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Anatomy of the coronary artery and cardiac vein in the quail ventricle: patterns are distinct from those in mouse and human hearts

Short title: Anatomy of quail coronary vessels

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Abstract

Coronary vessel development has been investigated in avian and mouse embryonic hearts. Quail embryos are a useful tool to examine vascular development, particularly because the QH1 antibody and transgenic quail line, Tg (tie1:H2B-eYFP), are useful to trace endothelial cells. However, there are only a few descriptions of the quail coronary vessels. Using ink injection coronary angiography, we examined the course of coronary vessels in the fetal quail heart. The major coronary arteries were the right and left septal arteries, which respectively branched off from the right and left coronary stems. The right septal artery ran posteriorly (dorsally) and penetrated the ventricular free wall to distribute to the posterior surface of the ventricles. The left septal artery ran anteriorly (ventrally) and penetrated the ventricular free wall to distribute to the anterior surface of the ventricles. The right and left circumflex arteries were directed posteriorly along the atrioventricular sulci. The cardiac veins consisted of three major tributaries: the middle, great, and anterior cardiac veins. The middle cardiac vein ascended along the posterior interventricular sulcus and emptied into the right atrium. The great cardiac vein ran along the anterior interventricular sulcus, entered the space between the left atrium and conus arteriosus and emptied into the right atrium behind the aortic bulb. The anterior cardiac vein drained the anterior surface of the right ventricle and connected to the anterior base of the right atrium. The course of coronary vessels in the quail heart was basically the same as that observed in chick but was different from those of mouse and human.

Key words: anatomy, avian species, cardiac vein, coronary artery, quail heart

Mini-abstract

Quail major coronary vessels consist of right and left septal arteries; and middle, great and anterior cardiac veins. Quail coronary patterns are distinct from those of mouse and human hearts.

Introduction

The coronary circulatory system is essential to maintain nutrients and oxygen provision for the cardiac muscle to function throughout life. The coronary circulation starts immediately after metamorphosis, during which embryos change their anatomy and physiology to form those of fetuses. At this time, the way oxygen is supplied to the cardiac muscle changes dramatically, i.e. diffusion from the endocardium is replaced by the adult coronary circulatory system consisting of coronary arteries and veins. Impaired development of the coronary vessels leads to life-threatening defects, including aberrant origins of the coronary artery and coronary arteriovenous fistula (Pe´rez-Pomares et al. 2016). Coronary arteriosclerosis causes ischemic heart disease in adult life. Revascularization of the ischemic or infarcted lesions is a potential therapeutic strategy to restore cardiac contractility. Therefore, it is important to understand the mechanisms regulating coronary vessel formation in order to develop the revascularization therapies (Sedmera and Watanabe 2006).

The development of the coronary system has been examined extensively in avian and mouse models (Reese et al. 2002; Tian et al. 2015). In avian models, the proepicardial organ, which consists of

surface mesothelium and a sinus venosus-derived inner core mesenchyme, generates the coronary vascular system of the ventricular free wall (Kamimura et al. 2018). Genetic tracing experiments demonstrated that the endothelial cells lining the sinus venosus and ventricles are the major sources of coronary vascular endothelium. Although the origin of coronary vessels has been concluded, the mechanisms leading to coronary vessel patterning as well as arteriovenous segregation processes are largely unknown (Nakajima and Imanaka-Yoshida 2013; Tian et al. 2015).

Mammalian and avian hearts have two coronary artery system, in which the right and left coronary arteries originate, respectively, from the right and left aortic sinuses. However, the patterns and courses of coronary vessels are very different between species. In human hearts, coronary arteries course along the interventricular and coronary sulci subjacent to the epicardium, whereas mouse coronary arteries course intramurally. In birds, the major branches of coronary artery are the septal arteries that branch off from the coronary stem, but there exist some differences in coronary patterning between birds (Myczkowski, 1960; Lindsay and Smith 1965; Bezuidenhout 1984). Quail embryonic hearts are a useful tool to examine vascular development, because the quail endothelium-specific antibody QH1 and transgenic quail model, Tg (tie1:H2B-eYFP), are available to trace endothelial cells (Pardanaud et al. 1987; Sato and Lansford 2013). However, there have been few published studies presenting the actual macroscopic anatomy of the quail coronary vessels (Fitzgerald 1969). In the present report, using ink injection coronary angiography we observed the origin and course of coronary arteries and veins in fetal quail heart. The major coronary arteries were the right and left septal arteries, which respectively branched off from the right and left

76 coronary stems. Cardiac veins were classified into three major veins including the middle, great, and
77 anterior cardiac veins according to their opening into the right atrium.
78
79 **Materials and Methods**
80 Fertilized quail eggs (Quail COSMOS, Toyohashi, Japan) were incubated at 37.5°C and 60% humidity.
81 Embryos were staged by days of incubation (embryonic day, E) and using the Hamburger and Hamilton
82 system (1951) adapted into quail (Ainsworth et al. 2010), and E6 to 14 (stage 29 to 43) hearts were
83 examined. The number of embryos examined is tabulated in Table 1. Eggs were placed on ice for 30
84 minutes to stop the heart-beat, the embryo was extirpated and put in ice-cooled phosphate buffered saline
85 (PBS). The thoracic cavity was opened, then a pulled glass needle was inserted into the ascending aorta,
86 and 4% paraformaldehyde (PFA)/PBS was gently injected. To observe the coronary artery, 20% carbon
87 ink (PLATINUM, Tokyo, Japan) in PBS was injected into the ascending aorta. The resulting hearts were
88 extirpated and re-fixed in 4% PFA/PBS at 4°C for more than 12 hours. The fixed hearts were immersed in
89 a graded series of glycerin/0.5% potassium hydroxide (1:3, 15 minutes; 1:1, 30 minutes; 3:1, 2 hours) for
90 transparency. To observe the cardiac vein, 20% carbon ink/2% gelatin in PBS was injected into the
91 ascending aorta, after the cardiac veins connecting to right atrium were visualized, the hearts were
92 removed and re-fixed in ice-cooled 4% PFA/PBS for more than 48 hours. Gelatin was used to keep the
93 carbon ink from diffusing out of the cardiac vein. Samples were observed using a stereoscopic
94 microscope and photographed. Animal handling and procedures were approved by the Osaka City

University Animal Care and Use Committee, as set forth in the NIH Guide for the Care and Use of Laboratory Animals (Eighth Edition).

Results

Coronary arteries

The right coronary stem, which originated from the right aortic sinus, gave off surface and deep branches. The surface arteries included the conus branch (cb in Fig. 1A), subepicardial branches of the right ventricular free wall (rvb in Fig. 1A), and the right circumflex branch (cx in Fig. 1A). The right circumflex branch ran along the right coronary sulcus. It gave off right atrial branches along the pectinate muscles as well as terminal branches on the right lateral surface of the right ventricle. The deep artery, the right septal artery, was thicker than the right circumflex artery (sa in Fig. 1B). The right septal artery pierced the supraventricular crista to enter into the interventricular septum (right side of the yellow dotted line in Fig. 1B and gray area in Fig. 1B') and gave off branches to the posterior (dorsal) aspect of the interventricular septum and apex. The peripheries of the right septal artery penetrated the ventricular free wall transmurally at the posterior interventricular sulcus and distributed on the posterior surface of both ventricles and the apex (small arrows in Fig. 1C).

The left coronary stem, which originated from the left aortic sinus, gave off the interatrial branch, left septal artery, left conus branch, and left circumflex branch. The left circumflex branch ran into the left coronary sulcus (cx in Fig. 1D) and terminated at the left posterolateral wall of the ventricle. The deep

114 thick artery, the left septal artery, pierced the infundibulum to enter the interventricular septum (sa in Fig.
115 1E) and gave off branches toward the anterior (ventral) aspect of the interventricular septum and apex
116 (left side of the yellow dotted line in Fig. 1E and gray area in Fig. 1E'). The peripheries of the left septal
117 artery penetrated the ventricular free wall and distributed onto the surface of the left ventricular free wall
118 and apex (small arrows in Fig. 1D and E).
119
120 **Cardiac veins**
121 Cardiac veins were classified into three major veins according to their openings into the right atrium, i.e.
122 middle cardiac vein, great cardiac vein, and anterior cardiac vein. The middle cardiac vein was the largest
123 vein and was observed in all samples examined (20/20) (mcv in Fig. 2A). The middle cardiac vein, which
124 drained from the posterior surface of both ventricles including the apex, ran along the posterior
125 interventricular sulcus and emptied into the base of the left precaval vein (left superior vena cava) before
126 E9 (stage 36-37) and emptied into the sinus venosus of the right atrium after E10 (stage 38-39). The left
127 circumflex vein (cx in Fig. 2A), which originated from the left lateral wall of the left ventricle and passed
128 into the left coronary sulcus, was observed in 14 hearts (14/20) and terminated at the left precaval vein
129 (5/14), right atrium (5/14) or middle cardiac vein (4/14). Small cardiac veins were observed in 5 (5/20)
130 hearts and joined into the middle cardiac vein (scv in Fig. 2A).
131 The great cardiac vein consisted of two major segments, the anterior interventricular segment and a
132 downstream basal segment. The anterior interventricular segment ascended along the left lateral side of

133 the anterior interventricular sulcus (aivs in Fig. 2B) and entered the space between the pulmonary trunk
134 and left auricle to continue the basal segment (bs in Fig. 2B). The basal segment ran along the anterior
135 basal rim of the left atrium (accompanying the left coronary artery stem) and finally emptied into the right
136 atrium behind the base of the ascending aorta (open arrowhead in Fig. 2B). In 2 of 18 hearts, no apparent
137 interventricular segment was observed. The left conus vein was observed in all samples with a visible
138 great cardiac vein (18/18). A direct anastomosis between the great cardiac vein and left circumflex vein
139 was detected in 6 samples (6/18).
140 The anterior cardiac vein, which drained from the anterior wall of the right ventricle via several
141 tributaries and the right conus vein, emptied into the base of the right auricle (acv and open arrowhead in
142 Fig. 2C). The opening of the anterior cardiac vein had a single orifice (13/16; 3 openings were found in
143 one sample and undetectable in 2 samples).
144
145 **Discussion**
146 **Coronary artery**
147 In quail hearts, the main coronary arteries were the right and left septal arteries, which respectively
148 branched off from the right and left coronary stems and penetrated the supraventricular crista and
149 infundibulum to enter the interventricular septum. These deep arteries distributed into the interventricular
150 septum, subsequently penetrated the ventricular free wall to exit into the subepicardial space, and
151 distributed into the ventricular surface and apex (Fig. 3A). The anatomy of quail coronary arteries

152 resembled chick and phalanger (a marsupial, Dowd 1974) but were different from monotremes (Dowd
153 1969), rodents and human hearts (Halpern 1957; Fernandez et al. 2008; Loukas et al. 2009a).
154 In mice, the right and left coronary arteries originated, respectively, from the right and left aortic
155 sinuses and course intramurally immediately after originating. The right coronary artery runs into the
156 right coronary sulcus, giving off an acute marginal branch and turns obliquely toward the apex as a dorsal
157 interventricular branch in C57BL/6 strains (Fernandez et al. 2008) or right ventricular distal branch in
158 Swiss albino mouse (Yoldas et al. 2010). The septal artery predominantly branches off from the right
159 coronary stem in several mice including Balb/c, Swiss albino, and wild mice, whereas the septal artery
160 originates evenly from the right, left or both coronary stems in strain C57BL/6 (Lopez-Garcia et al. 2016).
161 The left coronary artery gave off two major branches, the left circumflex artery in the left coronary sulcus
162 terminating at the crux and the obtuse branch along the obtuse margin to the apex in strain C56BL/6
163 (Fernandez et al. 2008), whereas it was the paraconal interventricular branch in Swiss albino mouse
164 (Yoldas et al. 2010). These observations indicated that the fundamental patterns/courses of coronary
165 arteries are distinct between not only species but also strains. Unusual anatomical variations/anomalies
166 including a single ostium, high take-off, and aortic intramural course occur with relatively high incidence
167 in certain strains (Lopez-Garcia et al. 2016). Therefore, knowledge of the species/strain-specific
168 topographical coronary anatomy is necessary to investigate coronary biology.
169
170 **Cardiac vein**

171 The quail cardiac vein system consisted of three cardiac veins according to their openings into the right
172 atrium: the middle cardiac vein, great cardiac vein, and anterior cardiac vein (Fig. 3). The patterns of
173 quail cardiac veins were similar to those observed in chick hearts (Lindsay 1967). The most characteristic
174 feature of the quail cardiac veins was the course of the great cardiac vein. In this vein, the anterior
175 interventricular segment ascended the lateral aspect of the interventricular sulcus followed by the basal
176 segment. The basal segment ran between the left atrium and conus arteriosus and opened solely into the
177 right atrium behind the aortic bulbs. This type of great cardiac vein is commonly observed in chicks (78%
178 [60/78] Lindsay 1967), monotremes (Dowd 1969), and phalangers (marsupials) (Dowd 1974), but rarely
179 in pigs (Alejandro Gómez et al. 2015) and humans (0.3% [1/337], Kawashima et al. 2003). The middle
180 cardiac vein is the largest cardiac vein in birds, and it drains from the apex and posterior ventricular
181 surface, ascends along the interventricular sulcus, and opens into the right atrium. The middle cardiac
182 vein is commonly observed in birds as well as in mammals, suggesting that the middle cardiac vein is
183 conserved across species. The anterior cardiac vein drained the anterior free wall of the right ventricle via
184 the right conal vein and several tributaries of the anterior ventricular wall. These tributaries united into a
185 single canal to open the anterior basal rim of the right auricle. The course and opening of the quail
186 anterior cardiac vein resembled with those in chicks and humans, in which one (most common) to three
187 anterior cardiac veins receive tributaries from the right ventricular free wall, empty the right atrium via
188 the luminal vein (Lindsay 1967; von Ludinghausen 1987; Loukas et al. 2009b).
189 The course of cardiac veins in the mouse heart resembles that in rats, but different from that in

190 humans or quails (Ciszek et al. 2007; Krešáková et al. 2015). In mouse cardiac veins, three major cardiac
191 veins emptying to the coronary sinus have been identified. These include the left cardiac vein (the largest
192 cardiac vein and comparable to the human left marginal vein), caudal vein (middle cardiac vein), and
193 right cardiac vein (right marginal vein). There is no great cardiac vein running in the anterior
194 interventricular sulcus. The remarkable features of the mouse/rat cardiac vein are the conal veins, in
195 which the right conal vein courses on the ventral aspect of the left ventricular outflow tract and opens into
196 the right atrium, and the left conal vein runs behind the pulmonary trunk and connects with the right conal
197 vein, right atrium, or right cranial caval vein. Therefore, the conal veins surrounding the great arteries are
198 similar to the peritruncal endothelial plexus (peritruncal ring) observed in embryonic hearts (Ando et al.
199 2004). It may be suggested that the left conal vein passing behind the great arteries (pulmonary trunk and
200 aortic bulb) is equivalent to the basal segment of the great cardiac vein in avian species.
201
202 **Coronary arteriovenous fistula**
203 In our observations, carbon ink injected into the aorta in E7 to 9 (stage 32 to 37) hearts delineated
204 directly not only the coronary arteries but also the major cardiac veins without apparent staining of the
205 ventricular free wall. This observation suggested direct connections between the coronary arteries and
206 veins at the onset of and immediately after coronary circulation starts. The direct connection between the
207 major coronary arteries and veins was consistent with the observations that the peritruncal endothelial
208 plexus surrounding the outflow tract remodels into the main coronary arteries and cardiac veins

(Vrancken Peeters et al. 1997; Tomanek et al. 2006). The direct connection was not evident from E10 (stage 38-39) onward. Therefore, the capillary beds interposing the arteries and veins may rapidly develop after the coronary circulation starts. Coronary arteriovenous fistula (a type of congenital heart defect), in which the right coronary artery connect the right atrium without a capillary bed (Pe´rez-Pomares et al. 2016), may occur due to the persistence of the direct connection of the coronary artery and cardiac vein.

We described the topographical anatomy of the quail coronary arteries and cardiac veins. The major coronary arteries of the quail heart are the right and left septal arteries, which respectively originate from the right ant and left coronary stems. The cardiac veins are classified into the middle, great, and anterior cardiac veins according to their openings into the right atrium. The course of the quail coronary vessels was basically the same as that in chick heart but was different from mouse and human hearts.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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293

294 **Figure legends**

295 **Figure 1**

296 Right and left coronary arteries. A) Surface branches of the right coronary artery include the conus branch

297 (cb), branches on the right ventricle (rvb), and right circumflex branch (cx). B) Right septal artery (sa).

298 The right ventricular free wall was removed to show the surface of the ventricular septum (right side of

299 the dotted line in B and gray color in B'). C) Peripheral branches of the right septal artery penetrate the

300 ventricular wall at the posterior interventricular sulcus (arrows) and distribute onto the posterior surface

301 of the ventricle. D) Surface branches of the left coronary artery including the interatrial branch (iab),

302 conus branch (cb), and left circumflex branch (cx). E) Left septal artery (sa). The right ventricular free

303 wall was removed to show the surface of the ventricular septum (left side of the dotted line in E and gray

304 color in E'). Peripheries of the left septal artery penetrated the ventricular free wall to distribute onto the

305 left ventricular surface (arrows). A and D, E9.0 (stage 36-37) heart; B, C and E, E12.0 (stage 42); Ao,

306 aorta; cb, conus branch; cx, circumflex branch; iab, interatrial branch; LV, left ventricle; Pt, pulmonary

307 trunk; RA, right ventricle; rvb, branches on the right ventricle; sa, septal artery; Bar, 500 μm.

308

309 **Figure 2**

310 Cardiac veins. A) Middle cardiac vein (mcv). In this sample, the middle cardiac vein receives the left

311 circumflex vein (cx) and small cardiac vein (scv). B) The great cardiac vein consists of the anterior

312 interventricular segment (aivs) and its downstream basal segment (bs). The basal segment runs between

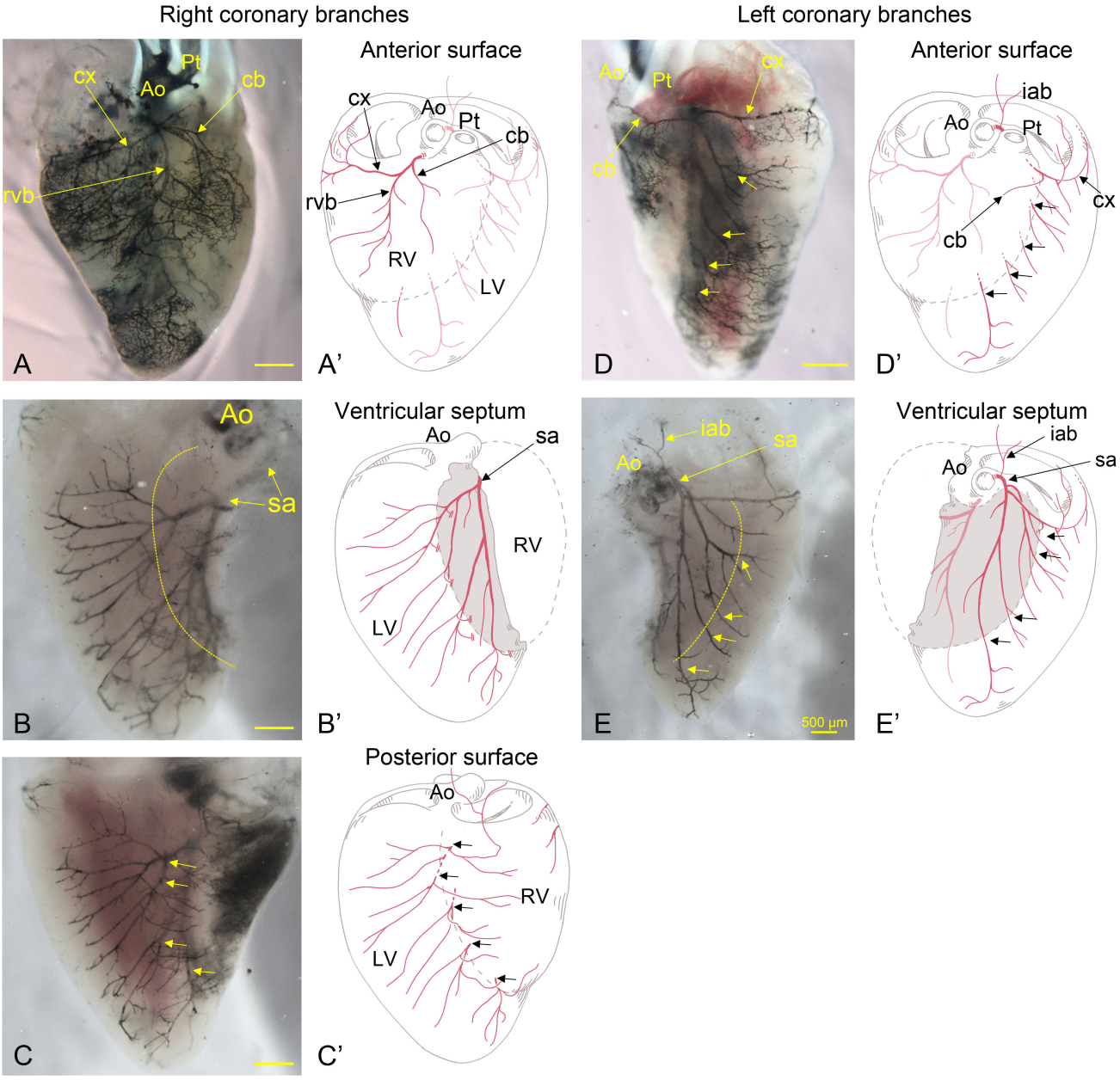
313 the left atrium and great arteries to empty the right atrium behind the aortic bulb (open arrowhead). C)
314 Anterior cardiac vein (acv) drains from the anterior right ventricular wall and empties into the base of the
315 right auricle (open arrowhead). A, E7.25 (stage 32) heart; B, E8.0 (stage 35); C, E7.0 (stage 32); acv,
316 anterior cardiac vein; aivs, anterior interventricular segment of great cardiac vein; Ao, aorta; bs, basal
317 segment of great cardiac vein; cx, left circumflex vein; LV, left ventricle; Pt, pulmonary trunk; RV, right
318 ventricle; scv, small cardiac vein; Bar, 500 μm.
319
320 **Figure 3**
321 Schematic showing the coronary arteries and cardiac veins of the fetal quail heart. A) The major coronary
322 arteries are the right and left septal arteries (rsa and lsa), which respectively originate from the right and
323 left coronary stems. The right septal artery pierces the supraventricular crista and left septal artery
324 infundibulum to enter the ventricular septum (gray color). Peripheries of the right and left septal arteries
325 penetrate the ventricular free wall at the posterior and anterior interventricular sulci, respectively, and
326 distribute over the ventricular surface. B) The cardiac veins consist of three major veins according to their
327 openings into the right atrium, the middle cardiac vein (mcv), great cardiac vein, and anterior cardiac vein
328 (acv). The most characteristic feature of the quail cardiac veins is the course of the great cardiac vein,
329 which ascends along the anterior interventricular sulcus (anterior interventricular segment, aivs) and then
330 courses between the left atrium and great arteries (basal segment, bs) to open into the right atrium. Note
331 that panel A shows the ventricular septum seen form the right ventricle after removing the right

ventricular free wall and panel B shows the cardiac base after removing the atria. acv, anterior cardiac vein; aivs and bs, anterior interventricular segment and basal segment of the great cardiac vein; Ao, aorta; lcx, left circumflex branch; lsa, left septal artery; mcv, middle cardiac vein; MV, mitral valve; Pt, pulmonary trunk; rcx, right circumflex branch; rsa, right septal artery; TV, tricuspid valve.

337 Table 1 Number of hearts examined

E	6	7	8	9	10	11	12	13	14	Total
HH	29-30	32-33	35	36-37	38-39	40	42	42	43	
Artery	4	4	2	11	11	29	5	6	10	82
Vein		4	3	3	2	3	5			20

338 E, embryonic day; HH, Hamburger and Hamilton stage adapted into quail.


Right coronary branches
Left coronary branches
Anterior surface
Anterior surface
cx
Ao
Pt
cb
rvb
RV
LV
A
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Ventricular septum
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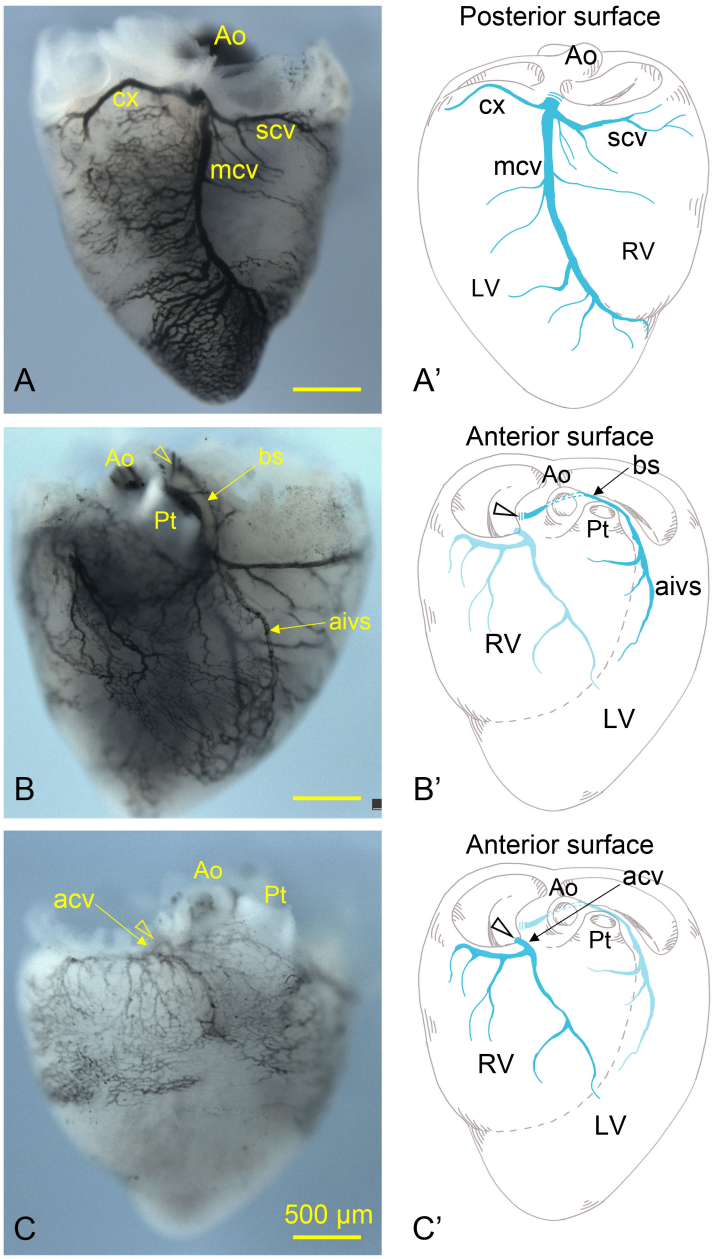
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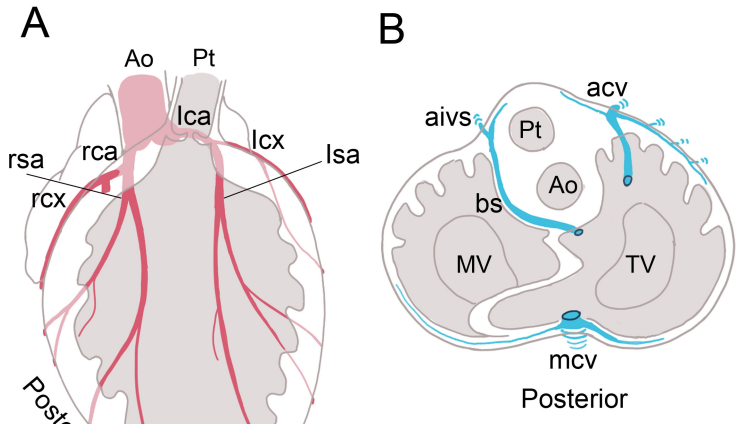
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