J. Anat. (1993) 182, pp. 87–94, with 3 figures Printed in Great Britain

The atrioventricular valves of the mouse I. A scanning electron microscope study

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(*Accepted 24 November 1992*)

ABSTRACT

This paper reports a scanning electron microscope study of the morphology of the atrioventricular (AV) valves in the mouse. The leaflet tissue of the 2 AV valves consists of a continuous veil that shows no commissures or clefts. In all instances, the chordae that arise from the papillary system merge with the free border of the leaflet tissue. No distinct terminations of chordae were observed on the ventricular face of the valves. The leaflet tissue of the right AV valve can be divided into parietal and septal components on the basis of the insertion into the ventricular wall and of the papillary system. While the septal component is similar in shape, location and tension apparatus to the septal tricuspid leaflet in man, the parietal component appears to correspond to the anterior and posterior human leaflets. This segment of the valve is served by 3 papillary muscles that arise from the septal wall. The right AV valve is not a tricuspid structure from the morphological standpoint, but appears to function as such because of the particular attachment of the papillary muscles. The leaflet tissue of the mitral valve is served by 2 papillary muscles, anterior and posterior, which consist of muscular trabeculae extending from the heart apex to the base of the valve. These muscles remain associated with the ventricular wall. The leaflet tissue attaches directly to these papillary muscles, which give rise to a very small number of slender chordae. There are thus several important differences between the AV valves of the mouse and man. It is stressed that extrapolation between species cannot safely be made without a thorough knowledge of normal embryology and anatomy.

INTRODUCTION

The normal anatomy of the atrioventricular (AV) valves in man is well known (Gross & Kugel, 1931; Silvermann & Hurst, 1968; Lam et al. 1970; Silver et al. 1971; Anderson & Becker, 1992). Mitral and tricuspid valves guard the left and right AV orifices, the valve leaflets being attached to the papillary muscles by chordae tendinae. However, some aspects of the development of these valves are still under discussion (Magovern et al. 1986; Wenink & Gittenberger-de Groot, 1986; Wenink, 1992). Most of our knowledge of human cardiac embryology is derived from the study of the developmental anatomy of different animal species. The results thus obtained are often extrapolated to man, assuming that both the development and the final anatomy of a particular region of the heart is similar between species. The same kind of inference is used to explain the development of different heart malformations. The problem with this approach is that these conclusions are reached assuming some developmental or anatomical facts that may be imperfectly known or even erroneous (Anderson & Wenink, 1988).

The mouse is generally considered to be an excellent model for studying heart development. Furthermore, the availability of mouse models of congenital heart disease involving the atrioventricular region (Layton, 1978; Miyabara, 1990; Morishima et al. 1990; Icardo & Sanchez de Vega, 1991) underscores the need for a detailed knowledge of the anatomy of this region. However, a full account of the normal anatomy of the AV valves in the mouse has, to our knowledge, not been provided to date. Also, the spatial arrangement (and the identification) of the different structural components of the valve leaflets have been insufficiently investigated. We have therefore undertaken a thorough study of the AV valves of the normal mouse.

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Similarities and dissimilarities between the AV valves of the mouse and man are highlighted.

MATERIALS AND METHODS

Mice of the Swiss albino strain were used in this study. 40 mice (20 for each valve) aged 21 d (at weaning) were anaesthetised with ether. The thoracic wall was opened and the hearts extracted. The hearts were washed thoroughly with phosphate-buffered saline (PBS) through the atria and ventricles to clear blood. The tricuspid valve was exposed by opening the right ventricle following the direction of the pulmonary artery. This was done by cutting through the right atrium and ventricle following the right border of the heart, or by cutting through the anterior ventricular wall. The mitral valve was exposed by opening the left ventricle following the direction of the aorta, cutting through the left atrium and ventricle and following the left border of the heart, or by cutting through the anterior ventricular wall. The hearts thus dissected were further washed with PBS and fixed open in 3% glutaraldehyde in PBS, pH 7.3. After fixation, the hearts were dehydrated in graded concentrations of acetone, dried by the critical point method using CO_2 as the transitional fluid, coated with gold and examined in a scanning electron microscope (Philips, SEM 501). To study the morphology of the AV orifices, 6 additional hearts were processed similarly and observed in cranial views after removal of the atrial walls. Most of this study was performed in young animals because the size of the heart makes them easier to manipulate under the SEM. Twelve more hearts from adult (6 months) and old (1 y) animals were also processed to exclude the possibility of age changes in valve morphology.

RESULTS

Figure 1 shows, in a cranial view, the location and shape of the valve orifices of the mouse heart. The tricuspid orifice is slit-shaped and appears oriented in an anteroposterior direction. The mitral orifice is rounded or slightly oval and appears oriented almost at a right angle to the tricuspid valve. The aortic orifice is wedged between the 2 AV orifices; the pulmonary orifice is anterior and to the left of the aortic one.

The tricuspid valve

The leaflet tissue of the tricuspid valve consists of a continuous curtain that occupies the right AV orifice (Figs 2, 3) and descends into the ventricular cavity. Small curved breaches appear in 20% of the hearts studied at the posterior end of the valve continuum (Fig. 3). These breaches are much less frequent at the anterior end of the valve. The arrangement of the right AV orifice permits the recognition in this continuous curtain of mural (septal) and parietal (right) components. As is shown below, the 2 segments differ in their site of insertion and in the tension apparatus which supports them.

The septal component of the valve inserts to the septal margin of the right AV orifice (Figs 2, 3). The free border of this segment is usually very irregular and shows numerous indentations between the attachment sites of the different chordae (Fig. 3). The chordae are usually short and slender, variable in number and location, and arise directly from the septal wall or from the base of very small papillary muscles. These chordae reach the free border of the leaflet tissue (Figs 2, 3) and merge with it. Some of the chordae appear to be formed by infolding of the endocardial covering and, in some cases, the valve tissue attaches directly to the septal wall (Fig. 3). Distinct papillary muscles giving rise to fan-shaped chordae that radiated out from its tip to reach the free margin of the leaflet tissue were only observed on 6 occasions (Fig. 2). These muscles were always very small; 5 of them were located in the middle of the septum and the 6th in a posterior position. Chordae and flat ribbons arising directly from the septal wall

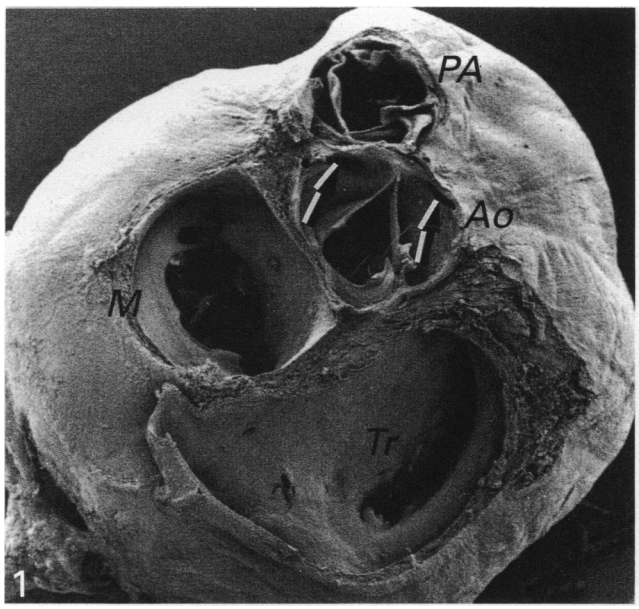

Fig. 1. Survey view of the valve orifices of the mouse heart after dissection of the atrial walls. Unless stated otherwise, all figures are for juvenile hearts. The tricuspid orifice (*Tr*) is slit-shaped, while the mitral one (*M*) is oval. The aortic (*Ao*) and the pulmonary (*PA*) sigmoid valves are exposed. The 2 arrows in the aorta are placed in the coronary sinuses and point to the coronary orifices. × 33.

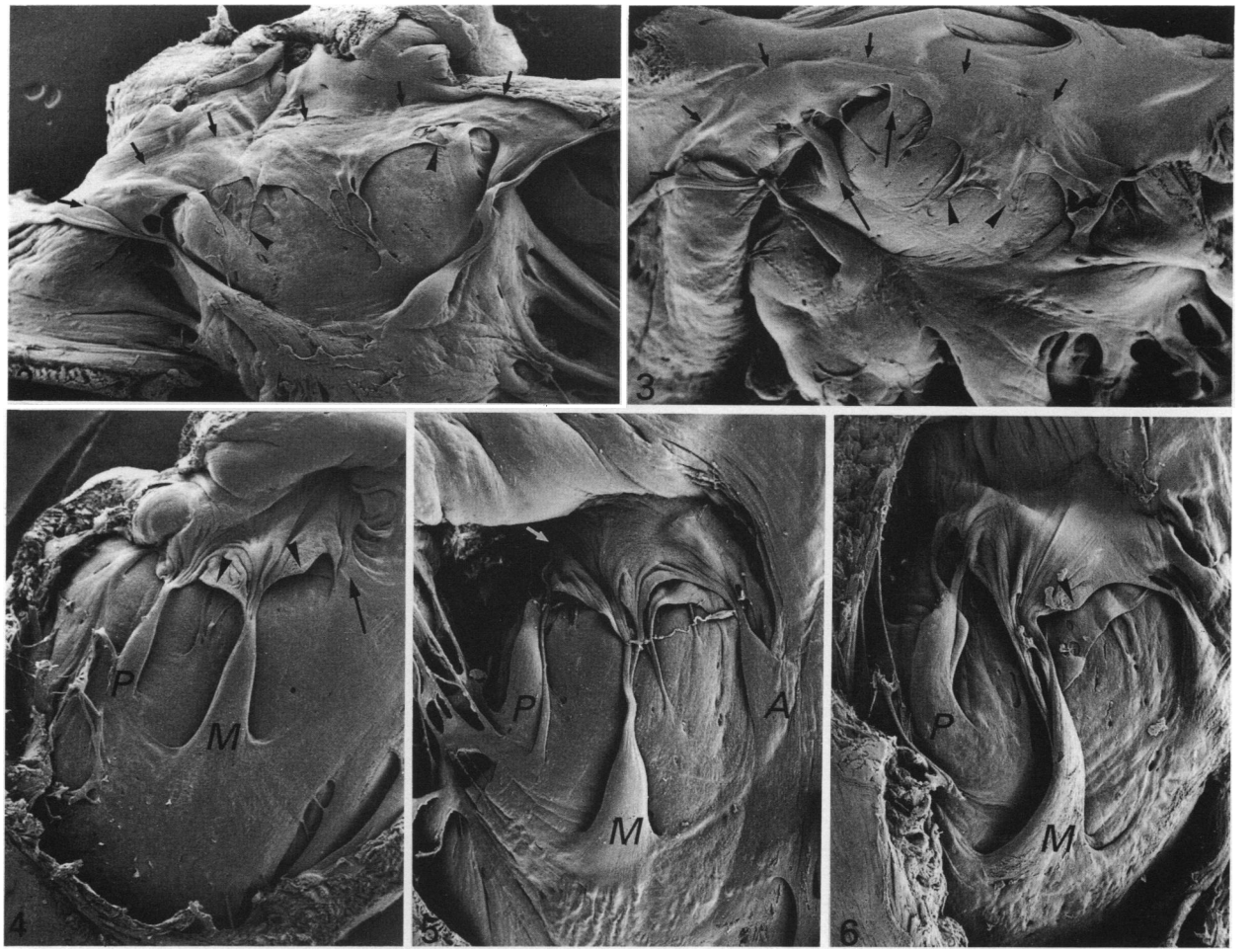

Fig. 2. Survey view of the right AV valve of the mouse. The right ventricle has been opened by cutting through the free ventricular wall. This exposes the atrial face of the valve. Small arrows indicate the base of the valve. The valve tissue appears as a continuous curtain with no commissures. The septal component of the valve is supported by 2 slender chordae (arrowheads) and by a small papillary muscle (in the centre of the figure) which gives rise to fan-shaped chordae. All these chordae merge with the free border of the valve tissue. The papillary muscles which serve the parietal component have been distorted by the dissection procedure. ×23.

Fig. 3. Survey view of the right AV valve after a similar dissection to that shown in Figure 2. In this heart, the septal component of the valve shows a dentate and very irregular free border. The valve tissue is supported by some free chordae, being directly attached to the septal wall at 2 points (arrowheads). Some slender chordae run under the septal leaflet tissue. Two muscular chordae (large arrows) support the posterior end of the AV valve. ×28.

Figs 4–6. Survey views of the right AV valve complex of the mouse after dissection of the free ventricular wall. The ventricular face of the parietal component of the valve and its papillary apparatus is exposed in each instance. The atrial face of the septal component appears under the parietal face. All the papillary muscles which serve the parietal component arise from the septal wall. The middle (*M*) papillary muscle is conus-shaped and gives origin to a strut of chordae tissue (Fig. 4), and 2–3 struts and chordae (Figs 5, 6) that reach the free border of the leaflet tissue and merge with it. The posterior (*P*) papillary muscle is also conus-shaped but can be single (Fig. 4) or double (Figs 5, 6), and gives origin to a strut (Fig. 4) or to thick chordae (Figs 5, 6). A single ending of a chorda in the ventricular face of the parietal component is seen in Figure 5 (arrow). The anterior (*A*) papillary muscle is absent in Figure 4, being represented by direct attachment of the valve to the septal ventricular wall (arrow). It can also be single and conus-shaped (Fig. 5), or double (Fig. 6). In the latter instance, the anterior papillary muscle is represented by a conus-shaped muscle and a thick chorda with the appearance of being muscular. Free chordae are common at the posterior end of the right ventricle. These chordae extend between the free ventricular wall and the base of the posterior papillary muscle. Arrowheads in Figures 4 and 6 indicate scalloping at the free border of the parietal cusp. Figure 4, ×28; Figures 5 and 6, ×40.

were observed (Figs 2, 3) coursing under the ventricular face of the septal leaflet tissue. However, most of these extended from one point of the septal wall to another and very few reached the basal portion of the valve tissue.

The parietal component of the right AV valve inserts into the right margin of the right AV orifice, from the anterior to the posterior end. This part of the valve is served by 3 papillary muscles that arise from the septal ventricular wall (Figs 4–6). These are here called anterior, middle and posterior, according to their location on the right side of the ventricular septum. The free edge of the parietal valve segment usually shows a scalloped appearance between the

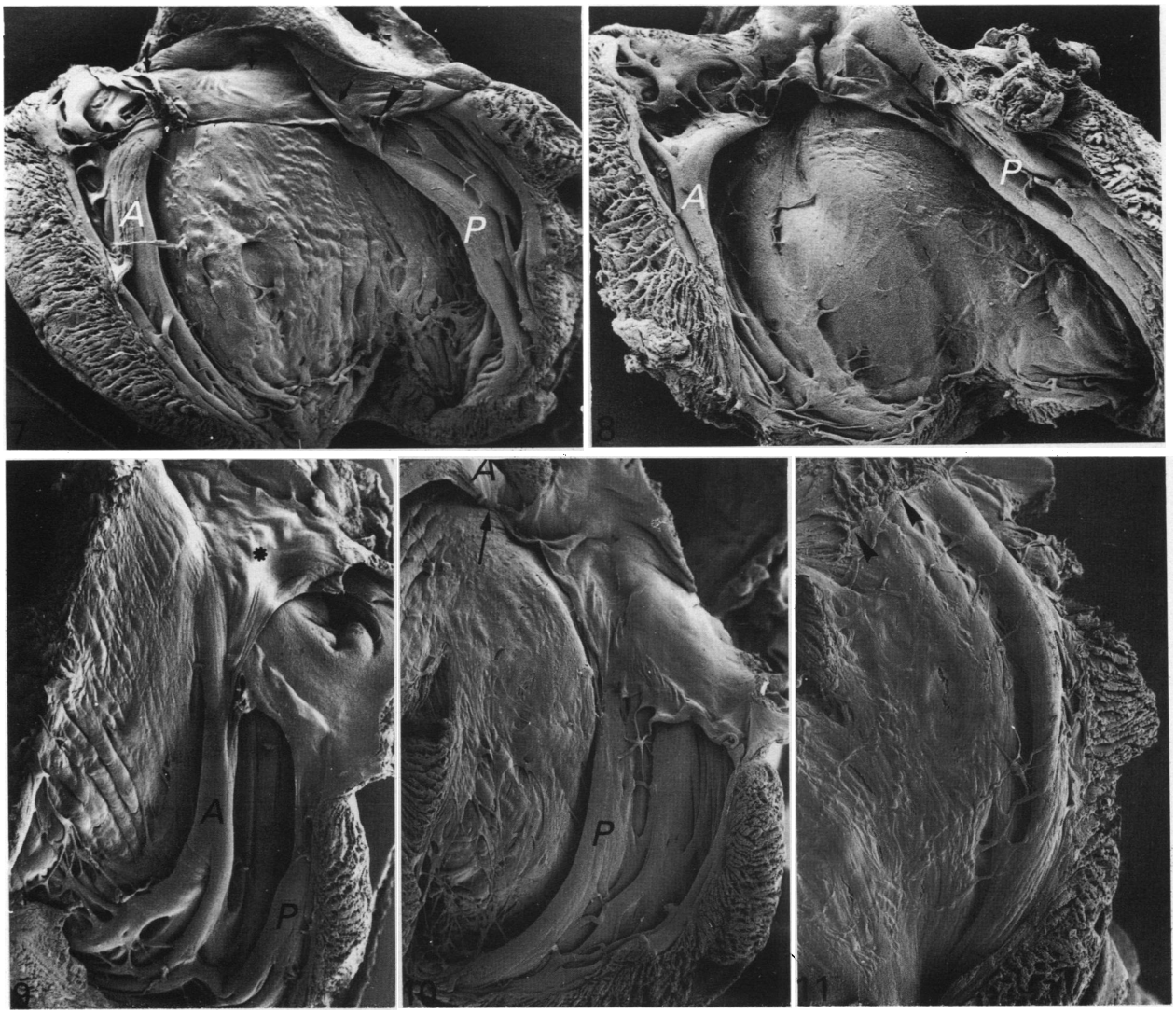

Fig. 7. Survey view of the left ventricle and the left AV valve. The left ventricle has been opened by cutting through the left ventricular wall. The atrial face of the mitral valve, the mitral valve apparatus and the left side of the interventricular septum are exposed. Small arrows indicate the base of the valve. The mitral valve is supported by 2 papillary muscles, anterior (*A*) and posterior (*P*), which run from the ventricular apex to the base of the mitral valve. The leaflet tissue is a continuous curtain that is attached directly to the papillary muscles. Note the small number and the shortness of the free chordae (arrowhead) that arise from the papillary complex and reach the valve tissue. In every case they merge with the free border of the cusp. The free border of the mitral valve tissue does not show clefts or scallops. The posterior muscle is continuous with muscular bands that are located along the free ventricular wall. The anterior muscle becomes more independent at its tip but still remains fully attached to the ventricular wall. × 30.

Fig. 8. Survey view of the left ventricle in a dissection similar to that shown in Figure 7. Small arrows indicate the base of the valve. The posterior papillary muscle (*P*) shows a similar morphology, but the chordae that attach this muscle to the leaflet tissue are more apparent. The chordae merge with the free border of the leaflet tissue. The tip of the anterior papillary muscle (*A*) is more independent from the ventricular wall than that shown in the previous figure, but still remains attached to the ventricular wall by free chordae and trabeculae. × 27.

Fig. 9. Detailed view of the mitral complex after dissection of the anterior wall of the left ventricle. The anterior papillary muscle (*A*) runs from the heart apex to the base of the valve. It appears as if this muscle is independent in its middle portion. The mitral tissue is directly attached to this muscle. Note the absence of chordae. The area of aortomitral continuity (asterisk) is a continuous mantle of fibrous tissue. The sigmoid valve of the aorta can be observed above the aortomitral continuity. The posterior papillary muscle (*P*) with its leaflet tissue attachment is also present. No chordae are observed at this point. × 27.

Fig. 10. Detailed view of the mitral complex after dissection of the anterior wall of the left ventricle. The mitral leaflet attaches directly to the posterior papillary muscle (*P*). Only some short and very slender chordae can be observed. No chordae are observed at the point of attachment (arrow) of the mitral tissue to the anterior papillary muscle (*A*). × 26.

Fig. 11. This picture shows a detail of one of the muscular bands which extends from the heart apex to the base of the mitral valve (arrowheads), running along the free wall of the left ventricle. Numerous free chordae attach these muscles to the ventricular wall. The papillary muscles which serve the mitral valve appear to be part of this system. × 37.

attachment of the 3 papillary muscles. The absence of clefts is noteworthy. The middle papillary muscle is usually larger than the others, more constant in shape and location, and arises from the middle of the septal ventricular wall in a position closer to the heart apex than the other two. This papillary muscle is cone-shaped, possesses a thin tip, and serves most of the parietal side of the valve. Characteristically, the middle papillary muscle gives rise to flat ribbons or struts of chordal tissue which reach the free border of the leaflet tissue and merge with it. The only instance in which one of the chordae reached the ventricular face of the parietal segment of the valve is shown in Figure 4. In half of the cases, the middle papillary muscle presented either a bifurcated tip, or the flat ribbon that originates from a single tip later divided into 2–3 ribbons (or struts) that reached the valve tissue. The main ribbons or struts appeared to continue within the leaflet tissue radiating towards the valvular annulus (Figs 4–6). Only on 2 occasions did we observe a middle papillary muscle giving rise to fan-shaped chordae. The base of the middle papillary muscle, in most cases, was joined to the other 2 papillary muscles by curved reliefs of the ventricular wall. The anterior relief appeared continuous with (or forming part of) the septomarginal trabecula (Figs 5, 6).

The anterior papillary muscle is usually smaller than the middle. It serves the anterior fourth of the parietal component and the anterior area of the AV orifice. Its size and shape are very variable (Figs 4–6). In half of the cases this papillary muscle was a flattened conus with a triangular base (Fig. 5). In 5 instances it appeared as a simple relief of the ventricular wall (Fig. 4), in 2 cases it appeared duplicated (Fig. 6) and, in 3 other instances, it was replaced by several flat ribbons and struts. This muscle gives rise to 1–2 flat ribbons or struts that attach to the free border of the leaflet tissue. In a few hearts we observed the presence of muscular chordae which merged with the leaflet tissue.

The posterior papillary muscle serves the posterior fourth of the parietal segment. When single, it is conus-shaped in most hearts (Fig. 4). However, it often appears duplicated, with the 2 muscles either being similar or very dissimilar in size (Figs 5, 6). It can also be bifurcated at its tip. In either instance the tip gives origin to flat ribbons and struts that reach the leaflet tissue. The posterior area of the right AV valve is normally free of chordae endings, although chordae arising from the posterior papillary muscle may sometimes reach the leaflet tissue (Fig. 2). When a breach of the leaflet tissue is present, free and muscular chordae merge with the leaflet tissue (Fig. 3) in this area.

Strands of chordae tissue (false chordae) were frequently observed extending between the free ventricular wall and the papillary muscle apparatus at the posterior end of the right ventricle (Figs 4–6). Only rarely did these chordae reach the valve leaflets. The presence of interchordal ligaments was less frequent.

The mitral valve

The leaflet tissue of the mitral valve is a continuous veil which shows a smooth and regular free edge (Figs 7, 8), with no commissures, scallops or clefts. Two papillary muscles serve the mitral valve: one posterior and another anterior. The 2 left papillary muscles arise from the heart apex (Figs 7–10). This apex is very trabeculated and the origin of the 2 papillary muscles is also trabeculated, showing an infinite number of variations. The 2 muscles ascend in the ventricle following the left border, separate from each other at the middle of the ventricular length, and reach the valvular annulus (see Fig. 9). These papillary muscles do not become isolated from the ventricular wall, but remain in continuity with the trabecular complex. Prominent trabeculations course along the free wall of the left ventricle, from the apex to the base (Fig. 11), and the papillary muscles appear to be part of this system. The leaflet tissue attaches directly to the papillary muscles, although the presence of some slender chordae near or at the site of the leaflet-muscle junction is frequent (Figs 7–10). The anterior papillary muscle is somewhat different, since in half of the hearts its tip became independent from the ventricular wall (Figs 7, 8). False chordae are a constant feature at the base of the left ventricle, and some are associated with basal origin of the 2 papillary muscles. Septoparietal muscular bundles were not observed at any time.

The AV valves of adult and old animals showed the same morphological appearance as those in the juvenile hearts (Figs 12, 13). When the hearts were excised and placed in PBS, the right AV orifice showed, in beating hearts, a triangular appearance. This was also patent when the valve was seen from below in sliced hearts (Fig. 13). The mural component and the posterior end of the valve tissue, that appears corrugated in Figure 1, forms the base of the triangle and presents, during ventricular contraction, little or no movement. The vertex of the triangle corresponds to the chordal attachment of the so-called middle papillary muscle (Fig. 13). Thus the parietal component of the right AV valve, when apposed to the

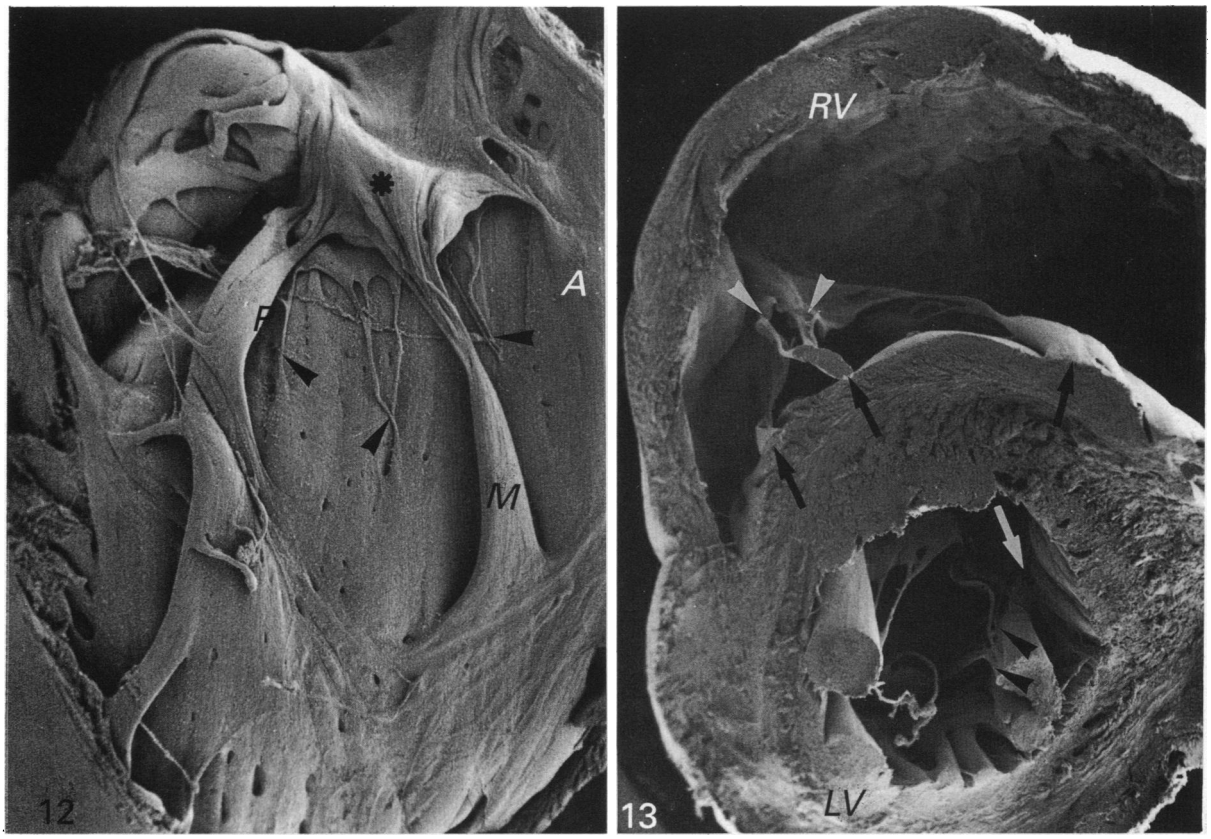

Fig. 12. Survey view of the right AV valve obtained from an adult animal after dissection of the free ventricular wall. General morphology is similar to that shown in Figures 4–6. The parietal component (asterisk) of the valve is served by 3 papillary muscles that originate from the right side of the ventricular septum. The anterior papillary muscle (*A*) is a simple relief of the ventricular wall, the middle one (*M*) is conus-shaped, and the posterior one (*P*) presents a bifurcated tip. Free chordae connect this muscle to the parietal ventricular wall. No chordae end in the ventricular face of the valve tissue. The septal component of the valve is served by slender chordae that arise directly from the septal wall (arrowheads). × 30.

Fig. 13. This figure shows a slice of the heart obtained from an old mouse. The slice is seen from below. The right (*RV*) and the left (*LV*) ventricles, and the interventricular septum, are present. In the RV, the right AV valve shows a triangular opening. The vertex of this triangle corresponds to the attachment of the middle papillary muscle (white arrowheads). The septal origin of the 3 papillary muscles (black arrows) which serve the parietal component of this valve is clear. In the LV, the 2 papillary muscles appear as thick trabeculae that run towards the base of the valve. The anterior papillary muscle presents a free tip that reaches the valve annulus (white arrow). The leaflet tissue attaches directly (black arrowheads) or by means of slender chordae to the papillary muscles. × 30.

mural component to close the valvular orifice, appears divided into 2 functional parts. This division is not apparent morphologically. The mitral valve closes in a fish-mouth fashion, showing an oblique commissure. The limits of the commissure correspond to the attachment of the leaflet tissue to the papillary muscles. This commissure divides the leaflet tissue into 2 components: one anterior and on the right (aortic) and another posterior and on the left (mural) (see Figs 1 and 13).

DISCUSSION

Several of the features arising from this study deserve to be highlighted. We have found a considerable variation in AV valve morphology among individual hearts, especially at the level of the papillary muscles and chordae system. A high degree of morphological variation has also been reported in human AV valves (Silverman & Hurst, 1968; Lam et al. 1970; Roberts, 1983). The AV valve orifices in the mouse are not circular as in man, and they appear oriented at a right angle with respect to each other.

The leaflet component of the 2 AV valves consists of a continuous mantle of valvular tissue that shows no deep indentations or clefts. This is more patent in the case of the mitral valve. It is thus a difficult task to separate these continuous skirts into distinct leaflets. In man, this distinction has classically been based on the presence of fan-like chordae surmounting a papillary muscle and on the presence of indentations of variable depth in the leaflet tissue (Lam et al. 1970; Silver et al. 1971). In the light of the present results, a similar classification cannot be made for mouse AV

valves. Anderson & Becker (1992) have recently proposed an alternative way of differentiating separate leaflets in the valve tissue. A leaflet is considered to be the segment of the valve tissue that makes up a functional part of the valve. It follows that a commissure is the junction between adjacent leaflets when the valve is closed (Anderson & Becker, 1992). Following this criterion we can divide the valve tissue of the mouse into separate leaflets.

As for the right AV valve, the septal component of the leaflet tissue is comparable in shape, location and tension apparatus to the septal tricuspid leaflet in humans (Anderson & Becker, 1992). By homology, the parietal component of the right AV valve should correspond to the anterior and posterior leaflets of the human tricuspid valve. Observation of the beating hearts (see also Fig. 13) reveals that this valve opens and closes in a triangular fashion, the vertex of the triangle corresponding to the attachment of the so-called middle papillary muscle. Thus the right AV valve of the mouse works like a tricuspid valve (similar to the human tricuspid), although there is not a separation into distinct leaflets from the morphological standpoint. Another interesting fact is that all the papillary muscles which serve the right AV valve arise from the septal wall; none originates from the free ventricular wall. Furthermore, most of the chordae in the mouse are struts and flat ribbons (instead of free or fan-shaped chordae) which merge with the leaflet tissue. Also, the ventricular face of the right AV valve is virtually free of chordae endings; the presence of muscular chordae is much more frequent than in the human heart and basal chordae are only detected at the level of the septal cusp. The striking location of the papillary muscles of the right AV valve appears to respond to functional demands. The septal leaflet is normally attached to the septal ventricular wall directly, or by means of very short chordae. Hence its mobility is very restricted. During ventricular systole, contraction of the papillary muscles brings the parietal leaflet against the septal side of the AV orifice, effectively preventing blood regurgitation. Should the papillary muscles arise from the anterior and posterior ventricular wall, contraction of the musculature would open the right AV orifice, resulting in valve insufficiency.

The leaflet tissue of the mitral valve is a continuous veil that attaches directly to the papillary muscles. The leaflet tissue of the human mitral valve is also a continuous curtain (Harken et al. 1952), but its free border shows clefts and 'scallops' that are not observed in the mouse heart. It is curious that the left papillary muscles of the mouse do not become completely independent from the ventricular wall. They ascend from the apex to reach the valvular annulus, and only give rise to a very limited number of free chordae. Only the anterior papillary muscle sometimes becomes independent at its tip. Interestingly, papillary muscles running from the heart apex to the valvular annulus, together with the absence of chordae tendinae, have been described in malformed human mitral valves (Wenink et al. 1986). These malformations are believed to be due to deficient or arrested undermining during the embryonic and fetal periods, resulting in a lack of separation of the papillary muscles from the ventricular wall. Thus the mitral valve of the mouse appears to constitute a lower step in the phylogenetic ladder when compared with the human mitral valve. It is unclear at this time whether something similar could be said about the right AV valve. Despite these differences in the papillary and chordal systems, the arrangement of the leaflet tissue is similar to that observed in the human mitral valve.

It is surprising that the morphological differences observed here between the AV valves of the mouse and man have not been pointed out previously. In short, it appears as if most authors have tacitly assumed the universality of valve morphology, overlooking the existence of interspecies differences. General studies of valvular morphology in mammals (Navaratnam, 1980) have not reported significant differences from the human heart. However, the AV valves of the rat (preliminary observations) present the same general morphology as those of the mouse, and it is possible that they may also be similar for other rodents. Interspecies differences between the rat and mouse have also been found, for example, in the density of innervation of the AV valves and chordae tendinae (Williams et al. 1990).

Knowledge of these differences is important not only from the embryological standpoint but also in the context of heart malformations involving the AV region. For example, a high proportion of *iv/iv* mice possess a common AV canal (Icardo & Sanchez de Vega, 1991). In these mice, the right end of the anterior bridging leaflet does not reach the anterior ventricular wall to connect with the anterior papillary muscle, as occurs in a small number of human specimens with nominally the same malformation. The reason for this difference is now clear. In the mouse, no papillary muscles arise from the anterior ventricular wall. The example could be applied to other areas of the heart as well. It is stressed that extrapolation cannot safely be made between species without a full knowledge of the normal embryology and anatomy.

ACKNOWLEDGEMENTS

The authors wish to thank Gema Viar for her expert technical assistance. Thanks are also due to the Marcelino Botin Foundation for continued financial support.

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