. The left conal vein drained the left circumference of the arterial cone (conus arteriosus), the origin of the pulmonary trunk (truncus pulmonalis), left atrium (atrium sinistrum), and proximal third of the left ventricle (ventriculus sinister). The first tributary of the left conal vein, the most cranial vein, drained the blood from the ventral side of the pulmonary trunk and proximal portion of the left ventricle. The middle vein often originated in the region of the paraconal interventricular groove (sulcus interventricularis paraconalis) in the proximal third of the heart. Alternatively, in 4 of the 36 cases (11.1%), the middle vein arose in the distal third of the left ventricle and received small branches from the left side of the heart. In addition, 4 cases (11.1%) demonstrated collateral veins between the left conal and left cardiac veins (Figure 1). A third tributary of the left conal vein, present in 20 rats (55.6%), typically was located caudally, arose on the left auricle due to the confluence of several fine veins, drained the ventral side of the left auricle, and merged with cranial and middle vein to form a common trunk. Thereafter the left conal vein ran dorsally, entered the space between the pulmonary trunk and left atrium and emptied the medial surface of the right cranial caval vein (vena cava cranialis dextra) in all 36 specimens.

The left cardiac vein (vena cordis sinistra) is a large tributary of the coronary sinus, just before the sinus opens into the right atrium. The left cardiac vein typically began at the apex of heart (apex cordis); in 4 cases (11.1%; Figure 1), the left cardiac vein arose from the distal third of the left ventricle. If this vein did not reach the apex of the heart, the related region was drained by branches of the right cardiac vein (Figure 2) and the major caudal vein. In 2 cases (5.6%), the left cardiac vein originated as 2 veins, and in 1 case (2.8%) as 3 veins, which fused into a single, main vessel. In 34 cases (94.4%), the left cardiac vein ran around the left border, ascended dorsocaudally toward the base of the heart, and terminated into the coronary sinus. In the remaining 2 cases (5.6%), the left cardiac vein entered the coronary sinus, together with the major caudal vein. Throughout its entire course, the left cardiac vein received numerous small cardiac veins from the wall of the left ventricle, which entered the left cardiac vein at right angles, parallel to one to another. Collateral veins between the left cardiac and left conal veins were present in 4 cases (11.1%; Figure 1).

The major caudal vein (vena caudalis major) was formed by the union of numerous branches from the caudal portion of the left and right ventricles, in the middle third of the heart. In 3 cases (8.3%), the major caudal vein formed near the apex of heart. The major caudal vein ran directly and dorsally toward the base of the heart and ended in the coronary sinus in 23 cases (63.9%) or in the right atrium in 7 cases (19.4%; Figure 3). In 3 cases (8.3%), the major caudal vein was part of a common root was formed by the major caudal, right cardiac, and cranial cardiac veins. The major caudal and right cardiac veins merged into a single trunk in 2 rats (5.6%). In the remaining case (2.8%), a common root comprising the major caudal, minor caudal, right cardiac, and cranial cardiac veins was formed before it opened into the caudal part of the right atrium (Figure 4).

The right cardiac vein (vena cordis dextra) drained the right ventricle and emerged as several small veins in the distal third of the right ventricle. In 4 cases (11.1%), the right cardiac vein arose at the apex of the heart and collected blood from the left ventricle. The right cardiac vein formed in the proximal third of the right ventricle in 3 cases (8.3%). The right cardiac vein curved around the right ventricular margin and entered the caudal portion of the right atrium; however in 2 cases (5.6%), the right cardiac vein emptied into the major caudal vein. The right cardiac vein received the cranial cardiac vein in 10 cases (27.8%). The right cardiac vein opened in the right atrium as a single vessel or with other veins (Table 1).

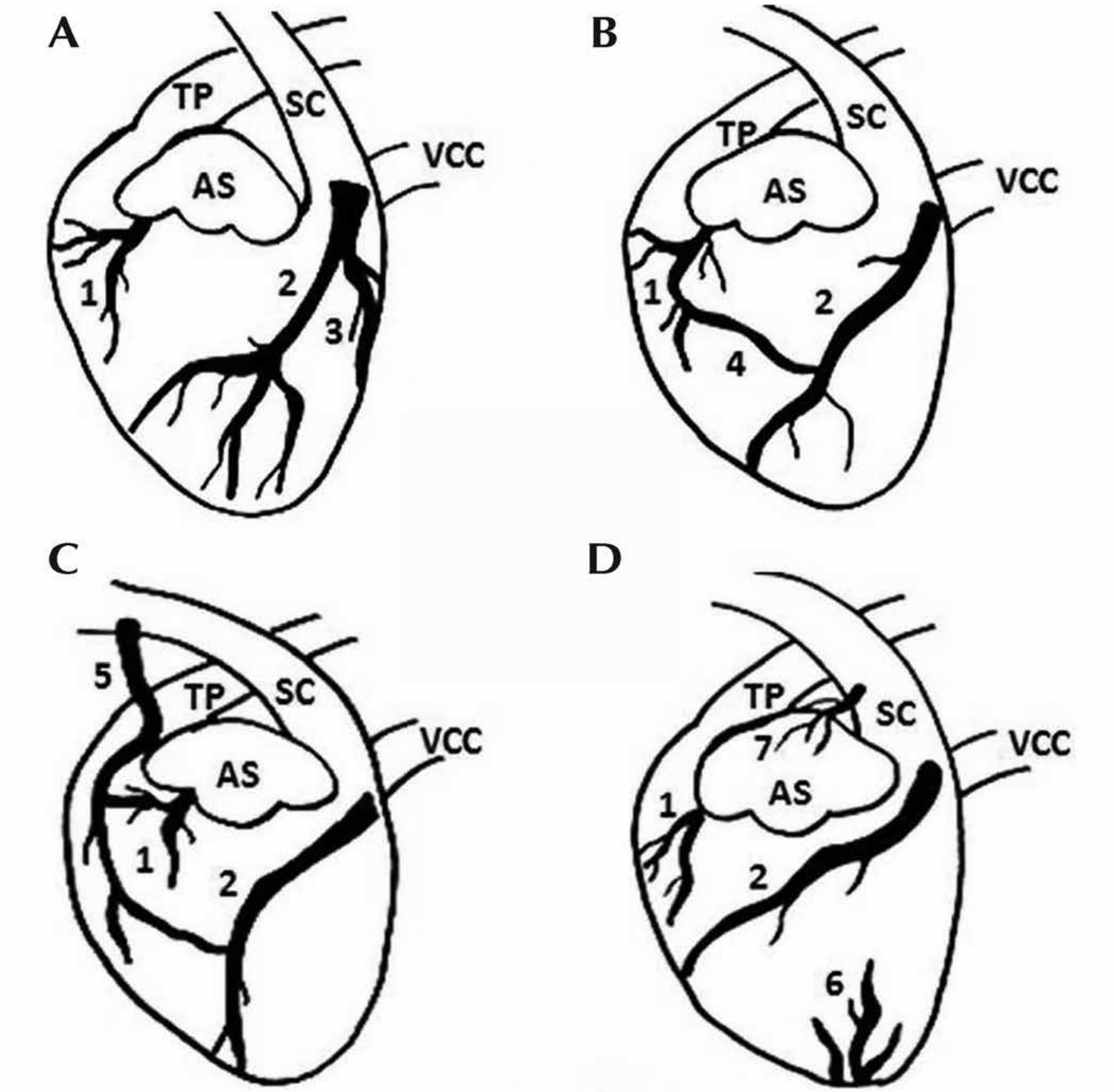

Figure 2. Veins of the left surface of the heart and some observed variations. AS, atrium sinistrum; SC, sinus coronarius; TP, truncus pulmonalis; VCC, vena cava caudalis; 1, vena coni arteriosi sinistra; 2, vena cordis sinistra; 3, vena caudalis major; 4, collateral vein; 5, conoanastomotic vein; 6, vena cordis dextra; 7, vena atrii sinistri.

The minor caudal veins (venae caudales minores) were present in only 6 rats (16.7%), drained the area between the major caudal and right cardiac veins, and emptied into the right atrium. There were 2 minor caudal veins in 2 cases (5.6%; Figure 4), and 3 cases (8.3%) each had a single minor caudal vein. In species other than rats, the related region is drained by branches of major caudal and right cardiac veins. The minor caudal veins established a common trunk with the major caudal, right cardiac, and cranial cardiac veins in 1 case (2.8%; Table 1).

The cranial cardiac vein (vena cordis cranialis) was inconsistent and was present in only 21 cases (58.3%; Table 2). The cranial cardiac vein manifested as a single vein in 7 cases (19.4%; Figure 5) or as a tributary of the right cardiac vein in 10 cases (27.8%; Figure 6). In 3 cases (8.3%), the cranial cardiac vein formed a common trunk with the major caudal and right cardiac veins, and in 1 case (2.8%), the cranial cardiac vein was integrated with major caudal, right cardiac, and minor caudal veins. The cranial cardiac vein was located between the right cardiac and right conal veins, drained the blood from the cranial portion of the proximal third of the right ventricle, advanced caudodorsally, and terminated in the right atrium.

The right conal vein (vena coni arteriosi dextra) drained the blood from the right part of the pulmonary trunk, arterial cone, and proximal third of the right ventricle (Figure 5); ran directly to the base of heart and opened into the right atrium; and was mostly covered by the right auricle. The cranial branch of the right conal vein anastomosed with the conoanastomotic vein.

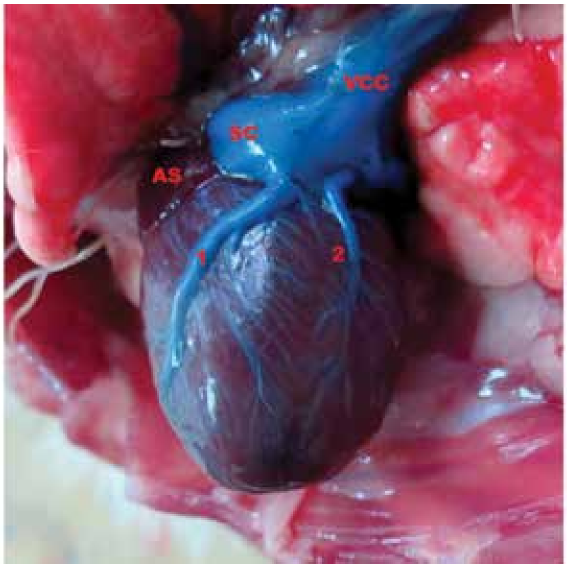

Figure 3. The left ventricular border of the rat heart, colored latex. VCC, vena cava caudalis; SC, sinus coronarius; AS, auricula sinistra; 1, vena cordis sinistra; 2, vena caudalis major.

The conoanastomotic vein, found in 24 cases (66.7%), arose on the right surface of the conus; ran from the right side of the heart, across the arch of aorta (arcus aortae), to the left side; and emptied into the ventromedial surface of the left cranial vena cava. In 2 cases (5.6%), the conoanastomotic vein arose on the middle third of the left ventricle, caudally from the left conal vein; ran around the pulmonary trunk; and curved cranially to enter the left cranial vena cava. The conoanastomotic vein anastomosed with branches of the left conal and left cardiac veins (Figure 2).

Left atrial veins (venae atrii sinistri) were present in 27 cases (75%), drained the dorsal surface of the left atrium, and opened into the coronary sinus as its first tributary (Figure 2).

Discussion

The cardiac drainage in rats differs from that in larger animals and shows an unusual arrangement of the cardiac veins. Only those of mice were similar in pattern.[8] The greatest difference between rats and other animals is the presence of the left cranial vena cava, which is characteristic of rats, and the common right cranial vena cava. A left cranial vena cava also occurs in other rodents, such as mice,[8] and rabbits.[34] Only a few cases of left cranial vena cava have been described in cats, cattle,[27] and marsupials.[11] Humans have only the right (cranial) superior vein. During human prenatal development, the left (cranial) superior vena cava, via the brachiocephalic vein, connects with the right (cranial) superior vein, which then drains into the right atrium.[16] In humans, a left cranial vena cava was reported as a rare variation termed the left superior caval vein in 0.3% of participants and 5% of patients with congenital heart malformations.[7]

The coronary sinus was present in most domestic animals[22] and humans,[16,20] porcupines,[2] rats,[13] and mice[8] but not rabbits.[3,34] In humans, the coronary sinus is considered the most important vein of the heart, draining practically all of the left ventricular wall and adjacent areas and part of the right ventricle, thereby accounting for approximately 85% of the coronary blood flow.[12] According to previous reports,[8,13] the term 'coronary sinus' is used to designate the terminal segment of the left cranial caval vein, between the orifice of the azygos vein and the opening of the left cranial caval vein into the right atrium. Some authors[33] have suggested that the coronary sinus is the cranial continuation of the great cardiac vein, whereas others[1,5] have proposed the coronary sinus to be the continuation of the left azygos vein. The coronary sinus drained blood from the left ventricle in rats and consistently collected flow from the left cardiac vein as well as the major caudal vein (23 cases, 63.9%) and left atrial veins (27 cases, 75%).

The route and direction of the left cardiac vein are very similar to those of the left marginal vein in humans and pigs.[24] In the current rat study, the left cardiac vein originated as 1 (91.6%), 2 (5.6%) or 3 (2.8%) veins and emptied into the coronary sinus in 34 of the 36 cases evaluated. In the remaining 2 cases (5.6%), the left cardiac vein opened to the coronary sinus, together with the major caudal vein. In mice, the left cardiac vein entered the coronary sinus by way of a single opening in 20 specimens (43.4%), it merged with the major caudal vein in 22 specimens (47.8%), or it joined a common anastomosis between the opening of the left cardiac vein and the major cardiac vein in 8 cases (17.4%).[8] We noted collateral veins between the left cardiac and left conal veins in 4 cases (11.1%). The presence of the collateral veins has not previously been described in rats, but they occurred at an equivalent position in domestic animals[22] and rabbits,[34] specifically , between the paraconal interventricular and left marginal veins. The arrangement of these 2 veins in these other species approximately corresponds to the left conal and left cardiac veins in rats.

The major and minor caudal veins were observed at the caudal part of rat hearts, similar to the arrangement in the hearts of mice. Whereas the major caudal vein of rats was present as a single vein or a vein that formed a common trunk with other veins, the minor caudal veins occurred in only 6 cases, as 1 (8.3%) or 2 (5.6%) veins or as a common root (2.8%). In contrast, minor cardiac veins in mice were present in 38 cases (82.6%): 20 cases had a single minor caudal vein, 12 cases had 2, 6 cases had 3, and 7 cases lacked minor caudal veins.[8] In rats, the major caudal vein opened to the sinus coronarius or right atrium, whereas the minor caudal veins entered the right atrium. In mice, these veins emptied into the coronary sinus or right atrium by a common opening with the right cardiac vein; the more complicated opening system was present in 11 cases.[8] A venous arch parallel to the coronary sinus in mice collected several caudal veins and sometimes included ostia of the left and right cardiac veins.[8] This pattern was not observed in rats. Caudal veins of the heart have not been reported to occur in domestic animals or humans, but their course can be compared with that of the middle cardiac vein.[21]

The right ventricle of rats was predominantly drained by the right cardiac vein, which typically entered the right atrium or, in 2 cases (5.6%), the major caudal vein. In domestic animals including rabbits, the veins comprising the right cardiac veins (the right marginal ventricular, proximal ventricular, distal ventricular, and conal veins) all have different origins, but all drain the right ventricle and unite to form the right semicircumflex vein, which opens into the right atrium.[1,5,22,34] According to one study,[8] the most frequent pattern of the right cardiac vein in rabbits consists of 2 main branches, which merge into a single trunk and enter the right atrium. In 15 cases, a single trunk of the right cardiac vein was detected in rabbits and shared an opening with the minor caudal veins or right conal vein.[8] The cranial cardiac vein of rats drained the right ventricle as a single vein (21 cases, 5.3%) or as a tributary of the right cardiac vein (10 cases) or merged with other veins. In contrast with our study, the cranial cardiac vein was present in only 4 cases in mice (8.7%).[8]

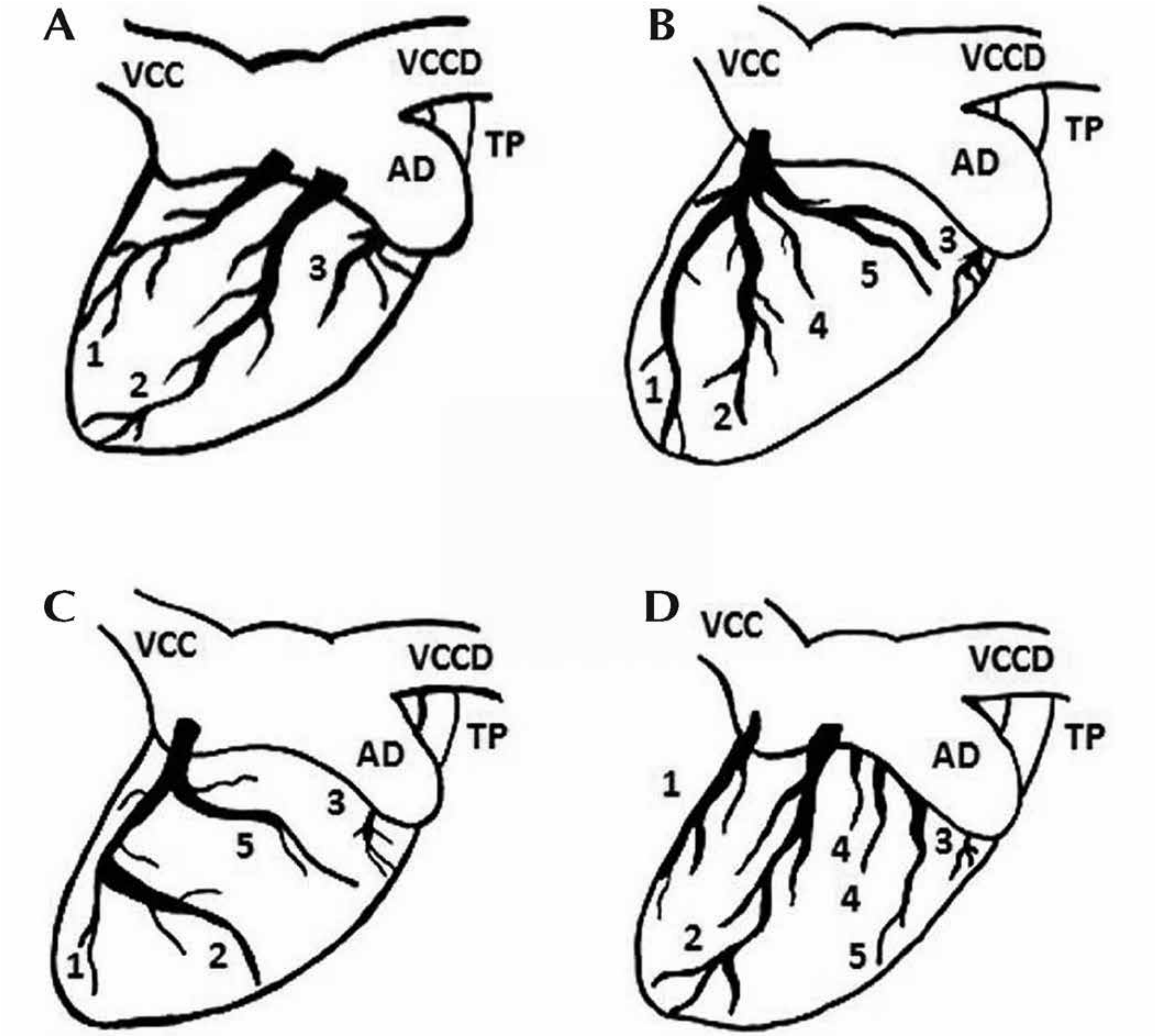

Figure 4. Several variations of the right surface of the heart in the rat. AD, atrium dextrum; VCC, vena cava caudalis; VCCD, vena cava cranialis dextra, TP, truncus pulmonalis, 1, vena caudalis major; 2, vena cordis dextra; 3, vena coni artesiosi dextra; 4, vena caudales minors; 5, vena cordis cranialis.

Table 1. Cardiac veins comprising the common root in rats (n = 36)

	No. of cases	Frequency (%)
LCV + MCV	2	5.6
MCV + RCV + CCV	3	8.3
RCV + MCV	2	5.6
MCV + MiCV + RCV + CCV	1	2.8
RCV + CCV	10	27.8

CCV, cranial cardiac vein; LCV, left cardiac vein; MCV, major caudal vein; MiCV, minor caudal veins; RCV, right cordal vein.

Table 2. Coronary veins variably present in rats (n = 36)

	No. of cases (n)	Frequency (%)
Cranial cardiac vein	21	58.3
Minor caudal veins	6	16.7
Conoanastomotic vein	24	66.7
Left atrial veins	27	75.0

A very interesting venous drainage pattern occurs in the region of the pulmonary trunk and arterial cone. Compared with other mammals, rats retain a more primitive venous system, because the region of the pulmonary trunk, arterial cone, and descending aorta are drained by 2 separate veins. The one from the right side of the arterial cone passed through the conoanastomotic vein, which emptied into the left cranial vena cava. The conoanastomotic vein was present in 24 cases (66.7%) that we evaluated and does not occur in other animals but corresponds of the median cephalic vein in frogs.[13] The anastomosis between the left cranial caval and right conal veins, which together are comparable to the conoanastomotic vein, occurred in only a single case in mice.[8] Another study[13] described the existence of this vein in 55 rats (79.7%), in which the left conal vein drained the left side of the arterial cone into the right cranial caval vein. The left conal vein appears to retain the characteristics of the cephalic vein of eels.[13] Therefore, the primitive features

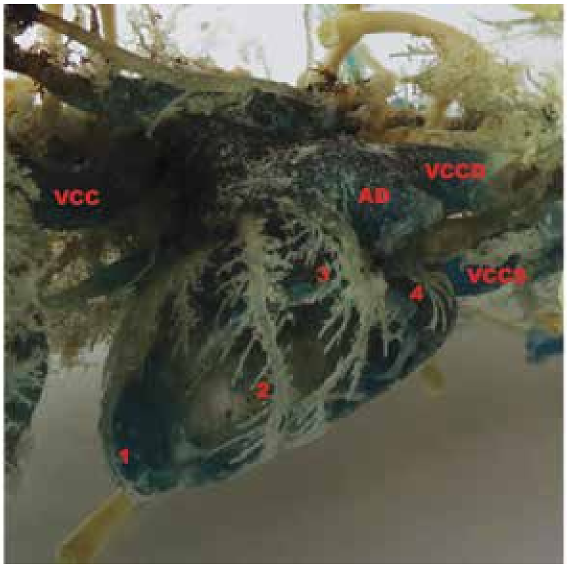

Figure 5. The right surface of the rat heart. VCC, vena cava caudalis; VCCD, vena cava cranialis dextra; VCCS, vena cava cranialis sinistra; AD, atrium dextrum; 1, vena caudalis major; 2, vena cordis dextra; 3, vena cordis cranialis; 4, vena coni arteriosi dextra.

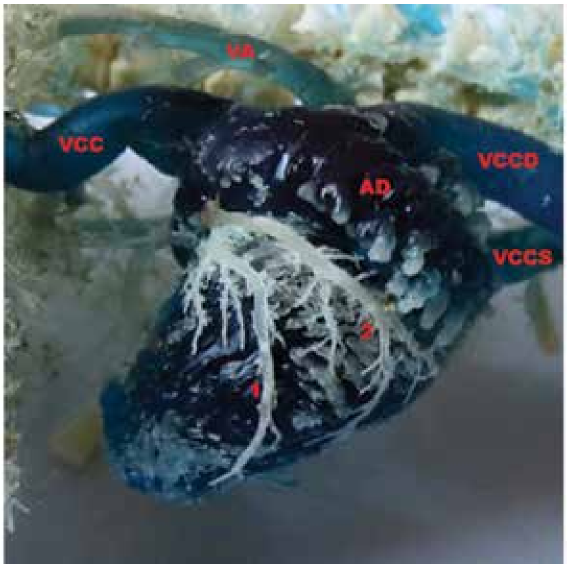

Figure 6. The common root formed between the vena cordis dextra (RCV) and vena cordis cranialis (CCV). VCC, vena cava caudalis; VCCD, vena cava cranialis dextra; VCCS, vena cava cranialis sinistra; AD, atrium dextrum; VA, vena azygos; 1, RCV; 2, CCV.

of cardiac drainage that are demonstrated in lower life forms (fishes and amphibians) are retained in rats but lost by other mammals.[13] In rats, the right conal vein consistently drained the right side of the conus, unlike the situation in other species. The left conal vein in rats entered the right cranial caval vein, whereas the right conal vein emptied into the right atrium in both rats and mice.[8] In rabbits and domestic animals, the left conal vein entered the paraconal interventricular vein,[1,34] and the right conal vein terminated in the right circumflex vein.

In a study of the variable system of the conal veins in mice,[8] the left and right conal veins usually anastomosed in front of the pulmonary root to the prepulmonary conal venous arch (arcus venosus coni arteriosi prepulmonalis), but this situation was not observed in the present study. Several mice demonstrated an anastomosis between the right and left conal veins and the prepulmonary conal venous arch.[8] This variation has been called the circulus venosus coni arteriosi and has been described to occur in rats,[13] but only during the embryonic period, as a plexus around the arterial cone, but not in adult rats, in agreement with our current findings.

The left atrium of rats is drained by the left atrial veins (75%) and caudal branch of the left conal vein (55.6%). Interestingly venous drainage of the right atrium was not apparent, consistent with previous observations in mice and rats.[8,13]

In conclusion, morphologic variability was manifested by differences in the presence, position, extent, and size of cardiac veins. These data suggest that the highest variability in the rat heart exists primarily in the region of the right ventricle. Knowing the anatomic configuration and variability of the major veins of the rat heart is necessary for understanding the normal structure of the venous system and can provide important information regarding future experimental studies, including cardiovascular procedures.

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