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CLOSURE OF THE DUCTUS ARTERIOSUS IN NORMAL AND MALFORMED HUMAN HEART*)

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ABSTRACT

Histopathological studies were made on 9 necropsy specimens of ductus arteriosus with hypoplastic left heart syndrome and I with rubella syndrome. A control group of 40 normal specimens were also studied. In the 17th week of gestation, ductus arteriosus was composed of few elastic fibers, a thick continuous internal elastic lamina and a wide hypocellular area. In the 8th month of gestation, there was a disruption of the internal elastic laminas, partially degeneration on inner layer of the media and circular fashion arrangement of smooth muscle fibers. In the 40th week of gestation, there was a thickening of the intima, a regular arrangement of muscle fibers in the outer layer of the media, cell degeneration between the intima and the outer layer of the media, presence of cleft tissue in the inner and outer layer of the media, an irregular arrangement and a whorl-like muscle nodles in the intermediate layer of the media. In the term fetuses, there was prominent mounds and disruption of the internal elastic lamina, and disintegretion of medial structure.

In a case with rubella syndrome there was an absence of disruption of the internal elastic lamina and of mounds or intimal thickening and presence of abundant elastic fibers in the media as in the aorta. In a case with hypoplastic left heart syndrome the internal lamina was thick and continuous, and no mounds were observed. There was aboundant elastic fibers in the media, while in 5 hearts there was a lower mounds, disruption of internal elastic lamina and relatively well developed elastic fibers in the media. Two hearts with hypoplastic left heart syndrome showed normal ductus arteriosus. Based on the data from this observation it was suggested that congenital structural anomalies of the ducutus arteriosus play an important role in the formation of patent ductus arteriosus.

INTRODUCTION

Normal mode of closure of the ductus arteriosus (DA) is not well documented yet. In 1963, Kovalicik[1] observed that spiral strips or rings cut from the DA of sheep and guinea pig fetuses and suspended in warm Tyrode or Ringer's solution contracted as the O_2 concentration of the gas passing through the solution was increased, and relaxed when O_2 was

*) 今村甲，岡本直正：正常及び異常ヒト心の動脈管閉鎖

Table 1. Number cases

	Total	Gestational Age (month)							neonate			
		4	5	6	7	8	9	10	1	2	3d	1m
Normal	45	5	7	13	5	1	4	8	1		1	
Hypo-A*	9				1			6		2		
Rubella	1											1

*Hypo-A; hypoplastic left heart syndrome

replaced by N_2. He concluded that O_2 causes constriction of the DA by a direct action on the smooth muscle. Thus, it has been believed by most of investigators that O_2 plays an important role in the natural closure of the DA. However, a question arises as to whether or not the O_2 deficiency may definitively be related to patency of the DA.

There have been many reports that the incidence of complication of the respiratory distress syndrome (RDS) is high in preterm infants with patent ductus arteriosus (PDA) and a number of investigators believe that PDA results from hypoxia due to respiratory distress[2,3].

On the other hand, Deslingneres et al[4] described that there was observed no histological difference in the DA between the patients with RDS and those without.

In this respect, one has to consider separately PDA in patients with congenital cardiac deformity viable with patency or requiring surgical treatment, and PDA in premature infants. PDA in the latter has a possibility of natural closure with the advance of age.

Recently it has been clarified that indomethacin, an inhibitor of prostaglandin synthesis, is useful in closing the DA in premature infants, but the other reports deny the effectiveness in infants weighing under 1,000 g in body weight. A question arises as to whether or not there is any peculiar histological difference between indomethacin effective and ineffective PDAs.

Subsequent to our previous report[5] on the closure of the DA in normal and malformed human hearts, we obtained additional cases and general discussion is made here on listological findings of the DA in an attempt to clarify the problem described above.

MATERIALS AND METHODS

The specimens of the DA of human fetal and neonatal hearts were collected from Department of Genetico-pathology, Research Institute for Nuclear Medicine and Biology, Hiroshima University, and from the Nagasaki Central Hospital. These cases consisted of normal and abnormal DA as shown in Table 1.

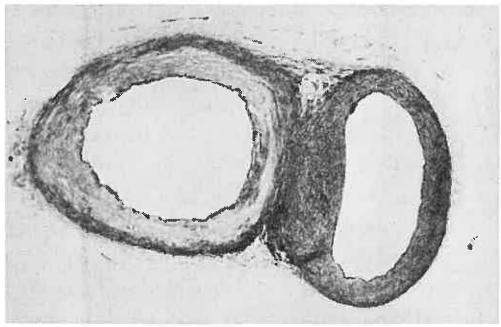

Fig. 1. Transverse section of the DA (left) and the pulmonary artery (right). 17 week of gestation. (Weigert's elastic stain). DA is very scanty of elastic fibers in the media, while the pulmonary artery shows abundant and thick elastic fibers.

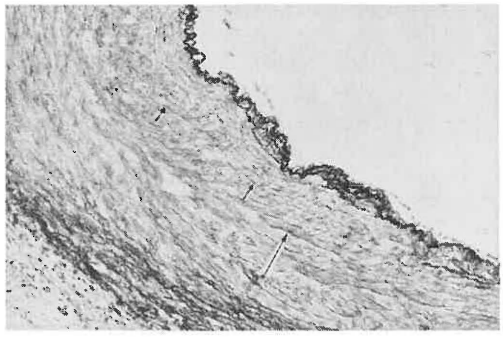

Fig. 2. Higher magnification of the DA shown in Fig. 1. The elastic fibers are sparce, frail and fragmented (→).

The DA was sectioned transversely or longitudinally, and histological sections were stained with H. E., Weigert elastic or elastica van Gieson methods. Some specimens were observed by electron microscope after usual fixation, embedding and staining.

The DA that might be naturally closed during early postnatal kife was defined as normal and what might be patent even in adult life was defined as abnormal.

RESULTS

I. *Normal ductus arteriosus*

Histologically, the DA differed from the aorta and pulmonary artery which were rich in elastic fibers. The DA essentially consisted of smooth muscle fibers and few elastic fibers.

In the 17th week of gestation, as shown in Fig. 1, 2 and 3, the pulmonary artery was composed of abundant elastic fibers, whereas in the DA few elastic fibers, a thick continuous internal elastic lamina and a wide hypocellular area were observed. Electron microscopically, endothelial cells which contained sparse glycogen particles, a continuous internal elastic lamina with granular to rod shaped tiny elastic fibers, obliquely arranged smooth muscle-like cells beneath the lamina, widened intercellular spaces containing mainly amorphous materials suggestive of mucopolysaccharide and scanty elastic and collagen fibers in caveola were observed in the DA (Fig. 3). Cells in the media were considered to be smooth muscle cells, but they could not be defined so since no myofilament was detected.

In the 8th month of gestation as shown in Fig. 4 and 5 intimal mounds or cushions protruding into the lumen were observed, and the internal elastic lamina was disrupted. The lumen of the DA was narrowed. Cells in the inner layer of the media were partially degenerated. In the outer layer, smooth muscle fibers were arranged in a circular fashion.

In the 40th week of gestation, as shown in Fig. 6, 7 and 8 the thickening of the intima

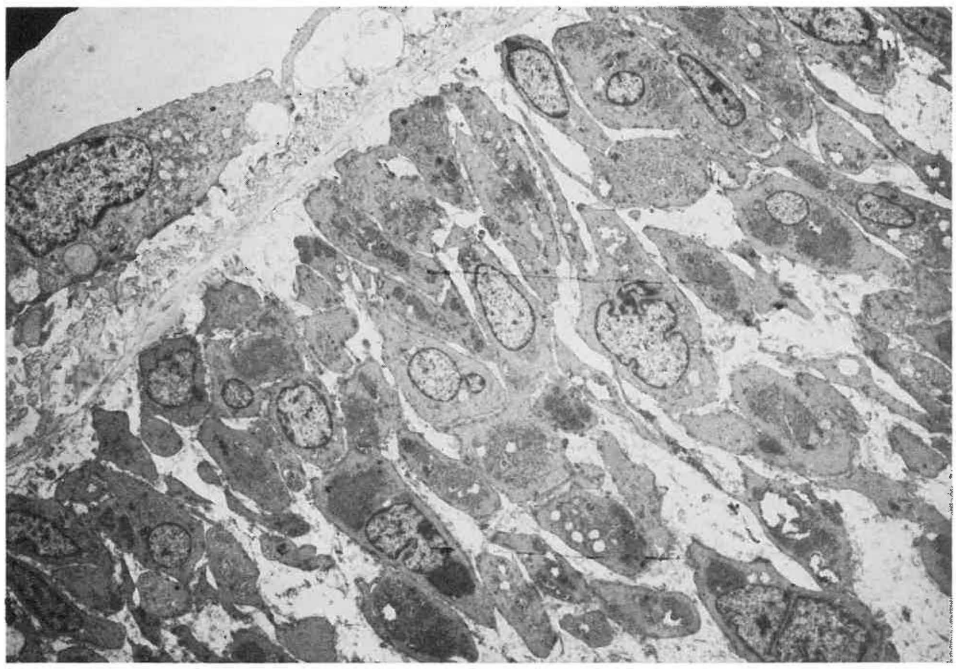

Fig. 3. Electron microscopic feature of transverse section of DA. 17 week of gestation. Endothelial cells contained sparce glycogen particles, a continuous internal elastic lamina with granular to rod shaped tiny elastic fibers, obliquely arranged smooth muscle-like cells beneath the lamina, widened inter-cellular spaces containing mainly amorphous materials suggestive of mucopolysaccharide.

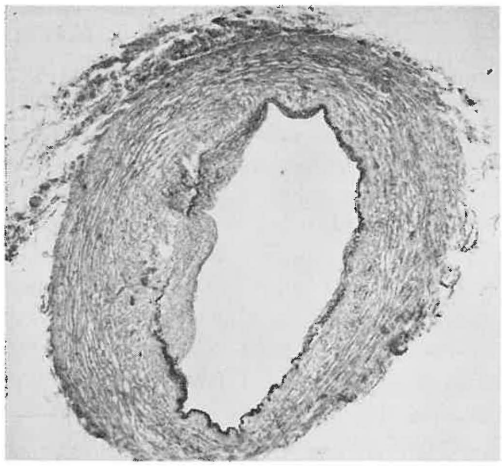

Fig. 4. Transverse section of the DA. 8 months of gestation. (Weigert's elastic stain). Intimal mounds protruded into the lumen, and internal elastic lamina beneath the mounds is disrupted.

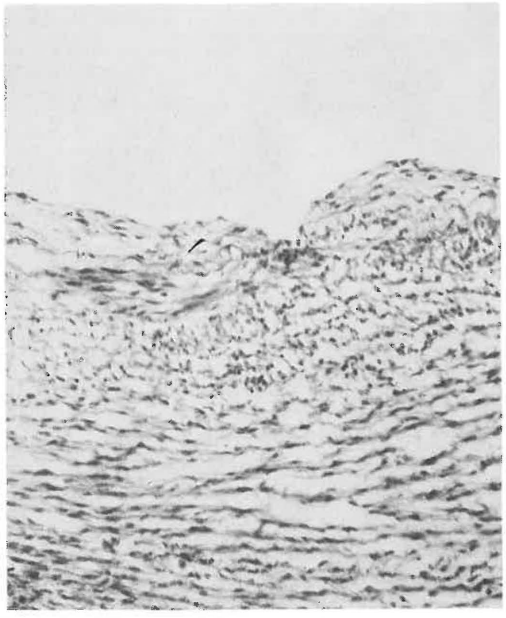

Fig. 5. Transverse section of the DA. 8 months of gestation. (HE stain). Cells in the inner layer of the media are partially degenerated.

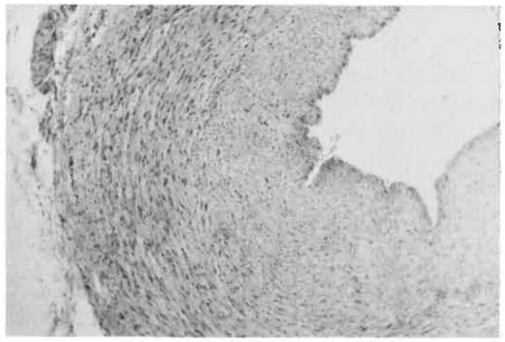

Fig. 6. Transverse section of the DA. 40th week of gestation. (HE stain). Thickening of the intima is prominent.

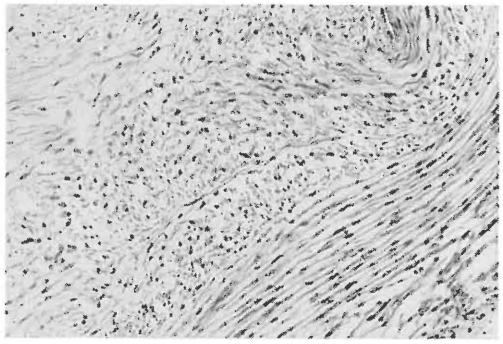

Fig. 7. Transverse section of the DA. 40th week of gestation. (HE stain). Arrangement of muscle fibers in the outer layer of the media (below) are still regular. The intermediate zone between the intima (left upper) and the outer layer of the media shows cell degeneration.

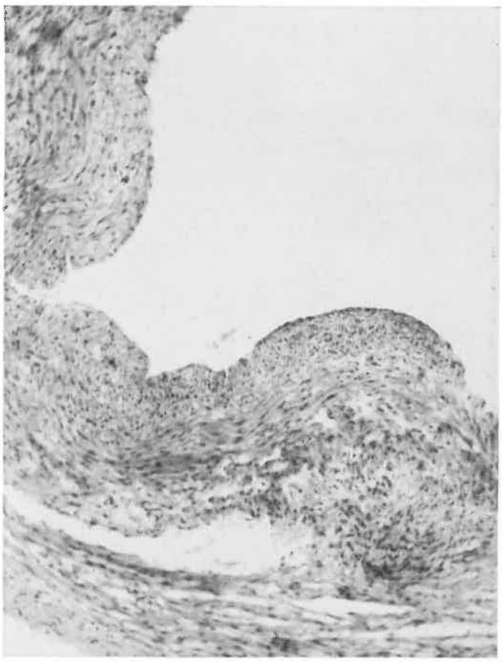

Fig. 8. Transverse section of the DA. 40th week of gestation. (HE stain). In the inner layer of the media beneath the thickned intima, the usual structural pattern of the media is lost and whorl-like muscular nodules is present.

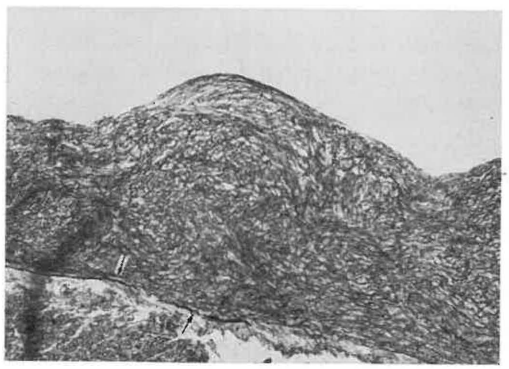

Fig. 9. Sagittal section of the DA. 40th week of gestation. (Weigert's elastic stain). Disruption and narrowing of the internal elastic lamina (→).

was prominent, but the arrangement of muscle fibers in the outer layer of the media were still regular. The intermediate zone between the intima and the outer of the media showed cell degeneration which is characteristic in the term stage. In the inner and outer layers of the media, a cleft of tissue was noticed. Although this may be an artefactial phenomenon, it can be considered to be a locus minoris which is easily disrupted by artificial effects. Smooth muscle fiber in the intermediate layer of the media showed an irregular arrangement and partially showed a whorl-like muscular nodules.

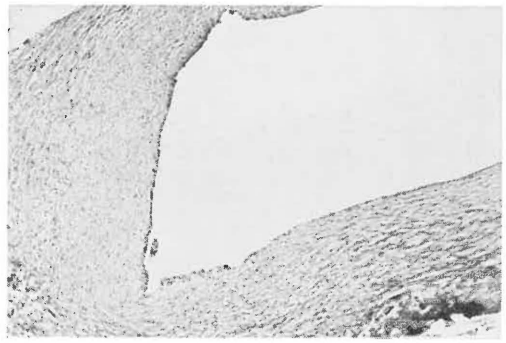

Fig. 10. Transverse section of the DA. One month old infant with rubella syndrome. (Elastica Van Gieson's stain). The presence of abundant elastic fibers in the media as in the aorta. Absence of disruption of the internal elastic lamina and of intimal thickening.

In the term fetuses, the DA showed prominent mounds and disruption of the internal elastic lamina, subsequent narrowing of the lumen and disintegretion of medial structure.

One day after birth, as shown in Fig. 9 the DA showed similar findings with those of term fetuses. No histological difference in the DA was observed between preterm or term stillborns and neonates within 3 days after birth.

Thus, the histological structure of normal DA changed with the advance of fetal age, and it was assumed to behave to accomplish the natural closure very easily.

II. *Abnormal ductus arteriosus*

In a case with rubella syndrome who was born at 42 weeks of gestation and weighed 1,700 g at birth, as shown in Fig. 10, the histological structure of the DA differed from that of normal term fetus in absence of disruption of the internal elastic lamina and of mounds or intimal thickening and the presence of abundant elastic fibers in the media as in the aorta.

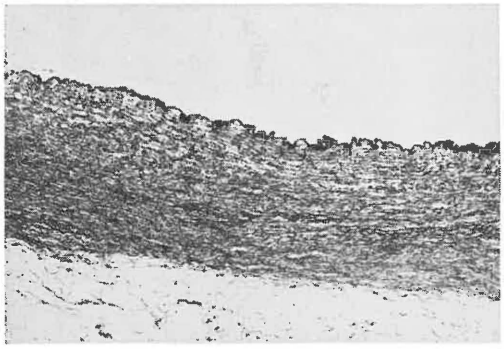

Fig. 11. Sagittal section of the DA in an infant who lived 2 days with hypoplastic left heart syndrome. (Weigert's elastic stain). The internal elastic lamina is thick and continuous, and no mounds are observed. The media contains abundant elastic fibers.

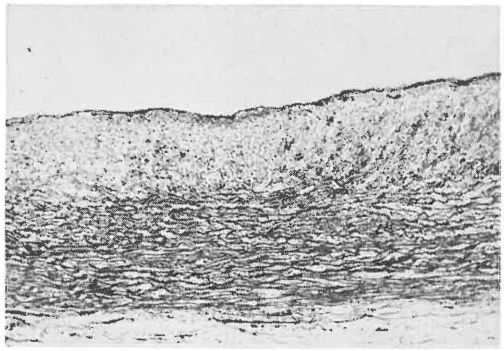

Fig. 12. Sagittal section of the DA in an infant with hypoplastic left heart syndrome. (Weigert's elastic stain). The internal elastic lamina is thick and continuous, and no mounds are observed. The outer layer of the media containing abundant elastic fibers.

Table 2. Classification of hypoplasia of the aorta (aortic hypoplasia) and hypoplastic left heart syndrome

1) Isolated hypoplasia of the ascending aorta.
   a. The ascending aorta is small and the pulmonary artery is large, with no dilatatation of the right heart, and with a relatively normal sized left ventricle.
   b. The ascending aorta is small and the pulmonary artery is large, with dilatation of the right atrium, ventricle, pulmonary artery, and with no hypoplastic left ventricle.
   c. With dilatation of the right atrium and ventricle and correspondingly small left sided heart. The most commonly associated anomaly is a coarctation of the aorta or tubular hypoplasia.
2) "Hypoplastic left ventricle syndrome"
   The basic features of this group are: (1) rudimentary left ventricle, (2) dilatation and hypertrophy of right-sided chambers, (3) small- to normal-sized left atrium, (4) hypoplastic ascending aorta, and (5) widely patent ductus arteriosus.*
3) Hypoplasia of the ascending aorta with ventricular septal defect.**
4) Coexistent hypoplastic ascending aorta and diaphragmatic hernia.
   These groups are associated with left diaphragmatic hernia.***
5) Coexistent hypoplastic ascending aorta and abdominal hernia (eventration).

Other associated conditions include: *aortic valve atresia, mitral valve atresia or stenosis, and atresia,, hypoplasia of the aortic arch, coarctation of the aorta, bicuspid aortic valve, herniation and prolapse of the valve of the foramen ovale into the right atrial cavity;** coarctation of the aorta, patent foramen ovale, bicuspid aortic valve or bicuspid aortic and pulmonic valves; ***bilateral or unilateral absence of pulmonary artericsy and lungs, mild or severe hypoplasia of the left lung.

In a case with hypoplastic left heart syndrome which is of mitral atresia and hypoplastic aortic arch who survived for two days after birth, as shown in Fig. 11, the internal elastic lamina was thick and continuous, and no mounds were observed. The media containing abundant elastic fibers resembled that of the aorta or pulmonary artery.

In a fetus of the 40th week of age with hypoplastic left heart syndrome, similar findings with those of normal neonates were observed. These findings observed in hypoplastic left heart

syndrome suggested the difficulty of natural closure of the ductus arteriosus (Fig. 12).

Hypoplasia of the aorta and hypoplastic left heart syndrome have been classified in detail by Okamoto[6] as shown in Table 2. The DA in every type of isolated hypoplasia of the ascending aorta and hypoplastic left heart syndrome was examined histologically, but no specific or identifiable findings were detected. Seven cases of abnormal DA were observed among 9 cases of these anomalies. One of the remaining two cases showed normal ductus. The other case showed an intermediate form of normal and abnormal ductus. In this case, a lower mound, disrupted internal elastic lamina and relatively well developed elastic fibers in the media were noted. This fact indicates that the DA of hypoplastic left heart syndrome is not always abnormal in the structure, and there are intermediate forms.

DISCUSSION

In the fetal period, the DA is classified into normal and abnormal from the structural view point, and their sequences are already determined[7].

Patterson[8] reported that the wall of hereditary patency of the DA such as the aorta and pulmonary artery in poodle consisted of rich elastic fibers. Thus, in general, it is assumed that the structure of abnormal PDA which persists through adult life may be determined genetically. Normal DA changes the structure with fetal age, and prominent intimal thickening, disruption of the internal elastic lamina and degeneration of the media occur at term. These findings may indicate the preparatory states for natural closure in postnatal life.

On the other hand, the internal elastic lamina in abnormal DA is continuous even at term as in early fetal period. Intimal thickening and mounds are not observed, and elastic fibers in the media are abundant as in the aorta and pulmonary artery. Such a ductus may retain its abnormal structure after birth and natural closure may not occur.

In the premature infants with PDA, the type of ductus may be classified as normal, and the capability of natural closure may be retained if they survive until complete maturity comparable with 40 weeks of fetal age.

Recently, it has been clarified that administration of indomethacin to premature infants with PDA suffering from cardiac failure is effective to close the DA. Coceani and Olley[9] stated that prostaglandin E_1 and E_2 may have a role in maintaining the patency of the ductus prior to birth and that the ductus closes as it is weakened. The relaxant action of prostaglandin E_1 and E_2 develops fully under anaerobic condition. On the other hand, the force to keep the DA patent may be weakened in high O_2 concentration, resulting in closure of the DA.

It has been well documented that indomethacin is effective in some cases but not effective in some others to close PDA in premature infants. Particularly, failure of indomethacin to close PDA in infants weighing under 1,000 g[10,11] has been reported by many investigators. This fact suggests that the ability of closure of the PDA in these immature infants is still immature to react to this drug.

Before the discovery of indomethacin, the therapy for PDA or its complication such as cardiac failure had been conservative waiting until maturity, when the DA would show natural closure, although there were many cases of death due to cardiac or respiratory failure in premature infants with PDA before the discovery of this drug. Recent progress in treatment of PDA with indomethacin has increased the survival rate though ineffective cases have also been experienced. The individual difference in effectiveness of the drug may be attributed to the individual difference in the genetically and environmentally determined structure and the conditions of receptors of the DA.

Most of the cases with hypoplastic left heart syndrome showing abnormal or nearly abnormal structure of the DA are provided with requirements for survival, but it has to be noted that normal structure remains in some cases which may result in cardiac failure.

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