THE CONCEPT OF DOUBLE INLET- DOUBLE OUTLET RIGHT VENTRICLE: A DISTINCT CONGENITAL HEART DISEASE

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Abstract

The aim of this study was to estimate the incidence and to analyze the anatomy of double inlet-double outlet right ventricle complex and its associated cardiac anomalies in our autopsy series.

Among the 1640 hearts with congenital heart disease of our Anatomical Collection, we reviewed the specimens with double inlet-double outlet right ventricle, according to the sequential-segmental analysis, identifying associated cardiac anomalies and examining lung histology to assess the presence of pulmonary vascular disease.

We identified 14 hearts with double inlet-double outlet right ventricle (0,85%). Right atrial isomerism was observed in 10 hearts, situs solitus in 3 and left atrial isomerism in 1. Regarding the mode of atrioventricular connection, all hearts but one had a common atrioventricular valve. Systemic or pulmonary venous abnormalities were noted in all patients with atrial isomerism. In 9 patients a valvular or subvalvular pulmonary stenosis was present.

Among the functionally “univentricular hearts", double inlet- double outlet right ventricle represents a peculiar entity, mostly in association with right atrial isomerism. Multiple cardiac anomalies are associated and may complicate surgical repair.

Keywords: congenital heart disease, double inlet right ventricle, double outlet right ventricle, univentricular heart.

Highlights:

- Double inlet-double outlet right ventricle represents a rare morphological complex
- Right isomerism with anomalous pulmonary venous return is frequent
- Common atrioventricular valve is often present
- Valvular or subvalvular pulmonary stenosis protects the lungs from hypertensive pulmonary disease
- Univentricular repair is feasible

Abbreviations:

AV	= atrioventricular
CHD	= congenital heart disease
DIRV	= Double Inlet Right Ventricle
DORV	= Double Outlet Right Ventricle
DI-DORV	= Double Inlet-Double Outlet Right Ventricle
LV	= left ventricle
RV	= right ventricle
VA	= ventriculo-arterial
VSD	= ventricular septal defect

1. Introduction

Among the spectrum of the functionally "univentricular hearts" [1,2], double inlet-double outlet right ventricle (DI-DORV) represents a distinct morphologic entity.

During cardiac development, the common atrium and common ventricle are separated by the atrioventricular (AV) canal (derived from first heart field)[3], from which later both mitral and tricuspid valves originate. Due to exaggerated rightward shift of the AV canal, the putative mitral orifice predominantly connects to the right ventricle (RV) [4,5], shaping a double inlet right ventricle (DIRV). The RV and the outflow tracts derive from a second heart field [3]. Persistence of the origin of both great arteries from the right ventricle accounts for double-outlet right ventricle (DORV).

When defining DI-DORV, some controversies are found in the literature. Following sequential-segmental analysis [6-8] and classifying univentricular AV connections according to our terminology (double inlet , absent right or absent left [9]), a DIRV is identified when both atria are mostly connected to the morphologically RV, regardless of the morphology of the AV valves (either through two separate or a common AV orifice). Some other authors, however, classify univentricular AV connection focusing on how the AV valves drain into the main ventricular chamber (double inlet, common inlet, single inlet) [10] and therefore, the presence of a common AV valve has been considered incompatible with the diagnosis of DI-DORV in previous case series [11,12]. We recognize that the latter approach is employed in classical pediatric cardiology texts [10], however, we prefer to maintain our own terminology, since we have been using it in our recent paper [9].

The association of common AV orifice and DORV is well known and has been extensively described [13-16], especially in the spectrum of canal malformation. However, from the above-described perspective of sequential-segmental analysis, only those hearts that have a common AV

valve connecting both atria primarily to a dominant RV (i.e. by more than 75%) should be properly considered as DIRV [9, 17,18]. Furthermore, some authors included among DI-DORV also cases of DIRV with pulmonary or aortic atresia [11,19, 20], but in terms of sequential classification those hearts should be referred as having single outlet RV when the atretic ventriculo-arterial connection cannot be ascertained.

We reviewed DI-DORV specimens from our Anatomical Collection of congenital heart disease (CHD) in order to investigate the incidence and the anatomical features of DI-DORV hearts, as defined by sequential-segmental analysis, with the aim to help the in vivo diagnosis and the surgical decision making.

2. Methods

Within the Anatomical Collection of CHD of the Cardiovascular Pathology Registry of the University of Padua, consisting of 1640 specimens collected from 1966 to 2015, we selected cases of DIRV associated with DORV. According to sequential-segmental analysis [6-9], we defined DIRV as the univentricular AV connection in which both atria are mostly connected to the morphologically RV through two separate AV valves or a common AV valve (or more than one and a half). The RV was identified according to its anatomical landmarks (coarse trabeculations, trabecula septo-marginalis and Lancisi muscle), and the left ventricle (LV) identified by smooth endocardial surface of the basal ventricular septum. DORV was identified as a ventriculo-arterial (VA) connection in which both great arteries (or more than one and a half) arise from the RV [6-9], excluding hearts with pulmonary or aortic atresia (single outlet).

Of these hearts, categorized as DI-DORV according to their AV and VA connections, we took note of the atrial situs, the mode of AV connection (two valves or common valve), the ventricular loop, the great arteries relations (aorta to the right or left, anterior or posterior, or side-by-side to the

pulmonary artery), the heart position (levocardia, mesocardia or dextrocardia), and the aortic arch side.

In addition, a detailed inspection of intracardiac anatomy and associated anomalies was performed. Anomalies of the systemic and pulmonary venous drainage, presence of atrial septal defect or common atrium, morphology of the AV valves, type of ventricular septal defect, ventricular and infundibular morphology, presence and type of left or right outflow obstruction, morphology of the aortic arch and origin of brachiocephalic arteries and patency of ductus arteriosus were analyzed and recorded.

Pulmonary histology was performed in order to evaluate the pulmonary arterial vascular tree. Hematoxylin-eosin and Elastic Van Gieson stain were used. The lesions were classified in grades according to Heath Edwards classification [21].

Patients' gender and age at death were retrieved from Cardiovascular Pathology Registry database.

Qualitative anatomic variables are described with absolute number and percentages. Due to the small sample size, no statistical analysis has been performed.

3. Results

3.1 DIRV and DI-DORV hearts

Among our 1640 hearts with congenital abnormalities, we found 23 hearts with DIRV. In two third of cases the atrial situs was right isomerism (Table 1). VA connection was DORV in 14 patients, accounting for an overall incidence of DI-DORV of 0,85%. In the remaining 9 cases of DIRV, they were associated with pulmonary atresia in 5 and with aortic atresia in 4 (Table 1).

3.2 Age and gender

Of the 14 hearts fulfilling the anatomic criteria for diagnosis of DI-DORV, 7 belonged to male patients. Patients age at death ranged from 1 day to 42 years. Atrial situs solitus was present in 3 cases (1 males, 2 females, age range 15 days-13 years), right isomerism in 10 (4 males, 6 females, age range 1 day-42 years) and left isomerism in a 20 years old male patient. No patient had Down syndrome.

3.3 Morphologic features of DI-DORV hearts

All hearts showed a dominant ventricle of right morphology, characterized by coarse apical trabeculations, prominent trabecula septo marginalis and a hypoplastic ventricular chamber of left morphology, with fine apical trabeculations and smooth basal septum. The hypoplastic LV was identified in all cases and was located in postero-inferior position, on the left in hearts with d-ventricular loop and on the right in hearts with l- ventricular loop (Table 2). Dextrocardia was present in 6 cases.

The position of the aorta relative to the pulmonary artery was right anterior in 5 cases, left anterior in 4, on the right, side-by-side, in 3 and right posterior in 2.

Two separate AV valves, with straddling left valve, were present only in 1 patient with atrial situs solitus (Figure 1), whereas a common AV valve was noted in all the remaining 13 (Figures 2-3). The common AV valve showed a free-floating superior leaflet in 10 hearts.

In 8 hearts there was a persistent left superior vena cava (SVC) in the presence of a right SVC, in one heart there was a persistent left SVC without right SVC. Interruption of inferior vena cava (IVC) was noted in 2 cases. The coronary sinus was absent in all cases with right isomerism.

In the 3 cases with atrial situs solitus the pulmonary venous drainage was normal, with all pulmonary veins draining in the left atrium. In the single case with left isomerism the pulmonary venous drainage was symmetric with 2 pulmonary veins draining in the left sided atrium and 2 in

right sided atrium. In this case both atria showed left morphology. The pulmonary venous drainage was considered anomalous in all 10 cases with right atrial isomerism (Figure 2A), for the presence of a bilateral morphologically right atrium. The pulmonary veins drained into right SVC in 4, into left SVC in 1 and in 5 directly into the atrium, which was right sided in 3 and left sided in 2. In 3 of the 5 cases with direct atrial drainage, the pulmonary veins drained into the same atrium receiving the caval return.

An atrial septal defect fossa ovalis type was also noted in 8 and a common atrium in 6 hearts.

All hearts presented a bilateral infundibulum.

Obstruction of the right outflow was present in 9 of 14 hearts. A muscular subvalvular pulmonary stenosis was noted in 7 cases due to hypertrophied infundibular myocardium and deviation of the infundibular septum (Figure 3A), was isolated in 2 cases and associated to a valvular stenosis in 5 (tricuspid stenotic pulmonary valve in 3 and bicuspid stenotic pulmonary valve in 2). A unicuspid, stenotic pulmonary valve was noted in one heart with subpulmonary stenosis due to accessory AV fibrous tissue. In the case with left atrial isomerism the pulmonary stenosis was only at valvular level, due to the presence of a bicuspid and stenotic pulmonary valve.

Subaortic stenosis was found only in the case with hypoplastic aortic arch.

Other associated anomalies are reported in Table 2.

Surgery was performed in 7 patients and consisted in pulmonary banding in 2, aorto-pulmonary shunt in 2 and in univentricular repair with bidirectional cavo- pulmonary anastomosis in 3 cases. All patients died within the first week after surgery.

3.4 Lung histology

Lung histology was performed in 11 patients, 7 with and 4 without pulmonary outflow obstruction. No case had irreversible pulmonary vascular disease (>grade 2). All patients without pulmonary obstruction were less than 3 months old.

4.Discussion

Since Munoz-Castellanos first description in 1969 [22], other authors have reported one or several either autopsied or clinical cases of DI-DORV (Table 3) [2,4, 5, 11, 12, 19, 20, 22-30]. Largest autopsied series were collected by Quero-Jiménez et al. [23] (5 cases), Van Praagh et al. [24] (6 cases), Keeton et al. [19] (7 cases). Saleeb et al.[11], Kawahira et al. [12]and Wang et al. [30] published the largest clinical series of DI-DORV.

Our collection of 14 specimens is, to our knowledge, the largest post-mortem series reported so far of DI-DORV hearts defined according to sequential-segmental analysis. In two thirds of our DIRV cases a DORV was also present (Table 1), and this should be kept in mind during clinical assessment and surgical decision making.

4.1 Anatomical characteristics

Preoperative definition of cardiac situs is then of paramount importance for surgical repair, because left and right atrial isomerism are almost always associated with systemic or pulmonary venous return abnormalities. In the present study, we found that right atrial isomerism actually represents the most frequent atrial situs (10 out of 14 hearts), followed by situs solitus (3 hearts) and left atrial isomerism (1 case), while no heart presented situs inversus. Cases of situs inversus have been reported [24, 26] or excluded in previous studies [28].

As expected, systemic or pulmonary venous abnormalities were noted in all patients with atrial isomerism of our series. Regarding the mode of AV connection, all hearts but one had a common AV valve.

It has to be considered that our case series is post-mortem, and this could explain the high prevalence of atrial isomerism, which may have precluded a complete surgical repair because of the complex systemic or pulmonary venous associated abnormalities.

We did not investigate histologically the course of the conducting tissue. However, previous reports showed that, in functionally "univentricular hearts" of right ventricular type, the AV bundle arises from a normally located posterior AV node and descends onto the posterior wall of the main chamber, either onto the trabecular septum or a posterior trabecula at the crux cordis [19, 31], in contrast to hearts of either left or indeterminate ventricular type. Therefore, a preoperative diagnosis of right ventricular morphology helps to locate the AV bundle and to prevent surgical heart block.

4.2 Physiopathological implications

Physiopathology of DI-DORV, such as other functionally single ventricle conditions, depends on systemic and pulmonary venous return, flow across the atrial septum, inflow obstruction, AV valve regurgitation, outflow obstruction and pulmonary vascular resistances. Previous clinical studies reported rare incidence of severe AV valve regurgitation in double inlet ventricle [12, 32].

A key feature is the presence of pulmonary outflow obstruction, which prevents pulmonary blood overload. Pulmonary outflow obstruction was present in 9 out of our 14 hearts. Muscular subpulmonary obstruction was the most frequent but also dysplastic or unicuspid or bicuspid pulmonary valves were noted (Table 2). Muscular subpulmonary stenosis was not present in hearts of younger patients, suggesting progressive pulmonary subvalvular obstruction with age. No case of irreversible pulmonary vascular disease was detected.

4.3 Current surgical options

Surgical palliation (creation of an aorto-pulmonary shunt to ensure adequate pulmonary flow or pulmonary banding in patients without pulmonary obstruction to prevent pulmonary blood overload and hypertension) and, at a later stage, Fontan univentricular repair are nowadays available operative procedures for DI-DORV patients. There are only anecdotal data about late outcome after biventricular repair for DI-DORV [11, 33]. However, in double inlet LV, biventricular repair carries a higher early surgical mortality and showed no real benefits in terms of exercise tolerance when

compared the univentricular repair, which still represents the technique of choice [11-12]. On the other hand, univentricular repair in the presence of a dominant morphologically RV carries a higher risk of future hemodynamic impairment, compared with "univentricular hearts" of left morphology. This is keeping with the general opinion that the structure of the RV is suboptimal to play the role of systemic ventricle [32, 34]. Cardiac transplant [35] is also an option but limited organ availability reduces chances of the latter solution. Accordingly, the optimal surgical treatment for DI-DORV patients still remains controversial and many patients can survive until adult age without repair, thanks to pulmonary stenosis.

5. Conclusion

DI-DORV is a rare congenital anatomo-maldevelopmental complex that might present with different associated anomalies, the knowledge of which is of paramount importance for preoperative assessment and surgical planning. Survival of these patients is influenced by the presence of pulmonary stenosis, that prevents the onset of hypertensive pulmonary disease. Besides eligibility for a univentricular or biventricular repair, associated anomalies such as anomalous pulmonary and systemic venous returns in the setting of atrial isomerism may significantly adverse DI-DORV patient operability.

Table and figure legends

Table 1. Atrial situs and VA connections in hearts with DIRV

Table 2. DI-DORV hearts morphology

Table 3. Previously reported cases of DI-DORV

*Figure 1***.** Double inlet-double outlet right ventricle in situs solitus. A) Two separate AV valves drain into the morphologically RV. The left AV valve (*) straddles and overrides the ventricular septum more than the 50%. The left ventricle was hypoplastic. B) View of the large right ventricle that receives blood from both atria through two separate AV valves and gives origin to both the vast arteries (the probe is inserted into the pulmonary outflow).

*Figure 2***.** Double inlet-double outlet right ventricle in right atrial isomerism. A) Anterior view of the heart. Both the atrial appendages show right morphology (right isomerism). A supracardiac total anomalous pulmonary venous drainage (*) is present draining to the right sided superior vena cava. B) The left ventricle is extremely hypoplastic. C) View into the right side of the heart: a common atrium is divided by a narrow band (arrow) and a common AV valve drains mostly into the RV.

Figure 3. Double inlet-double outlet right ventricle with pulmonary stenosis. A) View from the apex of the RV: a common AV valve is visible, mostly aligned with the morphologically RV. Note the subpulmonary fibro-muscular stenosis (arrow). B) View from the left-posterior perspective shows a hypoplastic LV and more than 75% of the common AV valve drains into the right ventricle.

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Table 1

Atrial Situs	DIRV	Ventriculo-arterial connections		
		DORV	Single Aortic Outlet (pulmonary atresia)	Single Pulmonary Outlet (aortic atresia)
Solitus	6 (26)	**3**	1	2
Left isomerism	2 (9)	**1**	-	1
Right isomerism	15 (65)	**10**	4	1
Total	23 (100)	**14 (60)**	5 (22)	4 (18)

Data are shown as N (%). DIRV = Double Inlet Right Ventricle; DORV= Double Outlet Right Ventricle.

Table 2

n	Gender	Age	Atrial situs	AV/VA connections	AV mode	Ventricular loop	Heart position	Great arteries relation	Systemic veins drainage	Coronary sinus	Pulmonary veins drainage	Atrium	Ventricular septal defect	Left ventricle	Infundibulum	Left outflow	Right outflow	Pulmonary valve	Aortic arch	PDA	Surgery
1	F	13y	solitus	DI-DORV	straddling left valve	d-loop	levocardia	right anterior Ao			normal	ASD	perimembranous posterior	hypoplastic	bilateral		muscular sub pulmonary stenosis	tricuspid stenotic	left		bidirectional cavo-pulmonary anastomosis
2	M	15d	solitus	DI-DORV	common valve	d-loop	levocardia	right posterior Ao	persistent left SVC		normal	common		hypoplastic	bilateral				left	left	pulmonary banding
3	F	18d	solitus	DI-DORV	common valve	d-loop	levocardia	right posterior Ao			normal	common		hypoplastic	bilateral				left	left	pulmonary banding
4	M	20y	left isomerism	DI-DORV	common valve	d-loop	levocardia	right anterior Ao	persistent left SVC, interrupted IVC		2 veins to each atrium	common		hypoplastic	bilateral			bicuspid stenotic	right		
5	F	1,5y	right isomerism	DI-DORV	common valve	d-loop	levocardia	right anterior Ao		absent	TAPVC to right sided atrium	ASD		hypoplastic	bilateral		accessory AV fibrous 4tissue	unicuspid stenotic	right	left	aorto-pulmonary anastomosis
6	F	15y	right isomerism	DI-DORV	common valve	d-loop	levocardia	right anterior Ao	persistent left SVC	absent	TAPVC to right SVC	common		hypoplastic	bilateral		muscular sub pulmonary stenosis	tricuspid stenotic	right		bidirectional cavo -pulmonary anastomosis
7	M	1,5 m	right isomerism	DI-DORV	common valve	d-loop	levocardia	right Ao		absent	TAPVC to right sided atrium	common	muscular trabecular	hypoplastic	bilateral				right		
8	F	42y	right isomerism	DI-DORV	common valve	d-loop	levocardia	right anterior Ao		absent	**TAPVC to left sided atrium**	ASD		hypoplastic	bilateral		muscular sub pulmonary stenosis	bicuspid stenotic	left		
9	F	7y	right isomerism	DI-DORV	common valve	d-loop	dextrocardia	left anterior Ao	persistent left SVC	absent	TAPVC to right SVC	ASD		hypoplastic	bilateral		muscular sub pulmonary stenosis	tricuspid stenotic	left		
10	F	1m	right isomerism	DI-DORV	common valve	d-loop	dextrocardia	right Ao	persistent left SVC	absent	**TAPVC to left sided atrium**	ASD		hypoplastic	bilateral	sub aortic stenosis			left, hypoplastic	left	aorto-pulmonary anastomosis
11	F	3m	right isomerism	DI-DORV	common valve	l-loop	dextrocardia	right Ao	left SVC, interrupted IVC	absent	TAPVC to left SVC	common		hypoplastic	bilateral		,		left, Ao coarctation	left	
12	M	4y	right isomerism	DI-DORV	common valve	l-loop	dextrocardia	left anterior Ao	persistent left SVC	absent	TAPVC to right SVC	ASD		hypoplastic	bilateral		muscular sub pulmonary stenosis	bicuspid stenotic	right		
13	M	6m	right isomerism	DI-DORV	common valve	l-loop	dextrocardia	left anterior Ao	persistent left SVC	absent	TAPVC to right-sided atrium	ASD		hypoplastic	bilateral		muscular sub pulmonary stenosis		left	left	bidirectional cavo-pulmonary anastomosis
14	M	2d	right isomerism	DI-DORV	common valve	l-loop	dextrocardia	left anterior Ao	persistent left SVC	absent	TAPVC to right SVC	ASD		hypoplastic	bilateral		muscular sub pulmonary stenosis		left	left	

Data are shown as N. ASD=atrial septal defect; Ao=aorta; AV=atrioventricular; d=days; DIRV=double inlet right ventricle; DORV=double outlet right ventricle; IVC=inferior vena cava; m=months; PDA=patent ductus arteriosus; Po=pulmonary; SVC=superior vena cava; TAPVC=totally anomalous pulmonary venous connection; VA=ventriculo-arterial; y=years.

Table 3

	Year	Total cases	Age	Cases type		Atrial situs				AV valve	
				Clinical	Autoptical	Solitus	Inversus	Right isomerism	Left isomerism	2 valves	Common valve
Munoz-Castellanos et al. [22]	1969	1	3y	1	1*	1	0	0	0	1	0
Quero-Jiménez et al. [23]	1973	5	3d-4m	5	5*	-	-	-	-	-	-
Munoz-Castellanos et al. [4]	1973	2	3-6 y	0	2	2	0	0	0	2	0
Tandon et al. [5]	1973	1	1,5 m	0	1	1	0	0	0	2	0
Van Praagh et al. [24]	1979	6	1d-15y	0	6	2	1	3	0	2	4
Soto et al. [25]	1979	7	1-27 y	7	1*	6	0	0	1	7	0
Keeton et al. [19]	1979	7+	-	0	7	4	0	3	0	3	4
Shinebourne et al.[26]	1980	8	1d-9m	8	-	4	2	2	0	6	2
Girod et al. [20]	1984	1+	-	0	1	1	0	0	0	1	0
Thies et al. [27]	1985	5	2d-31 y	5	0	2	0	1	2	2	3
Thies et al. [28]	1986	9	-	9	0	7	0	1	2	4	5
Kawahira et al [12]	2001	51++	-	51++	0	-°°	-°°	-°°	-°°	12	39
Saleeb et al. [11]	2010	20+	1d-50y	16	7*	20	0	0	0	20	-**
Frescura, Thiene [2]	2014	9	1d-42y	0	9	1	0	7	1	1	8

Data are presented as absolute number. AV=atrioventricular; d=days; DI-DORV=double inlet-double outlet right ventricle; m=months; y=years

+cases of DIRV with pulmonary atresia described by authors as DI-DORV have been excluded

++authors included DIRV with pulmonary atresia as DI-DORV but total amount of those is unknown

*autopsy performed in cases included also in clinical group

** common AV valve was considered as exclusion criteria for DI-DORV

°° atrial situs and associated morphologic anomalies are reported for all cases of double ventricle