Original Article

Solitary coronary ostium in the aorta in Syrian hamsters.
A morphological study of 130 cases

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Received 9 May 2005; received in revised form 27 June 2005; accepted 6 July 2005

Abstract

Background: Solitary coronary ostium in the aorta (SCOA) is a rare anomaly, the pathogenesis of which remains uncertain. The lack of an animal model is one of the reasons why little understanding of this question has been gained. The aim was to examine the coronary distribution patterns associated with SCOA in laboratory inbred Syrian hamsters. Methods: The study concerns 130 cases detected in a database consisting of 1202 internal casts of the heart, great arterial trunks, and coronary arteries. Results: In 21 (16.2%) cases, the solitary ostium was located in the left aortic sinus. In a further 58 (44.6%) cases, it was in the right aortic sinus. In the remaining 51 (39.2%) cases, the ostium was in the right side of the ventral aortic sinus of a bicuspid aortic valve. The distribution patterns were classified according to the location of the solitary ostium and the presence, or absence, and course of the main coronary arterial vessels. Overall, 14 categories were established, 10 of which had their counterpart in man. Conclusions: The findings reported substantiate the use of the present inbred Syrian hamsters for further studying the morphogenesis of the SCOA. The results of a statistical analysis indicate that when a sole coronary ostium becomes established in the aortic root, the development of the resultant anomalous coronary arterial tree tends to happen through preferential pathways. In addition, they indicate that the branching mode of the coronary tree and the condition of the aortic valve are independent traits. © 2005 Elsevier Inc. All rights reserved.

Keywords: Coronary arteries; Coronary ostium; Anomaly; Syrian hamster

1. Introduction

Solitary coronary ostium in the aorta (SCOA), in the absence of other major cardiovascular malformations, is a rare congenital anomaly, with an estimated incidence of 0.04% to 0.24% in the general population and a frequency of 0.2% to 0.66% in angiographic series (see Desmet et al. [1] and Petit and Reig [2], for reviews). SCOA is commonly considered a benign coronary artery abnormality, unless congenital or acquired obstructive disease is present in the proximal single coronary trunk [3–5]. However, some coronary artery distributions associated with SCOA have been related to sudden death because of myocardial ischemia during or just after severe exertion [6–16].

The various coronary patterns that can be assigned to SCOA have been the subject of several attempts at classification to facilitate their anatomical description and clinical significance [1,13,17–21]. However, current knowledge on the pathophysiology of such patterns is scarce. In addition, the morphogenetic deviations leading to the formation of a coronary arterial tree connected to the aorta through a solitary ostium remain unknown.

The lack of an animal model is one of the reasons why little understanding of these questions has been gained. In this regard, a colony of Syrian hamsters subjected to systematic inbreeding in our laboratory may provide an appropriate model. The colony shows a high incidence of both congenital anomalies of the origin and course of...
The most frequent coronary artery abnormality is the right SCOA (RSCOA), also reported as single right coronary artery. The left SCOA (LSCOA), described as single left coronary artery in previous reports, is less frequent.

A classification of the coronary artery distribution patterns associated with SCOA in our Syrian hamsters is presented in Fig. 1. Branching patterns of the coronary arteries in inbred Syrian hamsters. Type N: normal coronary artery pattern. Types 1A1–1B1: left solitary ostium in aorta. Types 2A1–2E1: right solitary ostium in aorta. In Types 1A1, 1A2, and 1B1, the aortic valve was tricuspid. In Types 2A4 and 2B2, the aortic valve was bicuspid. The remaining types were found in association with a tricuspid (normal) or with a bicuspid aortic valve. For further explanation, see the text and Table 1. DI, dorsal interventricular branch; LCx, left circumflex branch; OM, obtuse marginal branch; RC, right coronary artery; S, septal artery; VI, ventral interventricular branch.
suitable, taking into account that they might be used for further investigation into the morphogenesis and functional effects of this defective origin of the coronary arterial tree. The main goals of the present study were (1) to describe the different patterns associated with SCOA, according to the ostial location and both the sequence of origin and course of the main coronary branches, (2) to classify the patterns on the basis of morphological criteria, (3) to establish the...

Fig. 2. Internal casts of the heart, great arterial vessels, and coronary arteries in inbred Syrian hamsters having an SCOA. (A) Type 1A1. The right coronary artery arising from the left main coronary artery crosses through the infundibular septum to the right atrioventricular sulcus. (B) Type 2A1. The left main coronary artery originates from the single coronary artery trunk and crosses the infundibular septum to the left side of the heart. The septal artery arises from the left main coronary artery. The arrow indicates the left circumflex branch. (C) Type 2A2. The left main coronary artery originates from the single coronary artery trunk and runs intramyocardially, coursing ventral to the right ventricular outflow tract to the left side of the heart. The arrow points to the left circumflex branch. (D) Type 2A3. The left main coronary artery surrounds dorsally the aorta. The arrow points to the left aortic sinus. (E) Type 2E1. Single right coronary artery. The left ventricle is irrigated by the right coronary artery and by branches coming from the septal artery (black arrows). The white arrow points to the proximal segment of the right coronary artery. Ao, aorta; DI, dorsal interventricular branch; LCx, left circumflex branch; LV, left ventricle; OM, obtuse marginal branch; PA, pulmonary artery; RA, right atrium; RC, right coronary artery; RV, right ventricle; S, septal artery; VI, ventral interventricular branch.
possible relationships between SCOA patterns and bicuspid aortic valve, and (4) to compare the SCOA distribution patterns in the Syrian hamster with those occurring in man.

2. Methods

2.1. Animals

The animals used belonged to a colony subjected to systematic inbreeding by crossing siblings or, occasionally, the offspring of siblings. The incidence of coronary artery anomalies and congenital bicuspid aortic valves is relatively high in the colony, which originated from an unrelated pair with normal coronary arteries and aortic valves [23,24]. In the family, 39 inbred generations with more than 3400 animals were produced. The arrangement of the coronary arteries and the condition of the aortic valve were assessed by means of a corrosion-cast technique in 1202 specimens. The resulting internal casts of the heart, great arterial trunks, and coronary arteries constituted the database searched in the present study for the diagnosis of SCOA. The criteria used to identify the specimens with SCOA were (1) the presence of a sole coronary artery trunk arising from the aortic root, and 2) the absence of any coronary artery vessel originating from the pulmonary artery.

The animals were handled in accordance with the Spanish Regulations for the Protection of Experimental Animals (Real Decreto 223/1988). They were housed in polypropylene cages in a room in which both the temperature and the photoperiod were controlled. Commercial mouse food (A.04 Panlab, Barcelona, Spain) and water were given ad libitum from the time of weaning. There was no known exposure of the animals to teratogenic agents. The hamsters were killed by overdosing with chloroform or with carbon dioxide at a concentration of 75% delivered into a chamber. In all cases, the heart was exposed by means of a thoracotomy at the level of the fifth intercostal space.

2.2. Techniques

The distribution of the coronary arteries was examined by means of a corrosion-cast technique [27]. Vinyl resin (Rhodopas AX 85/15) in a 20% ketone solution was injected via a cannula placed in the ventral aorta through the apex of the left ventricle. In some cases, the right ventricle and the pulmonary artery were also injected. Internal casts of the ventricles and arterial vessels were obtained by macerating the specimens in a 20% hydrochloric acid bath.

2.3. Statistical methods

The x² test was used to seek for (1) any significant difference between the incidences of the different coronary artery patterns associated with SCOA and (2) any significant association between such anomalous patterns and the condition of the aortic valve. A probability of .05 or less was required as evidence for a significant difference.

2.4. Nomenclature

For a clear presentation of our observations concerning the SCOA in the Syrian hamster and to prevent potential, terminological confusion, we will briefly describe the main features of the normal coronary artery pattern of this rodent species. The nomenclature used is that proposed by Sans-Coma et al. [27].

The hamster heart has no interventricular grooves, and both coronary arteries, right and left, become intramyocardial shortly after they originate from the aorta. The right coronary artery (Fig. 1, N), which supplies the right side of the heart, runs parallel to the right atrioventricular sulcus, reaching usually the dorsal interventricular boundary. After surpassing the acute margin of the heart, the vessel gives off a branch that crosses the right ventricle dorsal wall more or less obliquely. Thereafter, this branch turns towards the apex of the heart as a dorsal interventricular branch. The left coronary artery (Fig. 1, N), which irrigates the left side of the heart, divides into the left circumflex branch and the obtuse marginal branch. The interventricular septum is supplied by a well-developed septal artery. In most cases (70%), the septal artery arises from the left coronary artery. In other cases (26%), it originates from the right coronary artery. Sometimes (4%), however, it originates from a separate ostium in the aorta.

3. Results

Overall, 130 (64 males, 66 females) of the 1202 hamsters displayed an SCOA. All of them were sacrificed according to our preestablished research protocol.

In 21 (16.2%) of the 130 specimens, the aortic valve was tricuspid (normal) and a solitary coronary ostium was placed in the left aortic sinus. A further 58 (44.6%) animals, also displaying a tricuspid aortic valve, had a sole coronary ostium situated in the right aortic sinus. In the remaining 51 (39.2%) hamsters, the aortic valve was bicuspid. In all of these valves, there were two aortic sinuses, a dorsal and a ventral, and the solitary coronary ostium was placed in the right side of the ventral sinus. In this study, no statistically significant differences related to sex were observed with regard to both the coronary artery distribution patterns and aortic valve morphology. Therefore, male and female data were pooled.

3.1. Left SCOA (LSCOA)

In all specimens (n=21) with LSCOA, the left main coronary artery bifurcated into the left circumflex branch and obtuse marginal branch. In 14 specimens, a right
In the other seven specimens, the right coronary artery was absent (Pattern 1B: single left coronary artery). The right ventricle was irrigated by branches arising from the septal artery, left circumflex branch, and obtuse marginal branch, as well as from a ventral intraventricular branch that originated from the left main coronary artery (Type 1B1; Fig. 1).

3.2. Right SCOA (RSCOA)

The following descriptions concern the coronary artery distribution patterns associated with a solitary coronary ostium situated either in the right aortic sinus of a normal aortic valve or in the right side of the ventral aortic sinus of a bicuspid aortic valve. In all cases \(n=109\), a single coronary artery trunk arose from the solitary ostium. This trunk gave off a normally branching right coronary artery.

In 50 specimens, a more or less developed left main coronary artery arose from the single coronary trunk. In 48 of these cases, the left main coronary artery ran to the left side of the heart, where it divided into left circumflex branch and obtuse marginal branch (Pattern 2A). The left main coronary artery crossed the infundibular septum in 34 of these 48 cases (Type 2A1; Fig. 1; 2B), whereas it coursed ventral to the right ventricular outflow tract, within the ventricular wall, in another 12 (Type 2A2; Fig. 1; Fig. 2C) and surrounded the aorta dorsally in the remaining two (Type 2A3; Fig. 1; Fig. 2D). In the other two specimens, the left main coronary artery was very short; it bifurcated into the left circumflex branch and obtuse marginal branch, which ran through the infundibular septum to reach the left side of the heart (Type 2A4; Fig. 1).

In 13 specimens, there was no left main coronary artery; the left circumflex branch and the obtuse marginal branch originated independently from each other from the right coronary artery (Pattern 2B). In 10 of these cases, the left circumflex branch ran to the left through the infundibular septum, while the obtuse marginal branch coursed to the left through the ventral wall of the right ventricle (Type 2B1; Fig. 1). In another case, the obtuse marginal branch ran to the left through the infundibular septum, and the left circumflex branch passed ventral to the right ventricle (Type 2B2; Fig. 1). In the remaining two cases, the left circumflex branch coursed to the left dorsal to the aorta.

#### Table 1

<table>
<thead>
<tr>
<th>Solitary coronary ostium in aorta in Syrian hamsters</th>
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<tbody>
<tr>
<td>1. Solitary ostium in the left aortic sinus (LSCOA)</td>
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<tr>
<td>Pattern 1A. Associated with an aberrant coursing RC that originates from the LMC and courses to the right AVS</td>
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<tr>
<td>Type 1A2. Ventral to the RV outflow tract, within the ventricular wall (SR: IB1)</td>
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<tr>
<td>Pattern 1B. Unassociated with an aberrant coursing RC</td>
</tr>
<tr>
<td>Type 1B1. Single left coronary artery (SR: IA)</td>
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<tr>
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<tr>
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<tr>
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<tr>
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Equivalencies in man are given in parentheses. They correspond to the categories described by Shirani and Roberts [20].

| coronary artery arose from the left main coronary artery and ran toward the right atrioventricular sulcus (Pattern 1A). The right coronary artery crossed the infundibular septum in 13 cases (Type 1A1 ; Fig. 1; Fig. 2A). In the remaining case, it ran ventral to the right ventricular outflow tract within the ventricular wall (Type 1A2; Fig. 1). |

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**Table 2**

<table>
<thead>
<tr>
<th>Coronary artery distribution types of RSCOA, and results of the ( \chi^2 ) contingency test</th>
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<tbody>
<tr>
<td>2A1</td>
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<td>O</td>
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<td>E</td>
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<tr>
<td>( \chi^2 )</td>
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E=expected values; O=observed values; tn=total number of specimens. See Table 1 and text for the definitions of the distribution Types 2A1 to 2E1.

* \( P<.05 \).  
** \( P<.01 \).  
*** \( P<.001 \).
while the obtuse marginal branch coursed ventral to the right ventricle (Type 2B3; Fig. 1).

In 34 specimens, the left circumflex branch was absent (Pattern 2C). The right coronary artery widely supplied the dorsal, interventricular boundary, supplying the territory that is usually irrigated by the left circumflex branch. The obtuse marginal branch, which arose from the right coronary artery, coursed intramyocardially behind the pulmonary artery in 21 cases (Type 2C1; Fig. 1). In the remaining 13 cases, it ran ventral to the right ventricle (Type 2C2; Fig. 1).

In two specimens, there was no obtuse marginal branch (Pattern 2D). The left circumflex branch arose from the right coronary artery and coursed to the left side of the heart dorsal to the aorta. Most of the left ventricle was supplied by branches coming from the septal artery (Type 2D1; Fig. 1).

Finally, in 10 specimens, there was no component of the left coronary artery (Pattern 2E: single right coronary artery). The left ventricle was supplied by the right coronary artery, which surpassed the dorsal interventricular limit, as well as by numerous branches of the septal artery (Type 2E1; Fig. 1; Fig. 2E).

All these observations are summarized in Table 1.

### 3.3. Statistical analysis

To determine if the present data substantiate any significant difference between the incidences of the 11 coronary artery distribution types associated with a RSCOA, a $\chi^2$ contingency test was performed under the null hypothesis that the values obtained were at random. The results of the test are given in Table 2. The computed value of the $\chi^2$ statistic is 105.74, with 10 degrees of freedom. Therefore, the null hypothesis is rejected at $P<.001$. As also shown in Table 2, the major departure from homogeneity is due to the relatively large fraction of specimens displaying the coronary artery Types 2A1 or 2C1.

Another $\chi^2$ contingency test sought for any association between the coronary artery distribution patterns (2A–E) associated with an RSCOA and the condition (tricuspid vs. bicuspid) of the aortic valve, under the null hypothesis that they are independent events. Table 3 shows the results of the test. The computed value of the $\chi^2$ statistic is 2.056, with 4 degrees of freedom. Therefore, the null hypothesis is accepted at $P>.70$.

### 4. Discussion

The arrangement of the coronary arteries in the Syrian hamster diverges from that in man in two main aspects: (1) the coronary arteries of the hamster have an intramyocardial, and not a subepicardial, course, and (2) the interventricular septum of the hamster is mainly supplied by a well-developed septal artery, instead of by perforating branches derived from arteries running along the interventricular sulci of the heart (see Von Lüdinghausen et al. [29] for a review). On the other hand, both coronary artery arrangements share the following basic features: (1) the existence of a right coronary artery that courses in the right atrioventricular sulcus, provides branches to the free wall of the right ventricle, surpasses the acute margin of the heart, usually gives off the dorsal interventricular branch (equivalent to the posterior descending branch of man), and reaches the crux cordis, sometimes extending towards the left ventricle, and (2) the presence of a left coronary artery composed of two elementary units, namely, the left circumflex branch in the Syrian hamster, which corresponds to the left circumflex artery in man, and the obtuse marginal branch in the Syrian hamster, which is equivalent to the left anterior descending artery in man. It should be noted here that a true ventral interventricular branch is usually lacking in the Syrian hamster. When such a vessel exists, it seldom reaches the apex of the heart [27].

The present report proposes a classification of the coronary artery distribution patterns recorded in the Syrian hamster in association with an SCOa (Table 1). The classification is based on the location of the solitary ostium, taking into account the condition of the aortic root, and the presence, or absence, and course of the main coronary arterial trunks and branches. These criteria do not substantially differ from those used by Shirani and Roberts [20] to establish a classification of SCOa in man, except for the fact that, in our hamsters, a considerable proportion of SCOAs occurred in association with a bicuspid aortic valve. Nonetheless, a comparison between both classifications can be done without major difficulties.

In both the Syrian hamster and man, two main groups of SCOa can be recognized, namely, LSCOa, characterized by the presence of a solitary coronary ostium placed in the left aortic sinus, and RSCOa, which comprises the cases in which the solitary ostium is located in the right aortic sinus, or, in the case of Syrian hamster, in the right side of the ventral aortic sinus of a bicuspid aortic valve. Shirani and Roberts [20] refer to a potential third group characterized by the existence of a solitary ostium located in the posterior aortic sinus, although they state that there is no reported example of this anomaly in humans.
In man, the estimated frequency of RSCOA (51%) is somewhat higher than that of LSCOA (49%; [2]). In the present hamsters, this difference is much higher (84% of RSCOA vs. 16% of LSCOA), a fact that we are unable to explain. However, it should be emphasized that the percentages of anomalous coronary artery patterns reported herein correspond to a specific inbred Syrian hamster colony and not to the whole species.

As given in Table 1, all types of LSCOA (1A1, 1A2, and 1B1) observed in the Syrian hamster have their counterpart in man. This is also the case for Types 2A1–2A3, 2B3, 2C1, 2C2, and 2E1 of RSCOA detected in the hamster. In contrast, Types 2A4, 2B1, and 2B2 have no matching part in man. In these types, both the left circumflex branch and obtuse marginal branch run through the infundibular septum to reach the left side of the heart. Finally, Type 2D1 has no counterpart in man. In this case, the obtuse marginal branch is lacking, and most part of the left ventricle is supplied by branches coming from the septal artery. Despite these minor differences, we believe that the present findings substantiate the use of Syrian hamsters for further studying the morphogenesis of the SCOA.

In man, the course of a major coronary artery vessel in between the aorta and the pulmonary artery is considered to be at risk of myocardial ischemia and even sudden death during or just after strenuous exercise [6,7,11,15]. The clinical relevance of this coronary artery arrangement in the Syrian hamster (Types 1A1, 2A1, and 2C1) remains uncertain because none of the affected animals had been subjected to severe exercise. All of them were in good general condition when they were sacrificed.

The results of the statistical analysis indicate that the occurrence of the coronary distribution types associated with RSCOA in the present hamsters is not random. Types 2A1 and 2C1 are significantly more frequent than any other type. Type 2A1 is characterized by the presence of a left main coronary artery that crosses the infundibular septum to reach the left side of the heart, where it divides into left circumflex branch and obtuse marginal branch. Type 2C1 diverges from this coronary arrangement in that there is no left circumflex branch; the territory usually supplied by this vessel is irrigated by a long branch proceeding from the right coronary artery.

The number of cases of LSCOA reported herein was too small to apply statistical analysis. However, the data obtained indicate that (1) Pattern 1B, which corresponds to the concept of single left coronary artery, is less frequent than Pattern 1A, characterized by the occurrence of an anomalous coursing right coronary artery, and (2) within Pattern 1A, the incidence of Type 1A1, where the right coronary artery crosses the infundibular septum, is notably higher than that of Type 1A2, where the right coronary artery courses anterior to the right ventricle.

These findings suggest that when a sole coronary ostium becomes established in the aortic root, the development of the resultant anomalous coronary arterial tree tends to happen through preferential pathways.

Previous work showed that in the Syrian hamster, the RSCOA and the anomalous origin of the left coronary artery, either from the pulmonary artery or from the dorsal aortic sinus, are associated with the bicuspid condition of the aortic valve [22–24]. In contrast, the LSCOA has been recorded only in association with a tricuspid aortic valve aortic valve (see Sans-Coma et al. [26]).

It has been proposed that the relationship between the bicuspid aortic valve and the abovementioned anomalies in the origin of the coronary arteries may have a morphogenetic basis [24] because they develop during embryonic life. After the division of the embryonic cardiac outflow tract, the right and left valve primordia normally grow as two independent mesenchymal cushions (tricuspid aortic valves). Sometimes, however, a single ventral cushion forms (bicuspid aortic valves) as a result of the fusion of the right and left cushions [30]. The coronary artery stems develop from a capillary plexus that covers the embryonic heart and specifically penetrates the developing aortic sinuses. This process is known as coronary ingrowth (see Bogers et al. [31], Bernanke and Velkey [32], and Fernández [33,34] for reviews). Failure of this connection leads to anomalies in the origin of the coronary arteries. We already hypothesized that anomalous behaviour of the neural crest cells that populate the embryonic cardiac outflow tract might account for the formation of both bicuspid aortic valves and anomalies in the origin of the coronary arteries, thereby resulting in a strong association of these congenital defects in our inbred colony of Syrian hamsters [24]. Several independent lines of evidence support this view [35–38].

The maturation of the coronary capillary plexus into the final coronary artery pattern is based on a differentiation process named arterialization (see Fernández [33,34] and Carmeliet [39] for reviews). Upon connection to the aorta, some capillary vessels of the coronary plexus acquire a layer of vascular smooth muscle cells that stabilizes the vessels, avoiding their regression and forming the main coronary artery stems. The arterialization progresses proximal-to-distally, from the coronary ostia to the apex of the heart, forming the main coronary artery trunks and the small coronary arterioles later. Most probably, deviations in the arterialization process may lead to the anomalous coronary artery patterns observed in the Syrian hamsters. As mentioned above, the strong association between anomalies of the aortic valve and anomalies in the origin of the coronary arteries suggest that they result from a single developmental diathesis, in which the neural crest plays a primary role. In contrast, the results of the present statistical analysis indicate that the bicuspid condition of the aortic valve and the anomalous coronary artery distribution patterns are independent traits. This suggests that they have different morphogenetic origin. In this regard, it should be underscored that the coronary arterialization is somehow induced by the differentiation of precursors of the cardiac
parasympathetic ganglia [36, 37]. Thus, it would be worthwhile to further study the topographic distribution of the parasympathetic nerve system in hamsters having anomalous coronary artery distribution patterns.

Acknowledgments

This study was supported by Grant BOS2002-03333 from the D.G.E.S. (Ministerio de Ciencia y Tecnologia, Spain). Teresa Fernández-Gallego is the recipient of a fellowship from the Fundación Hospital Universitario Carlos Haya, Málaga, Spain. The authors thank L. Vida, Málaga, for his technical assistance.

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