

A new anatomic approach of the ventricular septal defect in the interruption of the aortic arch

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Abstract

The aim of this study was to analyse the anatomy of the ventricular septal defect (VSD) in heart specimens with interruption of the aortic arch (IAA) in order to explore the hypothesis of different embryologic mechanisms for the different anatomic types of IAA. We examined 42 human heart specimens, 25 with IAA as the main disease with concordant atrioventricular and ventriculo-arterial connections and two distinct great arteries, and 17 hearts with IAA associated with other malformations [six common arterial trunk (CAT), five double-outlet right ventricle (DORV), three transposition of the great arteries (TGA), three atrioventricular septal defect (AVSD)]. The interruption was classified according to Celoria and Patton. We focused on the anatomy of the VSD viewed from the right ventricular side. There were 15 IAA type A, 27 type B, no type C. The VSD in IAA type B was always an outlet VSD, located between the two limbs of the septal band, with posterior malalignment of the outlet septum in hearts with concordant ventriculo-arterial connections, without any fibrous tricuspid-aortic continuity. In addition, the aortic arch was always completely absent. Conversely, the VSD in IAA type A could be of any type (outlet in six, muscular in four, central perimembranous in two, inlet in three) and the aortic arch was either atretic or absent. In addition, IAA type B, when found in the setting of another anomaly, was always associated with neural crest-related anomalies (CAT and DORV), whereas IAA type A was found in association with anomalies not related to the neural crest (TGA and AVSD). These results reinforce the hypothesis that different pathogenic mechanisms are responsible for the two types of IAA, and the inclusion of IAA type B in the group of neural crest defects. Conversely, IAA type A could be due to overlapping mechanisms: flow-related defect (coarctation-like) and neural crest contribution.

Key words: congenital heart disease; interruption aortic arch; ventricular septal defect.

Introduction

Interruption of the aortic arch (IAA) is a rare congenital heart defect accounting for about 1% of all congenital heart disease (Van Praagh et al. 1971; Khoshnood et al. 2012). It is rapidly fatal if untreated. The aortic arch can be atretic, when the arch and the descending aorta are still connected anatomically with a fibrous cord, or absent, when there is no anatomic connection between the proximal part of the aortic arch and the descending aorta (Abbott, 1927; Blake et al. 1962; Roberts et al. 1962; Moller

& Edwards, 1965; Van Praagh et al. 1971; Higgins et al. 1977).

The most commonly used classification is that of Celoria and Patton, based on the site of interruption (Celoria & Patton, 1959). In type A, the interruption is located distal to the left subclavian artery, in type B, between the left subclavian and the left carotid artery, and in type C, between the innominate and the left carotid artery (Fig. 1).

These three types are considered very different from a developmental point of view (Celoria & Patton, 1959; Van Mierop & Kutsche, 1984). Types B and C may be due to a lack of development of the fourth aortic arch and are supposed to belong to neural crest defects. Type A is considered to be an extreme form of coarctation, occurring later, after the proximal migration of the seventh intersegmental artery.

The most frequently associated anomaly is the ventricular septal defect (VSD), present in more than 90% of patients

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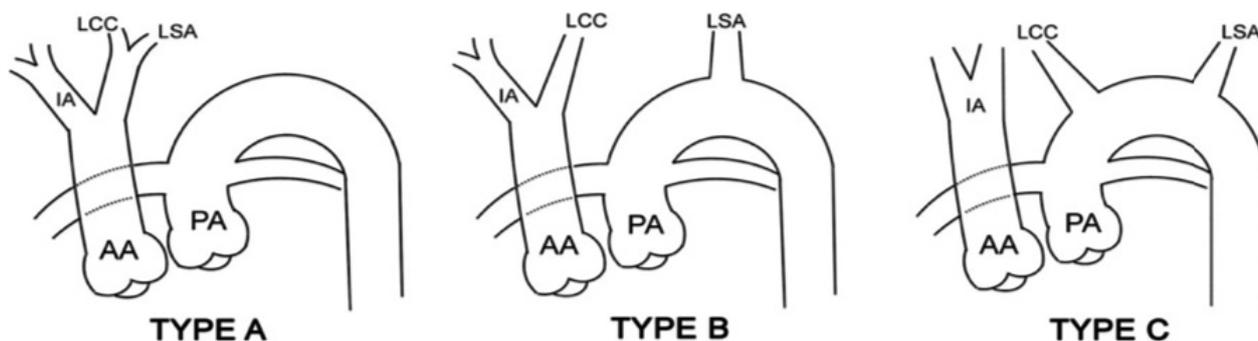


Fig. 1 Anatomical types of interruption of aortic arch according to Celoria and Patton classification. AA: aortic arch, IA: innominate artery, LCC: left common carotid artery, LSA: left subclavian artery, PA: pulmonary artery.

(Van Praagh et al. 1971). Interruption of the aortic arch can also be associated with more complex lesions such as double outlet right ventricle, common arterial trunk or atrioventricular septal defect.

In our anatomic study on human heart specimens, we focused on the relations between the anatomy of the IAA and that of the VSD in order to explore the possible link between the embryological mechanisms and the anatomical type of IAA.

Material and methods

Material

Among the 1423 human heart specimens of the anatomic collection of the French Reference Center for Complex Congenital Heart Defects (M3C), 45 have an interrupted aortic arch. In 28 specimens, interrupted aortic arch is the main disease, with concordant atrioventricular and ventriculo-arterial connections, and two distinct great arteries. Seventeen specimens have an IAA in the setting of another malformation: six hearts with common arterial trunk (CAT), three hearts with transposition of the great arteries (TGA), five hearts with double outlet right ventricle (DORV) and three hearts with complete atrioventricular septal defect (AVSD).

Three hearts with IAA but no VSD were excluded from the study, two with IAA type A and an aortopulmonary window, and one with IAA type B and an intact interventricular septum.

The 42 hearts included in the study were classified according to the classification of Celoria and Patton: 15 specimens had IAA type A and 27 specimens IAA type B. There was no type C.

We looked for associated anatomic anomalies and the presence or absence of DiGeorge syndrome using the patient's records. DiGeorge syndrome was confirmed genetically for some patients. For other hearts that are more ancient in the collection, DiGeorge syndrome was suspected when there was no thymus found by the surgeon.

Methods

The aortic arch of each heart specimen was examined carefully and any variation in arterial pattern noted. For each specimen, we looked at whether the aortic arch was absent or atretic with

an anatomic connection between the aortic arch and the descending aorta. For hearts with previous surgery, we used the description by the surgeons during the intervention to assess the presence or the absence of fibrous continuity between the ascending and the descending aorta. The intracardiac anatomy of each heart specimen was studied with particular attention paid to the VSD. This channel between the ventricles can also be described as an interventricular communication, especially in the setting of DORV, in which the hole that will be closed by the surgeon is not a hole within the ventricular septum itself and thus a plane surface, but a curved surface between malaligned septal structures which are normally aligned in the normal heart (Spicer et al. 2014a). However, in this study we use the term 'VSD' to describe any type of channel between the ventricles. We carefully describe the geographical location of the VSD relative to the landmarks of the right ventricular aspect of the ventricular septum, then the anatomical details of the borders and rims of the VSD, and the relation between the tricuspid and the aortic valves. We looked for a fibrous continuity between these two valves, particularly which tricuspid leaflet was involved in this continuity. To describe fully the types of VSD, the terminology we use must be precise. We classified the VSDs in four main types according to the Eleventh Iteration of the International Classification of Diseases (ICD-11, Franklin et al. 2017; Fig. 2).

Outlet VSD

An outlet VSD was defined as a VSD opening to the outlet of the right ventricle and located between the two limbs of the septal band (Mostefa-Kara et al. 2015). There were some variations observed, especially regarding the postero-inferior rim of the VSD, which can be fibrous (with fibrous continuity between the aortic and the anterior leaflet of the tricuspid valve) or muscular, due to a fusion between the posterior limb of the septal band and the ventriculo-infundibular fold. The other anatomical variation is the muscular or fibrous nature of the outlet (conal) septum: when the outlet septum is muscular, the VSD is a malalignment type outlet VSD; when the outlet septum is fibrous or absent the VSD is dubbed doubly committed or juxta-arterial. In hearts with DORV, the outlet VSD is called subaortic when the outlet septum is attached to the anterior limb of the septal band, subpulmonary when the outlet septum is attached to the posterior limb of the septal band, and doubly committed if the outlet septum is distant from the limbs of the septal band (in this case usually fibrous or absent).

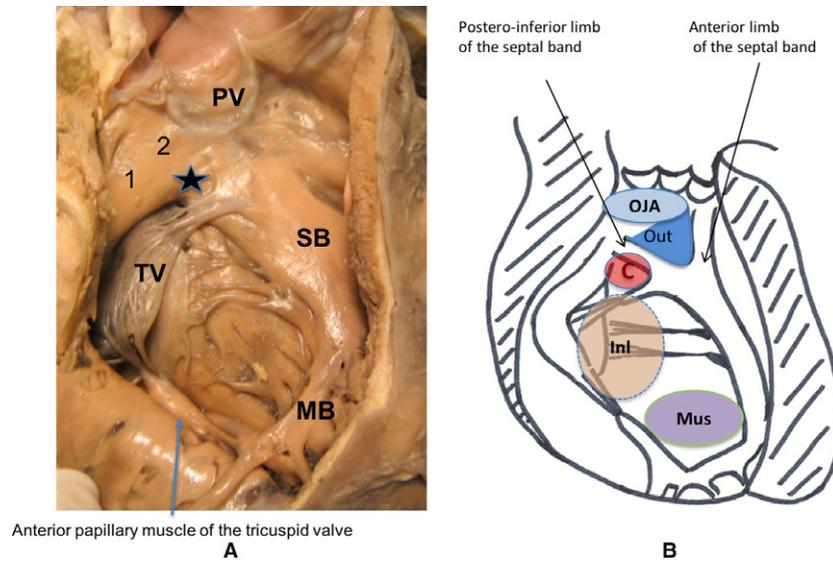


Fig. 2 (A): Right ventricular aspect of the ventricular septum in a normal heart. The muscular bands of the right ventricle are: the ventriculo-infundibular fold [VIF, including parietal band (1) and subpulmonary conus (2)]; (star) is showing the site of insertion of the supra-ventricular crest between the limbs of the septal band; the septal band or septomarginal trabeculation (SB) with its two limbs, antero-superior and postero-inferior, the moderator band (MB); the anterior papillary muscle of the tricuspid valve. PV: pulmonary valve; TV: tricuspid valve. (B) Four main anatomic types of ventricular septal defects viewed from the right ventricle. (C) Central VSD. Inl: Inlet VSD, M: muscular VSD, OJA: outlet juxta arterial VSD, Out: outlet VSD, T: tricuspid valve, VIF: ventriculo-infundibular fold.

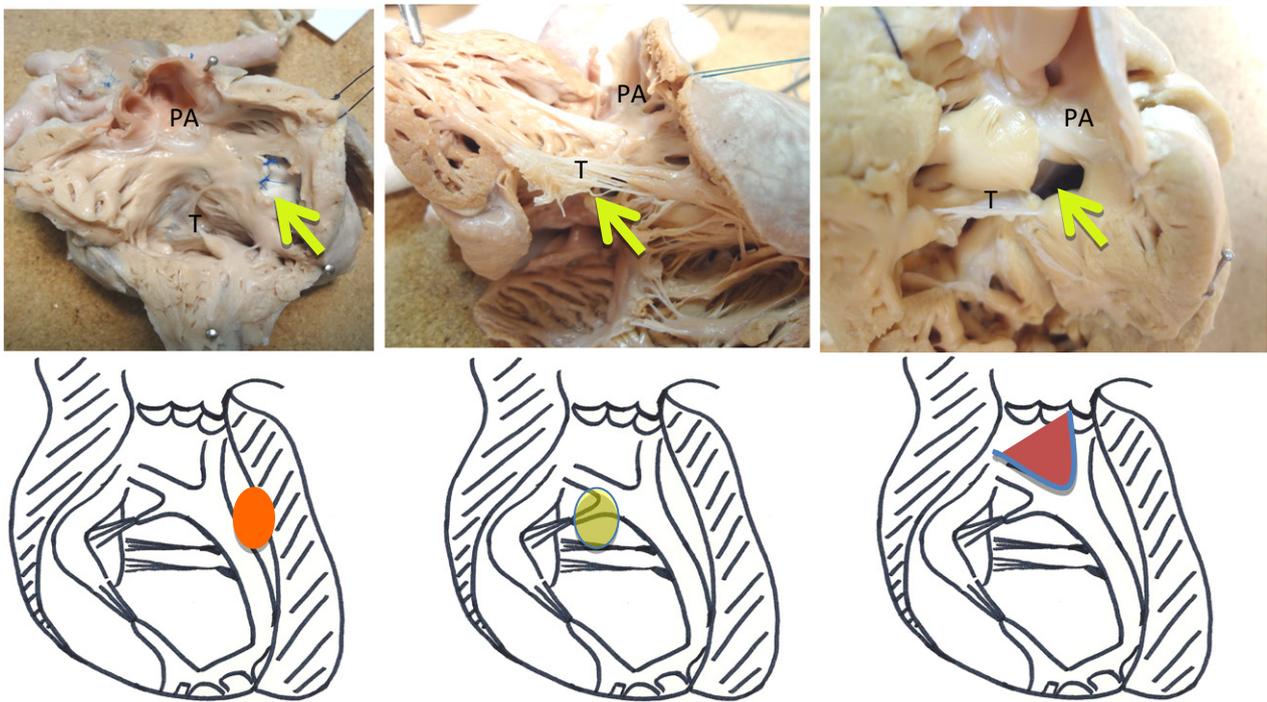


Fig. 3 VSD phenotypes in interruption aortic arch type A. (A) Muscular VSD closed on this image with a patch. (B) Central perimembranous VSD, under the posterior rim of the septal band and behind the septal leaflet of the tricuspid valve. (C) Outlet VSD between the two rims of the septal band. PA: pulmonary artery, T: tricuspid valve.

Inlet VSDs

An inlet VSD was defined as a VSD present at the borders of, or within the posterior-inferior part of, the

interventricular septum, behind the full length of the septal leaflet of the tricuspid valve, opening in the inlet of the ventricular septum. These VSD can be immediately adjacent to

the atrioventricular valves or have entirely muscular borders (inlet muscular defects).

Muscular trabecular VSD

Muscular trabecular VSD is located in the muscular septum and bordered entirely by trabecular septum.

Central perimembranous VSD

Central perimembranous VSD was defined by its location below the posterior limb of the septal band and under the ventriculo-infundibular fold. This VSD is different from the malalignment outlet VSD with a fibrous postero-inferior rim because of its geographical location, but also because the fibrous continuity involves the septal leaflet of the tricuspid valve and not the anterior leaflet, contrary to the outlet VSD (Mostefa-Kara et al. 2015).

We also looked for the nature, muscular or fibrous, of the outlet septum and its orientation relative to the axis of the remainder muscular ventricular septum. The associated anomalies are defined.

Statistical analysis

STATVIEW software was used for data analysis. The qualitative anatomic variables were presented with percentages. A Chi-square test analysis was used to evaluate possible differences between the parameters. Statistical significance was assessed using a cut-off *P*-value of 0.05.

Results

Anatomy of the aortic arch

The aortic arch was left-sided in all but two hearts, where the arch was right-sided. In those latter specimens, interruption of the aortic arch was type B.

Among the 15 specimens with IAA type A, the aortic arch was absent in six, atretic in six and unknown in three because of previous surgery. The aortic arch was absent in all 27 hearts with IAA type B.

We found a retro oesophageal right subclavian artery in six hearts with IAA type B and in two hearts with IAA type A.

Anatomy of the VSD according to type of IAA

In the 15 hearts with IAA type A, the VSD was muscular within the trabecular septum in four, central perimembranous in two, outlet with posterior malalignment of the outlet septum in six, and inlet in three (Fig. 3).

In the 27 heart specimens with IAA type B, the VSD was always an outlet VSD located between the two limbs of the septal band.

Hearts with interruption of aortic arch as the main disease

Among the nine specimens with IAA type A as the main disease, the VSD was trabecular muscular in three, central perimembranous in two and outlet in four. When the VSD was

an outlet VSD, the postero-inferior rim of the VSD was muscular in two and fibrous, with a fibrous continuity between the aortic valve and the anterior leaflet of the tricuspid valve, in two (Table 1).

Among the 16 specimens with IAA type B, the VSD was always of the outlet type, located between the two limbs of the septal band, with a muscular postero-inferior rim in all, without any fibrous continuity between the leaflets of the aortic valve and the tricuspid valve (Fig. 4). In three hearts the VSD was doubly committed and juxta-arterial with a fibrous outlet septum between the two arterial valves in two hearts and an extreme hypoplasia of the outlet septum with a muscular raphe in one heart.

We found a statistically significant difference between IAA type A and B as regards the types of VSD, with an outlet VSD present in 4/9 specimens in type A and 16/16 in type B ($P = 0.001$).

Hearts with IAA in the setting of another cardiac heart defects

In the common arterial trunk associated with IAA, the interruption of the aortic arch was always type B (6/6 CAT) with an absent connection between the ascending and the descending aorta, and the VSD was always an outlet VSD.

In heart specimens with DORV, the interruption of the aortic arch was type B in all specimens (5/5) and the aortic arch was absent in all. The VSD was always an outlet VSD. The VSD was subpulmonary in three hearts with a deviated outlet septum creating a subaortic obstruction; subaortic in one heart with bilateral conus, and a small aortic annulus; and doubly committed in one heart.

In TGA associated with IAA, the interruption was always type A with an absent aortic arch. The VSD was of the outlet type in two heart specimens and muscular in one.

In complete AVSD associated with IAA, the interruption was always type A but of the atretic type, and the VSD was, as expected, always an inlet VSD.

Nature of subaortic obstruction according to type of IAA

In hearts with IAA type B and concordant ventriculo-arterial connections, the VSD was of the outlet type with postero-caudal deviation of the outlet septum, creating a subaortic obstruction as shown in Fig. 4, regardless of whether the outlet septum was muscular or fibrous. In hearts with an IAA type A and muscular trabecular, central perimembranous or inlet VSD, the outlet septum was located normally between the two limbs of the septal band and not deviated. The subaortic obstruction in these hearts was multifactorial and caused by the small size of the aortic annulus, an abnormal anterolateral muscle bundle of the left ventricle (muscle of Moutaert) and/or mitral anomalies.

Table 1 Types of VSD according to the anatomical type of CHD.

Cardiac heart defects (CHD)	Interruption (type A)				Interruption (type B)				VSD phenotype							
	Atretic arch		Absent arch		Unknown		Absent arch		Outlet		Membranous		Muscular		Inlet	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
IAA type A as main CHD, n = 9	3 (33%)	3 (33%)	3 (33%)	0 (0%)	3 (33%)	0 (0%)	0 (0%)	0 (0%)	4 (44%)	2 (22%)	3 (33%)	0 (0%)	0 (0%)			
IAA type B as main CHD, n = 16	0 (0%)	0 (0%)	0 (0%)	0 (0%)	16 (100%)	0 (0%)	0 (0%)	16 (100%)	16 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)			
IAA associated with CAT, n = 5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (100%)	6 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)			
IAA associated with DORV, n = 5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (100%)	5 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)			
IAA associated with TGA, n = 3	0 (0%)	0 (0%)	3 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (65%)	2 (65%)	1 (33%)	0 (0%)	0 (0%)	0 (0%)			
IAA associated with complete AVSD, n = 3	3 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (100%)			

Associated anomalies according to IAA type

Table 2 shows the details of the associated anomalies. The aortic valve was bicuspid in eight specimens, all with IAA type B. The fusion pattern of the leaflets was right-left (R-L) in seven hearts (without a raphe in five) and right-non coronary (R-N) in one with a raphe. In 19 hearts we noted the presence of an anomalous muscle bundle in the anterolateral wall of the left ventricle, which participated in the obstruction of the left ventricular outflow tract. DiGeorge syndrome was found in two hearts with type A and four hearts with type B. There was no significant difference between the two types of IAA relative to the associated anomalies, except for the presence of a bicuspid aortic valve, found in eight specimens with IAA type B and none with type A ($P = 0.01$).

Discussion

Interruption of the aortic arch and ventricular septal defect

An interventricular communication is almost invariably present in interruption of the aortic arch. When the ventricular septum is intact, there is usually an aorto-pulmonary window, as it was the case for two of our specimens with IAA type A (Ho et al. 1983). Interrupted aortic arch without VSD and without aortopulmonary window, as in one of our specimens with IAA type B, was an exception but it has already been described in the literature (Cazavet et al. 2012).

In this study, we showed that the distribution of the VSD phenotypes differs markedly depending on the type of interruption of the aortic arch.

The VSD in interruption of the aortic arch type B was always the same, an outlet VSD located between the two limbs of the septal band, with posterior malalignment of the outlet septum in hearts with concordant ventriculo-arterial connections. This feature has been reported by Oppenheimer-Dekker et al. (1982) and Van Mierop & Kutsche, (1984) in previous anatomical studies. We demonstrated in an earlier anatomic study that the VSD in cardiac neural crest defects is always an outlet VSD (Mostefa-Kara et al. 2015), which can be easily explained by embryology.

The 'cardiac neural crest defects' and the 'second heart field defects' are observed experimentally after ablation of the cardiac neural crest or of the anterior part of the second heart field. Although the genes that regulate each population of cells are distinct, these two populations interact, which probably explains, at least in part, the overlapping phenotypes. These phenotypes include complete absence of septation of the outflow tract (common arterial trunk) and malalignment defects (DORV with subaortic or doubly committed VSD, tetralogy of Fallot and variants, outlet VSD with overriding aorta, interrupted aortic arch type B;

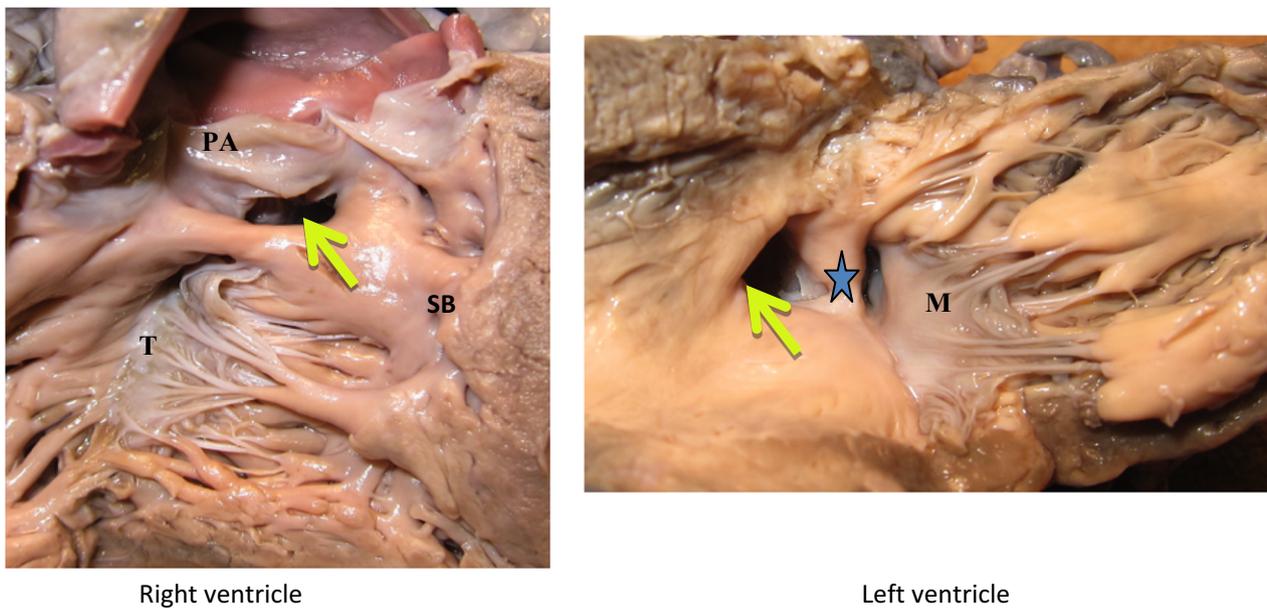


Fig. 4 Outlet VSD in interruption of aortic arch type B. The VSD is always an outlet VSD located between the two rims of the septal band viewed from the right ventricle (A), viewed from the left ventricle with the posterior deviation of the outlet septum (showed by a star). T: tricuspid valve. M: mitral valve, PA: pulmonary artery, SB: septal band.

Table 2 Associated abnormalities in hearts with IAA.

Associated abnormalities	IAA type A, n = 15	IAA type B, n = 27
Right aortic arch	0 (0%)	2 (7%)
Retro-oesophageal RSCA	2 (13%)	6 (22%)
Bicuspid aortic valve	0 (0%)	8 (30%)
Muscle of Moutaert	10 (66%)	9 (33%)
Left superior caval vein	0 (0%)	2 (7%)
DiGeorge syndrome	2 (13%)	4 (15%)

Hutson & Kirby, 2007). Malalignment defects are due to a lack of elongation of the outflow tract during the different phases of cardiac looping (Yelbuz et al. 2002), preventing normal wedging of the aortic valve between tricuspid and mitral valves, with an outflow tract that is shorter and straighter than normal (al-Marsafawy et al. 1995; Waldo et al., 2005a,b). All malalignment defects include a ventricular septal defect, due to the malalignment and to the absence of fusion between the outlet septum and the rest of the ventricular septum. The outlet septum then becomes an exclusively right ventricular structure, except in IAA type B, in which it is deviated within the left ventricular outflow tract (Soto et al. 1989; Yelbuz et al. 2002; Bailliard et al. 2015). This posterocaudal deviation of the outlet septum could be explained by an excess of rotation of the outflow tract during wedging, as assessed by the absence of aortic overriding in this case. However, contrary to the normal

heart in which there is an aortic-tricuspid fibrous continuity via the atrioventricular membranous septum, disrupting the muscular fusion between the ventriculo-infundibular fold and the postero-inferior limb of the septal band or septomarginal trabeculation (Mostefa-Kara et al. 2015), in our anatomical study we found that the borders of the VSD in IAA type B were always muscular, without fibrous continuity between the tricuspid and the aortic valve. This might also be explained by an excess of rotation of the outflow tract during the wedging phase (Ho et al. 1983). Finally, we found that all heart specimens with IAA type B had complete absence of the aortic arch. This favours the hypothesis of Celoria and Patton about the pathogenesis of IAA type B, which might be due to an early involution of the left fourth aortic arch, and is another argument for including IAA type B in the group of cardiac neural crest and/or second heart field defects (Celoria & Patton, 1959).

In our anatomic collection, we found six heart specimens with CAT and IAA (CAT with pulmonary dominance or type A4 of the modified Van Praagh classification; Van Praagh, 1987). A common arterial trunk is defined by a single vessel originating from the heart, with a common arterial valve, giving rise in that order to the coronary arteries, at least one pulmonary artery and systemic arteries (Jacobs, 2000). A common arterial trunk almost always includes a VSD, which is always an outlet VSD, located between the two limbs of the septal band (Ho et al. 1983; Russell et al. 2011). There is no outlet septum, the superior rim of the VSD being formed by the common arterial valve. In our anatomical study, all six specimens with CAT and IAA had an outlet

VSD and, in addition, the IAA was always type B, with an absent aortic arch. This is also the case in animal models such as the mouse embryos lacking the neurovascular guidance molecule semaphoring 3C, which display CAT and IAA type B or C (Feiner et al. 2001).

We also found five specimens with DORV and IAA. In all of them, the VSD was an outlet VSD, committed to the great arteries (subaortic VSD in one heart, subpulmonary VSD in three, doubly committed VSD in one). DORV with subaortic or doubly committed VSD are considered to belong to the group of cardiac neural crest and/or second heart field defects, whereas DORV with subpulmonary VSD are considered to be related to TGA. However, the anatomical type of IAA was different in DORV with subpulmonary VSD and in TGA: type B, with absent aortic arch, in DORV with subpulmonary VSD (like in other types of DORV), type A in TGA. These results raise some intriguing developmental questions, particularly a possible participation of the second heart field in DORV with subpulmonary VSD (Mahle et al. 2008).

By contrast, we found that the VSD in IAA type A can be of any type: outlet, inlet, central perimembranous or muscular. This affirms that IAA type A is aetiologically and pathologically distinct from IAA type B (Celoria & Patton, 1959; Van Mierop & Kutsche, 1984). In the former patients, the left subclavian artery has migrated to its normal position, which clearly indicates that at one time during development the isthmus part of the aortic arch must have been normal. This hypothesis is reinforced by the fact that in IAA type A the aortic arch can be either atretic or absent. Indeed, IAA type A and coarctation are closely related anomalies that may be prenatally acquired when IAA is of the atretic type (Kreutzer & Van Praagh, 2000; Mostefa-Kara et al. 2015).

In the three specimens with TGA and IAA, the anatomic type was always A with an absent aortic arch. The VSD phenotype was not constant: outlet in two, muscular in one. By contrast, in AVSD, the interruption was always type A and of the atretic type, closely similar to a coarctation of the aorta. The association between AVSD and IAA type A or coarctation has already been described in the literature. The scooped-out aspect of the interventricular septum results in a narrowed left ventricular outflow tract, which constitutes an anatomic substrate for subaortic obstruction. This particular anatomy of the left ventricular outflow tract probably favours reduced blood flow through the aortic arch during fetal life.

Interruption of aortic arch and associated anomalies

Bicuspid aortic valve

A bicuspid aortic valve was found exclusively in the group of IAA type B in our series. This finding is different from what is described in the literature. In Van Mierop & Kutsche's series (Van Mierop & Kutsche, 1984), the

frequency of the bicuspid valve was about 50% in IAA type A and 80% in IAA type B. This difference may be related to the small number of specimens in our study. However, the frequency of bicuspid aortic valve remains higher in IAA type B than in IAA type A in the literature; this could be explained by the embryological origin of the arterial valve, which involves neural crest cells (Anderson et al. 2012; Spicer et al. 2014b), especially for the development of the left and right aortic leaflets (Phillips et al. 2013). Interestingly, experimental studies indicate that R-L fusion is associated with VSD and coarctation of the aorta and would be related with alterations in cardiac neural crest cell signalling, whereas R-N fusion would be related with second heart field genes (Fernandez et al. 2009; Grewal et al. 2014).

DiGeorge syndrome

The association between DiGeorge syndrome and IAA type B is well known. However, we found only 4/27 hearts with this association in our study. This frequency is obviously underestimated because of the small number of specimens and the fact that the collection was started more than 50 years ago, with incomplete records and no genetic analysis. In addition, two hearts with isolated IAA type A were associated with DiGeorge syndrome. This association, albeit rare, has already been described in the literature (Moerman et al. 1980).

Limitations of the study

The principal limitation of our study is the small number of heart specimens with interruption of aortic arch, both as the main disease and associated with other malformations.

Conclusion

The phenotypes of both the VSD and the arch itself are clearly distinct in IAA type B and in IAA type A. The VSD in IAA type B is always the same, located between the two limbs of the septal band, with posterior malalignment of the outlet septum when the ventriculo-arterial connections are concordant, without any fibrous tricuspid-aortic continuity. In addition, the aortic arch is always completely absent. Conversely, the VSD in IAA type A can be of any type, and the aortic arch is either atretic or absent.

This reinforces the hypothesis of different pathogenic mechanisms responsible for the two anatomical types of IAA. In addition, IAA type B, when found in the setting of another anomaly, is associated with second heart field and/or cardiac neural crest anomalies, namely, CAT and DORV with subaortic and doubly committed VSD, but also DORV with subpulmonary VSD. By contrast, IAA type A is associated with anomalies not related to the neural crest, TGA and AVSD. Therefore, these findings confirm that IAA type B should be included in the group of neural crest and/or

second heart field defects. Conversely, the variability of the VSD type in IAA type A, as well as the possibility for the aortic arch to be either absent or atretic, could indicate overlapping mechanisms: flow-related defect (coarctation-like, with atretic aortic arch) and neural crest contribution, especially when associated with an outlet VSD.

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