

Original Article

Prenatal Diagnosis of Interrupted Aortic Arch: Usefulness of Three-Vessel and Four-Chamber Views

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Interrupted aortic arch (IAA) is fatal if not diagnosed. Prenatal diagnosis is helpful, but it is difficult to detect IAA and even more so to differentiate types A and B prenatally. Our objectives were to find a way to detect IAA using 2 views—three-vessel view (3VV) and four-chamber view (4CV)—and to differentiate between types A and B. We retrospectively analyzed fetal echocardiographic images and medical records of eight IAA patients. All eight patients had a ventricular septal defect (VSD) on 4CV. The aorta/main pulmonary artery (Ao/MPA) diameter ratio on 3VV was significantly low, which is characteristic of type B IAA. The left/right ventricular diameter (LV/RV) ratio on 4CV was 0.61 ± 0.17 for type A and almost 1.0 for type B. The thymus was not observed on 3VV in some type B IAA patients. These findings suggest that we could increase the number of prenatal diagnoses of IAA using the Ao/MPA ratio on 3VV and the presence of VSD on 4CV. Additionally, we could differentiate types A and B with the LV/RV ratio on 4CV, the Ao/MPA ratio, and the presence of a thymus on 3VV, which results in better management of IAA after birth.

Key words: interrupted aortic arch, three-vessel view, four-chamber view, aortic diameter/main pulmonary artery diameter ratio, ventricular septal defect

Interrupted aortic arch (IAA) is a rare disease in which ductal shock is caused when the arterial duct closes postnatally, making prenatal diagnosis crucial. Using the Celoria-Patton classification [1], we classified IAA into types A, B, and C according to the interruption site. In a previous study, 65% of cases were type B, 30% were type A, and 5% were type C [2]. Type A is rarely associated with the 22q11.2 deletion syndrome, whereas type B is closely related to it. The 22q11.2 deletion syndrome is characterized by various abnormalities, including palatal malformation, velopharyngeal incompetence, submucosal cleft palate, bifid uvula, cleft palate, and thymus

hypoplasia [3]. We are working toward being able to diagnose IAA more successfully and to differentiate type A from type B prenatally.

The development of ultrasonography (US) in general and fetal US imaging in particular has made it possible to diagnose IAA prenatally, but the diagnostic yield is still low, with only a few reports on useful screening methods [4-8]. It remains difficult to differentiate type A IAA from type B prenatally.

IAA has a low incidence, with 0.09 per 1,000 live births [9], making the investigation of multiple cases difficult. In addition, at first glance, IAA appears normal in a four-chamber view (4CV), and a long-axis view of the aortic arch is difficult to render. Thus,

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depending on the position and orientation of the fetus and its gestational age, screening for the presence of IAA is difficult. Compared to the long-axis views, observation is easier with short-axis view, *i.e.*, a three-vessel tracheal view (3VTV), three-vessel view (3VV), and 4CV. 3VTV is usually used for IAA screening, but 3VTV images are not clear, and we cannot confirm the presence of an interrupted aortic arch even if we change the timing of the imaging. Herein we describe 8 cases of IAA in which we retrospectively investigated the usefulness of 3VV and 4CV imaging to screen for fetal IAA.

Patients and Methods

The subjects were eight infants whose IAA was diagnosed and confirmed postnatally. They were among the 225 infants with congenital heart disease managed from the prenatal stage who had been born at the Okayama University Hospital Perinatal Center in the years 2008–2015. IAA was definitively diagnosed at 1 day of age based on the findings obtained by echocardiography and postnatal multidetector row computed tomography. Okayama University Hospital approved this study (No. 1512–014, December 22, 2015). The protocol for the study was open. It was posted for the public to read in our hospital and on the home page of our department's website. With this information, the informed parents or legal guardians of the infants could decline participation in the study if they so desired.

Using the Celoria-Patton classification [1], we categorized the 8 patients' IAA into types A, B, and C based on the interruption site. Type A was an interruption distal to the left subclavian artery. Type B was an interruption between the left common carotid artery and the left subclavian artery. The interruption for type C was between the left common carotid artery and the innominate artery [1]. Type A (and perhaps type C) IAA are thought to be due to abnormal flow *in utero* [9], which means that low blood flow caused the aorta to narrow during the fetal period.

Type A may be a severe form of coarctation of the aorta (CoA). By contrast, type B is considered a conotruncal defect along with tetralogy of Fallot and truncus arteriosus [9], and it is closely related to the 22q11.2 deletion syndrome [10]. In the present study, there were 4 cases of type A and 4 cases of type B, with no cases of type C. All patients were referred to

our hospital at the fetal stage. The median gestational age at the time of referral was 31 weeks, range 24–38 weeks. Most of the reasons for referral were abnormal 3VV images. Seven patients were managed as IAA or CoA from the fetal stage. The remaining patient was managed as a diaphragmatic hernia because IAA was not identified during the fetal stage. Among the 225 infants with congenital heart disease, only one was thought to have IAA and was diagnosed with CoA after birth.

At our hospital, 3 obstetricians performed the fetal echocardiography at the time of the referral assessments. The 4CV and 3VV images were then sent to the electronic medical records (EMRs) department, where they stored. We used these data for the present analyses. The aortic valve (AoV) and pulmonary valve diameters during systole along with the Ao diameter and the main pulmonary artery (MPA) diameter on 3VV were measured and saved in the EMRs. Based on these images and the saved EMRs, we retrospectively investigated the AoV diameter, the pulmonary valve diameter, the AoV/pulmonary valve ratio, and the Ao/MPA ratio obtained from 3VV images; the presence of ventricular septal defect (VSD); and the presence of a thymus. We then used the average diameters, which had been measured three times by 2 obstetricians, for the analyses.

We also carried out a comparative study for IAA with six control cases that were chosen because they were postnatally confirmed at our hospital to have a single VSD. There were only 6 single VSD cases among the 225 infants with congenital heart disease from the prenatal stage who were born at our hospital during the above-mentioned study period. Four had muscular VSD, and 2 had membranous VSD. Echocardiography had been performed at the median gestational age at the time of referral of 34.5 weeks (25–38 weeks).

Other authors have reported reference curves for the AoV diameter, pulmonary valve diameter, and AoV/pulmonary valve ratios [11–13]. We used a graph from the literature [9] for these values.

We used JMP®10.0.2 statistical software (SAS Institute Japan, Tokyo, Japan) for the statistical analyses. We also used a Wilcoxon test. A value of $p < 0.05$ was considered to indicate statistical significance. The US equipment used were the Volson E8 (GE Healthcare Japan, Tokyo, Japan) and Alpha 6

(Hitachi Aloka Medical, Tokyo, Japan) systems with convex-type probes (3.5 MHz).

Results

The characteristics of the eight IAA patients, including the diagnoses, complications, chromosome tests, birth weights, birth weeks, and surgery durations, are shown in Table 1. Relatively large VSDs were observed on fetal US in the outflow tract on 4CV images of all 8 patients. In a previous study, the MPA, Ao, and superior vena cava were observed to

be large, medium, and small, respectively, on normal 3VV images [14], whereas we observed their sizes to be large, small, and small, respectively, in all type A (Fig. 1A) and type B (Fig. 1B) cases.

In addition, the AoV diameter was smaller than those within the reference range (Fig. 2A), and the pulmonary valve diameter was larger (Fig. 2B). Although the reference value was essentially constant at 0.8–1.0 regardless of the gestational week [11,12], the average AoV/pulmonary valve ratio in the IAA patients was 0.49 ± 0.09 (Table 2). The average AoV/pulmonary valve ratio in the 6 control subjects

Table 1 Summary of 8 patients with interrupted aortic arch (IAA)

Pt.	Gestational wks at reference	Type	Diagnosis after birth	Complication	Thymic presence	Chromosome analysis	Birth week Birthweight	Operation time
1	32	A VSD	bicuspid aortic valve		Yes	normal	36w6d 3,038g	9th day after birth
2	31	A VSD	bicuspid aortic valve		Yes	—	39w6d 3,078g	4th day after birth
3	38	A VSD		cleft and palate diaphragmatic hernia	Yes	46,XX,dup(5)(q31.1q33.1)	39w3d 2,552g	20th day after birth
4	33	A VSD	mitral atresia DORV	hydrops fetal	Unknown	—	35w3d 3,989g	death
5	24	B VSD	truncus arteriosus		Yes	—	40w1d 3,124g	18th day after birth
6	30	B VSD			No	22q11.2deletion syndrome	41w0d 3,058g	11th day after birth
7	30	B VSD	bicuspid aortic valve	aplasia of soft palate	No	22q11.2deletion syndrome	37w3d 2,578g	10th day after birth
8	31	B VSD	bicuspid aortic valve	aplasia of soft palate	No	22q11.2deletion syndrome	39w3d 2,512g	4th day after birth

VSD, ventricular septal defect; DORV, double outlet right ventricle.

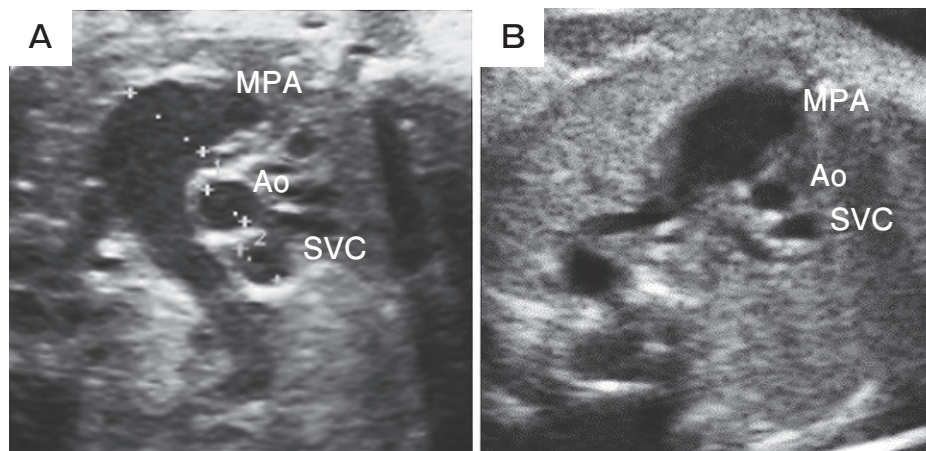


Fig. 1 **A:** Three-vessel view (3VV) of a case of interrupted aortic arch (IAA) type A. **B:** 3VV of a case of IAA type B. The main pulmonary artery (MPA), aorta (Ao), and superior vena cava (SVC) are observed as being large, small, and small, respectively. The MPA was enlarged, and the Ao was narrow. The Ao was the same size as, or smaller than, the SVC.

with a single VSD was 0.80 ± 0.08 (Table 3), which was significantly higher than that of the IAA patients ($p = 0.0019$) (Fig. 2C).

The average Ao/MPA ratio from the 3VV was 0.47 ± 0.10 , which was the same as the AoV/pulmo-

nary valve ratio (Table 2). The average Ao/MPA ratio measured on the 3VV was 0.53 ± 0.05 for type A and 0.41 ± 0.01 for type B. The type B infants had very low Ao/MPA ratios (0.33 and 0.29), whereas the type A infants did not (Table 2). The average left

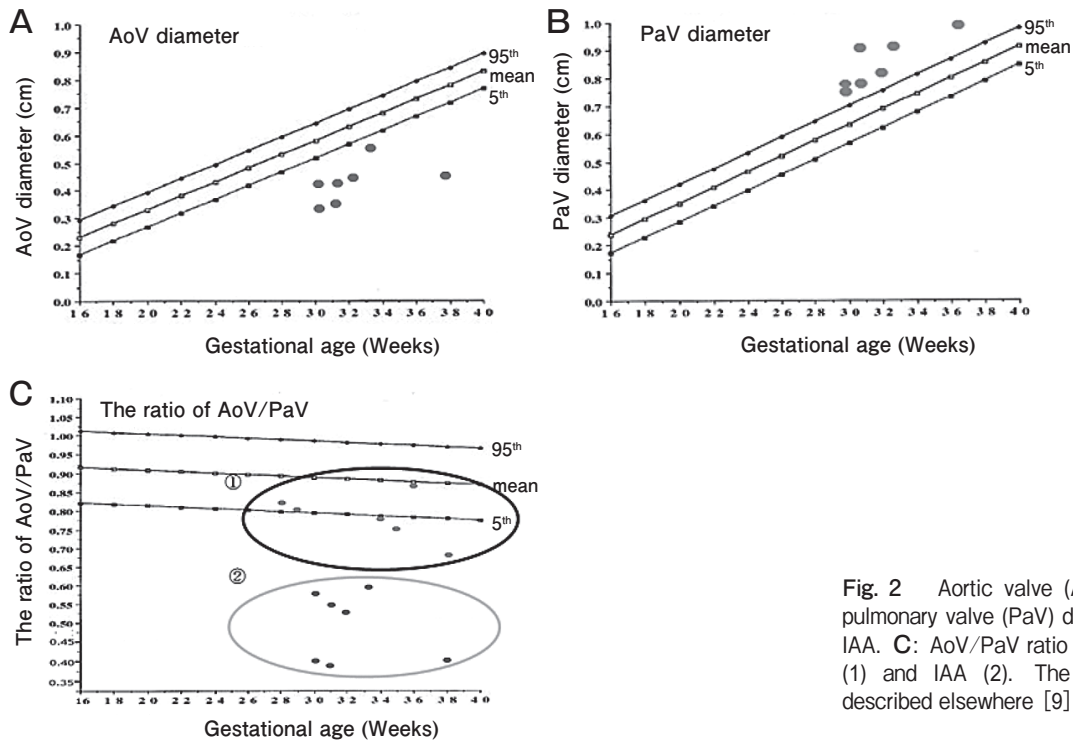


Fig. 2 Aortic valve (AoV) diameter (A) and pulmonary valve (PaV) diameter (B) of cases of IAA. C: AoV/PaV ratio in cases with only VSD (1) and IAA (2). The reference values are described elsewhere [9].

Table 2 Aortic valve/pulmonary valve and aorta/main pulmonary artery ratios on three-vessel views.

Case	Fetal age at time of echocardiography (wks)	AoV/pulmonary valve ratio	Ao/MPA ratio from 3VV	LV/RV ratio
Type A				
1	32	0.53	0.5	0.75
2	31	0.55	0.5	0.42
3	38	0.41	0.6	0.67
4	33	0.6	0.5	—
Average		0.52 ± 0.08	0.53 ± 0.05	0.61 ± 0.17
Type B				
5	24	—	0.5	1
6	30	0.4	0.5	1
7	30	0.57	0.33	1
8	31	0.38	0.29	1
Average		0.45 ± 0.10	0.41 ± 0.11	1
Average of all cases		0.49 ± 0.09	0.47 ± 0.10	0.8 ± 0.23

Ao, aorta; AoV, aortic valve; LV/RV, left ventricle/right ventricle diameters ratio; MPA, main pulmonary artery; 3VV, three-vessel views.

ventricle/right ventricle diameters (LV/RV) ratio was 0.61 ± 0.17 in the 3 type A cases (excluding the case complicated by mitral atresia), whereas it was almost 1.0 in the 4 type B cases (Table 2).

Fig. 3 shows postnatal chest CT scans and fetal US images in 3VV of types A and B. Aplasia/hypoplasia of the thymus was observed on a chest CT scan in a patient with type B IAA, which indicated a diagnosis of the 22q11.2 deletion syndrome (Fig. 3C). The

type A cases showed no aplasia/hypoplasia of the thymus (Fig. 3A). In fetal US images, the thymus was observed on 3VV of type A (Fig. 3B), whereas it was not observed on 3VV of type B (Fig. 3D).

Discussion

Based on our results, we suggest a method for fetal IAA screening using 3VV and 4CV images, which are frequently used for fetal echocardiography. Our present study revealed 2 important findings: (1) the low AoV/pulmonary valve ratio and the low Ao/MPA ratio on 3VV images, and (2) the detection of VSD at the outflow site on 4CV images. We also observed that the LV/RV and Ao/MPA ratios derived from 3VV images and the presence of the thymus on 3VV images were useful for differentiating type A from type B.

The Ao/MPA ratio on 3VV images and the VSD presence on 4CV images are important findings when screening for IAA. In the present patient series, the average Ao/MPA ratio was 0.47 ± 0.10 , and the Ao diameter was only about half the size of the MPA

Table 3 AoV/pulmonary valve ratio in single VSD cases

Control	Type of VSD	Fetal age at time of echocardiography (wks)	AoV/pulmonary valve ratio
1	Muscular	38	0.68
2	Muscular	32	0.87
3	Muscular	36	0.90
4	Muscular	29	0.82
5	Membranous	35	0.77
6	Membranous	34	0.78
Average		34.5 ± 3.2	0.80 ± 0.08

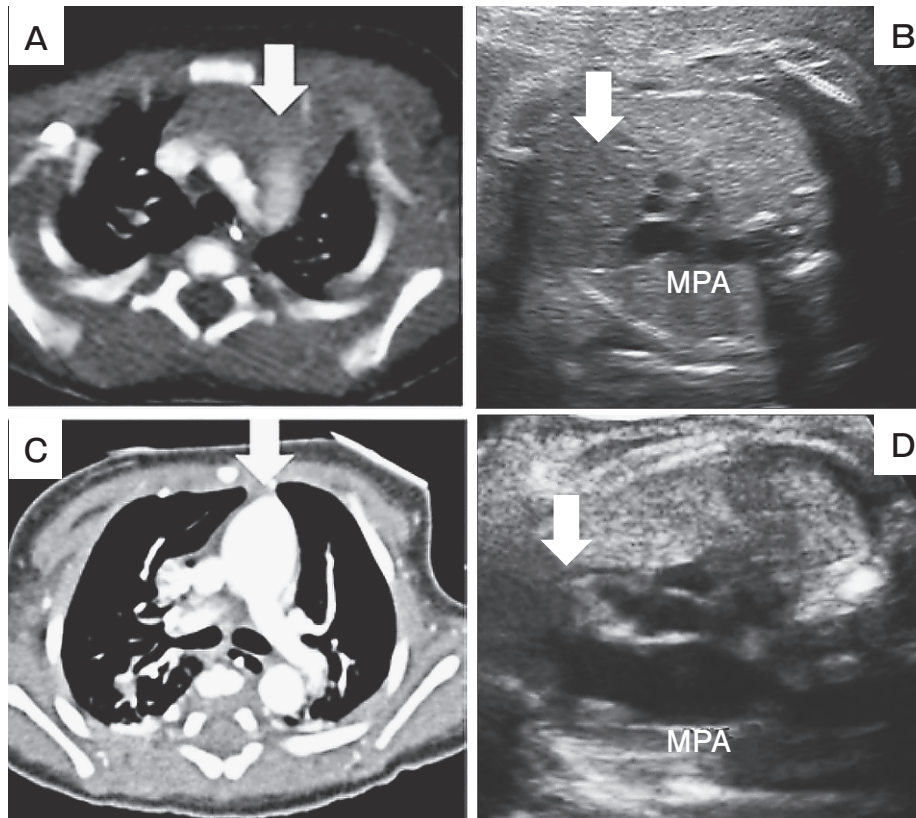


Fig. 3 Postnatal chest CT scan (A) and fetal US image near a 3VV (B) of IAA type A. The thymus is observed. The postnatal chest CT image (C) and fetal US image near 3VV (D) of IAA type B. Deletion/hypoplasia of the thymus is observed on a chest CT scan and fetal US image, indicating a diagnosis of 22q11.2 deletion syndrome.

diameter. Moreover, a relatively large VSD was observed at the outflow site in all eight IAA cases. Regarding VSD complicating IAAs, the data from some other reports [6–8] and our present patients are summarized in Table 4. VSD may be observed as a complication at a higher rate in type B than in type A. Moreover, we observed a significant difference in the AoV/pulmonary valve ratio between the IAA patients and the subjects with a single VSD. Therefore, when VSD is observed in the outflow tract and the Ao/MPA and AoV/pulmonary valve ratios are low, the aortic arch must be viewed in detail and evaluated for the presence of IAA.

Second, the LV/RV and Ao/MPA ratios derived from 3VV images and the presence of the thymus on 3VV images are useful for differentiating type A from type B. Regarding the Ao/MPA ratio from 3VV images, very low Ao/MPA ratios (0.33 and 0.29) were observed in the type B cases, whereas these low ratios were not observed in the type A cases. Our results showed that when the Ao is smaller than the MPA, particularly when the ratio is only approx. 1 : 3, type B may be present but not type A. Slodki *et al.* [8] also reported this difference.

In addition, the LV/RV ratio on the 4CV images was substantially greater (approx. 1.0) in type B compared to type A (0.61 ± 0.17) in this study, suggesting that there is no significant difference between the LV and RV diameters in type B but that the LV may be smaller than the RV in type A. Previous reports have noted that the LV is smaller than the RV in the case of CoA [15,16], suggesting that our results support the concept that type A IAA is a disease similar to CoA.

Vogel *et al.* [7] reported that the “Y” sign appears in type B IAA and that branching of the left subclavian artery from the arterial duct arch to the descending aorta is characteristic of type B IAA as well. These findings are seen in long-axis views but are

sometimes difficult to render. It was for this reason that we used the short-axis views to determine to what extent these features would be useful for differentiating types A and B.

Regarding the presence of the thymus on 3VV images, type A is rarely associated with the 22q11.2 deletion syndrome [17,18], whereas it is observed as a complication of type B in 60–70% of IAA type B cases [19–22]. When type B is suspected, the 22q11.2 deletion syndrome must be kept in mind. There are individual differences in the 22q11.2 deletion syndrome, regardless of the deficiency in the same part as the deletion [23].

Palatal abnormalities, which were observed in 69% of patients with 22q11.2 deletion syndrome [3]—particularly velopharyngeal incompetence, submucosal cleft palate, bifid uvula, and cleft palate—are difficult to detect *in utero*. Immunodeficiency (observed in 77% of patients with this syndrome) also occurs as a result of thymus hypoplasia [3]. In the present study, we observed that aplasia/hypoplasia of the thymus was present on postnatal chest CT scans of the type B patients, who also had 22q11.2 deletion syndrome. Volpe *et al.* [5] stated that prenatal screening for developmental defects of the thymus showed 75% sensitivity and 94% specificity in subjects with 22q11.2 deletion syndrome. In the present study, we retrospectively evaluated the fetal echocardiograms and observed that although the thymus was apparent on 3VV images of the type A IAA patients, the thymus was not apparent in the patients with type B and 22q11.2 deletion syndrome. When the thymus is not visualized, it is helpful to consider 22q11.2 syndrome. As noted earlier, infants with type B IAA have a greater possibility of having this syndrome compared to those with type A.

The screening method proposed in this study has 2 limitations. The first is that VSD in the outflow tract is sometimes not apparent during a single screening of 4CV images. It is important to observe the outflow tract carefully on 5CV images. The second limitation is differentiating type A from CoA. Some reports [15,16,24,25] have stated that CoA has a low Ao/MPA ratio. The method for differentiating type A from type B is as stated above. Differentiating type A from CoA, however, is difficult because of the absence of aortic isthmus blood flow: A non-patent fibrous thread is present in the isthmus [9]. Thus, it appears

Table 4 Incidence of VSD in type A and B interrupted aortic arch cases

Study	Type A VSD (+)	Type B VSD (+)
Volpe [6] (2010)	5/7 (71%)	15/15 (100%)
Vogel [7] (2010)	4/4 (100%)	14/14 (100%)
Slodki [8] (2011)	3/3 (100%)	5/5 (100%)
Hirano (this study)	4/4 (100%)	4/4 (100%)
Total	16/18 (89%)	38/38 (100%)

the similar anatomic locations, just distal to the left subclavian artery, between type A IAA and CoA, making it difficult to differentiate type A IAA and CoA.

We reviewed 8 cases of IAA and retrospectively examined the screening images to identify fetal IAA using 3VV and 4CV imaging, which is easier for screening than a long-axis view in these cases. When VSD is observed on 4CV and the AoV/pulmonary valve and Ao/MPA ratios derived from 3VV images are low, we must evaluate the patient for the presence of IAA. The Ao/MPA ratio and the presence of the thymus are useful for differentiating type A from type B. These findings suggest that we could increase the number of prenatal diagnoses of IAA using the Ao/MPA ratio derived from 3VV images and the presence of VSD on 4CV images. We could also differentiate type A from type B using the LV/RV ratio on 4CV images and the Ao/MPA ratio and the presence of aplasia/hypoplasia of the thymus on 3VV images, which might result in better management, including surgical intervention for IAA after birth.

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