Original Article

Contribution to the Diagnosis and Treatment of Pulmonary Arteriovenous Fistulae after a Bidirectional Glenn Operation

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Objective

To determine the incidence of pulmonary arteriovenous fistulae (PAVFs) after the bidirectional Glenn operation and the possible independent variables that could influence their appearance; to confirm the use of microbubble contrast echocardiography for the detection of PAVFs; and to test the sensitivity and specificity of pulmonary angiography.

Methods

From March 1990 to December 1995, 59 patients were operated upon. Their ages ranged from 2 to 132 months (mean, 32.7± 33.6). All underwent clinical and laboratory examinations, microbubble contrast echocardiography, and cardiac catheterization.

Results

Of the 54 survivors, 20 (37.0%) had PAVFs. The ages ranged from 2 to 132 months (mean, 29.6±29.7). In 13 (65%) patients, the bidirectional Glenn operation was performed on the right-hand side; in 2 (10.0%) patients, on the left-hand side; and in 5 (25%) patients, it was bicaval. The follow-up of the patients with PAVFs ranged from 4 to 84 months (mean, 32.4±21.65), and that of the patients without fistulae ranged from 1 to 77 months (mean, 23.4±18.8), with statistical significance (P=0.04). The PAVFs were diagnosed by use of microbubble contrast echocardiography in 20 cases; the examination was considered positive when return of microbubbles through the pulmonary veins was detected. PAVFs were observed in the right lung in 9 (45%) patients, in the left lung in 3 (15%) patients, and in both lungs in 8 (40%) patients. The pulmonary angiography showed alterations compatible with PAVFs in 16 patients, with a sensitivity of 80%.

Conclusion

The incidence of PAVFs after the bidirectional Glenn operation was high (37%). The time interval elapsed after the bidirectional Glenn operation was the only independent variable that significantly correlated with the appearance of PAVFs (P=0.04). Microbubble contrast echocardiography was the standard diagnostic method. The pulmonary angiography showed a sensitivity of 80.0%.

Keywords

pulmonary arteriovenous fistulae, bidirectional Glenn operation, microbubble contrast echocardiography

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Cyanogen congenital heart diseases, which behave functionally as univentricular heart, are usually characterized by a poor prognosis, unsatisfactory quality of life, and impossibility of surgical correction that reestablishes the normal cardiac anatomy.

In the past 4 decades, several proposals for palliative operations have been tested, initially in experimental animals, and then, if successful, in children with such defects. One of them, the Glenn operation, was based on the principle that systemic venous blood might reach the pulmonary circulation without the participation of the right cardiac cavities. This operation was experimentally proposed by Carlon et al [1] in 1951, successfully performed for the first time by Meshalkin [2] and Bakulev [3] in 1956, and diffused by Glenn [4] in 1958.

The classical Glenn operation, as this procedure has been known, remained unaltered for many years. Haller et al [5] experimentally introduced the concept of bilateral partial cavopulmonary anastomosis, in which the continuity between the pulmonary arteries was preserved by a terminolateral anastomosis between the superior vena cava and the right pulmonary artery.

Azzolina et al [6] performed that operation for the first time, which became known as the bidirectional Glenn operation. The major advantage of this technique was that the right pulmonary artery, not separated from the confluence, allowed the division of the blood volume of the superior vena cava between both lungs.

Mathur and Glenn [7] reported the late evolution of 56 patients out of 63 who underwent the classical Glenn operation and described for the first time the development of pulmonary arteriovenous fistulae in that type of operation. From this publication onwards, other studies reported such complications [8,9], decreasing the enthusiasm in regard to the classical Glenn operation, which was then abandoned in favor of the bidirectional Glenn operation [6, 10].

Methods

From March 1990 to December 1995, 59 patients with complex cyanogen congenital heart diseases underwent the bidirectional Glenn operation at our service. Five patients died, 4 immediately after the procedure and one during hospitalization. The 54 survivors comprised the case series of this study. Age, on the occasion of the operation, varied from 2 to 132 (mean, 31.4±33.56; median, 18.5) months, and 4 patients were less than 6 (range, 2 to 5; mean, 4.0) months. Of the 54 patients, 28 (51.9%) were of the male sex, and 26 (48.1%) were of the female sex. The heart

diseases were as follows: tricuspid atresia, 30 (56.0%); atrioventricular connection of the double-inlet type, 17 (31.5%); right ventricular double outflow tract, 4 (7.4%); Ebstein disease, 1 (1.7%); complete transposition of the great arteries, 1 (1.7%); and pulmonary atresia with intact ventricular septum, 1 (1.7%). The pulmonary valve had normal anatomy in 19 (35.2%) patients, was stenotic in 25 (46.3%), and atresic in 10 (18.5%).

The bidirectional Glenn operation was performed by anastomosing the right superior vena cava to the right pulmonary artery in 38 (70.4%) patients, to the left pulmonary artery in 6 (11.2%), and simultaneously to the right and left pulmonary arteries (bicaval bidirectional Glenn operation) in 8 (14.9%) patients. In the 2 (3.4%) remaining patients, the inferior vena cava was used for connection with the right pulmonary artery (inverted bidirectional Glenn operation). Blood flow from the ventricular cavity to the pulmonary trunk was maintained in 21 (38.9%) patients. It was abolished after the surgical ligature of the pulmonary trunk in 23 (42.6%) patients. In the other 10 (18.5%) patients, it never occurred due to the presence of pulmonary valve atresia.

All patients underwent periodical review every 3 months, which included, in addition to the complete clinical examination, electrocardiography at rest, chest radiography in the posteroanterior projection, pulse oximetry, measurement of the hematocrit and hemoglobin, microbubble contrast echocardiography with sequential analysis of the heart disease, and, finally, cardiac catheterization.

Transthoracic echocardiographic study was performed in 41 (76.0%) patients weighing less than 20 kg, and the transesophageal technique was used in 13 (24.0%) patients weighing 20 kg or more. The initial maximum dosage of 80 mg/kg of 20% chloral hydrate was used as a sedative for patients undergoing transthoracic echocardiography after a 3-hour fast. If the patient did not respond to sedation, 20% of the initial dosage was administered 20 minutes after the first dose. For transesophageal echocardiography, anesthesia was induced with propofol (1 to 2 mg/kg) and maintained with a dosage of approximately 100 μg/kg per minute. When necessary, concomitant inhalation with halothane was provided.

The venous access for microbubble injection was chosen according to the location of the bidirectional Glenn operation as follows: in patients with the bidirectional Glenn operation performed on the right- or left-hand side, the right or left brachial vein, respectively; in those with the bicaval bidirectional Glenn, the right and left brachial veins; and in those with the inverted bidirectional Glenn, the right femoral vein.

The contrast material consisted of 5.0 mL of saline solution with 0.5 mL of environmental air vigorously mixed by use of a system with 2 taps and 3 connections, producing an opaque saline solution rapidly injected into the patient's vein [11].

The confirmation of the diagnosis of pulmonary arteriovenous fistulae was obtained by detecting the echocardiographic contrast material (bubbles) in the pulmonary veins after a maximum of 8 cardiac cycles. The number of contrast material injections varied, and they were repeated as many times as necessary for the correct diagnosis.

The echocardiographic examinations were performed with the Ultramark-9 HDI model ATL (Advanced Technology Laboratories) apparatus, using a phased array transducer at a 5-3 MHz frequency, and a transesophageal biplane probe at a 5 MHz frequency. The 2-dimensional images were recorded on videotape for later analysis. The duration of the echocardiographic contrast material injection appeared on screen and was recorded on the videotape.

The conventional echocardiographic examination was based on the sequential analysis [12] for defining the anatomy of the heart disease and functionally assessing the bidirectional Glenn operation. Then, the contrasted examination was performed. The subcostal, 4-chamber apical, longitudinal parasternal, and suprasternal views were used for transthoracic examination. The 4-chamber medium transverse and longitudinal planes were used for the transesophageal examination.

The bidirectional Glenn operation was conventionally performed with or without extracorporeal circulation, depending on the surgeon's option. The inverted Glenn operation, which consisted of the construction of a tunnel inside the right atrium, allowing continuity of the inferior vena cava with the right pulmonary artery, was performed according to a previously published technique [13].

For confirming that the microbubbles do not cross the capillary barrier in the absence of pulmonary arteriovenous fistulae, a control group of 27 healthy children was used. Their ages ranged from 12 to 156 months (mean, 58.4±34.8; median, 48.0), and they underwent the same clinical, laboratorial, and echocardiographic protocol of the general case series, except for the hemodynamic study.

The statistical analysis was performed by calculating the arithmetic mean, standard deviation, and median for describing the continuous quantitative variables. The qualitative and categorical variables were expressed as percentages, and, for their comparison, the Pearson χ^2 (chi-square) test or the Fisher exact test was used. For comparisons of the means of the quantitative variables, the Student t test and the nonparametric Mann-Whitney test were used for independent populations. The actuarial curve was calculated for studying the accumulated probability of the time free from the event pulmonary arteriovenous fistulae. The possibility of the risk factors for the appearance of pulmonary arteriovenous fistulae was studied by using the multivariate logistic regression analysis with the conditional forward stepwise selection model. In all statistical tests, the significance level adopted was 0.05. For estimating the population parameters, 95% confidence intervals were calculated. The statistical calculations and analyses were performed with the SPSS program for Windows version 6.0.

Results

Fifty-four patients were followed up for the maximum period of 110 months (mean, 31.4±33.56; median, 18.5). Pulmonary arteriovenous fistulae were detected in 20 patients (37.0% - 95% CI: 24.1 - 49.9%).

The survival curve free from the event pulmonary arteriovenous fistula had a mean of 50.0 (95% CI: 39 - 61 months) and median of 48.0 (95% CI: 38 - 58 months), with a 37.0% accumulated probability of up to 84 months (fig. 1).

The age of 20 patients who developed pulmonary arteriovenous fistulae ranged, on the occasion of the bidirectional Glenn operation, from 2 to 132 months (mean, 29.6±29.72; median, 19.0). Twelve (60.0%) were males and 8 (40.0%) were females. The follow-up duration ranged from 4 to 84 months (mean, 4±21.65; median, 25.0), while in those who did not develop pulmonary

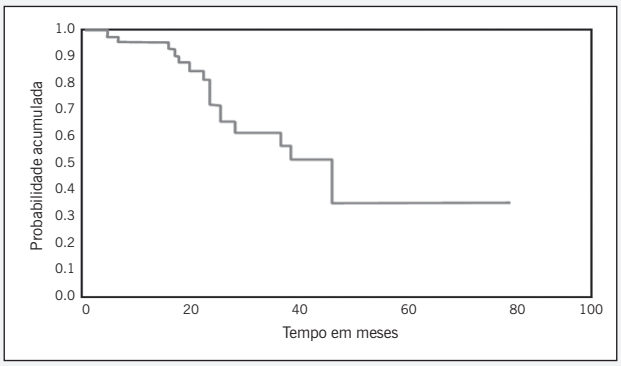

Fig. 1 - Pulmonary arteriovenous fistula event-free survival.

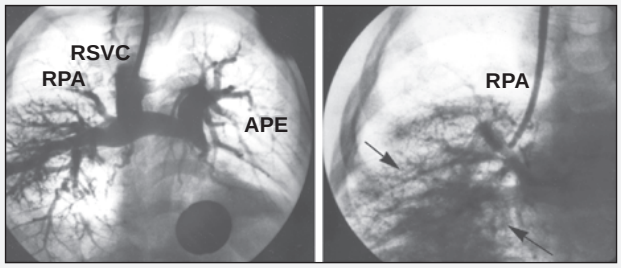

Fig. 2 - Case # 2 – Angiographic sequence in posteroanterior projection. A) contrast material injection into the right superior vena cava (RSVC), with opacification of both pulmonary arteries. Note the vascular dilations in the inferior lobe of the right lung, compatible with PAVFs; B) magnification of the right pulmonary artery (RPA), highlighting the angiomatoid lesions.

arteriovenous fistulae, the follow-up duration ranged from 1 to 77 months (mean, 23.4±18.84; median, 18.0; P=0.04), showing statistical significance. The comparison between the ages of the general case series and the event of pulmonary arteriovenous fistulae by using the class interval showed no statistical significance (P=0.48).

In the case series of 54 patients, 4 (6.8%) underwent the bidirectional Glenn operation before the age of 6 months (range, 2 to 5 months; mean, 4.0 months), and pulmonary arteriovenous fistulae were detected in 2 patients at the ages of 23 and 24 months (fig. 2).

When comparing the sex of the patients with and without fistulae, the P value was also not significant (P=0.41).

The most prevalent heart diseases among the patients developing pulmonary arteriovenous fistulae were tricuspid atresia in 10 (50.0%) and atrioventricular connection of the double-inlet type in 8 (40.0%) patients. The 2 remaining patients had right ventricular double outflow tract and complete transposition of the great arteries (10.0%). No statistical significance was observed between the 2 major groups of heart diseases in regard to the presence or absence of pulmonary arteriovenous fistulae (P=0.54).

Table I shows the diagnosis, *situs cordis* and visceral *situs*, associated defects and previous surgeries in each patient. No statistical significance was observed in regard to the *situs* and the development of pulmonary arteriovenous fistulae (P=0.18). The performance of palliative surgeries prior to the bidirectional Glenn operation was also not an independent variable with statistical significance (P=0.29).

As can be seen in table I, although lacking statistical significance due to the small size of the sample, 3 (75%) of the 4 patients with left atrial isomerism developed pulmonary arteriovenous fistulae (cases 6, 7, and 20) (fig. 3 and 4). All had atrioventricular connection of the double-inlet type to the ventricular cavity, which was morphologically right in 2, and morphologically left in one patient. In addition, they had a single atrioventricular valve and interruption of the hepatic segment of the inferior vena cava,

Table I – List of the pulmonary arteriovenous fistulae comprising the number of each case, the diagnosis, the *situs*, the anatomical arranges, and the previous operations (Prev Op)

Number	Diagnosis	*Situs*	Anatomical arranges	Prev Op
1	DIL	"SOLITUS"	PS, single AVV	LBT
2	TA	"SOLITUS"	no PS, restrictive ASD and VSD	-
3	DIL	"SOLITUS"	VAD, no PS	PTB
4	DIR	RAI	PS, single AVV	-
5	DIR	"INVERSUS"	PA, PDA	LBT
6	DIR	LAI	PS, single AVV	-
7	DIR	LAI	no PS, single AVV, single A	-
8	RVDOT	"SOLITUS"	PS, VSD not RGA	RBT
9	TA	"SOLITUS"	PA, PDA	RBT
10	TA	"SOLITUS"	no PS, single A, restrictive VSD	-
11	DIR	T INV, A SOLIT	PS, ALAVV	BROCK
12	TA	"SOLITUS"	PA, PDA	RBT
13	TA	"SOLITUS"	PA, PDA	RBT
14	TA	'SOLITUS"	PS	-
15	TA	'SOLITUS"	No PS	PTB
16	TA	"SOLITUS"	no PS	PTB
17	TGA	"SOLITUS"	PS, single AVV	-
18	TA	"SOLITUS"	no PS, restrictive VSD	
19	TA	"SOLITUS"	no PS, restrictive VSD	-
20	DIL	LAI	PA, PDA, single AVV	LBT

DIL - double inlet to the left univentricular cavity; DIR - double inlet to the right univentricular cavity; TA - tricuspid atresia; RVDOT - right ventricular double outflow tract; TGA - complete transposition of the great arteries; RAI - right atrial isomerism; LAI - left atrial isomerism; T INV - thoracic "*inversus*"; A SOLIT - abdominal "*solitus*"; PS - pulmonary stenosis; PA - pulmonary atresia; AVV - atrioventricular valve; ASD - atrial septal defect; PDA - patent *ductus arteriosus*; VSD - ventricular septal defect; single A - single atrium; VSD not RGA - ventricular septal defect not related to the great arteries; RBT - right Blalock-Taussig; LBT - left Blalock-Taussig; PTB - pulmonary trunk banding; VAD - ventriculoarterial discordance; ALAVV - atresic left atrioventricular valve.

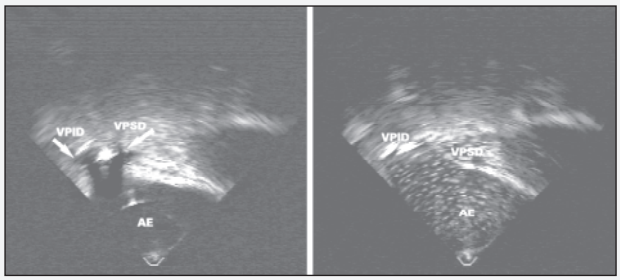

Fig. 3 - Case # 20 - A) transesophageal study with visualization of the right superior and inferior pulmonary veins (RSPV and RIPV) in a longitudinal view prior to contrast material injection; B) return of the contrast material through the right superior and inferior pulmonary veins, characterizing PAVFs in the entire right lung.

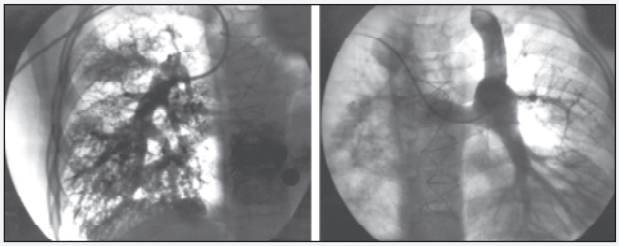

Fig. 4 - Case # 20 - A) injection of contrast material through the bidirectional Glenn operation to the right, with selective opacification of the right pulmonary artery, which shows diffuse angiomatoid dilations in the entire right lung. B) selective injection of contrast material into the left pulmonary artery through the bidirectional Glenn operation to the left, showing a normal angiographic appearance. RPA- right pulmonary artery; LPA- left pulmonary artery; RSVC- right superior vena cava; LSVC- left superior vena cava.

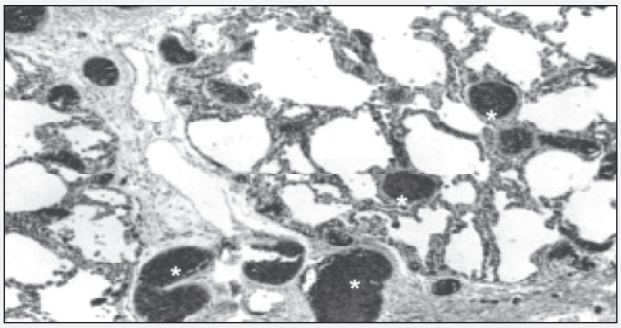

Fig. 5 – Microscopic view of the right lung showing ectatic * vessels in the pulmonary parenchyma and in fibrous septa (HE, 40x).

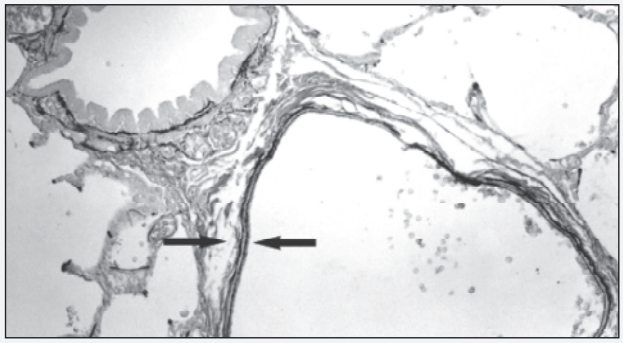

Fig. 6 – Markedly dilated bronchiolar artery with thin walls. This dilation gives the artery a venous aspect, but the 2 elastic laminae, which characterize the arterial lineage of the vessel, are clearly seen (Miller stain for elastic fibers, 100x).

with continuation and drainage through the azygos system in one patient and through the hemiazygos system in 2 others.

The pulmonary biopsy revealed pulmonary parenchyma with ectatic and congestive arterial and venous vascular network compatible with pulmonary arteriovenous fistulae (fig. 5 and 6).

In 13 (65.0%) of 20 patients with pulmonary arteriovenous fistulae, the right superior vena cava was used for connecting with the right pulmonary artery; in 2 (10.0%), the left superior vena cava was anastomosed to the left pulmonary artery; and in 5 (25.0%), both the left and right venae cavae were anastomosed to the respective left and right pulmonary arteries.

Blood flow from the ventricular cavity to the pulmonary trunk was maintained in 10 (50.0%) patients. In 5 (25.0%), blood flow was abolished by surgical ligature of the pulmonary trunk, and in the other 5, it never occurred due to the presence of pulmonary valve atresia. The comparative study considering the location of the operation and maintenance of the anterograde flow between the groups with and without pulmonary arteriovenous fistulae showed no statistical significance (P=0.31 and 0.19, respectively).

The duration of the follow-up of patients in whom pulmonary arteriovenous fistulae were detected after the bidirectional Glenn operation ranged from 4 to 84 months (mean, 32.4±21.65; median, 25.0). Six patients had progressive dyspnea and stable cyanosis on the occasion of the detection of the fistulae; 8 had progressive cyanosis; and 6 had progressive dyspnea and cyanosis.

On echocardiographic study, the duration between injection of the contrasted material and the appearance of the microbubbles in the pulmonary veins ranged from 3 to 8 seconds, which corresponded to the mean of 5 cardiac cycles (range, 4 to 7). As no contrast material was observed in the inferior vena cava and in the systemic return atrium, the possibility of systemic venous collaterals was excluded in 19 (95.0%) patients. In one (5.0%), the presence of microbubbles was observed in the inferior vena cava, which also allowed the diagnosis of systemic venovenous connection to that vein. In 9 (45.0%) patients, pulmonary arteriovenous fistulae were detected in the right lung; in 3 (15.0%) patients, in the left lung; and in 8 (40.0%) patients, in both lungs (tab. II). Of the 34 patients who developed no pulmonary arteriovenous fistulae, systemic venous collaterals were observed in 14 (41.1%) patients.

Of the 20 patients with pulmonary arteriovenous fistulae diagnosed on microbubble contrast echocardiography, pulmonary angiography detected fistulae in 16 (80.0%) due to the presence of one or more of the following factors: 1) reticular appearance of the lung parenchyma; 2) angiomatoid dilations of the lobar pulmonary arteries (figs. 2 and 4); 3) loss of the capillary phase; and 4) rapid arteriovenous transit. Four patients (cases 7, 13, 16, and 19) had no angiographic images of fistulae. Table III shows the echocardiographic and angiographic findings and the time interval between the bidirectional Glenn operation and the detection of the fistulae in 20 patients.

Angiography had a sensitivity of 80.0%, specificity of 100%, and positive and negative predictive values of 100% and 89.5%.

Of the 20 patients with pulmonary arteriovenous fistulae, 10 underwent total cavopulmonary operation; 2 (10.0%) died in the immediate phase due to hypoxemia and low cardiac output syndrome; 5 are awaiting surgical correction; and 4 are not indicated for surgery, because of the presence of bilateral diffuse fistulae in 2 patients, and hypoplasia of the pulmonary arteries, with a Nakata index [14] lower than 200 mm^2/m^2, in the other 2. One patient died after the hemodynamic restudy (case 8), which was performed for assessing the possibility of definitive correction (total cavopul-

Table II – Distribution of the PAVFs according to the site of the bidirectional Glenn operation

Site of operation	PAVFs					
	Right lung		Left lung		Both lungs	
	Nº	%	Nº	%	Nº	%
Right	8	40.0	1	5.0	4	20.0
Left	-	-	1	5.0	1	5.0
Right and left	1	5.0	1	5.0	3	15.0

monary operation). Of the 8 patients surviving the total cavopulmonary operation, disappearance of the pulmonary arteriovenous fistulae was detected in 3 (27.0%) patients (cases 2, 3, and 10) at 6, 26, and 36 months, respectively (figs. 7 and 8), according to contrast transesophageal echocardiography and hemodynamic study. On contrast transesophageal echocardiography performed 5 and 18 months after the operation, 2 patients (cases 11 and 15, respectively) had reversal of the left pulmonary fistulae, but not of the right pulmonary fistulae. In 3 patients (cases 4, 9, and 16), the pulmonary arteriovenous fistulae remained unaltered on contrast transesophageal echocardiography performed 20, 29, and 18 months after the operation, respectively.

The control group showed no return of microbubbles through the pulmonary veins, confirming the importance of contrast echocardiography for diagnosing the presence or absence of pulmonary arteriovenous fistulae.

Discussion

Pulmonary arteriovenous fistulae have been postulated as remnants of minute arteriovenous communications present in the fetus and neonatal infant, which, by dilation, become fistulous, causing precapillary shunts and arterial insaturation [15]. Injections of gelatinous calcium carbonate into the pulmonary arteries of stillborns showed the presence of vascular channels that go beyond the capillary bed and directly communicate the arterial and venous systems [16]. These channels may be responsible for the development of the pulmonary circulation, before the alveolar capillary network establishes. The lungs of neonates are more sensitive and the embryonic arteriovenous connections may persist, explaining the greater prevalence of pulmonary arteriovenous fistulae, which are clinically more significant in young infants [16].

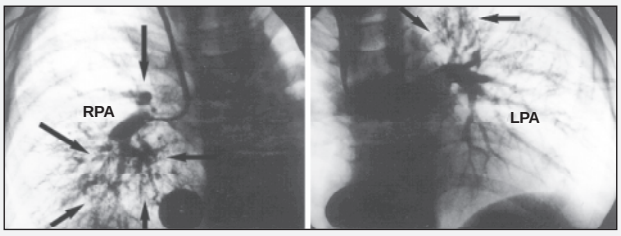

Fig. 7 – Case # 3 - A and B) Angiographic study of the bidirectional Glenn operation to the right showing angiomatoid dilations of the pulmonary vessels in the middle and inferior lobes of the right lung and in the hilum and superior lobe of the left lung (arrows). RPA- right pulmonary artery; LPA- left pulmonary artery.

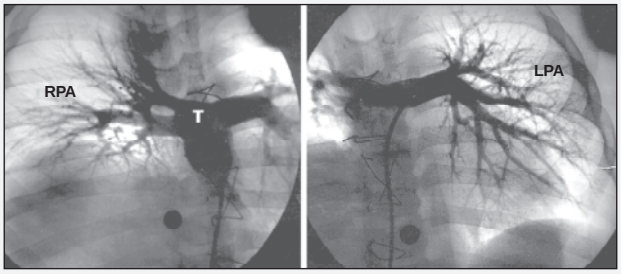

Fig. 8 - Case # 3 – Angiographic restudy 2 years after total cavopulmonary operation. A and B) Injection of contrast material into the tunnel that connects the inferior vena cava to the pulmonary arteries, showing a normal angiographic aspect, with complete disappearance of the vascular dilations in both lungs. RPA- right pulmonary artery; LPA- left pulmonary artery.

In our study, in the 20 patients who developed pulmonary arteriovenous fistulae, statistical significance was observed in regard to neither the intensity of the event nor the age on the occasion of the bidirectional Glenn operation. In 2 patients, pulmonary arteriovenous fistulae were detected earlier (cases 12 and 18), 6 and 4 months after surgery, respectively, and their ages on the occasion of surgery were 39 and 17 months (tab. III). In regard to the patients with diffuse pulmonary arteriovenous fistulae (cases 1, 6, and 20), their ages on the occasion of operation were 31, 53, and 46 months, and the pulmonary arteriovenous fistulae were detected at 26, 40, and 84 months of follow-up, respectively (tab. III). Therefore, their follow-up was longer than 2 years, confirming the impression obtained in our study and in the literature that, the longer that time, the greater the possibility of occurrence of pulmonary arteriovenous fistulae [9,17,18]. On the other hand, the 2 younger patients (cases 2 and 16), operated upon at the ages of 2 and 5 months, respectively, pulmonary arteriovenous fistulae were detected 23 and 24 months (tab. III) after surgery, without any relation between the precocity of the operation and the appearance of pulmonary arteriovenous fistulae.

Therefore, pulmonary arteriovenous fistulae seem to be related to the time of evolution after the bidirectional Glenn operation. Cloutier et al [9] reported a 25.0% incidence of the event in 20 patients studied during an 8.8-year follow-up. Kopf et al [17], studying 62 cases, reported the presence of pulmonary arteriovenous fistulae in 19 (31.0%), and the only predictive variable was the interval between the operation and the detection of fistulae ($P<0.05$). Trusler et al [18], studying 61 patients, detected the development of pulmonary arteriovenous fistulae in 13 (21.0%) patients. The mean follow-up of patients with fistulae after the bidirectional Glenn operation was 125.6 ± 28.5 months; the mean follow-up of those with no angiographic evidence of fistulae was 86.05 ± 37.0 months ($P=0.027$).

The pathogenesis of the pulmonary arteriovenous fistulae has not yet been clarified. It has been suggested [8,19] that patients with left atrial isomerism have a predisposition for the occurrence of pulmonary arteriovenous fistulae as part of the spectrum of incomplete development of organs affected by the syndrome, or that the fistulae are related to the biliary disease sometimes found in those patients. Studies carried out by Srivastava et al [20] have

Table III – Echocardiographic and angiographic findings and interval (Dt) in moths between the bidirectional Glenn operation and the detection of PAVFs in 20 patients.

N	Echocardiography	Angiography	Δt
1	Right lung	Diffuse: right lung	26
2	Right lung	Inferior lobe: right lung	23
3	Right and left lungs	Middle and inferior lobes: right lungSuperior lobe: left lung	48
4	Right and left lungs	Inferior lobe: right and left lungs	38
5	Right and left lungs	Inferior lobe: left lung	16
6	Right and left lungs	Diffuse: right lung. Hilum and superior lobe of the left lung	40
7	Left lung	No images of PAVFs	48
8	Right lung	Inferior lobe: right lung	24
9	Right and left lungs	Base of both lungs	24
10	Right lung	Base: right lung	18
11	Right and left lungs	Inferior lobe: right and left lungs	20
12	Right lung	Inferior lobe: right lung	6
13	Right lung	No images of PAVFs	26
14	Right and left lungs	Base of both lungs	29
15	Right and left lungs	Hilum and inferior lobe: left lung Base: right lung	17
16	Right lung	No images of PAVFs	24
17	Left lung	Superior lobe: left lobe	48
18	Right lung	Base: right lung	4
19	Left lung	No images of PAVFs	84
20	Right lung	Diffuse: right lung	84

reported a high incidence of pulmonary arteriovenous fistulae after the bidirectional Glenn operation in 6 of 28 (21.0%) patients with left atrial isomerism, with a mean follow-up of 4 years.

The bad distribution of the pulmonary flow may be another cause of appearance of pulmonary arteriovenous fistulae [21], because the passive pulmonary filling, without the propelling force of the right ventricle after the operation, results in an increase in the perfusion of the inferior lobe instead of the superior lobe. Although this bad distribution is present in some patients after the total cavopulmonary operation [9], pulmonary arteriovenous fistulae are not frequent complications.

Another cause could be the absence of pulsatile flow, but this possibility does not explain the appearance of pulmonary arteriovenous fistulae in patients with biliary atresia [22].

These considerations strongly suggest that the hepatic venous blood plays a role in preventing the pulmonary arteriovenous fistulae. Patients with hepatic cirrhosis [23,24] develop vascular dilations similar to those found after the bidirectional Glenn operation, impairing the precapillary and capillary regions of the pulmonary vessels. Although abnormal vasoactive agents were found in the hepatic venous blood of patients with cirrhosis [25,26], most patients with pulmonary arteriovenous fistulae consequent to the bidirectional Glenn operation have normal liver function [20].

This finding leads to the supposition that it is the absence of a normal hepatic factor, rather than the presence of an abnormal factor in the hepatic venous blood that produces pulmonary arteriovenous fistulae [20]. Lamberg et al [22] have reported that 2 patients with biliary atresia developed pulmonary arteriovenous fistulae, which reversed 3 months after orthotopic liver transplantation, suggesting that the return of the normal liver flow to the lungs was responsible for involution of the fistulae. Other studies [27,28] have also confirmed this hypothesis in adults with hepatic cirrhosis and children with biliary atresia.

On the other hand, the evidence of pulmonary arteriovenous fistulae in patients with left atrial isomerism with no cardiac anomalies [19,29], the close relation between biliary atresia and pulmonary arteriovenous fistulae [30-32], and worsening or appearance of fistulae after a total cavopulmonary operation [9] suggest that hepatic venous blood is partially responsible for, but does not play an exclusive role in the genesis of the pulmonary arteriovenous fistulae.

The studies by Moore et al [33], Knight and Mee [34], and Shah et al [35] confirm the hypothesis of the role played by the hepatic factor in the formation of the pulmonary arteriovenous fistulae by showing the appearance of fistulae after the Kawashima operation [32], and their partial [34] or complete [35] disappearance after the incorporation of the supra-hepatic veins into the pulmonary circulation. In our study, of the 8 patients with pulmonary arteriovenous fistulae undergoing total cavopulmonary operation, complete regression occurred in 3 and partial in 2, the latter with bilateral fistulae. A new investigation with a longer follow-up may have more favorable results.

Despite the evidence showing that the hepatic venous blood plays a role in the genesis of pulmonary arteriovenous fistulae, their causal agent has not been detected. Vasodilators originating in the mesenteric venous blood, such as glucagon, have been proposed as the major agents involved in the appearance of the fistulae [25]. Kawata et al [36] reported the appearance of pulmonary arteriovenous fistulae in 3 of 16 patients with left atrial isomerism and cyanogen congenital heart diseases and no previous operation, 2 of whom also had systemic arteriovenous fistulae. These results were compared with those of 50 patients with right atrial isomerism, but none of them developed fistulae, either pulmonary or systemic. One patient with left atrial isomerism and systemic and pulmonary arteriovenous fistulae had an elevation in somatostatin, an antagonist of glucagon, with values around 92.8 pg/mL, when the normal level is 28 pg/mL. The increase in somatostatin may reflect a homeostatic mechanism to prevent the excessive vasodilation caused by an unknown mediator, which may account for the appearance of the fistulae [36]. In addition, the unknown vasodilator agent may reach the systemic circulation without being metabolized by the liver, and, therefore, may similarly produce systemic arteriovenous fistulae.

Although the unknown vasodilator agent may be responsible for the genesis of both types of fistulae, other mechanisms may be involved, because the pulmonary arteriovenous fistulae appear

in patients with interruption of the hepatic segment of the inferior vena cava, with continuation and drainage through the azygos or hemiazygos system.

Those considerations again shed light onto the liver, because, as already cited, the pulmonary arteriovenous fistulae consequent to biliary atresia [22] or hepatic cirrhosis [25,26] reverse after orthotopic liver transplantation.

Although the unknown vasodilator agent may be responsible for the genesis of the pulmonary and systemic arteriovenous fistulae in patients with left atrial isomerism, other mechanisms may be implicated. The following hypothesis may be formulated: in these cases, vasodilator agents, such as glucagon and vasoactive intestinal peptides originating from the mesenteric circulation, are not metabolized by the liver and pass directly to the lungs, heart, and other organs, stimulating the formation of the fistulae. Hypersensitivity of the pulmonary endothelium or a reduction in the sensitivity of the pulmonary vasculature to an endogenous vasoconstrictor should be considered alternative mechanisms [36].

Recognizing the importance of the hepatic venous blood return to the lungs for preventing fistulae, Macé et al [37] and the group of this study [13] modified the procedure of the bidirectional Glenn operation to allow a first mandatory passage of hepatic blood through the lungs. Aiming at this, the right pulmonary artery was connected to the inferior vena cava, a procedure called the inverted bidirectional Glenn operation, whose technical details have already been described in a previous publication [13]. After surgery, blood of the inferior vena cava has to pass through the lungs, supplying them with the hypothetical hepatic factor. This technique was used in 2 patients in this series, who developed no pulmonary arteriovenous fistulae during 2 years of follow-up, when a total cavopulmonary operation was performed.

In regard to the prevention of the development of pulmonary arteriovenous fistulae, the literature has emphasized the possible benefits of pulsatile flow, both for the decrease in the incidence of the fistulae and for their reversal after the inclusion of hepatic venous blood [30,38,39].

In our study, anterograde pulmonary flow was maintained in 21 (39.0%) patients and was absent in 33 (61.0%) patients (P=0.19), nonsignificant for pulmonary arteriovenous fistulae.

Historically, the assessment of the presence of pulmonary arteriovenous fistulae has been difficult due to the lack of an appropriate investigation medium for the supervision of patients at risk for developing fistulae. Although pulmonary angiography and pulmonary perfusion study with technetium-99m macroaggregated albumin have been used for demonstrating pulmonary arteriovenous fistulae [9,18], these techniques are very uncomfortable and seem to be less reliable than contrast echocardiography [40, 41-43]. According to Bernstein et al [40], pulmonary angiography has low sensitivity, mainly in cases of localized and small fistulae. Those authors reported that pulmonary angiography allowed the diagnosis in only 2 of the 9 cases of fistulae. Chang et al [42] reported the detection of pulmonary arteriovenous fistulae by use of contrast echocardiography in 10 of 14 (71.0%) patients after the bidirectional Glenn operation, while pulmonary angiography provided the diagnosis in only 3 (21.0%).

In our study, the angiographic study of the pulmonary arteries was completely normal in 4 (20.0%) patients (cases 7, 13, 16, and 19) (tab. III), although the contrast echocardiographic studies repeated every 3 months were clearly positive. The sensitivity of angiography was 80.0%, and specificity was 100%. Our findings established that contrast echocardiography is the most sensitive method for detecting pulmonary arteriovenous fistulae, and should be performed as part of the echocardiographic routine for assessing all patients undergoing the bidirectional Glenn operation.

Special attention should be given to the contrast technique and the correct interpretation of the images to reduce the possibilities of false-positive or false-negative results. An inadequate formation of microbubbles may result in a false-negative. The contrast material should only be injected if the mixture is opaque, when it has a grayish color. The injection should be rapid. The quality of the mixture is more important than the volume injected. The injections may and should be repeated as many times as necessary. No type of complication was recorded in 207 examinations performed.

The false-positive diagnosis may occur in the presence of systemic venous collaterals, which develop between the superior vena cava and the systemic return atrium, or between the superior vena cava or the innominate vein and the inferior vena cava, or between the innominate vein and the pulmonary veins. Therefore, it is recommended that the diagnosis of pulmonary arteriovenous fistulae on contrast echocardiography should be considered positive when the microbubbles are detected returning through the pulmonary veins. To rule out the possibility of connections between the innominate vein and the pulmonary veins, a rare situation (less than 4%), occlusion of the innominate vein with a balloon and contrast injection are mandatory through a cardiac catheter [44].

One of the most intriguing aspects of pulmonary arteriovenous fistulae is the scarcity of therapeutic options available. If not treated, they result in significant morbidity and mortality. In those cases, the options are: to undo the Glenn anastomosis [45]; perform heart and lung transplantation [31]; create an ipsilateral axillary arteriovenous fistula [17]; and convert to a total cavopulmonary operation. In patients with left atrial isomerism and the bidirectional Glenn operation, the inclusion of the suprahepatic veins into pulmonary circulation [34, 35] or into the azygos system [46] has led to resolution of the fistulae.

In our experience, the reversal of the fistulae occurred after surgical complementation to total cavopulmonary, which was complete in 3 and partial in 2, as reported.

The natural history and clinical significance of the pulmonary arteriovenous fistulae have not been completely defined, and the best approach to such a severe complication is limited by the short follow-up of the patients. Although it is not possible, mainly in Brazil, to reduce the interval between the bidirectional Glenn operation and the total cavopulmonary operation, it is important to include contrast echocardiography as part of the investigative routine in patients undergoing the bidirectional Glenn operation. For those with a positive contrast study, cardiac catheterization is recommended for assessing the extension of the problem. Attention should be particularly directed at 2 population groups: the infants who undergo early operation, and the patients with an evolution time greater than 2 years. The results of this study indicate that all

children undergoing the bidirectional Glenn operation have a significant risk of developing pulmonary arteriovenous fistulae.

The results of the present study allowed the following conclusions: 1) the incidence of pulmonary arteriovenous fistulae after the bidirectional Glenn operation was high, with values around 37.0% (95% CI: 24.1 - 49.9%) in our case series; 2) the only independent variable that significantly correlated with the appearance of pulmonary arteriovenous fistulae was the time interval elapsed after the bidirectional Glenn operation, with an increased risk for those with an evolution time longer than 2 years (P=0.04); 3) contrast echocardiography was the standard method for diagnosing pulmonary arteriovenous fistulae, suggesting its use every 3 months for all patients undergoing the bidirectional Glenn operation; 4) pulmonary angiography proved to be a method with sensitivity of 80% and specificity of 100%, and positive and negative predictive values of 100% and 89.5%, respectively, for detecting pulmonary arteriovenous fistulae. The exclusion of fistulae was not considered a finding of apparent normality of the pulmonary vascular parenchyma; 5) in our study, total cavopulmonary operation was an appropriate treatment for pulmonary arteriovenous fistulae because of the inclusion of hepatic blood into the lungs.

Further investigation is mandatory for determining other risk factors involved in the pathogenesis of pulmonary arteriovenous fistulae, for confirming the still hypothetic hepatic factor, and also for identifying the substance(s) responsible for dilation of precapillary and capillary pulmonary vessels.

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