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Coronary artery anomalies and aortic valve morphology in the Syrian hamster

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SUMMARY

In the Syrian hamster, anomalies in the origin of the left coronary artery are significantly associated with the bicuspid condition of the aortic valve. In this species, bicuspid aortic valves are expressions of a trait, the variation of which takes the form of a phenotypic continuum, ranging from a tricuspid aortic valve with no commissural fusion to a bicuspid aortic valve with the aortic sinuses located in ventrodorsal orientation and devoid of any raphe. The intermediate stages of the continuum are represented by tricuspid aortic valves with a more or less extensive fusion of the ventral commissure and bicuspid aortic valves with a more or less developed raphe located in the ventral aortic sinus. The present study was designed to decide whether there is a gap between tricuspid and bicuspid aortic valves regarding the incidence of coronary artery anomalies, or whether this incidence varies according to the different tricuspid and bicuspid morphotypes of the continuum. The study was carried out in Syrian hamsters belonging to a single inbred family with a high incidence of tricuspid aortic valves with fusion of the ventral commissure, bicuspid aortic valves, and anomalies in the origin of the left coronary artery, i.e. single right coronary artery ostium in aorta, anomalous origin of the left coronary artery from the pulmonary artery, and anomalous origin of the left coronary artery from the dorsal aortic sinus. The specimens were examined by means of a stereomicroscope and, in several cases, scanning electron microscopy was also used. The relationships between anomalous coronary artery patterns and aortic valve morphologies were tested using a logistic regression model. The results obtained indicate that there is no discontinuity between tricuspid and bicuspid aortic valves regarding the incidence of coronary artery anomalies. The probability of occurrence of anomalous coronary artery patterns increases continuously according to the deviation degree of the aortic valve from its normal (tricuspid] design. The present findings suggest that in the Syrian hamster, the morphogenetic mechanisms involved in the formation of congenital anomalous aortic valves and anomalies in the origin of the left coronary artery, respectively, are strongly related from an aetiological viewpoint.

Keywords: Aortic valve; bicuspid aortic valve; coronary arteries; anomalies; heart; Syrian hamster

In the Syrian hamster (*Mesocricetus auratus*), the aortic valve is usually tricuspid, it has three aortic sinuses, right, left, and dorsal, three leaflets (cusps), and three fibrous interleaflet triangles of similar size in the subaortic outflow tract (Sans-Coma et al.1992). The interleaflet triangles are located in the right-dorsal, left-dorsal, and ventral positions, respectively. Two coronary arteries, the right and left, arise from the right and left aortic sinuses, respectively (Sans-Coma et al. 1993a). Both vessels become intramyocardial shortly after their origin from the aorta.

The occurrence of congenital bicuspid aortic valves (BAVs) in the Syrian hamster has been reported (Sans-Coma et al. 1992, 1993b, 1996). These defective valves are characterized by the existence of two aortic sinuses, a ventral and a dorsal, two leaflets, and two interleaflet triangles located one in the right or right-dorsal position and the other in the left or left-dorsal position.

In the Syrian hamster, BAVs are significantly associated with anomalies in the origin of the coronary arteries, i.e. single right coronary artery ostium in aorta (Sans- Coma et al. 1991), anomalous origin of the left coronary artery from the pulmonary artery (Sans-Coma et al. 1991, Cardo et al. 1994), and anomalous origin of the left coronary artery from the dorsal aortic sinus (Cardo et al. 1995).

Currently, the relationships between anomalous coronary artery patterns and aortic valve morphology in the Syrian hamster have been examined by considering two discrete classes of aortic valve conditions, namely, the tricuspid condition as opposed to the bicuspid condition. However, recent work (Sans-Coma et al. 1996) has shown that, at least in the hamster, BAVs are expressions of a trait, the variation of which takes the form of a phenotypic continuum, ranging from a tricuspid aortic valve (TAV) with no commissural fusion to a BAV devoid of any raphe. The intermediate stages of the continuum are represented by TAVs with a more or less extensive fusion of the ventral commissure and BAVs with a more or less developed raphe located in the ventral aortic sinus.

The present work was designed to decide whether there is a gap between TAVs and BAVs regarding the incidence of coronary artery anomalies, or whether this incidence varies according to the different tricuspid and bicuspid morphotypes of the aortic valve continuous spectrum. The study was carried out in Syrian hamsters belonging to a single inbred family with a high incidence of both aortic valve and coronary artery anomalies.

MATERIALS AND METHODS

Animals

The sample studied consisted of 968 (476 male, 492 female) Syrian hamsters, Mesocricetus auratus, aged 1-816 days; their weights ranged between 2.1 and 94.0 g. They belonged to a single family subjected to systematic inbreeding by crossing siblings or, occasionally, the offspring of siblings. As reported elsewhere (Sans-Coma et al. 1993b, 1996), the incidence of anomalous aortic valves and coronary arteries is relatively high in this family, which originated from an unrelated pair with tricuspid aortic valves and normal coronary arteries. In the family, 32 inbred generations with more than 1750 animals were produced. The estimated mean frequencies of BAVs and coronary artery anomalies in the whole family amounted to 41.5% and 32.2%, respectively. The specimens examined were chosen at random among those belonging to the inbred generations 4 to 28. Their inbreeding coefficients, calculated according to Falconer (1989), ranged between 0.594 and 1.

Matings were set up as a monogamous system, with males and females occupying separate polypropylene cages (49.0 x 24.5 x 15.0 cm). These were kept in a well ventilated room at 22-25°C, with no measures to protect the microbiological status of the animals, except routine hygiene. The light cycle was 14 h light and 10 h dark. After mating, gravid females were transferred to clean cages (24.5 x 24.5 x 15.0 cm). Nesting material was provided approximately 2 days prior to delivery. After weaning, hamsters were housed in individual cages. Commercial food (UAR/Panlab s.l. A.04) and water were given as required, starting at weaning.

The hamsters were handled in accordance with the Spanish Regulations for the Protection of Experimental Animals (Real Decreto 223/1988). There was no known exposure of the animals to teratogenic agents.

Techniques

The hamsters belonging to the inbred generations 4-16 (363 specimens; years: 1988- 1992) were killed by overdosing with chloroform. Those belonging to the inbred generations 17-24 (451 specimens; years 1993-1996) were deeply anaesthetized with diethyl ether in a chamber until they died. The remaining 154 specimens, belonging to the inbred generations 25-27 (years 1996- 1997), were sacrificed with carbon dioxide at a concentration of 75% delivered into a chamber.

Thereafter, the heart was exposed by means of a thoracotomy at the level of the fifth intercostal space and perfused through the ventricles with 0.1 M phosphate buffered saline (pH 7.3). Hearts were then removed, transferred to the same solution, and dissected to expose the cardiac semilunar valves and the main coronary artery trunks. The condition of the aortic valve and origin of the coronary arteries were assessed by means of a stereomicroscope equipped with an ocular micrometer.

In several cases, the aortic valve was removed and fixed by immersion in 1% paraformaldehyde and 2% glutaraldehyde in 0.05 M sodium cacodylate buffer (pH 7.3) with osmolarity adjusted to 330 miliosmol/l, for 3 h (ratio of fixative to tissue volume = 80: 1). Thereafter, the specimen was dehydrated in increasing concentrations of ethanol, dried by the critical point method, and gold sputter coated. Observations were made using a Jeol JSM-840 scanning electron microscope, operated at 10, 20, or 25 kV.

In the present study, the branching mode of the main coronary artery trunks could not be assessed because of the intramyocardial course of the coronary branches. It should be noted, therefore, that the relationships reported herein only refer to the origin of the main coronary artery trunks and the morphology of the aortic valve.

Statistical methods

In the present study, the branching mode of the main coronary artery trunks could not be assessed because of the intramyocardial course of the coronary branches. It should be noted, therefore, that the relationships reported herein only refer to the origin of the main coronary artery trunks and the morphology of the aortic valve. The I-test was used to test for any association between the arrangement in the origin of the coronary arteries and the tricuspid versus bicuspid design of the aortic valve. A probability of 0.05 or less was required as evidence for a significant association.

In order to analyse the possible influence of the different morphologies of the aortic valve on the occurrence of coronary artery anomalies, the following logistic regression was used:

$$P= e^{y}/(1+ e^{y})$$

in which P represents the probability of a coronary artery anomaly being present, e is the basis of the Napierian logarithms, and y is a regression equation of the following type:

$$y = \mathrm{a} + \mathrm{b} \times group$$

where the term group refers to six *groups* of valve conditions into which we divided the continuous spectrum of aortic valve morphology.

The SPSS software was used to obtain the logistic model, which was tested by means of a χ^2-test of goodness of fit. The estimation of the parameters a and b in equation (2) was by maximum likelihood and was tested by Wald's test (Wa1d 1943).

Nomenclature

The nomenclature used for aortic valve components was that of Angelini et al. (1989), McKay et al. (1992) and Sans-Coma et al. (1992). It should be noted, however, that we use the terms tricuspid and bicuspid instead of bifoliate and trifoliate, considering that the former are of much more common usage.

RESULTS

In the sample studied, no statistical difference related to sex was found with regard to the occurrence of coronary artery anomalies and aortic valve condition; hence, male and female data were pooled.

Anatomy of the aortic valve

In 496 (51.2%I of the 968 hamsters examined, the aortic valve displayed a tricuspid condition. It had three aortic sinuses and three leaflets. However, in most (n= 4721of these TAVs, the ventral commissure, between the right and left leaflets, was more or less fused. TAVs with no commissural fusion possessed interleaflet triangles of similar size (Fig la), whereas in TAVs with fusion of the ventral commissure, the ventral interleaflet triangle was decreased in size, according to the degree of the fusion (Figs lb and 2a). When the ventral commissure was completely fused, the ventral interleaflet triangle was lacking (Figs Ie and 2b). In that case, the basically tricuspid architecture of the valve could be recognized because the most cranial margin of the fused commissure was on the same level as the cranial margins of the other two commissures (see Sans-Coma et al. (1996) for a definition of the tricuspid condition of the aortic valve in the Syrian hamster).

The remaining 472 (48.8%) hamsters of the series had BAVs with the aortic sinuses in ventrodorsal orientation. In 275 of these BAVs a raphe was located in the ventral aortic sinus. The raphe varied in size, ranging from a raphe that widely encroached toward the leaflet, but did not reach the cranial level of the commissures (Figs 1d and 3a), to a raphe confined to the aortic wall (Figs 1e and 3b). The remaining 197 BAVs were devoid of any raphe (Fig 1f).

Although there was a continuous spectrum of TAV morphology in the sample studied, we considered three groups of TAVs for statistical purposes. The first group (74 cases) included both the TAVs with no commissural fusion and TAVs with a fusion of the ventral commissure that extended less than 33% of the distance between the most cephalic and most caudal margins of the valve. The second group (264 cases I was that of TAVs with a commissural fusion extending between 33% and 66% of this distance. The third group 1158 cases) consisted of the TAVs with a commissural fusion affecting more than 66% of the craniocaudal distance of the valve. These three groups will be referred to as TAV-O, TAV-1 and TAV-2, respectively.

Bicuspid aortic valves were also subjected to a continuous morphological variation. However, we established three groups of BAVs for the statistical analysis. The first group (183 cases) was formed by the BAVs with a raphe that reached the leaflet. The second group (92 cases) was that of BAVs with a more or less developed raphe confined to the aortic wall. The third group (197 cases) comprised the BAVs without raphe. These groups will be referred to as BAV-3, BAV-4 and BAV-S, respectively.

Arrangement of the coronary arteries

The origin of the coronary arteries was normal in 638 (65.9%) of the 968 hamsters. The right and left coronary arteries arose from the right and left aortic sinuses, respectively, when the aortic valve was tricuspid (Fig 4a). When it was bicuspid, they originated from the right and left sides of the ventral aortic sinus, respectively (Fig 4b).

In another 220 (22.7%) hamsters there was a single coronary artery ostium in the aorta. The ostium was located in the right aortic sinus when the valve was tricuspid (Fig 4c), and in the right side of the ventral aortic sinus when the valve was bicuspid (Fig 4d). As far as our observations allowed, a single coronary artery trunk arose from the single ostium and bifurcated soon into right and left coronary arteries.

In a further 57 (5.9%) hamsters, the left coronary artery originated from the left sinus of the pulmonary valve, whereas the right coronary artery arose from the right aortic sinus when the aortic valve was tricuspid (Fig 4e), and from the right side of the ventral aortic sinus when the valve was bicuspid (Fig4f).

In the remaining 53 (5.5%) hamsters, the left coronary artery arose from the dorsal aortic sinus. The right coronary artery originated from the right aortic sinus when the aortic valve was tricuspid (Fig 4g), and from the right side of the ventral aortic sinus when the valve was bicuspid (Fig 4h).

Statistical analysis

The distribution of coronary artery patterns according to the tricuspid or bicuspid condition of the aortic valve is given in Table 1. Overall, 105 (21.2%) of the 496 TAVs and 225 (47.7%) of the 472 BAVs were associated with anomalous origin of the left coronary artery. This difference is statistically significant ($P < 0.001$; χ^2-test). Significant differences between TAVs and BAVs were also detected for each abnormal coronary artery pattern (χ^2-test): single right coronary ostium in aorta ($P < 0.001$) anomalous origin of the left coronary artery from the pulmonary artery ($P < 0.05$), and anomalous origin of the left coronary artery from the dorsal aortic sinus ($P< 0.001$).

Table 2 shows the distribution of coronary artery patterns according to the six groups of aortic valve morphotypes defined above. These data were used for the logistic regression analysis using the hypothesis that the probability of occurrence of the present coronary artery anomalies might be explained as a function of the groups of valves. Logistic regressions were calculated for each coronary artery anomalous pattern and the whole set of coronary artery anomalies.

The significant regression equations obtained are:

$y = - 2.0976 + 0.3136 \times \text{group}$ for single coronary artery ostium in aorta;

$y = - 3.3332 + 0.2005 \times \text{group}$ for anomalous origin of the left coronary artery from the pulmonary artery;

$y= - 3.7581 +0.3101 \times \text{group}$ for anomalous origin of the left coronary artery from the posterior aortic sinus;

$y= -1.6783+0.3756 \times \text{group}$ for the whole set of coronary artery anomalies.

In these equations, the term group refers to the six groups of valves into which we divided the continuum spectrum of aortic valve morphology; it takes values between 0 and 5, namely: 0 for TAV-O,1 for TAV- I, 2 for TAV- 2,3 for BAV-3,4 for BAV-4,and 5 for BAV-5. The graphic representations of the respective logistic functions ($P = e^y/(1+e^y)$) are shown in Figs 5a-d.

DISCUSSION

Prior to the discussion of the results obtained, it should be noted that all of the 968 hamsters reported herein had already been used in previous anatomical studies on the normal and abnormal arrangement of the cardiac outflow tract components, including the coronary arteries. A considerable part of these studies concerned the bicuspid condition of the aortic valve, which is the most frequent congenital cardiac malformation in man (Roberts 1970, 1987). Another important part was devoted to congenital anomalies in the origin of the coronary arteries, the interest of which relied on the fact that most of the anomalo'us coronary artery patterns recorded in the Syrian hamster are very similar to those in humans (Sans-Coma et al. 1993a). Thus, the present inbred family seems to offer a suitable animal model to study the aetiology of several congenital aortic valve and coronary artery defects that are clinically relevant in man. Unfortunately, there are no alternative techniques to conduct further investigations in this field. This means that a number of hamsters should be sacrificed in the coming years. In this regard, we will emphasize that the use of both the chloroform and diethyl ether to kill hamsters was abolished in our laboratory at the end of 1996. Since then, we follow the recommendations of Close et al. (1996, 1997) for euthanasia of experimental animals.

Other aspects that should be emphasized prior to the discussion of our results are: (1) in the Syrian hamster, the normal condition, m the sense of most frequent condition, of the aortic valve is that displaying a tricuspid design without fusion of the ventral commissure (Sans-Coma et al. 1993b, 1996), (2) in this rodent species, the normal coronary artery pattern is characterized by the existence of two well-developed coronary arteries, the right and left, arising from the right and left aortic sinuses, respectively (Sans-Coma et al. 1993a), (3) a third coronary artery ostium in aorta resulting from the independent origin of either the conal branch or the septal artery is often present; the existence of such a supernumerary ostium falls within the limits of normality (Sans-Coma et al. 1993a) and (4) the high percentages of BAVs, TAVs with fusion of the ventral commissure, and anomalies in the origin of the left coronary artery in the Syrian hamster family under study are the product of systematic inbreeding (Sans-Coma et al. 1993b, Cardo et al. 1995).

Morphological relationships

The statistical results obtained (x2-tests) agree with those reported in previous studies (Sans-Coma et al. 1991, Cardo et al. 1994, 1995) in demonstrating that in the Syrian hamster, the coronary artery anomalies characterized by the anomalous origin of the left coronary artery are significantly associated with the bicuspid condition of the aortic valve. However, this statement does not describe the true status of the question. In fact, there is no discontinuity between TAVs and BAVs regarding the incidence of coronary artery anomalies. The logistic functions obtained indicate that the probability of occurrence of each coronary artery anomaly increases continuously, according to the deviation degree of the aortic valve from its normal design (Figs Sa-c). As a consequence, the probability of occurrence of the whole set of coronary artery anomalies also increases continuously from one end to the other of the aortic valve phenotypic spectrum; namely, from TAVs with no commissural fusion to BAVs devoid of any raphe (Fig 5d).

Single coronary artery ostium in aorta is the anomalous coronary artery pattern with the highest probability of occurrence (Fig Sa); the lowest probability concerns the anomalous origin of the left coronary artery from the pulmonary artery (Fig 5b). Nonetheless, the logistic functions of the three coronary artery anomalies (Figs Sa-c) display similar topologies. This suggests that their respective relationships with the morphology of the aortic valve rely on identical causality.

Morphogenetic relationships

Sans-Coma et al. (1996) showed that all variants of the aortic valve morphological spectrum occurring in the Syrian hamster develop from three mesenchymal valve cushions, right, left and dorsal, after normal septation of the conotruncus. The more or less extensive fusion of the right and left cushions at the beginning of the valvulogenesis is a key factor in the formation of the different types of BAVs with the aortic sinuses in ventrodorsal orientation and TAVs with a more or less extensive fusion of the ventral commissure. Hence, the continuous spectrum of aortic valve morphology seen in adult hamsters relies on an embryonic trait, the arrangement of the right and left aortic valve cushions, which also shows a continuous distribution; it ranges from two cushions that grow as independent units to two cushions that are completely fused, resulting in a single ventral cushion.

Martire et al. (1998) demonstrated that in the Syrian hamster, the coronary arteries develop by the sprouting of single endothelial cells of the peritruncal capillary plexus which contact the endothelium that covers the aortic wall. Hence, the proximal coronary arteries of the Syrian hamster grow into the aorta as occurs in birds (Bogers et al. 1989, Waldo et al. 1990, Mikawa & Fischman 1992, Poelmann et al. 1993). Moreover, Martire et al. (1998) showed that the anomalies in the origin of the left coronary artery are not the consequence of defective growth or abnormal arrangement of the peritrunca1 plexus. They result either from the lack of connection of the peritruncal capillary plexus to the left aortic sinus or from the connection of the anticipated left coronary artery system to the arterial tree at an erroneous site such as the pulmonary artery or the dorsal aortic sinus. Thus, the present coronary artery anomalies are due to a common primary cause, namely, the lack of penetration of the peritruncal capillary plexus into the aorta at its normal site, that is, at the left aortic sinus in TAVs or at the left side of the ventral aortic sinus in BAVs.

These data, together with the results reported herein, indicate that in the Syrian hamster, the probability that the peritruncal capillary plexus does not penetrate into the aorta at the normal site increases according to the degree of fushion of the right and left aortic valve cushions at the beginning of the valvulogenesis. This strongly suggests that both anomalous morphogenetic events are related from an aetiological viewpoint. However, the fact that they also occur independently denotes that there is no primary dependence between them, but some other cause predisposes to their concurrence.

Cardo et al. (1994, 1995) stated that in the Syrian hamster, congenital abnormal aortic valves and anomalies in the origin of the left coronary artery might be the product of a single developmental diathesis. They postulated an anomalous behaviour of the cells from the cardiac neural crest as the possible common underlying morphogenetic defect. This proposal relied on the following data: (1) in humans, defects of neural crest cells had been suggested as producing bicuspid aortic valves in combination with malformations of the aortic arch and other systems (Kappetein et al. 1991, Miyabara et al. 1993a,b); and (2) in the chick, ablation of the cardiac neural crest had been proved to produce anomalies in the origin of the coronary arteries, probably because of the spatial disorder caused by the absence of the neural crest cells on the development of the proximal coronary arteries (Hood& Rosenquist 19921.More recently, Sans-Coma et al. (1996) argued that in the Syrian hamster, anomalies in the cardiac neural crest cells might be responsible for the fusion of the left and right embryonic aortic valve cushions, which is a key factor in the formation of the present defective aortic valves. On the other hand, Martire et al. (1998) suggested that in the hamster, the lack of penetration of the peritruncal capillary plexus into the aorta at its normal site is due to the reduction of the territory that can be invaded by the plexus, an event that might be caused by a defective behaviour of the cells from the neural crest.

The preceding data suggest that in the Syrian hamster, anomalous behaviour of the cardiac neural crest cells might be the primary morphogenetic defect leading to anomalous aortic valves (BAVs and TAVs with commissural fusion) and anomalies in the origin of the left coronary artery. Further studies are needed, however, to verify this hypothesis.

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Table 1 Coronary artery patterns versus aortic valve conditions

CAP	TAV (%)	BAV (%)	n
Normal	391 (78.8)	247 (52.3)	638
SCAOA	71 (14.3)	149 (31.6)	220
ALCAPA	20 (4.1)	37 (7.8)	57
ALCADAS	14 (2.8)	39 (8.3)	53
N	496	472	968

CAP = coronary artery pattern; TAV = tricuspid aortic valve; BAV= bicuspid aortic valve; SCAOA=single coronary artery ostium in aorta; ALCAPA=anomalous left coronary artery from the pulmonary artery; ALCADAS=anomalous left coronary artery from the dorsal aortic sinus; n=total number of specimens

Table 2 Coronary artery patterns versus aortic valve morphotypes (TAV-0 to TAV-2 and BAV-3 to BAV-5)

CAP		TAV-0	TAV-1	TAV-2	BAV-3	BAV	BA V-5
Normal	n	64	214	113	102	45	100
	%	86.5	81.1	71.5	55.7	48.9	50.8
SCAOA	n	9	27	35	53	32	64
	%1	2.2	10.2	22.1	29.0	34.8	32.5
ALCAPA	n	0	15	5	15	5	l7
	%	0.0	5.7	3.2	8.2	5.4	8.6
ALCADAS	n	1	8	5	13	10	16
	%		3.0	3.2	7.1	10.9	8.1

See text for an explanation of the aortic valve morphotypes and Table 1 for the abbreviations

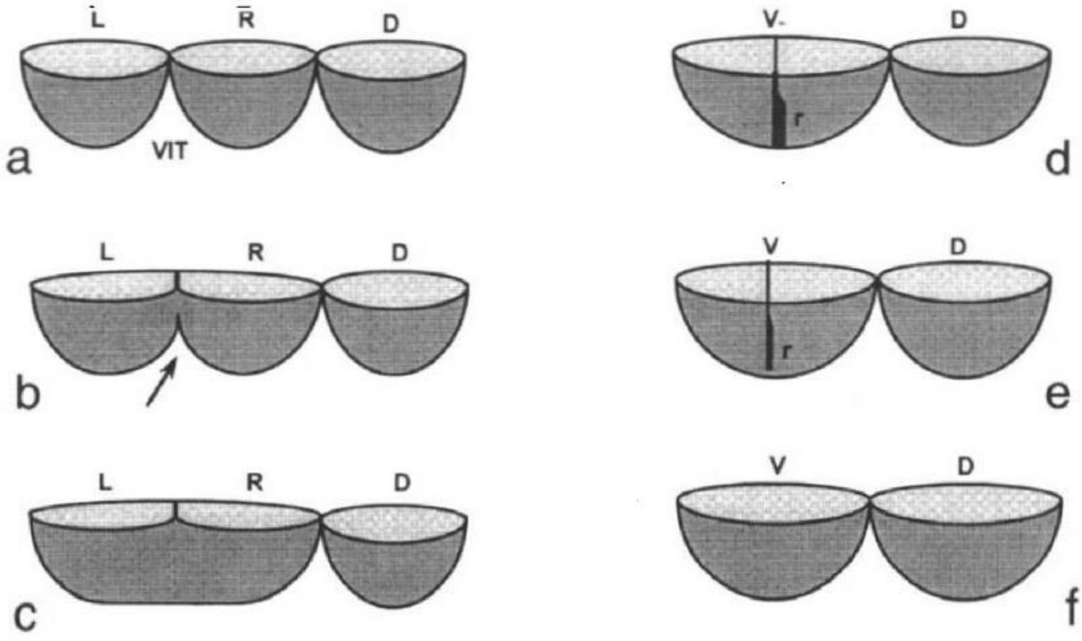

Figure 1. Aortic valve morphologies in Syrian hamsters. (a) Tricuspid aortic valve with no fusion of the ventral commissure and a well-developed ventral interleaflet triangle (VIT). (b) Tricuspid aortic valve with partial fusion of the ventral commissure. The ventral interleaflet triangle (arrow) is reduced in size. (c) Tricuspid aortic valve with complete fusion of the ventral commissure. The ventral interleaflet triangle is lacking. (d) Bicuspid aortic valve with a well-developed raphe (r) that encroaches toward the leaflet. (e) Bicuspid aortic valve with a raphe (r) confined to the aortic wall. (e) Bicuspid aortic valve devoid of any raphe. D= dorsal aortic sinus; L= left aortic sinus; R= right aortic sinus; V = ventral aortic sinus

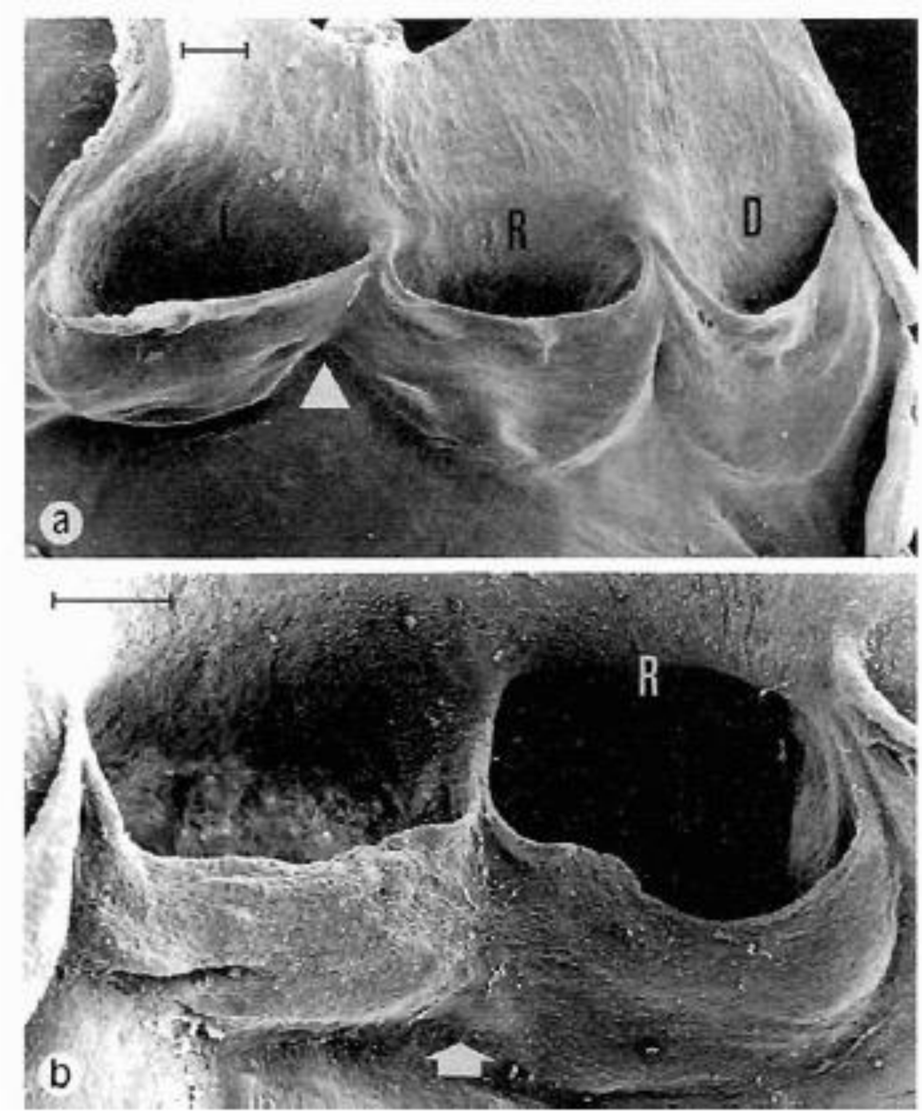

Figure 2 Scanning electron micrographs of tricuspid aortic valves from Syrian hamsters. (a) Tricuspid aortic valve with partial fusion of the ventral commissure. The ventral interleaflet triangle (triangle) is decreased in size. (b) Tricuspid aortic valve with complete fusion of the ventral commissure (arrow). The ventral interleaflet triangle is lacking. The specimen was opened through the dorsal aortic sinus to expose the ventral aspect of the valve. 0 = dorsal aortic sinus; L = left aortic sinus; R= right aortic sinus. Scale bars=200 μm

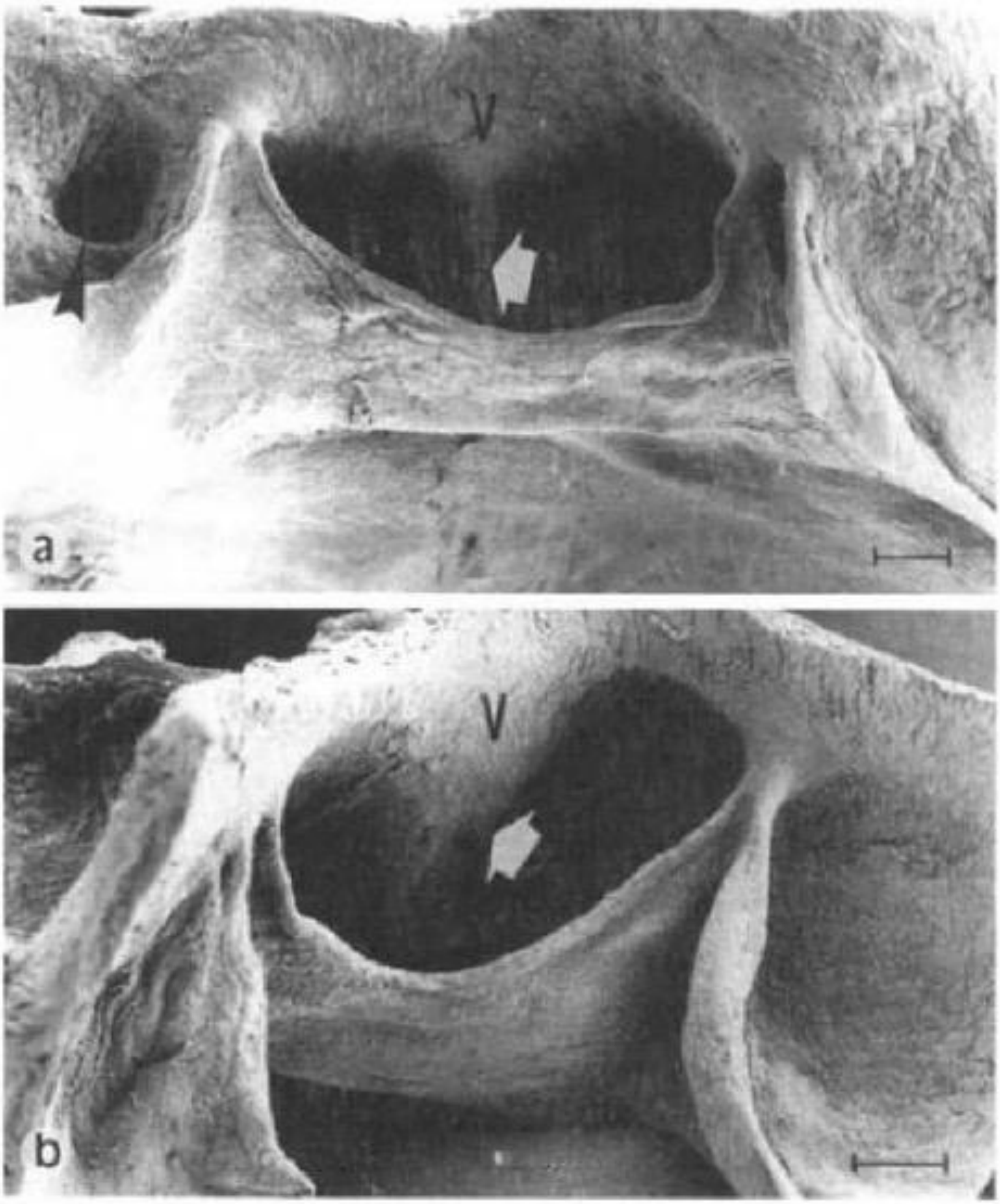

Fig 3 Scanning electron micrographs of bicuspid aortic valves from Syrian hamsters. The specimens were opened through the dorsal aortic sinus to expose the ventral aspect of the valve. (a) Bicuspid aortic valve with a raphe (arrow) located in the ventral aortic sinus (V). The raphe reaches the leaflet. The arrowhead points to the ostium of the left coronary artery that originates from the dorsal aortic sinus. (b) Bicuspid aortic valve with a raphe (arrow) confined to the wall of the ventral aortic sinus. Scale bars=200 μm

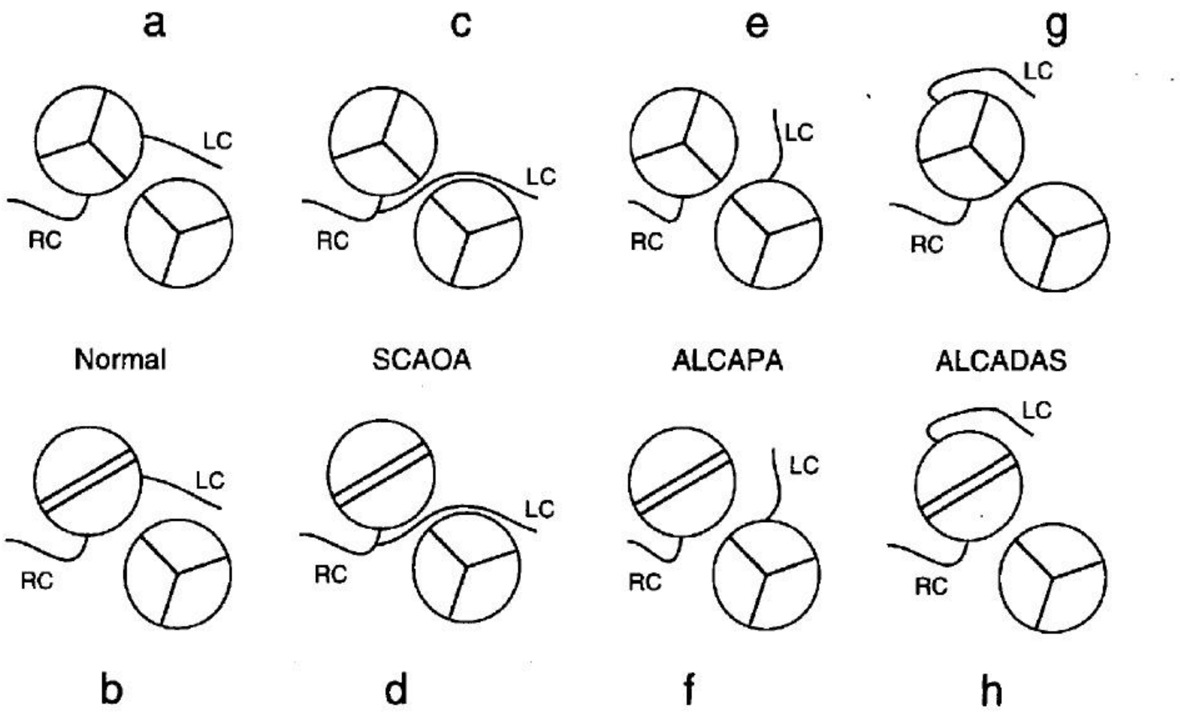

Figure 4 Coronary artery patterns in Syrian hamsters. Normal = Normal coronary artery pattern associated with tricuspid aortic valve (a) and bicuspid aortic valve (b). SCAOA = Single coronary artery ostium in aorta associated with tricuspid aortic valve (c) and bicuspid aortic valve (d). ALCAPA=anomalous origin of the left coronary artery from the pulmonary artery associated with tricuspid aortic valve (e) and bicuspid aortic valve (f). ALCADAS = anomalous origin of the left coronary artery from the dorsal aortic sinus associated with tricuspid aortic valve (g) and bicuspid aortic valve (h). LC= left coronary artery; RC= right coronary artery.

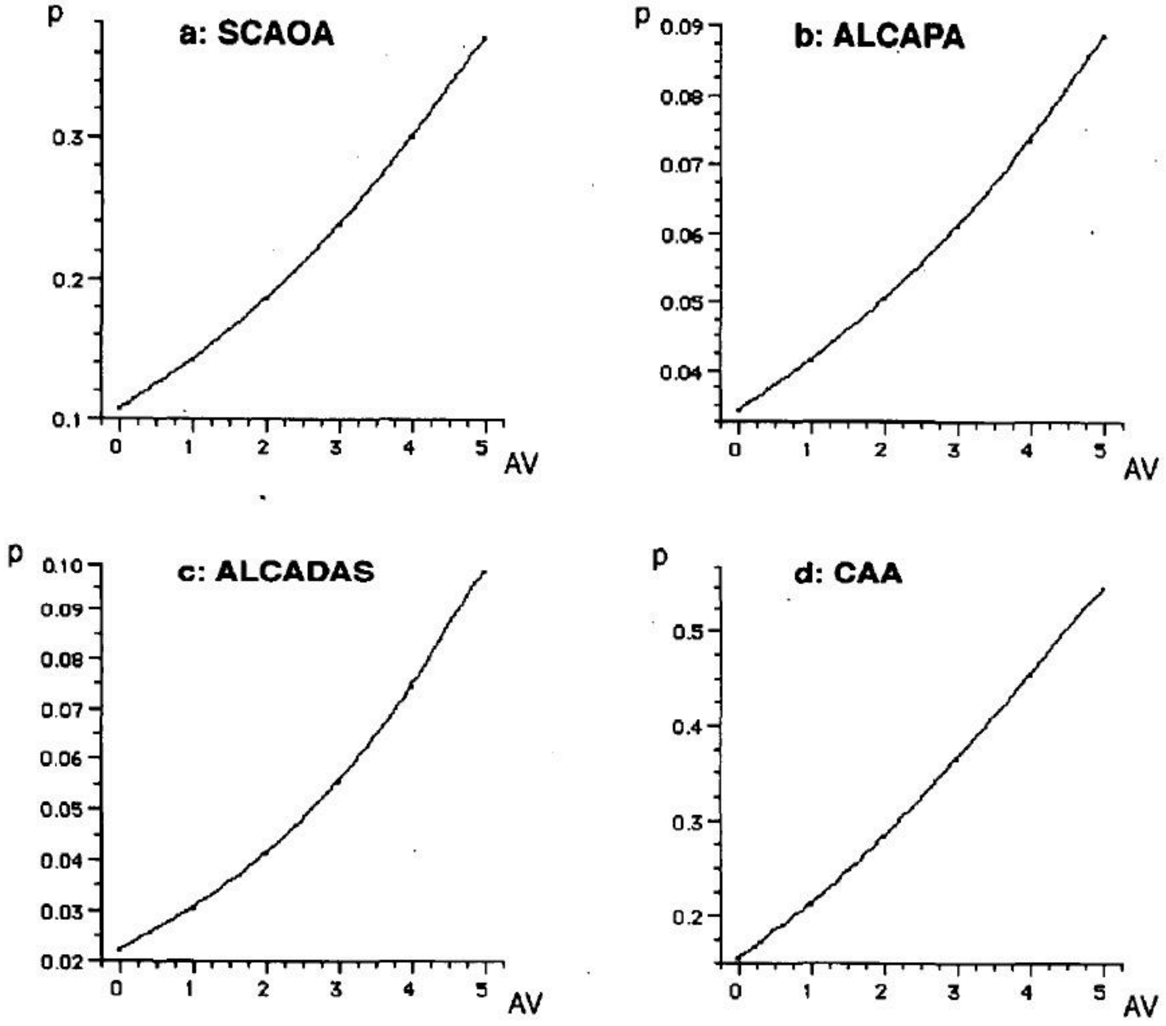

Figure 5 Graphic representations of the logistic functions ($P=e^y/(1+e^y)$) obtained, respectively. for (a) single coronary artery ostium in aorta (SCAOA). (b) anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA). (c) anomalous origin of the left coronary artery from the dorsal aortic sinus (ALCADAS). and (d) the whole set of coronary artery anomalies (CAA). P= probability of occurrence of the anomalous coronary pattern or patterns; AV=aortic valve morphotypes: 0= TAV-O; 1= TAV-l; 2= TAV-2; 3= BAV-3; 4= BAV-4; 5= BAV-5