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Origin and course of the coronary arteries in normal mice and in iv/iv mice

JOSÉ M. ICARDO AND ELVIRA COLVEE

Department of Anatomy and Cell Biology, University of Cantabria, Santander, Spain

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ABSTRACT

This paper reports on the origin and distribution of the coronary arteries in normal mice and in mice of the iv/iv strain, which show situs inversus and heterotaxia. The coronary arteries were studied by direct observation of the aortic sinuses with the scanning electron microscope, and by examination of vascular corrosion casts. In the normal mouse, the left and right coronaries (LC, RC) arise from the respective Valsalva sinus and course along the ventricular borders to reach the heart apex. Along this course the coronary arteries give off small branches at perpendicular or acute angles to supply the ventricles. The ventricular septum is supplied by the septal artery, which arises as a main branch from the right coronary. Conus arteries arise from the main coronary trunks, from the septal artery and/or directly from the Valsalva sinus. The vascular casts demonstrate the presence of intercoronary anastomoses. The origin of the coronary arteries was found to be abnormal in 84% of the iv/iv mice. These anomalies included double origin, high take-off, slit-like openings and the presence of a single coronary orifice. These anomalies occurred singly or in any combination, and were independent of heart situs. The septal artery originated from RC in most cases of situs solitus but originated predominantly from LC in situs inversus hearts. Except for this anomalous origin no statistical correlation was found between the coronary anomalies and heart situs or a particular mode of heterotaxia. The coronary anomalies observed in the iv/iv mice are similar to those found in human hearts. Most coronary anomalies appear to be due to defective connections between the aortic root and the developing coronaries. iv/iv mice may therefore constitute a good model to study the development of similar anomalies in the human heart.

Key words: Coronary arteries; mouse; heart; iv/iv mouse; vascular corrosion casts.

INTRODUCTION

In the normal heart, the coronary arteries arise from the left and right Valsalva sinus, reach the coronary sulcus and distribute through the heart myocardium following well known patterns (James, 1961; McAlpine, 1975). Coronary artery anomalies have often been described. They appear in $\sim 0.7\%$ of the adult population (Baltaxe & Wixson, 1977; Angelini, 1989) and include anomalous origin, course, or both (Roberts, 1986; Gaither et al. 1991; Roberts & Shirani, 1992; Shirani & Roberts, 1993; Bartorelli et al. 1994). The coronary pattern has been also described in human hearts with situs inversus totalis, where a mirror-image situation is normally found (Ilia et al. 1988; Blankenship & Ramires, 1991; Patti et al. 1999). Coronary anomalies, however, occur when the heart is abnormally located, or in the presence of abnormal venoatrial connections, although the number of cases reported is very small if there are no associated intracardiac malformations (Topaz et al. 1992; Yabe & Tsukahara, 1995; Shanoudy & Russell, 1996; Turchin et al. 2000). The rarity of these situations has precluded the analysis of large samples.

The mouse is a model which has been widely used to study several aspects of cardiovascular embryology, anatomy and physiology. These include the molecular determinants of coronary development (Bellomo et al. 2000; Tevosian et al. 2000), the control of arteriosclerosis (Isobe et al. 2000; Suzuki et al. 2000), the mechanisms of ischemia-reperfusion, and the regulation of infarct size (Scherrer-Crosbie et al. 1999;

Correspondence to Dr J. M. Icardo, Departamento de Anatomía y Biología Celular, Facultad de Medicina, Polígono de Cazoña, s/n, 39011-Santander, Spain. Tel.: +34 942 201924; fax: +34 942 201903; e-mail: icardojm@unican.es

Nossuli et al. 2000). Thus knowledge of murine coronary anatomy is very important and can serve as a reference point in developmental and clinical studies that use the mouse as a model.

Coronary artery patterns have been described in wild mice and in several small rodents (Ahmed et al. 1978; Vicentini et al. 1991; Durán et al. 1992; Sans-Coma et al. 1993). However, we could not find a similar study of the laboratory mouse, although analysis of the mouse coronaries has been approached by magnetic resonance imaging techniques (Burstein, 1991). Furthermore, reports on variations of the coronary vascular pattern in rodents are scarce (Arqué et al. 1986; Durán et al. 1992; Sans-Coma et al. 1993; Fernandez et al. 2000). Knowledge of these variations is equally important for relating functional and clinical studies to specific vascular anomalies.

The iv/iv strain of mice carries a spontaneous mutation characterised by randomisation of ventricular looping with half of the individuals exhibiting left hand ventricular topology (Hummel & Chapman, 1959). In addition, these mice show cardiac, visceral and venous heterotaxia (Hummel & Chapman, 1959; Layton, 1978; Icardo & Sanchez de Vega, 1991; Seo et al. 1992). In the course of previous studies with this mutant strain we observed that some newborns lagged behind their normal littermates, reached about 60% of normal size and weight, and died (or were killed by their mates) near weaning age. Serial sectioning of one of those hearts revealed that the right coronary showed a high take-off, was embedded in the aortic wall, and presented a long intraaortic course. Scanning electron microscope (SEM) examination of another heart showed high take-off for the 2 coronaries. This prompted us to study the anatomy of the coronary arteries in the hope that this mouse strain would be a good model for humans with similar anatomical settings. Thus the purpose of the present study was twofold: (1) to describe the coronary pattern in the normal laboratory mouse, and (2) to investigate the occurrence of coronary variations in the iv/iv mouse. The extracardiac branches, which supply the greater part of the 2 atria in rodents (Halpern, 1957) are not considered here.

MATERIALS AND METHODS

Healthy adult specimens of the iv/iv mutant strain (homozygous, C57BL/6, n = 70) and of the Swiss albino strain (n = 15) mice were used in this study. The animals were anaesthetised with ether and killed by cervical dislocation. Then the chests and abdominal walls were opened and the hearts (including the arch of the aorta) extracted. The relative position of the heart, stomach, gut and portal vein was recorded in each case. Spleen morphology was also recorded.

In 5 specimens (5 Swiss albino, 50 iv/iv), the origin of the aorta was dissected under a binocular microscope to expose the Valsalva sinuses and the origin of the coronary arteries. The samples were then dehydrated in graded acetone, dried by the critical-point method, mounted on aluminium stubs, coated with gold and observed with a Philips SEM 501.

To make vascular corrosion casts, 30 isolated hearts (10 Swiss albino, 20 iv/iv) were perfused with saline to clear the blood, and the arch of the aorta was clamped. Then the left ventricle was hand-injected with a 2-component resin (Mercox, Ladd Research Industries, VT, USA) for up to 4 min (Lametschwandtner et al. 1990). Filling of the main coronary arteries was controlled visually. The relevance of the different injection methods still remains to be discussed, but the presence of cellular imprints (see Fig. 3*a*, inset) is considered to be a good control of cast quality (Lametschwandtner et al. 1990). After the injection, the resin was allowed to cure for 15 min and the injected hearts were macerated in 30% NaOH at 60 °C to eliminate the soft tissues. Digestion of the soft tissues was controlled visually, occurring in $\sim$ 2 h. The resulting vascular casts were then washed thoroughly in distilled water, air-dried, and mounted as above for SEM observation. Some of the vascular casts were photographed with a binocular microscope (Wild Photomakroskop M400) before SEM processing.

Statistical significance of the coronary variations as related to the patterns of heterotaxia studied was analysed by using the Chi-square test for goodness of fit of the null hypothesis of an uniform distribution in each of the variables. Only a value smaller than 0.05 was considered to be significant.

RESULTS

Direct observation of the aortic root revealed that the normal mice showed a single coronary orifice in the left and in the right Valsalva sinus. However, only 16% of the iv/iv mice showed this type of arrangement (Fig. 1*a*). Variations are summarised in Figure 1 and include the presence of 2 coronary orifices in the same Valsalva sinus, a high take-off, a single coronary opening, and the occurrence of a coronary orifice shaped like a sinus and with a slit-like opening. Figure 1 also shows that all these variations may occur in association. For instance, a double coronary opening may be unilateral (Fig. 1*b*, *d*, *h*),

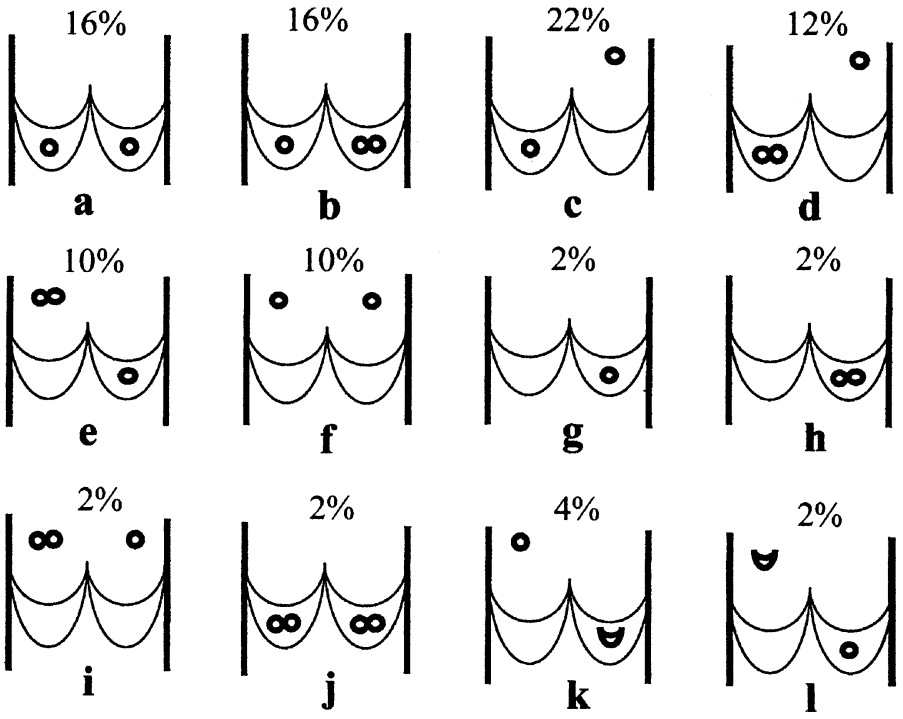

Fig. 1. This diagram summarises the findings on the origin of the coronary arteries in iv/iv mice (n = 50). The aorta has been opened longitudinally and the 2 coronary (facing) sinuses are seen from behind in an open-cut view. The origin of the arteries has been corrected for those hearts with situs inversus. The circles indicate the coronary origin, which can be single or double. A normal origin occurred in only 16% of the cases (*a*). The circle located above the Valsalva sinus indicates a high take-off (*c*–*f*, *i*, *k*–*l*, 62% of the cases). Absence of one coronary was seen in 2 specimens (*g*–*h*, 4% of the total). A coronary orifice with a slit-like opening occurred in 6% of the cases (*k*–*l*). Note that different anomalies may occur in association.

bilateral (Fig. 1*j*), be located within the Valsalva sinus (Fig. 1*b*, *d*, *h*, *j*), or present a high take-off (Fig. 1*e*, *i*). Figures 2 and 3 show several examples of normal and anomalous origin, combining direct observation of the Valsalva sinuses and vascular casts.

Observations on the distribution of the main coronary trunks in the normal mouse indicate that the left coronary runs along the lateral aspect of the left ventricle to reach the heart apex (Fig. 4). Along this course the left coronary may remain as a single trunk or give off up to 4 main branches. From these branches, thinner arteries arise at perpendicular or acute angles to supply the left ventricle. The right coronary divides soon after its origin into 2 main branches. One follows the right aspect of the heart branching off to vascularise the right ventricle. The other main division, the septal artery, is shorter and reaches the ventricular septum. This distribution pattern may change at the ventricular apex. This area of the heart was supplied by the left coronary in most cases (7 of 10, Fig. 4), by the right coronary in one case, and by the 2 arteries in another 2 cases. Crossing of the coronary branches and intercoronary anastomoses (Fig. 4) can also be observed. Small-calibre conus arteries arising from the main coronary trunks (Fig. 4), from the septal artery, and/or directly from the coronary sinuses (Fig. 2*b*), are observed in all cases.

All iv/iv hearts showed either a left hand or a right hand topology, and concordant atrioventricular and ventriculoarterial connections. In all cases, the morphologically left coronary supplied the left ventricle and the morphologically right coronary supplied the right ventricle. However, the origin of the septal artery was highly variable. This artery arose from the morphologically right coronary in 90% of the hearts with situs solitus (1 of 11) (Fig. 5*a*, *b*), while it originated from the morphologically left coronary in more than half of the hearts with situs inversus (5 of 9 cases) (Fig. 5*c*). In addition, the ventricular apex was supplied by the 2 coronaries in one third of the hearts (Fig. 5). When 1 coronary was absent, the remaining one supplied the 2 ventricles (Fig. 5*d*). It should be emphasised that, except for the variable origin of the septal artery, the coronary variations occurred with similar incidence in situs solitus and in situs inversus. In addition, mice with situs solitus or situs inversus totalis showed most often a normal coronary arrangement, while mice with visceral and/or venous heterotaxia showed a higher incidence

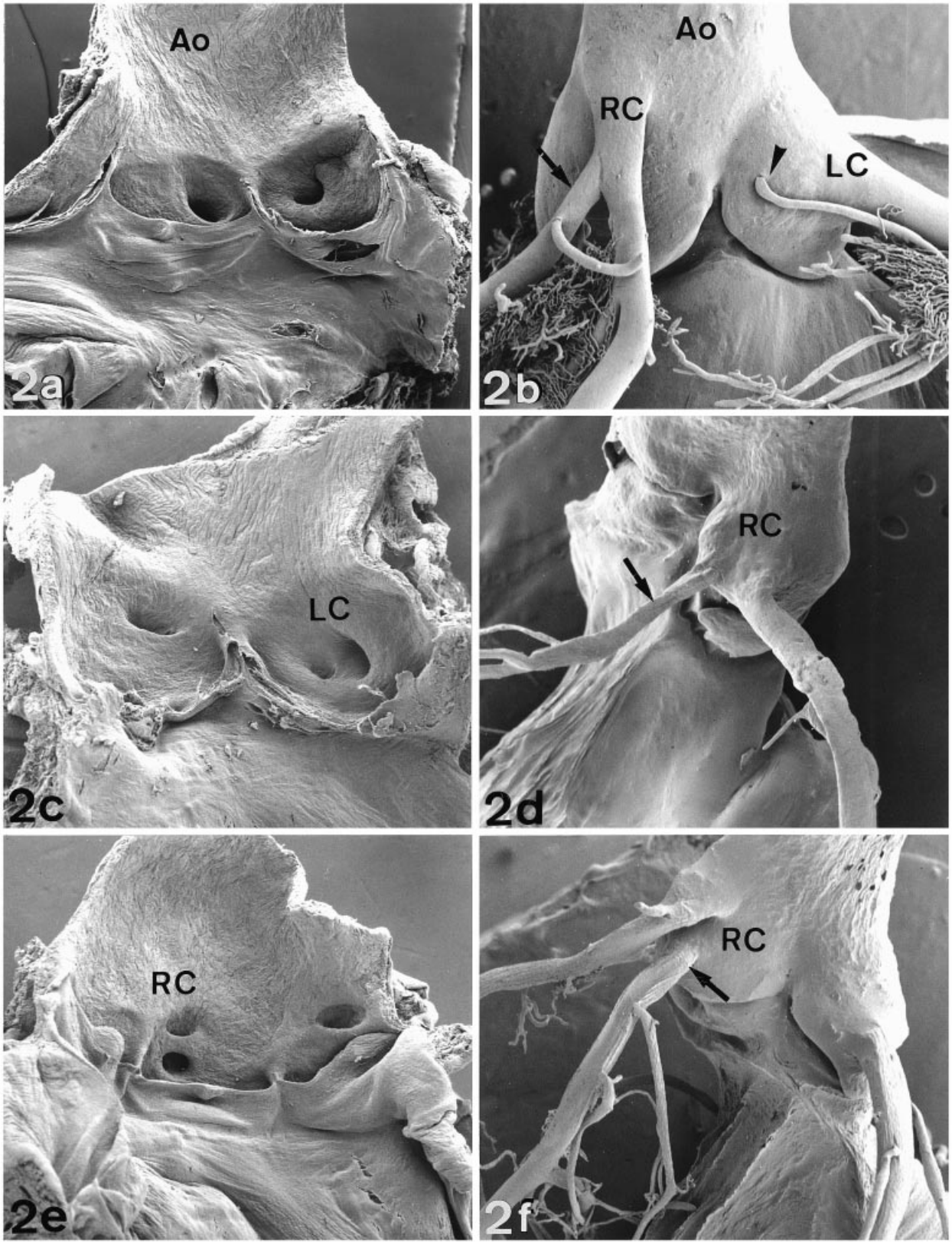

Fig. 2. SEM micrographs showing the origin of the coronary arteries in the normal mouse (*a*) and in iv/iv mice (*b*–*f*). Open-cut views (*a*, *c*, *e*) and vascular corrosion casts (*b*, *d*, *f*). Ao, aorta. LC, morphologically left coronary. RC, morphologically right coronary. (*a*) One coronary orifice arises from each coronary sinus in the normal mouse. (*b*) Situs solitus. The 2 coronaries arise from the corresponding sinus, although RC shows a slightly high origin. RC branches into the main right trunk and the septal artery (arrow). A conus artery (arrowhead) arises independently from the left coronary sinus. (*c*) Situs inversus. LC shows a double origin. The 2 orifices arrange side by side. (*d*) Situs inversus. The septal artery (arrow) arises independently from the right sinus. (*e*) Situs inversus. RC shows a double origin. The 2 orifices are located on top of each other. (*f*) Situs solitus. The origin of RC is double. The 2 arteries arise one on top of each other and are of similar size. Arrow indicates the septal artery. Magnifications, $\times 47$ (*a*, *c*, *e*); $\times 60$ (*b*, *d*); $\times 32$ (*f*).

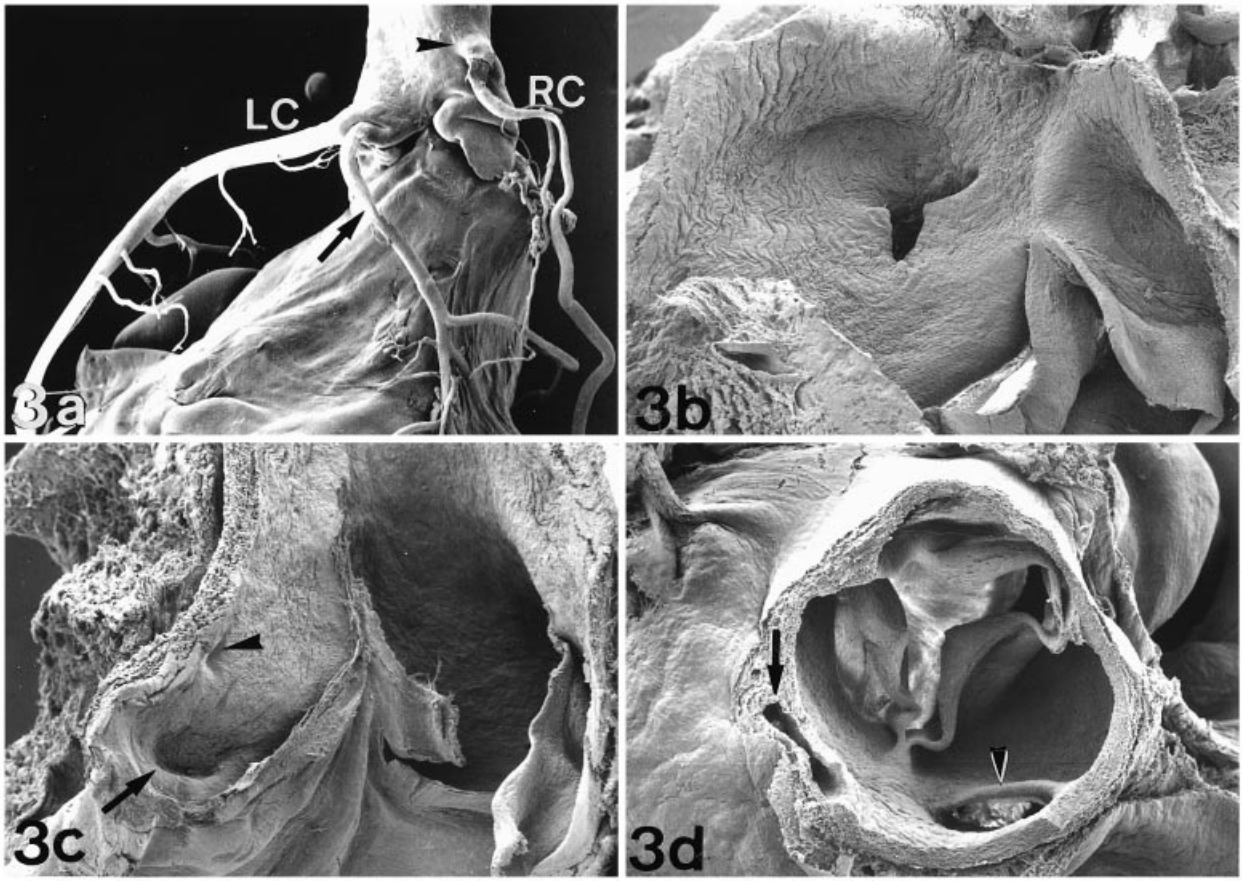

Fig. 3. SEM micrographs showing variations in the origin of the coronary arteries in iv/iv mice. LC, morphologically left coronary. RC, morphologically right coronary. (*a*) Vascular cast. Situs inversus. RC shows a high take-off (arrowhead). The septal artery (arrow) arises from LC. (*b*) Situs inversus. The orifice of origin of LC is sinus-like and shows a slit-like opening. (*c*) Situs inversus. The orifice of origin of RC is absent. A blind depression (arrow) seems to indicate the expected location of the coronary opening. A smaller depression (arrowhead) located in the wall of the Valsalva sinus is also blind. (*d*) Situs solitus. The origin of the aorta is viewed from above. LC has arisen above the left sinus and shows an intraaortic course (arrow). RC (arrowhead) also originates above the insertion of the aortic leaflets. Magnifications, ×22 (*a*); ×90 (*b*, *c*,); ×46 (*d*).

of anomalies. This was especially true in the cases with a single coronary orifice, in which there was always thoracic-abdominal discordance. However, except for the tendency of the septal artery to originate from the morphologically left coronary in situs inversus mice ($P > 0.05$), no statistically significant correlation could be established between specific coronary anomalies and a particular mode of heterotaxia.

DISCUSSION

In the normal mouse, the heart is supplied by 2 coronaries, left and right, which originate from the corresponding Valsalva sinus. In man, these sinuses are named the left and right 'facing' coronary sinuses because they face 2 sinuses of the pulmonary valve (Anderson & Becker, 1992). The same terminology can be applied in the mouse since the spatial relationships between the aortic and pulmonary roots are very similar (see fig. 1 from Icardo et al. 1993). After their origin, the coronary arteries course to the heart apex following the left and right borders, and supply the corresponding ventricle through thinner branches that arise at different angles from the main arterial trunks. In addition, most of the ventricular septum is supplied by the septal artery, which originates as a main division of the right coronary. This vascular pattern coincides with the descriptions previously published for several species of rodents (Ahmed et al. 1978; Durán et al. 1992, 1998). The existence of a septal artery in the mouse and in other rodents may seem striking, but it is common in species having intramyocardial coronary arteries (Durán et al. 1992). In man (James & Burch, 1958) and in other species (Christensen, 1962; Rowlatt, 1981), in which the main coronaries course mostly subepicardially,

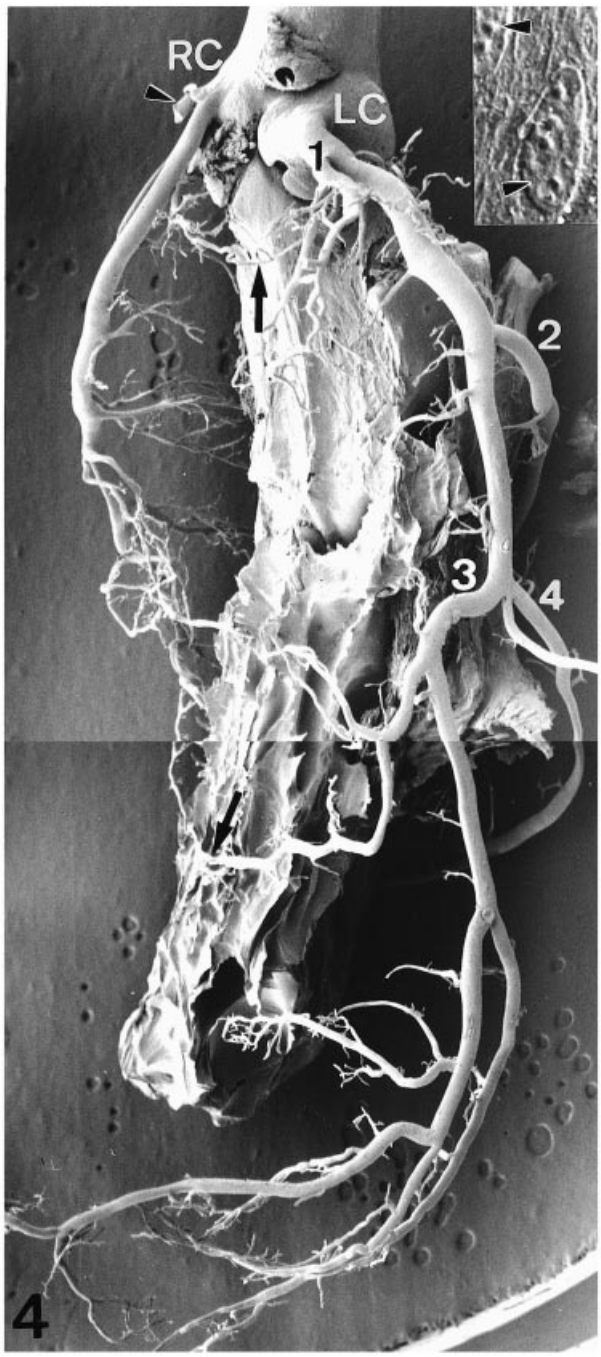

Fig. 4. Vascular corrosion cast from a normal mouse. Frontal view. The left (LC) and right (RC) coronaries arise from the respective coronary sinus. LC descends along the left aspect of the heart, gives off 4 main branches (1–4), and reaches the heart apex. Branches 1 and 3 supply the conus and the anterior part of the heart. Branches 2 and 4 supply the dorsal part of the heart. RC descends along the heart right aspect. The septal artery arises (arrowhead) as a main subdivision of RC, but has been lost in this specimen during manipulation of the cast. Arrows indicate intercoronary anastomoses between conus and ventricular branches. Inset: endothelial cell imprints. Nuclei are indicated by arrowheads. Magnification, ×30; inset, ×1950.

the septal artery is lacking and the ventricular septum is supplied through perforating vessels that originate from the ventricular branches.

Deviations from the normal coronary pattern occur frequently and, in many cases, they can be considered to be normal variants (Angelini, 1989): e.g. conus branches originating independently from the coronary sinuses, variations in the number of branches arising from the main coronary trunks, and the existence of left, right or balanced dominance at the ventricular apex. These variations have been described in other rodents (Sans-Coma et al. 1993; Fernandez et al. 2000), and are comparable to the situations described in humans (Allwork, 1987; Feinstein et al. 1988; Angelini, 1989). The origin of the septal artery deserves further comment. This artery supplies the ventricular septum, which is a basic structure in ventricular dynamics and contains the central conduction system. We have found that this artery originates from the right coronary in normal mice. Our results agree with previous data on rats and wild mice (Durán et al. 1992). However, in the Syrian hamster (Sans-Coma et al. 1993) and in other small rodents (Fernandez et al. 2000), the septal artery originates from the left coronary in most cases. Thus the existence of a predominant left or right septal pattern varies according to species. The right septal pattern seems to be a fixed anatomical arrangement in the mouse.

In animal studies, where a large number of specimens can be analysed, the origin of the coronary arteries has been found to be abnormal in less than 14% of the cases (Sans-Coma et al. 1989; Durán et al. 1992). This rate rose to 34% in an inbred family of Syrian hamsters having bicuspid aortic valve (Fernandez et al. 2000). The latter study cannot be compared with the present report because the coronary anomalies were associated with valve malformations. However, it indicates that, in the presence of an abnormal genetic background affecting the heart, the incidence of coronary anomalies is greatly increased. Accordingly, in this study 84% of the iv/iv mice showed an abnormal coronary origin. The association between the coronary anomalies and other heart anomalies can be ruled out. Heart malformations, even if mild, are not easily compatible with survival and reproduction in mice. Indeed, we have found only one case in which anomalies of the coronary origin (high take-off on both sides) were associated with partial fusion of the left and dorsal aortic valve leaflets. Fusion of the valve leaflets is most unusual in these mice and cannot be considered on statistical grounds. Thus the high incidence of coronary anomalies can be ascribed to the iv background. The predominant origin of the septal artery from the morphologically left coronary in situs

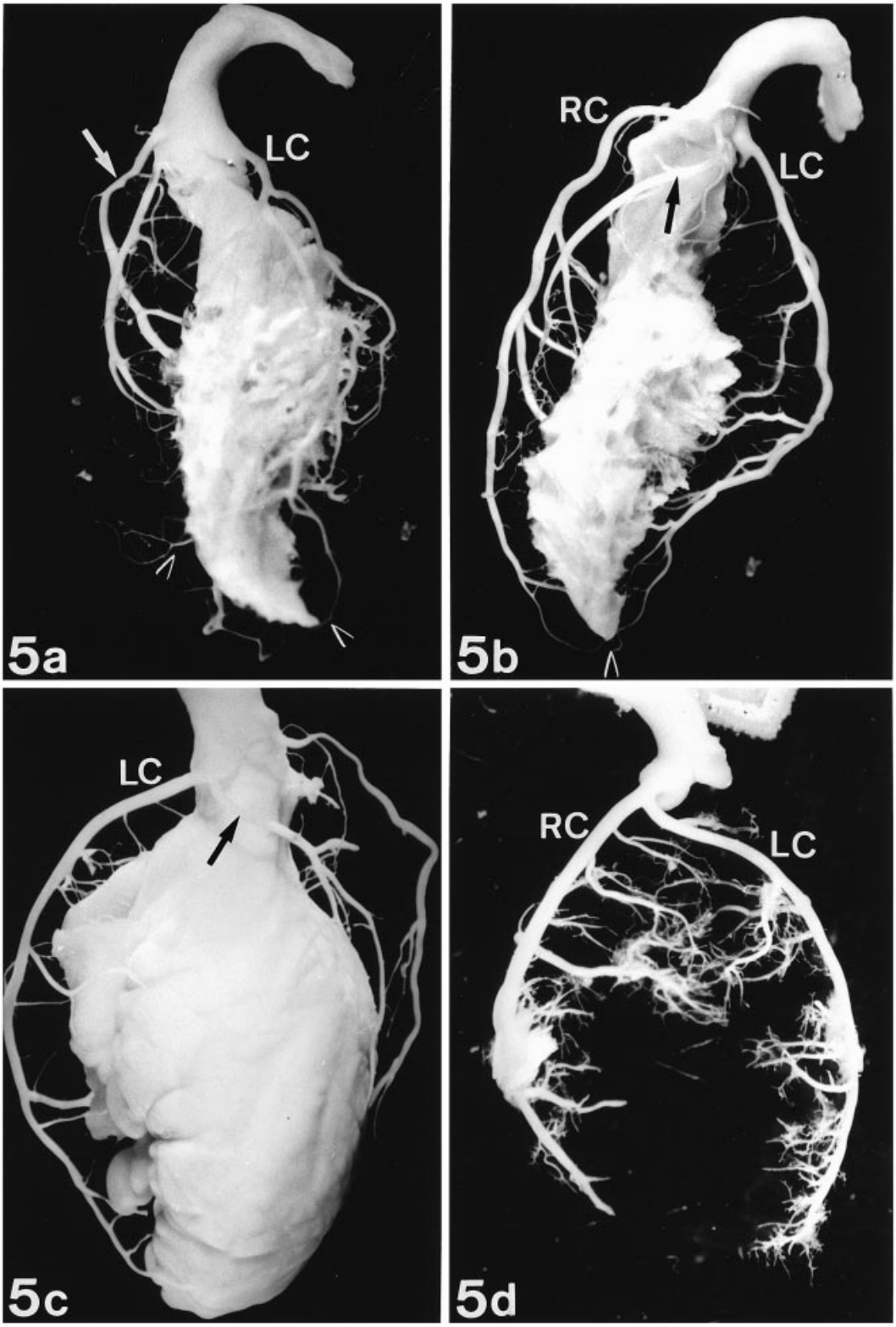

Fig. 5. Light microscope photographs illustrating coronary distribution in vascular corrosion casts of iv/iv mice. Frontal views. (LC), morphologically left coronary. (RC), morphologically right coronary. Arrow in panels *a-c* indicates the septal artery. (*a*) Situs solitus. Normal pattern. LC supplies the heart apex (arrowheads) and the septal artery arises from RC. (*b*) Situs solitus. RC shows an extended domain and reaches the heart apex where it seems to anastomose (arrowhead) with LC. The septal artery also arises from RC. (*c*) Situs inversus. The septal artery arises from LC. The 2 coronaries show sparse branching. (*d*) Situs solitus. A single coronary, arising from the right coronary sinus, bifurcates to supply the 2 ventricles. A distinct septal artery cannot be distinguished. $\times 20$.

inversus hearts appears also to be specific to the iv background. It should be emphasised that, in all cases, the distribution of the coronary trunks matched the ventricular mass arrangement. In all cases there were concordant atrioventricular and ventriculo-arterial connections. Despite this assertion, we cannot discount the possibility that a small number of cases had isomerism of the atrial appendages (Seo et al. 1992). However, identification of isomerism in mice is quite difficult (Icardo & Sanchez de Vega, 1991). Although other authors have reported on the utility of some external and internal characteristics of the atrial appendages to define atrial morphology (Seo et al. 1992; Webb et al. 1996), the incidence of isomerism in adult, healthy iv/iv mice is very small (less than 5%, Seo et al. 1992). While full knowledge of the arrangement of the heart and thoracic and abdominal organs is critical in the setting of heterotaxia in humans (Anderson, 1996; Uemura et al. 1995, 1999), the issue of isomerism appears to be secondary in the context of the present study.

The next question is whether the coronary anomalies found in the iv/iv mouse are comparable to those found in humans. First, the coronary distribution is different in mice and man. Second, coronary arteries are intramyocardial in mice while the main coronaries mostly run subepicardially in man. Thus only the anomalies in the coronary origin may be of any comparative significance. The literature contain many reports on the incidence of coronary anomalies, and similar anomalies to those reported here have often been described (Baltaxe & Wixson, 1977; Roberts, 1986; Yamanaka & Hobbs, 1990; Topaz et al. 1992; Li et al. 2000). The incidence of anomalies is very high in the so-termed heterotaxia syndrome (see, for a recent paper, Uemura et al. 1999), although the reports are very scarce if no heart malformations are associated (Wester et al. 1994; Yip et al. 1994; Yabe & Tsukahara, 1995; Shanoudy & Russell, 1996; Turchin et al. 2000). Despite this, data analyses indicate that the coronary anomalies may have a higher than expected frequency (Turchin et al. 2000). This coincides with the unexpectedly high incidence of anomalies reported here. We have not found any case of coronary arteries arising from the noncoronary (nonfacing) aortic sinus, or from one of the pulmonary sinuses, as has been reported in humans (Yabe & Tsukahara, 1995; Shanoudy & Russell, 1996). The possibility that we have missed such an abnormal origin is unlikely. The morphologically left and right main coronary trunks were present in every case studied, even when a single coronary orifice occurred. If these anomalies occur in the iv/iv mouse they may either be associated with gross heart malformations, or with compromised cardiac performance. Natural selection within the colony would have eliminated the individuals affected and, thus, may have introduced a natural bias in this study.

Finally, it has to be underscored that the coronary anomalies reported here appear to be exclusively related to anomalous connections between the developing coronaries and the aortic root. The establishment of the definitive coronary trunks is a tightly controlled event (Hutchins et al. 1988; Waldo et al. 1990) which occurs by interaction between the capillaries existing around the embryonic bulbus and the aortic root (Bogers et al. 1989; Waldo et al. 1990; Poelmann et al. 1993). Our hypothesis is that, as appears to occur in other areas of the developing heart (Icardo & Sanchez de Vega, 1991; Icardo et al. 1995), the signals which regulate specific morphogenetic events are overridden or lost in the iv/iv mice. The consequence in this particular case is that multiple coronary orifices and/or anomalous points of origin remain in adult life. The iv/iv mouse appears to be a good model to study the development of these anomalies.

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