Development of the coronary arteries in the embryonic human heart

Grove M. Hutchins, M.D., Abigail Kessler-Hanna, M.D., and G. William Moore, M.D., Ph.D.

ABSTRACT It is not known why the coronary arteries almost always originate only from the right and left aortic sinuses of Valsalva, since the structure and conditions appear to be the same for all six sinuses of the embryonic great arteries. We sought a possible mechanical explanation for the phenomenon by studying the development of the coronary vasculature in 351 staged, serially sectioned human embryos of Carnegie stades 9 through 23 from the Carnegie Embryological Collection. A plexus of blind epicardial capillaries appears on the heart in Carnegie stage 14 or 15 and acquires a coronary sinus connection in stage 15, 16, or 17. The connection of the proximal coronary arteries to the aorta does not appear until stage 18. We found no histologic features of the cardiac nerves or any other component of the tissues to account for the consistent origin of coronary arteries from the right and left aortic sinuses of Valsalva. However, serial section reconstructions showed that the two sinuses where coronary arteries develop acquire a positive transverse curvature and a negative longitudinal curvature, i.e., a catenoidal or saddle-shaped configuration, before the appearance of the coronary arteries. The four noncoronary sinuses also have a positive transverse curvature, but longitudinally, in contrast, they have a positive curvature or are straight. The results suggest that the coronary arteries originate from those sinuses of Valsalva where wall tension is increased by a catenoidal configuration.


IT IS A MATTER of observation that the coronary arteries almost always arise from the aorta, and more specifically, that they almost always originate from the two sinuses of Valsalva adjacent to the pulmonary trunk. The reason for this is not evident from review of the sequence of developmental processes in human embryos.1–7 Examination of the outflow tract and great artery area of normal human embryos in the Carnegie Embryological Collection suggests that the conditions around all six embryonic sinuses of Valsalva of the great arteries are similar at the time that the coronary arteries arise selectively from the right and left aortic sinuses in Carnegie stage 18.8 There are only a few reports describing the sequential changes in development of the coronary circulation in staged human embryos,9,10 and these studies are in disagreement as to the observations on formation of the aortic-to-coronary artery connection. There are several studies on the sequential development of the cardiac vasculature in chickens, rodents, and other species,11–16 but these do not address the question of coronary artery origin and are, in any case, difficult to compare to cardiogenesis in staged human embryos since the reported observations differ from those in human embryos. To examine the sequences of formation of the coronary vasculature and possible mechanisms that could account for the site of origin of the coronary arteries, we reviewed a large series of serial histologic sections of human embryos and prepared three-dimensional reconstructions of selected specimens.

Materials and methods

The serial histologic sections of 351 normal human embryos of Carnegie stages 9 through 23 in the Carnegie Embryological Collection at the University of California, Davis, were examined through the courtesy of Dr. Ronan O’Rahilly, Director of the Carnegie Embryological Laboratories. Most of the embryos in this collection have been catalogued.17–22 Embryos were examined histologically and the presence or absence of a number of anatomic features, especially of the cardiovascular system, was recorded. To prepare three-dimensional reconstructions, the histologic sections of selected embryos were photographed on Kodak Technical Pan 2415 film with use of a 35 mm camera mounted on a Leitz microscope with either a 1.0 X or 2.5 X objective lens. The number of photomicrographs for each embryo varied from every section to every fifth section in the sequence, depending on section thickness, size of the embryo, and rapidity of change in the anatomic relationships between

From the Department of Pathology of The Johns Hopkins Medical Institutions, Baltimore.

Supported in part by NIH grants HL-22963 and HL-34626 from The National Heart, Lung, and Blood Institute.

Address for correspondence: Dr. Grove M. Hutchins, Department of Pathology, The Johns Hopkins Hospital, Baltimore, MD 21205.

Received Oct. 19, 1987; revision accepted March 10, 1988.
adjacent sections. Images were prepared of the sections by projecting the negative and tracing the structures of interest. Alternatively, the negatives for each section used were placed on a 3M "800" microfiche-reader-printer, which magnified the image 94 times. The best exposure was determined and a print was made. The vertebral column and body wall were used for registration. Negatives of a 1 mm graticule, photographed with each embryo, were printed for accurate calibration of image magnification.

Two methods of reconstruction were used. For selected specimens a triaxial isometric reconstruction technique was used. For other specimens the images of the sections were entered into a microcomputer with use of a digitizing tablet and the images were reconstructed. Paper tracings or prints were stacked according to the best fit between adjacent images as determined by the body wall, vertebral column, and other structures. A line was established and used both as a reference line for the embryo as a whole and as a marker so that different sections could be oriented with respect to one another. For the computer-based reconstructions each tracing was placed on a Houston Instruments HIPAD digitizer and the outline of the great artery walls was entered. The X-Y coordinates for each point were transmitted to an Image-80 Image Analysis System (Laboratory Computer Systems, Inc., Cambridge, MA 02142) and the tracings were reconstructed and assembled as three-dimensional images with the use of the incorporated registration line and knowledge of section thickness and interval between tracings. The three-dimensional image could then be examined on the screen and oriented to examine the reconstruction from three orthogonal positions. When properly positioned the images were printed by a Prism Printer (Integral Data Systems, Inc., Milford, NH).

Results

The presence or absence of anatomic features of the outflow tract region of the heart and the coronary vasculature of the 351 embryos of Carnegie stages 9 through 23 judged to be in good condition and reviewed for this project are detailed in table 1. These data, which have been previously published in part, show that while some anatomic features appear abruptly within a stage, others may arise over two or even three different stages in individual embryos. The heart appears in stage 9, acquires asymmetry in stage 10, and has completed the major features of cardiogenesis by stage 19; during this interval the body length has increased over tenfold. Except for the final closure of the membranous interventricular septum, the outflow tract and great arteries have developed their definitive relationships and septation by this time. The coronary vasculature develops in a regular sequence of blood islands or capillaries, coronary venous connections, and the coronary arterial connections.

Blood islands. The first feature of the coronary vasculature to appear, seen in five of 45 stage 14 embryos and 24 of 31 stage 15 embryos, is the collection of blood islands, coronary cords, or incipient capillaries. These islands consist of a layer of endothelial cells distended by a collection of nucleated erythrocytes. At their earliest appearance, the structures are round and have no discernible connection with other islands or with the cavity of the ventricle. The first islands that are seen occur near the ventricular apex in the interventricular sulcus; subsequently they occur in the atrioventricular sulcus and then over other regions of the ventricles. With proliferation of the islands, they coalesce and form the rudiments of a network of vascular channels. The location of the first-formed islands suggest that they form preferentially in the sulci or indentations of the epicardial surface.

It seemed possible that the appearance of the epicardial blood islands was a function of increasing thickness of the compact portion of the myocardium, thereby removing the outer layers further from the intracavitary blood by the interposition of more muscle. To examine this question, the thickness of the compact layer and the distance from the epicardial to the endocardial surface was measured from the available photomicrographs of embryos of stages 9 through 16. The difference between the thickness of the compact myocardium and the endocardial-to-epicardial distance was the thickness of cardiac jelly that could be discerned in the photographs. Surprisingly, the results showed that appearance of the epicardial plexus correlated with the disappearance of cardiac jelly and not with increased wall thickness (table 2). The thickness of the compact part of the myocardial wall showed little change during the period when the plexus appeared, and the overall distance from the chamber cavity to the epicardium actually decreased. All stage 14 and 15 embryos with capillaries, 15 of 25 stage 14 embryos without capillaries, and the seven stage 15 embryos without capillaries all showed no measurable layer of cardiac jelly interposed between endocardium and myocardium.

Another difficult problem was the identification of any connections between the epicardial blood islands and the cavities of the ventricles. In no instance was it possible to show a convincing channel of communication between epicardial vessels and the intertrabecular space. Ten of the specimens of stages 17 through 22 had been injected. In one embryo (stage 17, CE 544) in which an injection of India ink had been made, there was ink within the ventricles and ink within a segment of epicardial plexus; however, no coronary-cameral communication could be identified, and it is probable that the ink had arrived in the coronary plexus by retrograde flow from the coronary vein.

Coronary veins. The establishment of a venous connection of the epicardial plexus to the coronary sinus was observed in one of 31 stage 15 embryos, 12 of 38
stage 16 embryos, and in 27 of 29 embryos in stage 17. With the establishment of the venous connection, there was a reduction in size of the epicardial blood islands, suggesting that they had been drained by the establishment of the venous connection.

**Coronary arteries.** Examination of the root of the aorta and pulmonary trunk showed no clear evidence of any blood vessel, endothelial sprout, or incipient coronary artery in any embryo, in any stage 17 or younger embryo, or in 16 of the 32 stage 18 embryos. In 16 other stage 18 embryos, the origins of the coronary arteries from the appropriate sinuses of Valsalva and their connection to the epicardial coronary plexus were present. Intermediate stages of formation of this connection were not observed; the proximal coronary arteries and their connections were either present or absent in all embryos examined. This observation suggested that the formation of the aorta-to-arterial connection of the coronary vasculature occurred rapidly. The anatomic nature of the establishment of the connection remained uncertain.

In the 16 embryos of stage 18 and in the 93 embryos of stages 19 through 23 with coronary arteries present, all coronary ostia were in the sinuses of Valsalva adjacent to the pulmonary trunk. The entire group of embryos studied were reviewed for any anatomic clue as

### TABLE 1
Presence of selected anatomic features in human embryos of the Carnegie Embryological Collection

<table>
<thead>
<tr>
<th>Carnegie stage</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of embryos</td>
<td>3</td>
<td>12</td>
<td>19</td>
<td>25</td>
<td>25</td>
<td>45</td>
<td>51</td>
<td>31</td>
<td>38</td>
<td>29</td>
</tr>
<tr>
<td>Crown-rump length*</td>
<td>1.8±0.6</td>
<td>2.2±0.8</td>
<td>3.1±0.8</td>
<td>3.8±0.7</td>
<td>4.9±0.7</td>
<td>6.5±0.9</td>
<td>7.8±1.1</td>
<td>9.7±1.5</td>
<td>12.4±1.2</td>
<td>15.0±1.5</td>
</tr>
<tr>
<td>Heart</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interventricular septum</td>
<td>3/19</td>
<td>23/25</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Outflow tract cushions divided</td>
<td>24/45</td>
<td>30/31</td>
<td>36/38</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Aortic sac subdivided</td>
<td>10/31</td>
<td>35/38</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Semilunar valves</td>
<td>3/31</td>
<td>32/38</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Outflow tract cushions joined</td>
<td>27/38</td>
<td>28/29</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Membranous interventricular septum closed</td>
<td>8/32</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary vasculature</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary capillaries</td>
<td>5/45</td>
<td>24/31</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Coronary veins</td>
<td>1/31</td>
<td>12/38</td>
<td>27/29</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Coronary arteries</td>
<td>16/32</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

+ = feature present in all embryos examined.
*Mean ± SD.

### TABLE 2
Measurements from embryos

<table>
<thead>
<tr>
<th>Carnegie stage</th>
<th>Number</th>
<th>Crown-rump length (mm)</th>
<th>Endocardium to epicardium (µm)</th>
<th>Cardiac jelly layer (µm)</th>
<th>Compact layer of myocardium (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>3</td>
<td>1.8±0.4</td>
<td>93±20</td>
<td>77±22</td>
<td>16±2</td>
</tr>
<tr>
<td>10</td>
<td>8</td>
<td>2.5±0.3</td>
<td>98±12</td>
<td>82±12</td>
<td>16±1</td>
</tr>
<tr>
<td>11</td>
<td>17</td>
<td>3.2±0.2</td>
<td>111±5</td>
<td>89±5</td>
<td>22±1</td>
</tr>
<tr>
<td>12</td>
<td>17</td>
<td>3.6±0.1</td>
<td>190±14</td>
<td>138±11</td>
<td>52±5</td>
</tr>
<tr>
<td>13</td>
<td>20</td>
<td>4.9±0.2</td>
<td>128±12</td>
<td>70±12</td>
<td>58±4</td>
</tr>
<tr>
<td>14</td>
<td>31</td>
<td>6.5±0.2</td>
<td>63±6</td>
<td>14±6</td>
<td>49±3</td>
</tr>
<tr>
<td>No BIs</td>
<td>25</td>
<td>6.4±0.2</td>
<td>63±7</td>
<td>17±7</td>
<td>46±3</td>
</tr>
<tr>
<td>Bs</td>
<td>6</td>
<td>6.8±0.5</td>
<td>62±6</td>
<td>0</td>
<td>62±6</td>
</tr>
<tr>
<td>15</td>
<td>29</td>
<td>7.8±0.2</td>
<td>56±2</td>
<td>0</td>
<td>56±2</td>
</tr>
<tr>
<td>No BIs</td>
<td>7</td>
<td>7.5±0.4</td>
<td>47±4</td>
<td>0</td>
<td>47±4</td>
</tr>
<tr>
<td>Bs</td>
<td>22</td>
<td>7.9±0.2</td>
<td>58±3</td>
<td>0</td>
<td>58±3</td>
</tr>
<tr>
<td>16</td>
<td>37</td>
<td>9.6±0.3</td>
<td>79±3</td>
<td>0</td>
<td>79±3</td>
</tr>
</tbody>
</table>

Values are mean ± SE.
Bs = blood islands.
TABLE 1 (Continued)

<table>
<thead>
<tr>
<th>Carnegie stage</th>
<th>19</th>
<th>20</th>
<th>21</th>
<th>22</th>
<th>23</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>18.4 ± 1.5</td>
<td>20.8 ± 1.4</td>
<td>22.7 ± 1.7</td>
<td>25.2 ± 1.3</td>
<td>28.7 ± 2.3</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

11/19 15/17 + + + 20/21
+ + + + +
+ + + + +
+ + + + +

18 and 21, 19 20 21 22 23
18.4 ± 1.5 20.8 ± 1.4 22.7 ± 1.7 25.2 ± 1.3 28.7 ± 2.3
+ + + + +
+ + + + +
+ + + + +
+ + + + +

The possibility that an anatomic configuration distinguished the two sinuses of Valsalva that give rise to the coronary arteries from the four that do not was suggested during the course of following the great arteries in the sequential serial histologic sections. The impression was gained that the aortic sinuses where the coronary arteries arose had a saddle-shaped configuration, and that the other sinuses were either outwardly convex or straight. To examine this impression further, the outflow tract–great artery relationships of two embryos were examined by isometric triaxial reconstructions. One embryo was of stage 17 and did not have coronary arteries. The other embryo was of stage 18 and had coronary arteries (figure 1). The results were the same for both embryos. The two aortic sinuses of Valsalva adjacent to the pulmonary trunk were shaped in such a manner that the curvature in the axial or longitudinal direction was outwardly concave and the curvature in the transverse or circumferential direction was outwardly convex. In contrast, the area of the noncoronary aortic sinus was outwardly convex in both the longitudinal and transverse directions. The three sinus of Valsalva regions of the pulmonary trunk were outwardly convex in the transverse direction and slightly convex or nearly straight in the axial direction. To further examine this matter, the same regions of six other stage 18 embryos were reconstructed by the computer and the three-dimensional images were positioned in anterior, superior, and lateral views (figure 2). The results in these six embryos showed the same configurations of the sinuses of Valsalva described above. Review of the serial histologic sections of the stage 17 and 18 embryos that had not been reconstructed also confirmed the presence of the different configuration of the aortic sinuses adjacent to the pulmonary trunk, from which the coronary arteries normally arise, as compared with the configurations of the other aortic and pulmonary sinuses.
Discussion

This study shows that there is a distinct progression in the development of the coronary vasculature. The earliest appearance of a coronary vascular bed is a group of round blood islands on the epicardium of the interventricular sulcus near the ventricular apex. These blood islands develop preferentially in the sulci of the heart, increase in number, and form a rudimentary plexus. The appearance of the blood islands follows the disappearance of the layer of cardiac jelly between the endocardium and myocardium, which is accompanied by a reduction of the endocardial-to-epicardial distance. Approximately one stage after the islands first appear, a venous connection is established between the coronary sinus and the plexus, and the latter becomes less prominent, presumably as a result of drainage of its contents. In stage 18, well after the appearance of the venous connection, an arterial connection to the epicardial plexus is established, with formation of the coronary artery ostia in the two aortic sinuses of Valsalva adjacent to the pulmonary trunk. The coronary arteries of the normal embryonic heart uniformly arise from these juxtapulmonary sinuses. We saw no clear evidence of any abortive budding, channeling, or other precursors of the coronary arteries in any of the sinuses before the appearance of the definitive connections.

The only anatomic feature we have found that could account for the selective origin of the coronary arteries from the two juxtapulmonary sinuses is the different shape of these two sinuses as compared with the other four. They have a saddle-shaped or catenoidal configuration and differ from the other aortic sinus and the three pulmonary sinuses, which are outwardly convex in shape. The importance of the catenoidal configuration is that it would produce an increase in the tension...
in that component of the wall as compared with tension in portions with an outwardly convex shape, provided there is a uniform transmural pressure difference across the walls of the great arteries. A catenoid is a surface generated by rotation of a catenary, the curve of repose of a chain suspended at both ends, around an axis (figure 3). The catenoid has the property that all points on its surface have orthogonal radii of curvature that are equal but opposite in direction; in effect, all points on the surface of a catenoid have net zero curvature. According to the Laplace relation, the pressure of a fluid contained within a membrane is a function of the tension in the membrane and its curvature.\textsuperscript{24, 25} Given equal transmembrane pressure differences, then the tension in a highly curved membrane will be less than that in a membrane with a lesser curvature. Applying these same considerations to a tissue membrane such as a blood vessel wall would suggest that where the curvature resembles the catenoid, i.e., has a saddle shape with a low net curvature, the wall tension will be greater than where the wall has a more positive curvature. We postulate that the explanation for the consistent origin of the coronary arteries from those sinuses with a catenoidal configuration is an increase in mural tension compared with that in the other potential sinuses of origin.

The anatomic observations of this study are largely in agreement with those of Hirakow,\textsuperscript{9} who studied 52 staged human embryos in the collection at Kyoto University. He described the same sequential development of coronary capillaries, coronary veins, and coronary arteries that we have observed in the embryos of the Carnegie Embryological Collection. Hirakow does not speculate on the reason for the consistent origin of the coronary arteries from the juxtapulmonary aortic sinuses of Valsalva. The other study on the development of the coronary vasculature in staged human embryos is by Conte and Pellegrini,\textsuperscript{10} who reviewed 33 embryos in the collection of the University of Pisa. These investigators describe the development of the epicardial plexus but then state that the veins and arteries arise simultaneously, the latter as a preferential selection among numerous buds in the aorta and pulmonary trunk. They do not suggest an explanation as to how the definitive coronary artery origins are selected from among the various possible sites of origin. Hackensellner,\textsuperscript{26} in a review of 63 human embryos ranging in length from 12 to 36 mm, reported similar observa-

\textbf{FIGURE 3.} Diagram of a catenoid. \textit{A}, A catenary, the curve of repose of a suspended chain, is rotated about an axis. \textit{B} and \textit{C}, Points on the catenoid have orthogonal curvatures that are equal but opposite in direction. Thus, the net curvature of the surface is zero at all points.
tions on endothelial budding. As noted above, our observations are more similar to those of Hirakow; we did not find convincing evidence of abortive vessels arising in the pulmonary or noncoronary aortic sinuses of Valsalva. We did observe small indentations of the endothelium into the arterial walls similar to those illustrated by Conte and Pellegrini and by Hackensellner, but we interpreted these areas as being secondary to changes that could have occurred with cessation of blood flow and contraction of the vessel or from preparation of the histologic sections. However, since the coronary arteries presumably do arise by endothelial outgrowth from the juxta- pulmonary aortic sinuses, it is attractive to speculate that such attempts at endothelial outgrowth are occurring throughout the sinuses but succeeding only where wall tension is elevated because of a saddle-shaped configuration.

Descriptions of the development of the coronary vasculature in other species emphasize the establishment of epicardial coronary vessels from the sinusoids with the eventual loss of capillary-sinusoidal connections. This phenomenon seems to be rare in the human embryo. We failed to encounter a single unequivocal example of a connection between the epicardial coronary vessels and the ventricular chambers in the specimens studied. There have been a number of reports of coronary-cameral fistulas occurring as abnormalities in the human heart, but evidence that these represent the persistence of a normal phase of development comes from comparative embryology. In humans, the first traces of the coronary vasculature are the distended blood islands that subsequently deflate with establishment of the venous connection. If the epicardial islands were derived from and in continuity with the cavity it would seem less likely that they would show this early and uniform distention.

If indeed the location of the coronary artery ostia is determined by the configuration of the roots of the great arteries, it would be reasonable to expect that in those situations in which the coronary arteries arise from ectopic sites there may have been an alteration in the normally catenoidal shape of the sinus. In transposition of the great arteries, the coronary arteries most commonly arise from the juxta-pulmonary aortic sinuses, even though the relative positions of the great arteries on the heart are altered. It is possible that in this condition the aortic root still retains a catenoidal shape for the sinuses of origin of the coronary arteries during the critical stages of development. This question cannot be answered at present.

In conclusion, the normal coronary vasculature of the embryonic human heart begins as a group of epicardial blood islands, endothelium-lined cysts filled with nucleated erythrocytes, in the apical interventricular sulcus at Carnegie stage 14 or 15. An epicardial capillary plexus forms from proliferation of these islands and a venous connection to the coronary sinus is established in stage 15, 16, or 17. Coronary artery origins do not appear until stage 18, and arise normally only from the juxta-pulmonary aortic sinuses. The only anatomic feature found to account for this selective site of origin is the distinctive saddle-shaped or catenoidal configuration of these two sinuses as compared with the other four. The catenoidal shape would be expected to increase mural tension within these sinuses, which may explain how the aortic endothelium could penetrate the mural tension preferentially at these points and establish connection with the epicardial coronary plexus.

References
Development of the coronary arteries in the embryonic human heart.
G M Hutchins, A Kessler-Hanna and G W Moore

*Circulation.* 1988;77:1250-1257
doi: 10.1161/01.CIR.77.6.1250
*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/77/6/1250

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation* is online at:
http://circ.ahajournals.org//subscriptions/