

Echocardiographic Follow-Up of Patent Foramen Ovale and the Factors Affecting Spontaneous Closure

Ali Yildirim,¹ Alperen Aydin,² Tefik Demir,¹ Fatma Aydin,² Birsan Ucar¹ and Zubeyir Kilic¹

Background: The aim of the present study was to evaluate the echocardiographic follow-up of patent foramen ovale, which is considered a potential etiological factor in various diseases, and to determine the factors affecting spontaneous closure.

Methods: Between January 2000 and June 2012, records of 918 patients with patent foramen ovale were retrospectively reviewed. Patency of less than 3 mm around the fossa ovalis is called patent foramen ovale. Patients with cyanotic congenital heart diseases, severe heart valve disorders and severe hemodynamic left to right shunts were excluded from the study. The patients were divided into three groups based on age; 1 day-1 month in group 1, 1 month-12 months in group 2, and more than 12 months in group 3.

Results: Of the 918 patients, 564 (61.4%) had spontaneous closure, 328 (35.8%) had patent foramen ovale continued, 15 (1.6%) patients had patent foramen ovale enlarged to 3-5 mm, 6 patients were enlarged to 5-8 mm, and in one patient patent foramen ovale reached to more than 8 mm size. Defect was spontaneously closed in 65.9% of the patients in group 1, 66.7% of the patients in group 2, and 52.3% of the patients in group 3. There was a negative correlation between the age of diagnosis and spontaneous closure ($p < 0.05$). Gender, prematurity and coexisting malformations such as patent ductus arteriosus and atrial septal aneurysm did not have any effect on spontaneous closure of patent foramen ovale ($p > 0.05$). However, ventricular septal defect and spontaneous closure of patent foramen ovale had a positive correlation ($p < 0.01$). No correlation was noted between the existence of atrial septal aneurysm, prematurity, and maturity of the patients.

Conclusions: The present study demonstrated that spontaneous closure rate of patent foramen ovale is high. Furthermore, a positive correlation was found between spontaneous closure of patent foramen ovale with early diagnosis and small defect size.

Key Words: Echocardiography • Patent foramen ovale • Spontaneous closure

INTRODUCTION

Foramen ovale is an oblique canal situated between the thin, membranous flexible flap-like septum primum and septum secundum, a thicker and harder muscular

structure to provide blood flow from the right to the left atrium during the intrauterine period. Patency of this embryonic remnant beyond labor is called patent foramen ovale.¹ The most common congenital anomaly that is seen with patent foramen ovale (PFO) is atrial septal aneurysm.² However, a full 75% of PFOs close spontaneously prior to the second year of life.

To date, few studies have been conducted focusing on echocardiographic follow-up of PFO. Previous studies have shown that a high percentage of PFOs close during the first year of life.^{3,4} The frequency of PFO diminishes as patient age increases, but the dimension can increase.⁵

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¹Department of Pediatric; ²Department of Pediatric Cardiology, Medical Faculty, Eskisehir Osmangazi University, Eskisehir, Turkey.

Address correspondence and reprint requests to: Dr. Ali Yildirim, Eskisehir Osmangazi Üniversitesi, Tıp Fakültesi, Pediatrik Kardiyoloji Bilim Dalı, 26480, Eskisehir, Turkey. Tel: 9 0 530 882 2319; Fax: 9 0 222 239 2979/7440; E-mail: yldirmaly@gmail.com

The aim of the present study was to evaluate the echocardiographic follow-up of PFO, which is considered as a potential etiological factor in various diseases, and to determine the factors affecting spontaneous closure.

METHODS AND MATERIALS

The records of 918 patients with PFO (age range is 1 day-170 months) who presented to the pediatric cardiology department between January 2000 and June 2012 were reviewed. Patients who were followed for at least 6 months with two echocardiographic evaluations were included in our study. The "patient information form" was used to record age, weight, underlying cardiac and non-cardiac diseases, gestational ages, reason of presentation to the hospital and echocardiographic evaluations. Consent for the study protocol was obtained from the ethics committee of Eskisehir Osmangazi University Medical School.

A review of the existing research indicated that there is no definitive diagnostic criteria for both PFO and atrial septal defect (ASD), and it is difficult to differentiate these two lesions.⁶⁻¹¹ A diagnosis of patent foramen ovale was confirmed when the presence of a shunt was

demonstrated with color flow in the 2-dimensional views of the fossa ovalis without drop-out, or when a tiny flap-like septum primum was detected in the left atrium and the septum secundum was seen in the right atrium in the presence of canal-type defect. In an analogous study by Radzik et al., patency of less than 3 mm around the fossa ovalis is called PFO if it is more than 3 mm, and was considered to be an atrial septal defect.⁶ Clear echocardiographic images can be obtained in pediatric populations where a diagnosis of PFO can then be readily made. However, difficulty often arises in adolescents and obese patients, where after transesophageal echocardiography can be utilized. Additionally, transesophageal echocardiography was performed especially in older children with a suspected defect in the 2-dimensional transthoracic echocardiographic imaging where no flow could be demonstrated in the color flow examination. For doubtful cases, the septal closure was determined using contrast studies with agitated 5% dextrose. PFO were observed from the subcostal view of the four-chamber and sagittal planes (Figure 1). Transesophageal echocardiography was performed in 84 patients with suspected PFO who did not have a diagnostic transthoracic echocardiography. Also, a contrast-enhanced echocardiography was performed on 16 patients in whom

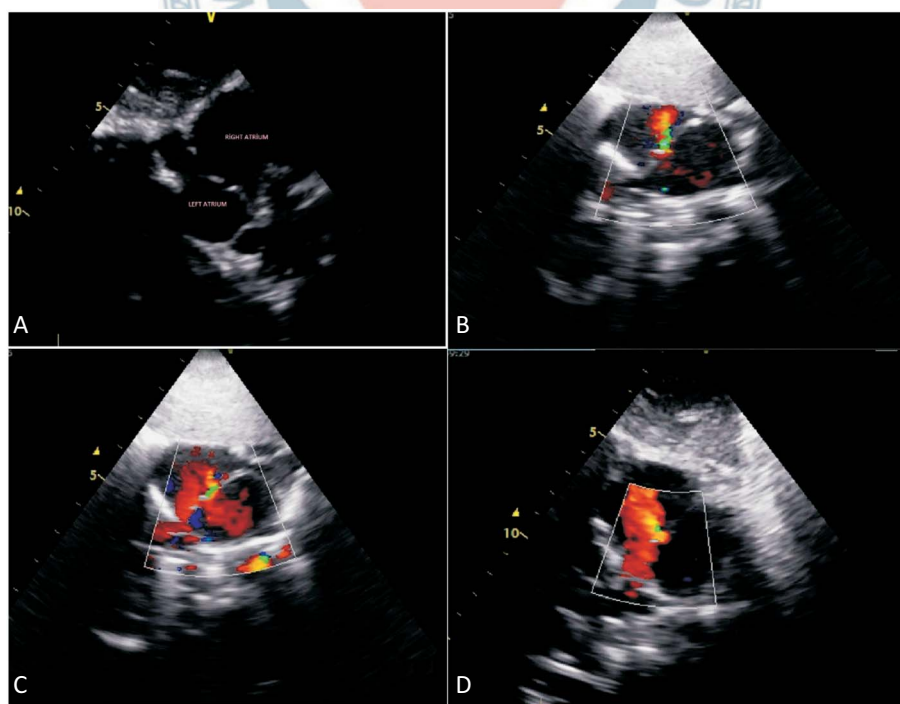


Figure 1. Echocardiographic view of patent foramen ovale.

definitive findings could not be obtained regarding the shunt.

Patients with cyanotic congenital heart diseases, severe heart valve disorders and severe hemodynamic left-to-right shunts were not included in the study. In cyanotic cardiac disease, severe valvular lesions and hemodynamically significant left-to-right shunt lesions (cardiac failure requiring treatment, pulmonary hypertension, or lesions associated with significant dilation in the left ventricle and left atrium and increased pressure) could prevent the closure of PFO or could result in the opening of an already closed lesion, by causing significant pressure elevation in the right or left atrium depending on the type of lesion. Therefore, these lesions were excluded from the study. Patients with large (ratio of defect diameter to annulus diameter was 50% or more) and medium ventricular septal defect (VSD) (ratio of defect annulus to aortic annulus diameter was between 33-50% and with left heart enlargement) and large patent ductus arteriosus (PDA) (left heart enlargement) were excluded from the study.

The patients were divided into three groups based on age, namely: 1 day-1 month in group 1, 1 month-12 months in group 2, and more than 12 months in group 3.

Echocardiographic evaluation

All of the echocardiographic assessments were performed by three different pediatric cardiologist using the Hewlett Packard Sonos (Model 5500) and 2-4 MHz and 4-8 MHz broadband probes or Vivid I with the 4-12 mHz probes.

The diameter of PFO and interatrial septal length was measured in a total of 15 randomly selected PFO patients between 1 and 10 years of age, where the intraobserver and interobserver variability was tested using Pearson's correlation analysis. In these randomly selected 15 patients, the intraobserver variability for PFO diameter and interatrial septal length were $r = 0.89$ and $r = 0.91$, respectively. The corresponding figures for interobserver variability were $r = 0.86$ and $r = 0.78$, respectively.

Statistical analysis

Statistical analysis of the data was done using SSPS 16.0 (SSPS Inc., Chicago, IL, USA). Continuous quantita-

tive data was expressed as n, mean and standard error (standard error of mean, SEM); qualitative data were expressed as n, median, minimum and maximum values. In comparing the two groups, the t-test was used for data with normal distribution, and the Mann-Whitney U test was performed for data with non-normally distributed variables. To demonstrate association between variables, Pearson's test was performed on data with normal distribution and Spearman's correlation test for the data with non-normal distribution. Chi-square test was applied to categorical data sets. The relation between these parameters was determined utilizing logistic regression analysis. A p value less than 0.05 was considered as significant.

RESULTS

A total of 918 patients were included in the study. Of these, 525 (57.3%) were male and 392 were (42.7%) were female, with a median age of 3 months (1 day-170 months). When diagnosis was classified based on age, 369 (40.2%) of the patients were in group 1 (1 day \leq 1 month), 246 (26%) were in group 2 (> 1 month- \leq 12 months) and 303 were (32.9%) in group 3 (> 12 months). The mean follow-up time for these patients was 12 months (6 months-122 months).

Of these patients, 564 (61.4%) had spontaneous closure, 328 (35.8%) had PFO continued, 15 (1.6%) patients had PFO enlarged to 3-5 mm, 6 patients had PFO enlarged to 5-8 mm, and one (0.1%) patient PFO expanded to greater than 8 mm in size.

Defect was spontaneously closed in 61.4% of the patients in group 1, 66.7% of the patients in group 2 and 52.3% of the patients in group 3. There was a negative correlation between the diagnosis age and spontaneous closure ($p < 0.05$). Echocardiographic progression of diameter of the defect based on the age groups was shown in Table 1.

Of the patients, 85 (9.3%) had VSD, 62 (6.8%) had atrial septal aneurysm and 59 (6.4%) had PDA. Gender, prematurity and coexisting malformations such as PDA and atrial septal aneurysm did not have any effect on spontaneous closure of PFO ($p > 0.05$). However, VSD and spontaneous closure of PFO did have a positive correlation ($p < 0.01$) (Table 2).

Table 1. Echocardiographic follow-up of defect size based on the age group

Age of first diagnosis	N	Spontaneous closure [n (%)]	≤ 3mm [n (%)]	> 3-≤ 5 mm [n (%)]	> 5-≤ 8 mm [n(%)]	> 8 mm [n(%)]
≤ 1 month	369	246 (66.6%)	113 (30.6%)	6 (1.6%)	4 (1.9%)	0
> 1-≤ 12 months	246	165 (67%)	79 (32.1%)	2 (0.8%)	0	0
> 12 months	303	159 (52.4%)	136 (44.8%)	7 (2.3%)	0	1 (0.3%)

Table 2. Factors affecting spontaneous closure of patent foramen ovale

	n	Spontaneous closure [n (%)]	Non closure [n (%)]	p value
Male/female	1.33	1.30	1.39	0.846
Prematurity	105	75 (71.4%)	30 (28.6%)	0.471
PDA (+)	59	30 (50.8%)	29 (49.2%)	0.378
VSD (+)	85	62 (72.9%)	23 (27.1%)	0.002
ASA (+)	62	34 (54.8%)	28 (45.2%)	0.415

ASA, atrial septal aneurysm; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

No correlation was noted between the existence of atrial septal aneurysm, prematurity and maturity of the patients. This study demonstrated that PFO closes earlier in term patients with PDA or VSD compared to preterm patients ($p < 0.01$) (Table 3).

When regression analysis of those factors affecting the progression of PFO (prematurity, gender, age at the time of diagnosis, PDA, VSD, defect diameter and atrial septal aneurysm) was performed, a positive correlation was found between spontaneous closure and early diagnosis ($p = 0.03$) and also with small defect diameter ($p < 0.001$) (Table 4).

DISCUSSION

PFO incidence is reported to be 20-34% in postmortem studies, and appears to decrease by age.⁵ Additionally, PFO was demonstrated to be responsible for the pathogenesis of various diseases.¹²⁻¹⁵ To date, there have been few studies published regarding echocardiographic progression of PFO and those factors affecting spontaneous closure. We aimed to investigate these factors in this study.

Similar to the literature, our study indicated that there was no gender difference and the most common congenital anomaly with PFO is atrial septal aneurysm

Table 3. Correlation of concurrent cardiac anomaly with the time of closure of patent foramen ovale based on the gestational age

Gestational age	Concurrent cardiac anomaly	n	Median (min-max) (month)	p value
Premature	PDA (+)	9	12 (9-18)	0.254
	PDA (-)	72	12 (6-60)	
	VSD (+)	11	12 (6-60)	0.105
	VSD (-)	70	12 (6-36)	
	ASA (+)	12	12 (8-24)	0.773
	ASA (-)	86	12 (6-56)	
Mature	VSD (+)	51	18 (6-84)	0.020
	VSD (-)	235	24 (6-180)	
	PDA (+)	21	12 (6-24)	0.004
	PDA (-)	267	24 (6-180)	
	ASA (+)	16	12 (8-36)	0.643
	ASA (-)	274	12 (6-54)	

ASA, atrial septal aneurysm; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

and VSD.^{16,17} No significant differences were found between the term and preterm babies in contrast to the study of Riggs et al.¹⁶

Our study has shown that VSD has a significant positive effect on the closure of PFO ($p < 0.01$). In the presence of PDA or VSD, the closure time of PFO was found to be significantly shorter in term babies ($p < 0.01$). The most common reason for the closure of PFO in the postnatal period is decreasing pressure of the pulmonary artery and right atrium in response to increased left atrium pressure. We think that in the presence of VSD or PDA, shorter spontaneous closure time of PFO can be the result of increased left atrium pressure associated with left-right shunt. VSD has a positive effect on the spontaneous closure of PFO in the whole study population; similarly, PDA has a positive effect on the closure in term babies in contrast to the Ghiglia et al. study.⁴ In healthy preterm infants of ≥ 30 weeks' gestation, duct closure typically occurs by the fourth day after birth, while preterm infants of < 30 weeks' gestation,

Table 4. Logistic regression analysis of the factors related to the closure of patent foramen ovale

Variables	β	SE	p value	OR	95%CI
Constant	0.564	0.389	0.147		
Age group (reference; less than 1 month)					
> 1 month-≤ 12 months	0.406	0.257	0.603	0.666	0.403-1.103
> 12 months	0.478	0.224	0.032	0.620	0.386-0.996
Gender (reference; male)					
Female	0.029	0.143	0.481	0.971	0.733-1.286
PFO diameter (reference; < 2 mm)					
≥ 2 mm-≤ 3 mm	0.601	0.144	0.002	0.548	0.414-0.726
ASA (reference; none)					
Present	0.232	0.283	0.103	1.261	0.724-2.197
Prematurity (reference; none)					
Present	0.375	0.223	0.259	1.078	0.696-1.670
VSD (reference; none)					
Present	0.461	0.265	0.342	0.631	0.375-1.061
PDA (reference; none)					
Present	0.535	0.287	0.934	0.586	0.334-1.028

ASA, atrial septal aneurysm; PDA, patent ductus arteriosus; PFO, patent foramen ovale; VSD, ventricular septal defect.

with severe respiratory distress, have a 65% incidence of PDA beyond the fourth day of life.^{21,22} PDA is a common clinical condition in preterm infants. Functional closure of the ductus arteriosus occurs in almost 50% of full-term infants by 24 hours, in 90% by 48 hours, and in all within 72 hours after birth. In preterm infants, since maturation is less well advanced as compared to a term baby, there may be a delay in the closure of functional openings or cardiac defects. PDA closes quickly after birth and the early closure of PDA does not increase the left atrial pressure. Therefore, we considered that PDA had no effect on the closure time of PFO.

Ghiglia et al.⁴ demonstrated that PFO diameter increased in 1% of the patients by the 12th month of life. The defect size was noted to be increased in 2.3% of the patients, and in one patient the diameter reached to 8 mm in our study. However, left atrial dilatation was not detected in these patients. Therefore, the increased diameter of PFO cannot be attributed to only the left atrial dilatation; these defects can enlarge in proportion to growth of the patient.

To assess the factors concurrently affecting the progression of PFO, logistic regression analysis was performed and a significant positive correlation was found between spontaneous closure and early diagnosis, and also with small defect size. Consistent with our study, Lin et al.²³ found a positive effect on the early diagnosis

of age and large interatrial openings. While a high spontaneous closure rate (66.6%) is expected in cases diagnosed at an early age, in the cases with late diagnosis, a lower rate of spontaneous closure (52.4%) is expected. Therefore, it is concluded that echocardiographic evaluation should be performed for follow-up in patients that are diagnosed at > 1 year of age. In our study, logistic regression analysis did not show any differential effects of PFO on spontaneous closure in those patients with or without VSD. On the other hand, for those patients with VSD (n = 85), there was a significant difference in those with spontaneous closure of PFO (n = 62) than those without spontaneous closure. However, the patients with (n = 85) or without (n = 827) VSD did not differ in terms of spontaneous closure rates. With regard to the transthoracic echocardiographic diagnosis of patent foramen ovale, no consensus exists in the published literature. In one study which investigated interatrial opening in the newborn period by Radzik et al.,⁶ it was stated that "Most patients of group I (defect < 3 mm) probably had an incompetent foramen ovate even if subjects with associated heart disease had been excluded; the female/male ratio of 0.6:1 in group I and spontaneous closure of the defect in all patients in this group favors this hypothesis".

Subsequently, Helgason et al.⁷ and Azhari et al.⁸ designed their studies on the basis of the definition pro-

posed by Radzik et al.,⁶ i.e. a value ≤ 3 mm was considered to be indicative of PFO. Although it is generally known that the cessation of interatrial shunt is not a clear-cut indicator of the anatomic closure of foramen ovale,⁹⁻¹¹ we preferred the term “spontaneous closure of interatrial opening” for patients whose shunt disappeared with color Doppler echocardiography in this study. There is some uncertainty in the published literature regarding the definition of small interatrial openings (< 3 mm) in fossa ovalis, with no clear-cut distinction between atrial septal defects and patent foramen ovale. As compared to many studies which reported on the follow-up of lesions equal to or greater than 3 mm in size in the fossa ovalis, those reporting on the follow-up lesions less than 3 mm in size are much more scarce. Despite certain limitations in our study, our objective was to provide a contribution to the existing literature data with information on the echocardiographic courses of these lesions, as well as to determine the differences between ASD and PFO in the differential diagnosis of smaller interatrial lesions. Our results showed that small interatrial openings at fossa ovalis may enlarge even if the baseline dimensions are less than 3 mm at the time of initial diagnosis. Does this mean that “these lesions were actually ASDs?” lesions with increasing diameter (particularly those reaching 8 mm) were potentially considered to represent ASDs. In our clinic, lesions under 3 mm were categorized as PFO, as proposed by Radzik et al. However, our observations showed that the defect diameter was not discriminative in the designation of small inter-atrial shunts.

As a result of our study, we concluded that PFO closure rate decreases when the first diagnosis is delayed. Furthermore, a positive correlation was found between spontaneous closure of PFO with early diagnosis and small defect size. In addition, the size of PFO can rarely increase in time, and thus it is appropriate to continue to follow these patients.

REFERENCES

1. Movsowitz C, Podolsky LA, Meyerowitz CB, et al. Patent foramen ovale: a non-functional embryological remnant or a potential cause of significant pathology? *J Am Soc Echocardiogr* 1992;5: 259-70.
2. Holmes DR Jr, Cohen H, Katz WE, Reeder GS. Patent foramen ovale, systemic embolization and closure. *Curr Probl Cardiol* 2004;29:56-94.
3. Ozcelik N, Atalay S, Tutar E, et al. The prevalence of interatrial septal openings in newborns and predictive factors for spontaneous closure. *Int J Cardiol* 2006;108:207-11.
4. Ghiglia S, Feslove V. Patency of foramen ovale in full term and preterm neonates. A follow-up study. *Pediatr Med Chir* 2008;30: 192-6.
5. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc* 1984;59:17-20.
6. Radzik D, Davignon A, Doesburg N, et al. Predictive factors for spontaneous closure of atrial septal defects diagnosed in the first 3 months of life. *J Am Coll Cardiology* 1993;22:851-3.
7. Helgason H, Jonsdottir G. Spontaneous closure of atrial septal defects. *Pediatr Cardiol* 1999;20:195-9.
8. Azhari N, Shihata MS, Al-Fatani A. Spontaneous closure of atrial septal defects within the oval fossa. *Cardiol Young* 2004;14:148-55.
9. Serafini O, Misuraca G, Greco F, et al. Prevalence of structural abnormalities of the atrial septum and their association with recent ischemic stroke or transient ischemic attack: echocardiographic evaluation in 18631 patients. *Ital Heart J Suppl* 2003; 4:39-45.
10. Beelke M, Angeli S, Del Sette M, et al. Prevalence of patent foramen ovale in subjects with obstructive sleep apnea: a transcranial Doppler ultrasound study. *Sleep Med* 2003;4:219-23.
11. Domitrz I, Mieszkowski J, Kwiecinski H. The prevalence of patent foramen ovale in patients with migraine. *Neurol Neurochir Pol* 2004;38:89-92.
12. Tembl J, Serena J, Segura T, et al. Electrocardiographic diagnosis of patent foramen ovale associated with ischemic stroke. *Stroke* 1998;29:2665-6.
13. Wilmhurst PT, Nightingale S, Walsh KP, Morrison WL. Effect on migraine of closure of cardiac right-to-left shunts to prevent recurrence of decompression illness or stroke or for haemodynamic reasons. *Lancet* 2000;356:1648-51.
14. Soliman A, Shanoudy H, Liu J, et al. Increased prevalence of patent foramen ovale in patients with severe chronic obstructive pulmonary disease. *J Am Soc Echocardiogr* 1999;12:99-105.
15. Calvert PA, Rana BS, Kydd AC, Shapiro LM. Patent foramen ovale: anatomy, outcomes and closure. *Nat Rev Cardiol* 2011;8:148-60.
16. Riggs T, Sharp S, Batton D, et al. Spontaneous closure of atrial septal defects in premature vs full-term neonates. *Pediatric Cardiology* 2000;21:129-34.
17. Olivares RA, Chan S, Lazar E, et al. Atrial septal aneurysm: a new classification in two hundred five adults. *J Am Soc Echocardiography* 1997;10:644-56.
18. Senocak F, Karademir S, Cabuk F, et al. Spontaneous closure of interatrial septal openings in infants: an echocardiographic study. *Int J Cardiol* 1996;53:221-6.
19. Holmes DR Jr, Cohen HA, Ruiz C. Patent foramen ovale, systemic embolization, and closure. *Curr Probl Cardiol* 2009;34:483-530.

20. Johansson MC, Eriksson P, Dellborg M. The significance of patent foramen ovale. A current review of associated conditions and treatment. *International Journal of Cardiology* 2009;134:17-24.
21. Nemerofsky SL, Parravicini E, Bateman D, et al. The ductus arteriosus rarely requires treatment in infants > 1000 grams. *Am J Perinatol* 2008;25:661-6.
22. Koch J, Hensley G, Roy L, et al. Prevalence of spontaneous closure of the ductus arteriosus in neonates at a birth weight of 1000 grams or less. *Pediatrics* 2006;117:1113-21.
23. Lin KM, Liang CD, Chien SJ, et al. Predictors for regression of large secundum atrial septal defects diagnosed in infancy. *Acta Cardiol Sin* 2013;29:82-7.

