Türk Kardiyol Dern Arş 1996; 24: 214-220

Contrast Echocardiography for Diagnosis of Pulmonary Arteriovenous Fistulae Late After Glenn Anastomosis

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KAVOPULMONER ANASTOMOZLAR SONRASI GELİŞEN PULMONER ARTERİOVENÖZ FİSTÜLLERİN TANISINDA KONTRAST EKOKARDİYOGRAFİ

Süperiyor vena kava-pulmoner arter anastomozunun (Glenn şantı) bilinen bir geç komplikasyonu olan pulmoner arteriovenöz fistüllerin (PAVF) sıklığının araştırılması ve tanıda kontrast ekokardiyografinin yerinin incelenmesi amacıyla, klasik veya iki-yönlü kavopulmoner anastomoz uygulanan, 21-38 (ort 28±4.8) yaşlarında 12 hasta,operasyondan 4-33 (ort 24±9) yıl sonra prospektif olarak değerlendirilmiştir. 11 hastaya kalp kateterizasyonu ve anjiografi, 6 hastaya manyetik rezonans görüntülemesi uygulanmış, sonuçlar kontrast ekokardiyografi bulguları ile karşılaştırılmıştır.

Kontrast ekokardiyografide 12 hastanın 8'inde bir üst ekstremite venine yapılan enjeksiyondan 1-8 saniye sonra sol atriyumda kontrast maddenin görülmesi ile PAVF tanısı konmuştur. Eko kontrastının sağ atriyumda belirlenmesi 2 hastada süperiyor vena kava ve sağ atriyum arasında rezidüel komünikasyon ve 1 hastada süperiyor vena kava ile inferiyor vena kava arası kollaterallerin varlığı ile açıklanmıştır. PAVF saptanan 8 hastada sistemik arteriyel oksijen satürasyonları istirahatte (% 51-94, ort. 75±15.3) ve modifiye Bruce protokolü ile egzersiz sonrasında (% 23-91, ort. 53±24.2) PAVF olmayan hastalardan daha düşük bulunmuştur (p<0.005). Sağ akciğerinde PAVF saptanan hastalarda sağ pulmoner arter basıncı normal iken, karşı akciğerde pulmoner hipertansiyon daha sık (ort. sol pulmoner arter basıncı 22-110 mmHg, p=0.014) bulunmuştur.

Kavopulmoner anastomoz uygulanan hastalarda özellikle geç dönemde sık görülen, siyanozda artma ve klinik deteriorasyon ile seyreden bir komplikasyon olan PAVF'lerin tanısında pratik ve hassas bir yöntem olduğu gösterilen kontrast ekokardiyografi, bu hastaların izleminde düzenli olarak uygulanmalıdır.

Anahtar kelimeler: *pulmoner arteriovenöz fistül, kavopulmoner anastomoz, kontrast ekokardiyografi*

The cavopulmonary anastomosis (Glenn shunt) introducted in the 1950's [1-3] for patients with cyanotic congenital heart disease has provided effective palliation over 30 years [4]. Although no longer used in lesions suitable for radical repair, there is renewed interest and use of the procedure for lesions deemed suitable for Fontan type operations, either as an initial bidirectional cavopulmonary shunt [5] or as part of the total cavopulmonary connection [6,7]. Its advantage over systemic-pulmonary artery shunts is the increase in pulmonary blood flow without volume overloading the main ventricle [3,5,8]. One of the undesirable long term complications is formation of pulmonary arteriovenous fistulae (PAVF) [4,9,10] which cause a decrease in arterial oxygen saturation and lead to clinical deterioration from increased cyanosis and decreased exercise capacity. Recognition of PAVF in the right lower lobe is difficult by angiography unless they are longstanding and associated with pulmonary venous dilatation; it depends on the speed of opacification of pulmonary veins which is rapid anyway in the low resistance right lung.

This study examines the use of two-dimensional contrast echocardiography for the detection of PAVF in 12 adult patients who had cavopulmonary anastomosis between 1961-1989, 4-33 (mean 24±9) years after the operation.

MATERIALS and METHODS

Patients: The records of all patients who underwent a cavopulmonary anastomosis referred to a unit specifically dealing with congenital heart disease in adolescents and adults were reviewed. There were 19 patients, seven died before the study. Twelve patients aged 21-38 (mean 28±4.8) years at the time of study were contacted and consented to participate in the study. Two of these 12 patients (cases 6&8) died after they had been studied.

The patients' data is summarized (Table 1). Eleven patients had a classical cavopulmonary shunt (Glenn) at age 1.5 months-14 years (mean 4±4.7 years), two of these and

Received December 18, 1995
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Table 1. Clinical data in 12 patients with a previous cavopulmonary anastomosis (Glenn).

Case	Age at study (years)	Age at Glenn (classical CPA) (years)	Age at bi-d CPA (years)	Duration of CPA (years)	Basic disease	Other operations	Age (years)
1	31	7/12		30	T.A. *, conc VA conn ASD, VSD, PS	Ao-LPA shunt Asc ao-mPA shunt	13 27
2	30	3		27	T.A. *, disc VA conn ASD, VSD, PS	B-T shunt (left) Ao-LPA shunt	1 8
3	22	9	11/12	21	T.A. *, conc VA conn ASD, PDA, no VSD	Fontan	9
4	33	7.5/12		32	T.A. *, conc VA conn ASD, VSD, PS	Ao-LPA shunt	3/12
5	27	1.5/12		27	T.A. ** Pulmonary atresia, ASD	B-T shunt (left)	26
6 (died, 1993)	24	14		10	T.A. *, conc VA conn ASD, VSD (restrictive)	Fontan	24
7	38	5		33	T.A. *, conc VA conn ASD, VSD, PS	B-T shunt (left) Infundibular resection	10/12 10
8 (died, 1993)	21		17	4	DILV, disc VA conn VSD	PAB B-T shunt (left)	3/12 10
9	28	4/12		27	T.A.*, conc VA conn ASD, VSD, PS	B-T shunt (left) Fontan	6 9
10	26	9	23	17	T.A. *, pulmonary atresia ASD, VSD	Fontan	23
11	29	8/12		28	T.A. *, conc VA conn ASD, VSD, PS	B-T shunt (left) Fontan)	8/12 12
12	31	2/12		31	T.A. *, conc VA conn ASD, VSD (restrictive)	B-T shunt (left) Fontan	12 21

** Usual atrial arrangement, absent right atrioventricular connection, **Usual atrial arrangement, imperforate right atrioventricular valve ao, aorta; ASD, atrial septal defect; B-T, Blalock-Taussig; bi-d, bidirectional; conc, concordant; conn, connections; CPA, cavopulmonary anastomosis; DILV, double-inlet ventricle; disc, discordant; LPA, left pulmonary artery; mPA, main pulmonary artery; PDA, patent arterial duct; PS, pulmonary stenosis; TA, tricuspid atresia; VA, ventriculoarterial; VSD, ventricular septal defect.*

another patient had bidirectional cavopulmonary shunts at age 11 months-23 years (mean 13±11.3 years). Eleven patients (cases 1-7,9-12) had tricuspid atresia (absent right atrioventricular connection in 10, imperforate right atrioventricular valve in one) with concordant ventriculoarterial connnections in 8, discordant ventriculoarterial connections in 1, pulmonary atresia in 2 patients and one (case 8) had double inlet left ventricle with discordant ventriculoarterial connections.

Four patients (cases 2,4,7,8) had undergone 5 previous palliative procedures before the cavopulmonary anastomosis (all had aortopulmonary shunts and one had pulmonary artery banding). One (case 11) had a left Blalock-Taussig shunt simultaneously with the Glenn shunt. One had infundibular resection (case 7) and 5 patients (cases 1,2,5,9,12) required aortopulmonary shunts 5-26.5 (mean 11±8) years after the Glenn shunt. Six patients (cases 3,6,9-12) had a subsequent Fontan operation, leaving the cavopulmonary anastomosis intact.

Method: After routine transthoracic echocardiography, contrast echocardiography was performed in the apical four-chamber view, visualising both atria and the pulmonary veins.

5 cc of the patient's blood was added to 5cc 5% Dextrose to produce a detergent effect and the mixture was vigorously agitated by transferring back and forth between two syringes connected by a three-way stopcock until a foam was formed. This solution was injected rapidly into the patient through a 19G butterfly needle or intravenous cannula inserted into a right antecubital vein, taking care that no foam was injected. An apical four-chamber view was recorded during the injection for later frame by frame review. The time of injection was noted and marked on the tape so that the duration between the injection of contrast material and appearance of microbubles in the left and right atria could be accurately measured. In the case of an intact superior vena cava-pulmonary artery anastomosis, no bubbles should appear in the right or left atria after an upper extremity peripheral venous injection. Therefore, the study was interpreted as positive for PAVF whenever echo contrast was seen to fill the left atrium from the pulmonary veins.

Cardiac catheterisation and angiography was performed in 11 patients, magnetic resonance imaging (MRI) was performed in 6 patients for further delineation of intra and extracardiac anatomy; the results were compared with the echocardiographic findings. Systemic arterial oxygen saturations at rest and during exercise using modified Bruce protocol were measured in all patients.

In one patient (case 1) PAVF were coil embolized and

contrast echocardiography was repeated after the procedure.

Statistical analysis was performed using the Student's t test and Fisher's exact test to compare difference between groups. A p value of less than 0.05 was considered significant. Values are expressed as mean ± 1 standard deviation (SD).

RESULTS

Table 2 shows the results of contrast echocardiography with previous Glenn anastomosis. In 7 of the 12 patients (cases 1-7), microbubbles appeared in the left atrium within 1,8 seconds after the injection of echo contrast, suggestive of PAVF (Figure 1). The differential diagnosis of other anomalies which may cause opacification of the left atrium, such as a systemic vein draining to the left atrium or pulmonary artery to left atrium communication, was made by echocardiography, angiography and/or MRI. In two patients (cases 1,7) bubbles appeared simultaneously in the right atrium, which was explained by residual communication between the superior vena cava and right atrium, confirmed by angiography and MRI. Both patients had atrial septal defects and to diagnose the PAVF, care was taken to detect filling of the left atrium from the right pulmonary veins. In case 8, a patient with right pulmonary artery pressure 30/22 (mean 26) mmHg and intact interatrial septum, the appearance of bubbles in the right atrium was due to flow down the azygos vein with huge collaterals which fed the inferior vena cava, and the delayed appearance of contrast after 13 seconds in the left atrium was due to venous collaterals which joined with the pulmonary veins, demonstrated by angiography. This was an example of an inappropriately performed bidirectional cavopulmonary shunt 4 years earlier, in the presence of raised pulmonary vascular resistance and the patient died while awaiting heart-lung transplantation.

Table 2. Contrast echocardiography findings, pulmonary artery pressure and arterial oxygen saturations in patients with a previous cavopulmonary anastomosis (Glenn).

Case	Echo contrast on c-TTE			PAVF verifeed by c-TTE	PAVF verified by angiography	PAP* (mm Hg)		Arterial oxygen saturation (%)	
	Location & timing of appearence		Direction			RPA	LPA	at rest	on exercise
	LA	RA							
1	4 sec	4 sec	rPV → LA SVC → RA	+	+	15/9 (13)	52/34 (42)	68	50
2	1 sec	-	rPV → LA	+	+	18/12 (16)	140/90 (110)	61	35
3	4 sec	-	rPV → LA	+	±			94	91
4	8 sec	-	rPV → LA	+	±	11/8 (10)	115/65 (80)	85	60
5	3 sec	-	rPV → LA	+	+			51	23
6	3 sec	-	rPV → LA	+	+	15/9 (13)		84	76
7	1 sec	1sec	rPV → LA SVC → RA	+	-	(9)	40/12 (22)	82	37
8	13 sec	13 sec	rPV → LA SVC → RA (via collaterals)	-	-	30/22 (26)		80	34
9	-	-	-	-	-	16/12 (13)	16/11 (12)	95	91
10	-	-	-	-	-	14/8 (10)	13/7 (8)	99	86
11	-	-	-	-	-	15/10 (13)	19/15 (16)	96	83
12	-	-	-	-	-	17/14 (16)	19/12 (16)	96	90

** Figures in parenthesis indicate mean pressures.*
c-TTE, contrast echocardiography; LA, left atrium; LPA, left pulmonary artery; PAP, pulmonary artery pressure; PAVF, pulmonary arteriovenous fistulae; RA, right atrium; RPA, right pulmonary artery; rPAV, right pulmonary veins, SVC, superior vena cava.

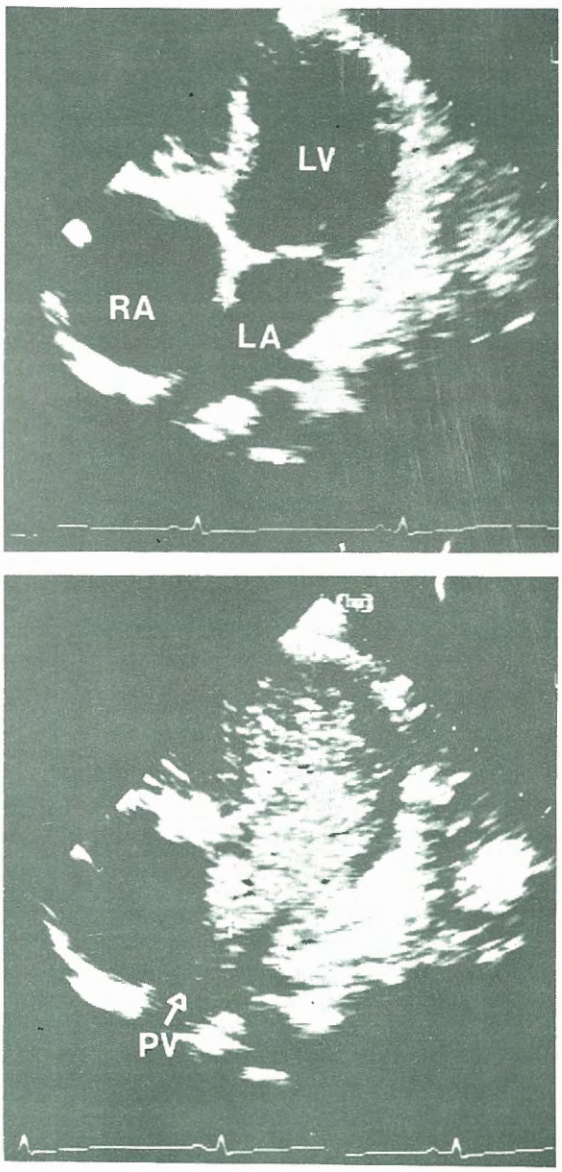

Figure 1. a) Two-dimensional echocardiogram from a patient with tricuspid atresia and a Glenn shunt (case 3), b) contrast medium fills the left atrium from the pulmonary veins, suggestive of PAVF.
LA: left atrium, LV: left ventricle, PV: pulmonary vein, RA: right atrium.

Cardiac catheterization with angiography in 6 of the 7 patients with early left atrial filling on contrast echocardiography, designated to have PAVF confirmed obvious fistulae in 4 (cases 1,2,6,7) (Figure 2) and probable in 2 (cases 4 and 5) (Table 2). Selective right pulmonary venous oxygen saturations had not been determined in these 2 patients (cases 4 and 5), but angiography showed early return of contrast material to the right pulmonary veins suggestive of PAVF. In the 4 patients in whom contrast echocardiography showed no early left atrial contrast, invasive investigation showed no suggestion of fistulae. Perfusion to the right lung was assessed by angiography in 8 patients (cases 1,2,4-6,9,11,12) and decreased flow to the right upper lobe was demonstrated in all, 5 of whom had PAVF.

The systemic arterial oxygen saturation at rest in 12 patients was 51-99 % (mean 82.5±15.4%), falling to 23-91% (mean 63±26%) on exercise (Table 2). In the 7 patients with early appearance of echo contrast in the left atrium, oxygen saturation at rest was 51-94% (mean 71±15.3%) falling to 23-91% (mean 53±24.3%) on exercise ($p<0.01$). In the 4 patients without early contrast in left atrium and no evidence of PAVF, excluding case 8 with massive collaterals from superior vena cava to inferior vena cava, oxygen saturation was 95-99% (mean 96.5±1.7) at rest, falling to 83-91% (mean 87.5±3.7%) on exercise ($p<0.05$). In the group with established PAVF, the arterial oxygen saturations were significantly lower than in those without PAVF both at rest ($p<0.005$) and on exercise ($p<0.005$). The decrease in arterial xygen saturation on exercise was greater in patients with PAVF ($p<0.05$).

The right pulmonary artery pressure was normal in all patients except case 8 (Table 2). The left pulmonary artery pressure was measured in only 4 (cases 1,2,4,7) of the 7 patients with contrast echocardiographic evidence of PAVF and was above 40 mm Hg systolic in all 4, left pulmonary artery mean pressure ranged from 22 to 110 mm Hg (Table 2). In the 4 patients without contrast echocardiographic evidence of PAVF (cases 9-12), systolic left pulmonary artery pressure was below 20 mm Hg, mean left pulmonary artery pressure was 8-16 mm Hg. Pulmonary hypertension in the contralateral lung was significantly more common in patients with PAVF ($p=0.014$).

The duration of cavopulmonary shunt in patients with PAVF was 10-33 (mean 25.7±8) years and in those without PAVF was 4-31 (mean 31.4±11) years, this difference was not significant.

Two patients (case 8 with massive venous collaterals and case 6 with PAVF) died, case 8 was awaiting heart-lung transplantation. Two patients (cases 1 and 2) were considered for transcatheter embolization of PAVF, but case 2 was found unsuitable because of the multiplicity and extensive nature of her fistulae (Figure 3); she has serious pulmonary hypertensive

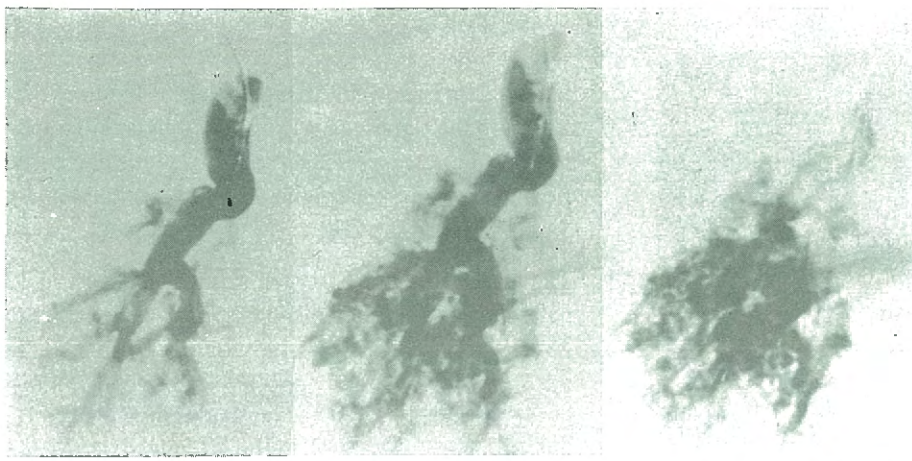

Figure 2. Angiogram with superior vena cava injection from a patient with tricuspid atresia and a Glenn shunt demonstrating decreased perfusion to the right upper and middle lobes (a), and early pulmonary venous return through the arteriovenous malformations in the right lower lobe (b,c).

changes with pressure at systemic level in the left lung and was shown to have a phaeochromocytoma. In case 1, three arteriovenous fistulae at the right lower lobe were occluded by coils and her resting arterial oxygen saturation rose from 68 to 80%; repeat contrast echo showed no rapid filling of the left atrium.

DISCUSSION

Since its first introduction by Gramiak and Shah [11] in 1969, contrast echocardiography has been used in the evaluation of various cardiac defects, including PAVF [12]. It is a safe [13,14], inexpensive and sensitive means of detecting PAVF. The rapid appearance of echo contrast in the left atrium after a peripheral venous injection is highly suggestive of intrapulmonary arteriovenous fistulae, because microbubbles obtained by standard contrast agents and hand agitation are normally cleared by the pulmonary capillary bed [15] unless a special sonication process is used to generate microbubbles of smaller (<10y) diameter, higher stability and persistence [16,17]. In PAVF however, blood will pass from the artery to the vein without traversing a capillary bed, thus appearing readily on the venous side of the arteriovenous malformation. After the cavopulmonary anastomosis, bubbles should appear in neither the right nor the left atria after injection of contrast material, because the superior vena cava-right atrium junction should be closed. When opacification of the left atrium is detected, care must be taken to note whether the bubbles fill the left atrium early through the pulmonary veins and before the right atrium or from the right atrium (if an unsuspected communication between the superior vena cava and right atrium persists), before accepting the presence of PAVF. Early appearance of contrast in left atrium could be demonstrated in 7 of the 12 patients in this study. Other possibilities causing early appearance of microbubbles in the left atrium in this setting are pulmonary artery to left atrium [18] or systemic vein to left atrium communication, left superior vena cava draining into an unroofed coronary sinus [13,19], which occasionally complicate tricuspid atresia, but all are rare. For the differential diagnosis, other investigations (angiography and/or MRI) were used in this series. Of the 3 patients in whom echo contrast appeared in the right a trium, angiography and/or MRI showed a residual superior vena cava-right atrium communication in two (cases 1,7) and downward flow in the azygos vein with huge collateral vessels "feeding" the inferior vena cava in one (case 8) which had developed because the bidirectional Glenn shunt was inappropriate with the elevated pulmonary artery pressure.

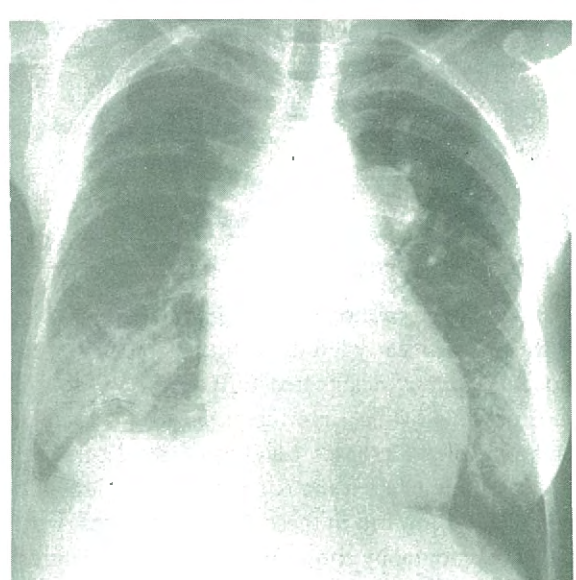

Figure 3. Chest x-ray from a patient with PAVF (case 2) showing angiomatoid malformations in the right lower lobe.

The contrast echocardiographic evidence of PAVF may be present before obvious angiographic abnormalities develop [9,20]. On angiography, the angiomatoid malformations involving the terminal arterial branches are visualized often in the right lower lobe by early pulmonary venous return into the pulmonary veins, but absence of these angiographic findings does not exclude the presence of smaller arteriovenous malformations unless pulmonary venous oxygen saturations are determined selectively. Of the 7 patients with contrast echocardiographic evidence of PAVF in this study, 6 had angiography which was suggestive of PAVF in 2 (cases 4,5) and demonstrated obvious PAVF in 4 (cases 1,2,6,7). Occasionally when large and longstanding the chest radiograph shows fistulae as in case 2.

In the group with PAVF recognized by contrast echo, the arterial oxygen saturations were significantly lower than in those without. Since it is sometimes difficult to detect whether the cause of cyanosis is from closing shunts, failed Fontan etc, contrast echocardiography is useful for sorting out this common problem in the supervision of such patients.

The most frequent causes of late deterioration after the Glenn shunt are decreased flow to the contralateral pulmonary artery [4,8,21], development of collaterals between the superior and inferior vena cavae [4,22,23] and formation of PAVF [4,9,10]. The pathogenesis of PAVF formation after the Glenn shunt remains unclear, but it is thought to be due to increased perfusion in the right lower lung fields where these fistulae occur. The normally present, constricted precapillary arteriovenous connections expand to become fistulous [8], increased resistance in the contralateral lung accelerate this process [4,20]. It is in part time-related, but the liver is also involved; where the hepatic venous blood is excluded from the pulmonary circuit, fistulae occur much quicker suggesting that some unknown factor(s) originating from the healthy liver play an inhibitory role during first passage through the lung, preventing the development of PAVF [24]. Significant correlations have been found between the development of PAVF and the presence of pulmonary hypertension in the contralateral lung [4], as well as the length of time since the cavopulmonary shunt [4,10]. In this series, PAVF with pulmonary hypertension in the contralateral lung was more common, the most extreme PAVF were in case 2 with serious pulmonary hypertension and pulmonary vascular disease in the left lung probably worsened if not induced by the phaeochromocytoma. No significant difference in the duration of the cavopulmonary shunt could be found between our patients with and without PAVF which was surprising. Abnormal distribution of blood flow between the right upper and lower lobes has been documented after the Glenn shunt [21,25,26]. Perfusion to the right lung assessed by angiography in [8] patients showed decreased flow to the right upper lobe in all 8,5 with PAVF. This abnormal distribution of perfusion in the right lung has been attributed to gravitational effects in the nonpulsatile, passive blood flow state. Although the bidirectional cavopulmonary anastomosis has the advantage of a more even distribution of flow to both lungs, the presence of a nonpulsatile, passive blood flow [27] and a similar abnormal distribution pattern [20] after both this procedure and total cavopulmonary connection and other Fontan-type operations renders them at risk for developing pulmonary arteriovenous malformations. Several studies have investigated the development of PAVF after the cavopulmonar shunt by angiography and contrast echocardiography and the prevalence has been reported to be 20-25%, mean %,20 years after the operation [4,10,20]. In our study, the occurrence of PAVF was higher (7/12) patients, 58%7, as determined by contrast echocardiography 4-33 (mean 24±9) years after the operation.

In view of the ease and accuracy with which contrast echocardiography can be used to detect PAVF as well as give useful information on other unsuspected anomalies, this test should be part of regular evaluation of patients with cavopulmonary connections or Fontan-type procedures, particularly when increasing cyanosis develops. It must not be assumed that increased cyanosis is due to failing shunts or falling output.

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