

Separate Origin of the Main Components of the Left Coronary Artery in Syrian Hamsters (*Mesocricetus auratus*)

A.C. Durán^{1*}, J.M. Arqué², B. Fernández¹, M.C. Fernández¹, T. Fernández-Gallego¹ & V. Sans-Coma¹

1. Department of Animal Biology, Faculty of Science, University of Málaga, 29071 Málaga

2. University Hospital Carlos Haya, 29011 Málaga, Spain

*Corresponding author: Tel.: +34 952 131847; fax: +34 952 131668; EMail: acduran@uma.es

Summary

This study describes a rare congenital coronary artery anomaly in the Syrian hamster; namely, the separate origin of the obtuse marginal and left circumflex arteries which are the main components of the left coronary artery. The hearts of nine affected animals were examined by means of a corrosion-cast technique and histology. The hamsters belonged to a laboratory-inbred family with a high incidence of coronary artery anomalies and bicuspid aortic valve. The aortic valve was tricuspid in three hamsters and bicuspid in the other six hamsters. In all cases, the right coronary artery was normal, whereas the left coronary artery main trunk was absent. The present anomalous coronary artery patterns could be classified into two main entities: (i) ectopic origin of the obtuse marginal artery from the right aortic sinus or from the right coronary artery, with the left circumflex artery arising from the left side of the aortic valve; and (ii) ectopic origin of both the obtuse marginal artery from the right aortic sinus or from the right coronary artery and left circumflex artery from the dorsal aortic sinus. In all cases, the obtuse marginal artery coursed to the right side of the heart through the ventral wall of the right ventricular outflow tract. When the left circumflex artery arose from the dorsal aortic sinus, it formed an acute angle with the aortic wall. This report seems to be the first to describe the separate origin of the main components of the left coronary artery in a non-human mammalian species. In man, the congenital coronary artery and aortic valve defects reported herein may entail the risk of clinical complications. However, none of the affected hamsters showed signs of disease.

Introduction

In the Syrian hamster, the blood supply to the heart takes place through two intramyocardial coronary arteries, right and left, arising from the right and left aortic sinuses respectively. The normal branching pattern of both arteries was described in detail by Sans-Coma et al. (1993). Moreover, a variety of congenital coronary artery anomalies has been reported in the Syrian hamster (see Sans-Coma et al., 1999; Fernández et al., 2000 for reviews). A considerable proportion of such anomalies concerns the anatomical origin of the left coronary artery: abnormal origin from the pulmonary artery (Sans-Coma et al., 2005), and from the right side of the aortic valve (Durán et al., 2006).

The left coronary artery of the Syrian hamster consists of two main components, the left circumflex artery (or branch) and the obtuse marginal artery (or branch). Normally, they arise from a common trunk, called left main coronary artery trunk, which becomes intramyocardial shortly after its origin from the aorta, and bifurcates at the level of the obtuse margin of the heart. The left circumflex artery runs more or less parallel to the left atrioventricular groove, terminating at a short distance of the *crux cordis*; it is equivalent to the left circumflex artery of man. The obtuse marginal artery runs along the obtuse margin down to the apex of the heart, irrigating the ventral wall of the left ventricle. Despite its anatomical location, the vessel is comparable with the left anterior descending coronary artery of man. In this regard, it should be born in mind that the hamster heart has no interventricular grooves and that a coronary arterial vessel running along the ventral interventricular boundary is seldom present. When it exists, it gives off the obtuse marginal artery (Sans-Coma et al., 1993).

The origin of the two main components of the left coronary artery from different aortic valve sinuses is well documented in man (see Roberts, 1987a; Virmani et al., 1989; Petit and Reig, 1993; Angelini et al., 1999 for extensive reviews). This condition was quoted three times in the Syrian hamster (Arqué et al., 1989, 1993; Sans-Coma et al., 1999), but no detailed description of the resulting coronary artery distribution patterns was included in these studies. To the best of our knowledge, the separate origin of the main components of the left coronary artery has not been reported for other non-human mammalian species.

The aims of our study were to: (i) describe these coronary artery anomalous patterns in Syrian hamsters, taking into account the condition of the aortic root and the origin of the septal artery, which, in the hamster, provides for the most part of the blood supply to the interventricular septum; and (ii) compare these patterns with those occurring in man.

Animals, Materials and Methods

Animals. Nine adult hamsters (four male and five female) belonging to a family

subjected to systematic inbreeding were included in this study. The incidence of coronary artery anomalies and bicuspid aortic valve is high in the family [see Fernández et al. (2000) for a description of the family, including housing, reproduction and management of the animals]. The hamsters were handled in accordance with the Spanish Regulations for the Protection of Experimental Animals (Real Decreto 223/ 1988; B.O.E. 18.03.1988). They were killed for examination by overdose inhalation of chloroform or carbondioxide at a concentration of 75%.

Eight of the nine affected hearts were comprised in a database in our laboratory consisting of 1202 internal casts of the heart, great arterial vessels and coronary arteries. The remaining specimen was found in a histological study of the coronary arteries of the Syrian hamster.

Corrosion-cast technique. Hearts were exposed by means of a thoracotomy at the level of the fifth intercostal space. Vinyl resin (Rhodopas® AX85/15; Rhone-Poulenc, Courbevoie, France) in a 20% ketone solution was injected via a cannula placed in the ventral aorta through the apex of the left ventricle. Internal casts of the left ventricle and arterial vessels were obtained by macerating the specimens in a 20% hydrochloric acid bath.

Histological techniques (light microscopy). The heart was fixed in 10% neutral formalin buffered with magnesium carbonate (ratio of fixative volume to tissue volume, 80:1), and embedded in Paraplast (Sigma Chemical Co., Poole, UK). Serial transverse sections (10 μ m) for light microscopy were stained with haematoxylin and eosin, orcein-picrofuchsin or Mallory's trichrome stains.

Nomenclature. The nomenclature used in this study is that of Sans-Coma et al. (1993) for coronary arteries and that of Sans-Coma et al. (1996) for aortic valve morphology.

Results

In three of the nine hamsters, the aortic valve was tricuspid (normal); three aortic sinuses were present, right, left, and dorsal, and three leaflets (or cusps). The other six hamsters possessed a bicuspid aortic valve, showing two aortic sinuses, ventral and dorsal, and two leaflets. In all hamsters, the right coronary artery was normal; it supplied the right side of the heart. The vessel arose from the right aortic sinus when the aortic valve was tricuspid or from the right side of the ventral aortic sinus when the valve was bicuspid.

In one of the three specimens with a tricuspid aortic valve, the obtuse marginal artery arose from the proximal segment of the right coronary artery, and the left circumflex artery from the left aortic sinus (Fig. 1, type a). The septal artery derived from the right coronary artery. In the other two specimens, a very short coronary artery trunk, originating from the right aortic sinus, split into the right coronary, obtuse marginal

and septal arteries. The left circumflex artery arose from the left aortic sinus (Fig. 1, type b and Fig. 2).

In two of the six specimens with a bicuspid aortic valve, the obtuse marginal artery originated from the right coronary artery, and the left circumflex artery from the left side of the ventral aortic sinus (Fig. 1, type c). In one case, the septal artery came from the right coronary artery; in the other case, it originated from the left circumflex artery (Fig. 1, type c: dotted lines). In another specimen, the obtuse marginal artery arose from the right coronary artery, and the left circumflex artery from the dorsal aortic sinus (Fig. 1, type d). The septal artery emerged from the right coronary artery. In a further two specimens, the right coronary, obtuse marginal and septal arteries arose from a very short coronary artery trunk arising from the right side of the ventral aortic sinus. The left circumflex artery originated from the dorsal aortic sinus (Fig. 1; type e). The remaining specimen was that examined by means of histological techniques. Its right coronary, obtuse marginal and septal arteries originated from three separate ostia located in the right side of the ventral aortic sinus, whereas its left circumflex artery arose from the dorsal aortic sinus (Fig. 1, type f, and Fig. 3).

In all hamsters examined, the anomalously originating obtuse marginal artery coursed to the right side of the heart through the ventral wall of the right ventricular outflow tract (Fig. 2). Having reached the obtuse margin, it turned towards the apex of the heart, running along the obtuse margin and giving off perpendicular branches to the ventral aspect of the left ventricle.

The left circumflex artery displayed a normal course when it originated from the left sinus of a tricuspid aortic valve or from the left side of the ventral sinus of a bicuspid aortic valve. The vessel ran almost parallel to the left atrioventricular groove, sending branches to the dorsal wall of the left ventricle. When the left circumflex artery came from the dorsal sinus of a tricuspid or a bicuspid aortic valve, it arose with an acute angle with respect to the aortic wall (Fig. 3).

According to the data concerning the internal casts examined, the incidence of an obtuse marginal artery arising from the right aortic sinus or from the right coronary artery, as isolated cardiac anomaly, was 0.25% (three of 1202 casts) in the inbred family. The incidence of the defect was 0.17% (two of 1202 casts) when it appeared in association with a bicuspid aortic valve. Finally, the incidence amounted to 0.25% (three of 1202 casts) when the defective obtuse marginal artery concurred with a bicuspid aortic valve and a left circumflex artery arising from the dorsal aortic sinus.

Discussion

Anatomy and nomenclature. When a coronary artery arises anomalously from a different-from-normal valve sinus, being its origin and proximal course abnormal, but not its territory of distribution, the name of the vessel should remain unchanged (Angelini et al., 1999). In the Syrian hamster, the obtuse marginal and left circumflex

arteries were described according to their distal vascularization territories, and not by their origin (Sans-Coma et al., 1993). On this basis, the present coronary anomalous patterns can be classified in two main entities, namely: (i) ectopic origin of the obtuse marginal artery from the right aortic sinus or from the right coronary artery, with the left circumflex artery arising from the left side of the aortic valve (types a-c); and (ii) ectopic origin of both the obtuse marginal artery from the right aortic sinus or from the right coronary artery and left circumflex artery from the dorsal aortic sinus (types d-f). In man, the anomalous origin of the left anterior descending artery from the right aortic sinus or from the right coronary artery, in combination with a left circumflex artery arising from the left aortic sinus, has been reported as isolated cardiac defect and in association with other congenital heart diseases (see Petit and Reig, 1993; Angelini et al., 1999 for reviews). However, there is no mention in the literature concerning the concurrence of such a defective left anterior descending artery with a left circumflex artery arising from the posterior (or non-coronary) aortic sinus (dorsal aortic sinus in non-human mammals).

In man, a left anterior descending artery coming from the right aortic sinus or from the right coronary artery can take one of four crossing pathways to reach the left side of the heart (Kimbiris et al., 1978; Roberts, 1987a; Click et al., 1989; Petit and Reig, 1993; Angelini et al., 1999). It may run: (i) behind the tricuspid and mitral valves, at the posterior atrioventricular groove (retrocardiac path); (ii) between the aorta and the pulmonary artery (preaortic or interarterial path); (iii) inside of the upper, anterior interventricular septum (intraseptal path); or (iv) anterior to the pulmonary artery (precardiac or prepulmonic path). In all hamsters examined in this study, the obtuse marginal artery coursed anterior to the right ventricular outflow tract, an arrangement equivalent to that of group (iv).

Incidence and association with other congenital disease. The incidence of obtuse marginal artery from the left aortic sinus of a normal aortic valve or from the right coronary artery as isolated cardiac anomaly was 0.25% in the hamsters examined. In man, the incidence of anomalous origin of the left anterior descending artery from the right aortic sinus or from the right coronary artery as isolated cardiac defect is eight to 25 times lower; it ranges between 0.01% and 0.03% in angiography surveys (Kimbiris et al., 1978; Click et al., 1989; Barriales-Villa et al., 2006). In this regard, it should be emphasized that the frequency of coronary artery anomalies is very high in our Syrian hamster family because of the systematic inbreeding. Probably, therefore, the incidence of the mentioned anomaly will be much lower in the normal hamster population.

In humans, a left anterior descending artery arising from the right aortic sinus or from the right coronary artery very often occurs in the presence of other congenital cardiac anomalies, especially tetralogy of Fallot and transposition of the great arteries (Dabizzi et al., 1980; Neufeld and Schneeweiss, 1983; Greenberg et al., 1989; Virmani et al., 1989). The association with a congenital bicuspid aortic has been

reported only once, namely, in a 20-year-old patient who died suddenly at rest due to incompetence of the anomalous valve (Virmani et al., 1989). The sole non-coronary, congenital cardiac malformation found in the nine hamsters examined in this study was the bicuspid aortic valve. Six (66.7%) specimens possessed such a defective valve. This percentage could be attributed to a random effect, basing on the fact that the frequency of bicuspid aortic valves is very high in our Syrian hamster family. However, the existence of an aetiological factor accounting for the association of the present coronary artery anomalous patterns with the bicuspid condition of the aortic valve cannot be ruled out. This proposal comes from the notion that in the Syrian hamster, the morphogenetic mechanisms involved in the formation of congenital bicuspid aortic valves and anomalies in the origin of the left coronary artery, respectively, are related from the aetiological viewpoint (Fernández et al., 2000).

Pathophysiology. In man, the preaortic pathway of an anomalous left anterior descending artery arising from the right aortic sinus or from the right coronary artery is considered a high-risk anatomic feature, because it has been found to be associated with myocardial ischaemia and even sudden death (Chaitman et al., 1976; Taylor et al., 1992). The other pathways are usually classified as low risk or benign (Coyle and Thomas, 2000). However, several cases have been reported in which the prepulmonic pathway was related to myocardial ischaemia, in the absence of significant atherosclerosis (Russo et al., 1991; Coyle and Thomas, 2000; Ono et al., 2003).

The origin of a coronary artery from the posterior aortic sinus is a rare anomaly in man (see Virmani et al., 1989; Arqué et al., 1993; Petit and Reig, 1993; Angelini et al., 1999 for reviews). It is a benign arrangement, unless it involves an acute, and not a perpendicular origin of the coronary artery trunk, in which case it might predispose the affected patients to increased risk of ostial stenosis and/or enhanced spasticity (Angelini et al., 1999).

In man, the congenital bicuspid aortic valve is the most frequent malformation seen in adults (Roberts, 1970, 1984, 1987b). It may occur as an isolated defect or in association with other congenital heart diseases. It has been repeatedly demonstrated that in the natural history, the bicuspid aortic valve entails the risk of complications such as aortic stenosis by dystrophic calcification, incompetence, and infective endocarditis (Fenoglio et al., 1977; Cheitlin et al., 1978; Roberts, 1987b; Giusti et al., 1991).

The obtuse marginal artery arising from the right aortic sinus or from the right coronary artery was the sole cardiac defect found in three of the nine hamster included in this study. The defect occurred in association with a bicuspid aortic valve in a further two hamsters, and in association with both a bicuspid aortic valve and a left circumflex artery arising from the dorsal aortic sinus in the remaining four. However, none of the nine hamsters showed signs of disease. All were in good general condition when they were killed, following our pre-established research

procedure. This might be explained by the following facts: (i) none of the affected hamsters had been subjected to severe exercise; (ii) the blood supply to the interventricular septum, which involves a considerable part of the conduction system, was ensured by a well-developed septal artery (see also Durán et al., 1992); and (iii) the bicuspid condition of the aortic valve seems to entail no risk of complications in the Syrian hamster under normal conditions (Sans-Coma et al., 2005).

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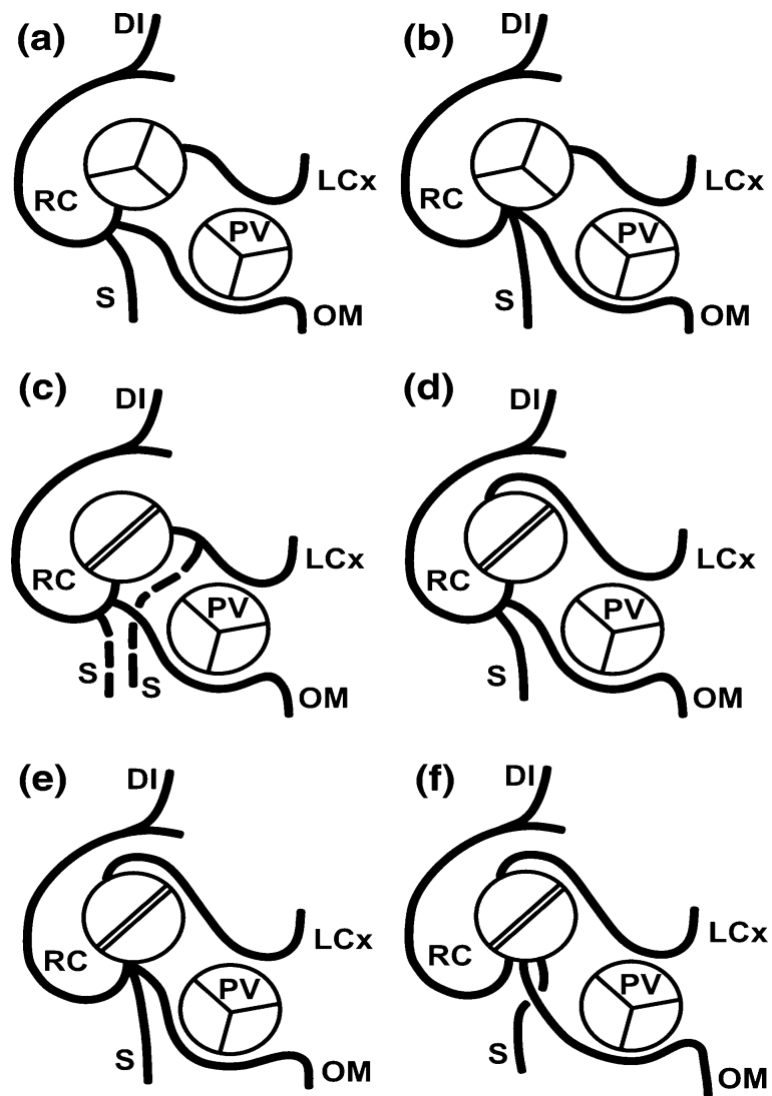


Figure 1. Separate origin of the obtuse marginal artery (OM) and left circumflex artery (LCx) in Syrian hamsters. (a–f): types of branching patterns. In types (a) and (b), the aortic valve was normal (tricuspid). Types (c–f) occurred in association with a bicuspid aortic valve. See text for further explanation. DI, dorsal interventricular branch; PV, pulmonary valve; RC, right coronary artery; S, septal artery.

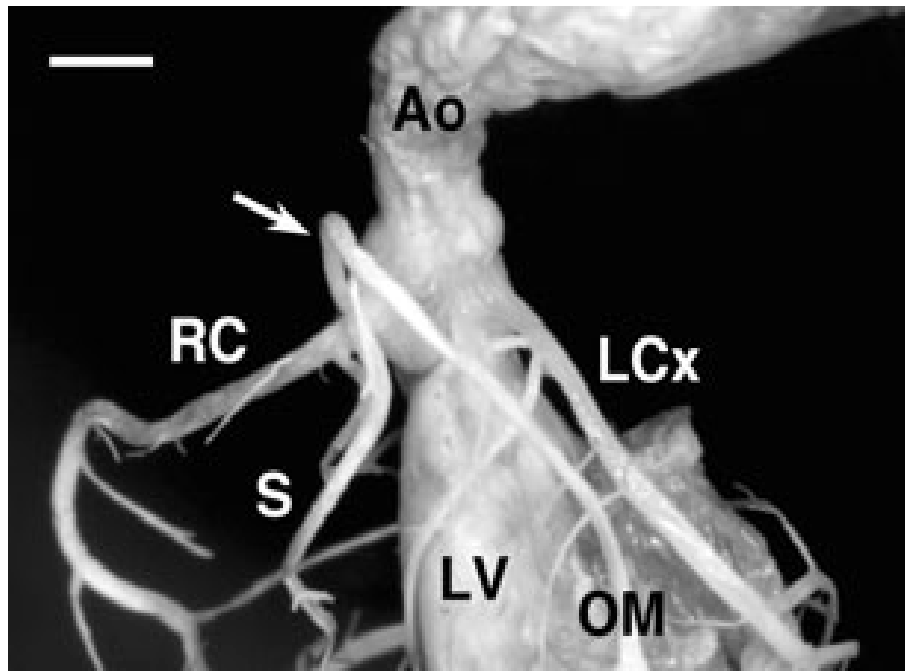


Figure 2. Internal cast of the left ventricle (LV), aorta (Ao) and coronary arteries of an adult Syrian hamster (ventral view). The aortic valve is normal (tricuspid). The right coronary (RC), obtuse marginal (OM) and septal (S) arteries arise from a very short coronary artery trunk coming from the right aortic sinus. Note that the obtuse marginal artery runs anterior to the right ventricular outflow tract (arrow), to reach the left side of the heart. The left circumflex artery (LCx), which originates from the left aortic sinus, shows a normal course (bar, 1 mm).

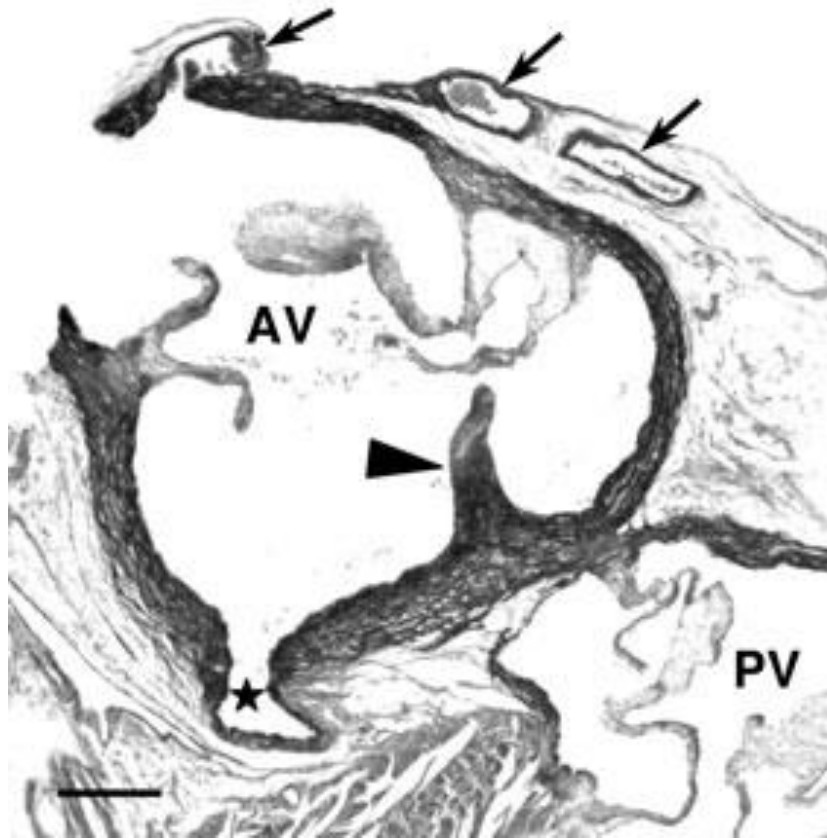


Figure 3. Transverse section of the aortic valve (AV) from an adult Syrian hamster. The aortic valve is bicuspid, with a well-developed raphe (arrowhead) placed in the ventral aortic sinus. The obtuse marginal artery (star) arises from an independent ostium located in the right side of the ventral aortic sinus. The left circumflex artery (arrows) originates from the dorsal aortic sinus, forming an acute angle with the aortic wall. See the text for further explanation. PV, pulmonary valve. Orcein-picrofuchsin (bar, 300 μ m).