*Pediatr Neonatol* 2008;49(6):234–239

ORIGINAL ARTICLE

# A Follow-up Study of Neonatal Interatrial Shunt with Echocardiography until Twelve to Fifteen Months of Age

Chi-Lin Ho[1,2], Sheng-Ling Jan[2,3]*, Ming-Chih Lin[2], Yun-Ching Fu[2,3]

[1]*Department of Pediatrics, Cheng-Ching Hospital, Taichung, Taiwan*
[2]*Division of Cardiology, Department of Pediatrics, Taichung Veterans General Hospital, Taichung, Taiwan*
[3]*Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan*

Received: May 20, 2008
Revised: Jul 7, 2008
Accepted: Sep 19, 2008

**KEY WORDS:**
echocardiography;
interatrial shunt;
neonate

**Objectives:** To assess the incidence and natural history of full-term neonates with interatrial shunt (IAS).
**Methods:** A follow-up study of 1389 neonates who received screening echocardiography between 2003 and 2006. Babies with IAS at 2 to 4 days of life underwent follow-up echocardiography at 2 to 4 months, 6 to 9 months and 12 to 15 months of age until closure of IAS.
**Results:** The ratio of IAS was 68.3% initially. No significant demographic differences were identified between infants with and without initial IAS. Among 949 neonates with initial IAS, 84.5% infants had a left-to-right interatrial shunt, 13.5% had bidirectional shunt and 2% had predominantly right-to-left shunt. The persistence rate of IAS at 12 to 15 months of age was 3.8% (44/1166). The initial size of IAS ranged from 1.2 to 7.7 mm (4.3±1.1 mm) detected by color Doppler flow mapping and cases were divided into three groups: small (≦5 mm), medium (5 to 8 mm) and large group (≧8 mm). There were 74.6% infants in the small group and 25.4% in the medium group initially. The neonates in the initial small group would always see their IAS close or else they would remain in the small group. Those in the final medium and large size groups always came from the initial medium group. The late closure rate of IAS was 93.9% of infants with initial IAS. The closure curves of initial small and medium sized groups were significantly different, and their late closure rates were 95.1% and 90.4%, respectively.
**Conclusions:** IAS was very common during early neonatal stage, but most cases would close after 1 year. The late closure rate of initial IAS was different if using a cutpoint of 5 mm.

## 1. Introduction

Interatrial shunt (IAS), caused by patent foramen ovale (PFO), functional incompetent valve of foramen ovale or secundum atrial septal defect (ASD), can be frequently detected by echocardiography during the neonatal period.[1–10] It does not influence hemodynamics in early infancy if not associated with other cardiopulmonary abnormalities.[3] However, it has been implicated as a risk factor for cardiovascular events with advancing age. Physicians face problems with follow-up plans and

*Corresponding author. Department of Pediatrics, Taichung Veterans General Hospital, 160 Section 3, Chung-Kang Road, Taichung 40705, Taiwan.
E-mail: sljan@vghtc.gov.tw

family anxiety if their baby's shunt persists. However, systemic studies with large cohort size, and detailed studies in the literature regarding use of neonatal screening echocardiography to evaluate full-term neonates with IAS, are sparse. In addition, with the development and improvement of innovative echocardiographic instruments, assessment of babies with IAS by echocardiography should be more sensitive and reliable. To assess the incidence and natural history of normal full-term neonates with IAS, we performed neonatal screening echocardiography and followed up at the outpatient department according to protocol. To the best of our knowledge, this prospective study is the largest case number series about full-term neonates with IAS to date.

## 2. Patients and Methods

A total of non-biased consecutive 1389 full-term infants (717 boys and 672 girls), with gestational ages ranging from 37 to 41.9 weeks, received screening echocardiography in a tertiary referral center between January 2003 and December 2004 after written informed consent was obtained from their parents. They were periodically followed up between 2003 and 2006. The mean gestational age was $38.9 \pm 1.2$ weeks, and mean birth weight was $3113 \pm 436$ g. The demographic data and perinatal history were recorded and analyzed. We excluded infants born to mothers who used special medication during pregnancy or had acute or chronic diseases that could affect the cardiovascular system of their babies. We also excluded symptomatic neonates admitted to the neonatal ward or neonates associated with other congenital heart defects except patent ductus arteriosus, patent foramen ovale and physiological valvular regurgitation. All enrolled infants underwent echocardiographic examinations between 2 and 4 days of life. The ultrasound scan we used was Sonos 5500 ultrasound system (Philips, Andover, MA, USA) with a 5- to 12-MHz multifrequency transducer for two-dimensional, continuous, directional spectral and color flow Doppler mapping images. All infants were examined by a well-experienced pediatric cardiologist, SL Jan, while they remained quiet in a supine position. The atrial septum was visualized from multiple aspects; parasternal short axis view, apical four-chamber view and subcostal four-chamber view, in order to assess the size, location and direction of interatrial shunt. The subcostal four-chamber view was used to focus on the atrial septum and measure the size of the interatrial shunt by color Doppler flow mapping. Serial follow-up echocardiograms were obtained according to the following schedule. Infants with IAS at 2 to 4 days of life underwent echocardiography at 2 to 4 months, 6 to 9 months, and 12 to 15 months of age. Babies without IAS underwent echocardiography selectively at 4 to 6 months of age to make sure of the absence of shunt.

Data are presented as mean value $\pm$ standard deviation, range or percentage. Statistical analysis was performed with *SPSS, Version 10.0 for Windows* (SPSS, Chicago, IL, USA). The Chi-square test or Student's *t* test according to unequal or equal variance was used to compare the data between neonates with and without IAS. Closure rate of the interatrial shunt was prepared by the Kaplan-Meier method, and differences between neonates with smaller and larger IAS sizes were evaluated using the log-rank test and $p$ values $<0.05$ were considered statistically significant.

## 3. Results

There were 949 newborns (485 boys and 464 girls) with IAS and 440 newborns (232 boys and 208 girls) without IAS detected by echocardiographic examination between 2 and 4 days of life, before being discharged. The demographic data and perinatal history are shown in the left column of the Table. The persistence rate of IAS was 68.3% (949/1389) initially, at 2 to 4 days of life. Among these neonates with initial IAS, there were 802 (84.5%) neonates with a left-to-right interatrial shunt, 128 (13.5%) with bidirectional shunt and 19 (2%) with predominantly right-to-left shunt detected by color Doppler flow mapping. During serial echocardiographic follow-up, only left-to-right shunts could be observed if the shunt persisted. The numbers of infants with IAS were 466 (232 boys and 234 girls), 148 (63 boys and 85 girls) and 44 cases (22 boys and 22 girls) at the 2- to 4-month, 6- to 9-month and 12- to 15-month follow-up period, respectively, and the rates of persistent IAS were 35.7% (466/1304), 12.2% (148/1212) and 3.8% (44/1166). There were 85, 92 and 46 infants with IAS lost to follow-up at the first, second and third follow-up, respectively. A detailed follow-up flow chart and numbers of babies with or without IAS and persistence rates at different ages are shown in Figures 1 and 2. A total of 152 babies without initial IAS underwent echocardiography at 4 to 6 months of age for following up neonatal patent ductus arteriosus or physiologic peripheral pulmonary stenosis detected by neonatal echocardiographic screening, or for checking for heart murmurs incidentally identified. Two infants had a small IAS, but both shunts had closed spontaneously at follow-up echocardiography 6 months later. They were not calculated statistically in this study.

The initial size of IAS ranged from 1.2 to 7.7 mm ($4.3 \pm 1.1$ mm) detected by echocardiography and

**Table** The demographic data, perinatal history and initial size of IAS in infants with or without IAS at different ages

| | IAS (−) initially ($n$=440) | IAS (+) initially ($n$=949) | $p$-value | IAS (+) initially but closure at follow up ($n$=682) | IAS (+) at final follow up ($n$=44) | $p$-value |
|---|---|---|---|---|---|---|
| Gender | 232M/208F | 485M/464F | 0.651 | 358M/324F | 22M/22F | 0.748 |
| BBW (g) | 3089±438 (1920–4912) | 3138±418 (1850–4800) | 0.05 | 3128±414 (1850–4800) | 3135±449 (2064–3970) | 0.908 |
| GA (wk) | 38.8±1.2 | 38.9±1.1 | 0.053 | 38.9±1.1 | 38.7±1.2 | 0.433 |
| Para gravity | 2±1 (1–4) | 2±1 (1–5) | 0.991 | 2±1 (1–5) | 2±1 (1–4) | 0.346 |
| Apgar 1 min | 8±1 (5–9) | 8±1 (5–9) | 0.945 | 8±1 (5–9) | 8±1 (6–8) | 0.233 |
| Apgar 5 min | 9±0 (7–10) | 9±0 (6–10) | 0.163 | 9±0 (6–10) | 9±1 (7–10) | 0.099 |
| Initial IAS size* (mm) | – | 4.3±1.1 (1.2–7.7) | – | 4.2±1.1 (1.2–7.7) | 4.6±1.3 (2–7.1) | 0.056 |

*Initial IAS size measured by the first echocardiographic examination during neonatal period. Data are presented as range and mean±standard deviation or range. BBW = birth body weight; GA = gestational age; NB = newborn; IAS = interatrial shunt.

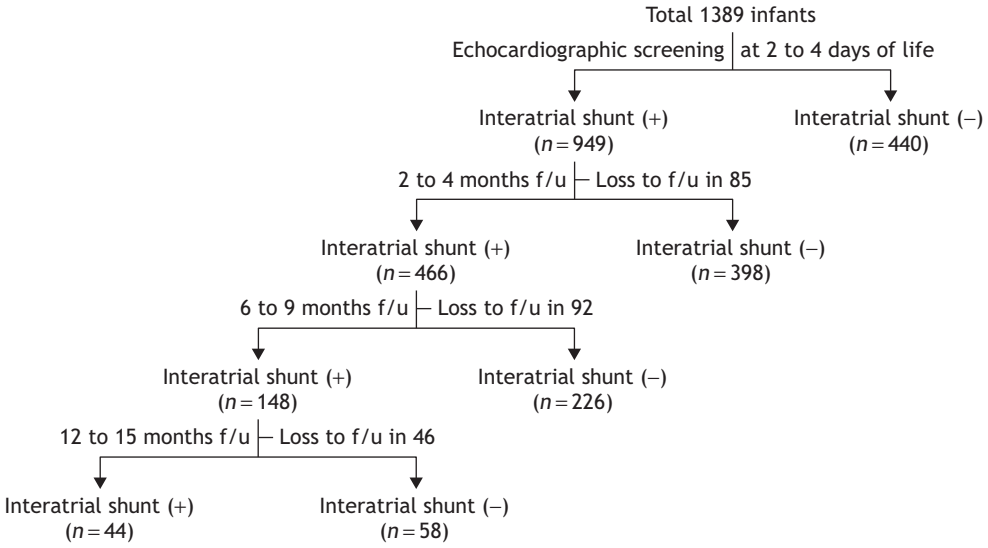


**Figure 1** Flow chart demonstrating the numbers of infants with or without interatrial shunt revealed by follow-up (f/u) echocardiography at the different periods.

cases were divided into three groups: small (≦5 mm), medium (5 to 8 mm) and large (≧8 mm).[11] Among the 949 neonates with initial IAS, there were 708 (74.6%) neonates in the small group, 241 (25.4%) in the medium group but none in the large group. After follow-up, there were 682 infants (358 boys and 324 girls) with initial IAS but late closure within 12 to 15 months of age, and 44 infants had persistent shunts beyond this age. Statistical analysis was performed for these 726 babies with initial IAS who were followed up completely. The demographic data and perinatal history are shown in the right column of the Table. There was no significant difference between patients with late closure and late persistence of IAS in gender, birth weight, gestational age, para gravity and Apgar scores. However, the IAS persistence group showed a trend of having larger initial diameter (4.6±1.3 mm) than that of the IAS closure group (4.2±1.1 mm), though the difference was not statistically significant ($p$=0.056). Among the 44 patients with late persistence of IAS, there were 38 cases (86.4%) in the small group, four (9.1%) in the medium and two (4.5%) in the large. All of the initial small group neonates ($n$=708) would see their IAS close, apart from 27 cases who would still remain in this group. The neonates in the final medium and large groups always started in the initial medium group ($n$=241). Totally, there

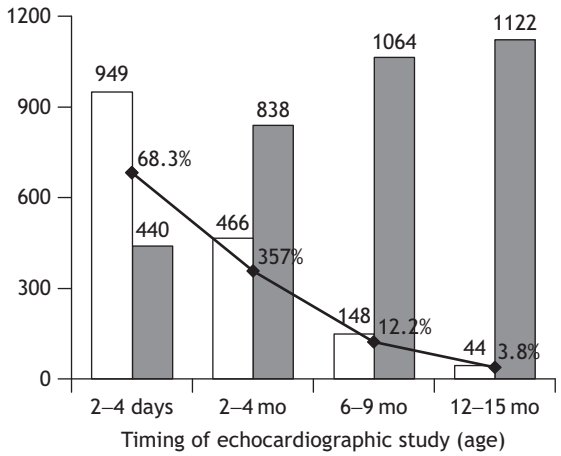


**Figure 2** The number of infants with (□) or without (■) interatrial shunt and the persistence rate (%) of interatrial shunt at different ages.

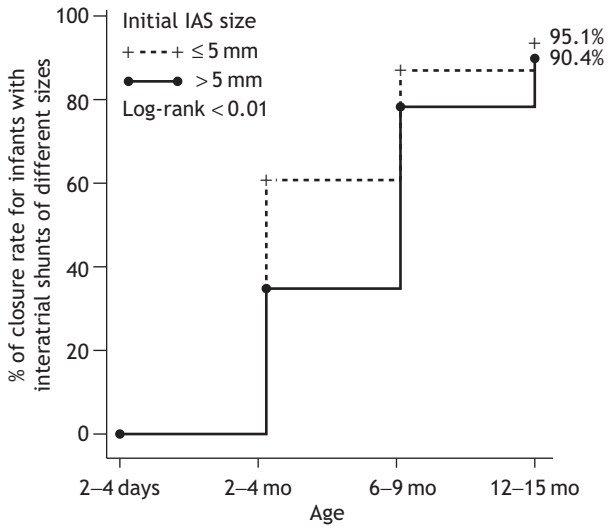


**Figure 3** Closure curves of initial interatrial shunts with different groups (≤5 mm and >5 mm). Significant differences between them were noted statistically.

were 726 patients with initial IAS who completed the 3 stages of echocardiographic studies until 12 to 15 months of age. Their final IAS closure rate was 93.9%. If we made a cutoff point by their initial size of IAS at 5 mm, we could find that the final IAS closure rate of those ≦5 mm was significantly higher than those >5 mm (95.1% *vs.* 90.4%, $p<0.01$ by log-rank test, Figure 3).

## 4. Discussion

Theoretically, foramen ovale is present in all normal newborns since premature closure of foramen ovale has been postulated to associate with serious congenital heart diseases such as hypoplastic left heart syndrome or nonimmune hydrops fetalis after birth.[12] After birth, the primary change in circulation is a shift in blood flow for gas exchange from the placenta to the lungs that causes serial hemodynamic changes. These include raised left atrial (LA) pressure as the result of an increase in systemic vascular resistance after interruption of the umbilical cord and rising pulmonary venous return to LA after lung expansion. In addition, right atrial (RA) pressure falls as a result of reducing blood return to RA after ductus venosus closure and decreasing pulmonary vascular resistance after lung expansion. The competent valve of the foramen ovale will be pressed to the interatrial limbus, and functional closure of the foramen ovale, without left-to-right interatrial shunt, occurs as a result of LA pressure in excess of RA pressure.

ASD versus PFO has been used for many years in neonatal echocardiographic reports if interatrial flow is noted around the foramen ovale. Some reports defined these interatrial shunts simply according to size by 4 mm, smaller shunt as PFO and larger as ASD.[13,14] However, concerning the term "patent" foramen ovale, it concerns the functional closure status of foramen ovale, and the right-to-left flow occurs when the RA pressure exceeds that of the LA. In adult series, it can only be detected by echocardiography with special methods such as contrast echocardiography,[15] a bubble test with the Valsalva maneuver,[16,17] accidentally by catheter probing in cardiac catheterization, or cadaveric study.[18] In our study, only 2% of neonates with initial IAS had with right-to-left shunts that would be classified as PFOs. However, most neonates with initial IAS had left-to-right (84.5%) or bidirectional (13.5%) shunts. Of course, the left-to-right shunt and bidirectional shunt were quite different from the concept of "patent foramen ovale". To explain the initial left-to-right shunt, Markhorst et al proposed a physiological fluid load at an early neonatal stage contributed to the shunt.[5] The valve of foramen ovale could not fully cover the foramen when the atrium was enlarged and the septum stretched. They reported the left-to-right shunt would disappear within 1 week after a transient period of physiological expansion in the early neonatal stage. As in our experience, this would be correct for infants with congenital heart disease complicated with congestive heart failure. But the hypothesis does not fit for normal babies with IAS beyond 1 week. In this study, there were still 35.7% of patients with IAS at 2 to 4 months of age and all of the interatrial shunts were from left to right. We propose that the thickening incompetent valve of foramen ovale and/or growing atrial septum could explain the late closure of IAS.[19–21] Interatrial flow through the intact-like atrial septum can usually be detected

by echocardiography during neonatal and infant periods, especially with two-dimensional and color Doppler flow mapping in dual screen. However, echocardiography struggles to differentiate between the soft and thin "incompetent" valve (functional) and structural incompetence (defect) due to the limitations of spatial resolution of ultrasound. We consider the gradual closure of foramen ovale will occur in those with an initial functional incompetent valve and/or small structural defect when the valve of foramen ovale has thickened and/or grown with age. In other words, a true structural defect, secundum ASD, could be identified after a thickening of the foramen ovale valve beyond 1 year of life if the interatrial flow and a left-to-right shunt persisted.

Because of an inability to distinguish between functional and structural incompetent valves by echocardiography,[22] we chose the term "interatrial shunt, IAS" in this study as it could also include right-to-left shunting PFO. Put simply, IAS around the foramen ovale during the early neonatal period has three conditions; PFO, a functionally incompetent foramen ovale valve and secundum ASD. The right-to-left shunting PFO was the least common and would not be detected at the next 2- to 4-month follow-up, as neither functional nor permanent closure. An initial left-to-right interatrial shunt but late closure could be attributed to an initial functional incompetent valve or a relatively small structural incompetence with growing atrial septum. IAS persisting beyond 1 year should be attributed to secundum ASD, a true structural defect.

Previous echocardiographic studies about neonatal IAS are few.[1–10] Among these, Senocak et al reported 415 neonates receiving echocardiographic screening in 1996.[6] Persistence rates of IAS were 68.7% within 1 week of life and 0.3% during an 18-month follow-up. Another larger case number series ($n=1072$) was reported by Ozcelik et al in 2006.[10] Persistence rates of IAS were 78.6% at 1 to 3 days of life and 1.7% at 12 months of age. However, our study showed a higher IAS persistence rate of 3.8% by 12 to 15 months of age, which might be a consequence of using the modern generation of echocardiographic instruments to detect the smaller cardiac lesions with higher sensitivity.

When informed that their babies had IAS, most parents were concerned about the natural history and closure rate of IAS. Although there were no significant differences between the initial IAS with late closure and late persistency in all parameters in our study, the difference in the initial size of IAS might be significant if more cases were included. In addition, if we chose a cutpoint of 5 mm IAS size for comparison, there were significantly different persistence rates between smaller ($\leqq 5$ mm) and larger ($>5$ mm) sizes.[23] Without regard for initial size, the overall late closure rate of IAS was 93.9% at 12 to 15 months of age calculated by the Kaplan-Meier survival method. If grouped according to initial IAS size, late closure rates of shunt were 95.1% and 90.4% in smaller and larger groups respectively. If shunt persisted, all of the initial small size of IAS would fall into the small group. Cases in the final medium and large size group came from the initial medium size group (2.5%, 6/241). Though these six cases has a shunt size $>5$ mm Hanslik et al[13] reported that spontaneous closure of secundum ASD was possible even for a large defect. They suggested that optional intervention for closure of a significant secundum ASD should be postponed until the patient was 6 years old if no clinical signs of heart failure presented. Those with IAS beyond 12 to 15 months of age still received regular OPD follow-up in our hospital.

## 5. Conclusion

In conclusion, the term "IAS" would be better than using simply "ASD versus PFO" in reports of neonatal screening echocardiography. Most neonates with initial IAS close during 12- to 15-month follow-up without symptoms. The closure rate of initial IAS beyond 1 year was significantly different if using a cutpoint of 5 mm in width for IAS.

## References

1. Shiraishi H, Ichihashi K, Kuramatsu T, et al. Left-to-right shunt via the foramen ovale in the early neonatal period: evaluation by Doppler color flow mapping. *J Cardiol* 1987; 17:559–66.
2. Fukazawa M, Fukushige J, Ueda K. Atrial septal defects in neonates with reference to spontaneous closure. *Am Heart J* 1988;116:123–7.
3. Hannu H, Pentti K, Henrik E, et al. Patency of foramen ovale: does it influence haemodynamics in newborn infants? *Early Hum Dev* 1989;20:281–7.
4. Hiraishi S, Agata Y, Saito K, et al. Interatrial shunt flow profiles in newborn infants: a colour flow and pulsed Doppler echocardiographic study. *Br Heart J* 1991;65:41–5.
5. Markhorst DG, Rothuis E, Sobotka-Plojhar M, et al. Transient foramen ovale incompetence in the normal newborn: an echocardiographic study. *Eur J Pediatr* 1995;154:667–71.
6. 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.
7. Hansen LK, Oxhoj H. High prevalence of interatrial communications during the first three months of life. *Pediatr Cardiol* 1997;18:83–5.
8. Connuck D, Sun JP, Super DM, et al. Incidence of patent ductus arteriosus and patent foramen ovale in normal infants. *Am J Cardiol* 2002;89:244–7.
9. Guntheroth WG, Schwaegler R, Trent E. Comparative roles of the atrial septal aneurysm versus patent foramen ovale in systemic embolization with inferences from neonatal studies. *Am J Cardiol* 2004;94:1341–3.

10. 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.
11. Radzik D, Davignon A, van Doesburg N, et al. Predictive factors for spontaneous closure of atrial septal defects diagnosed in the first 3 months of life. *J Am Coll Cardiol* 1993; 22:851–3.
12. Lev M, Arcilla R, Rimoldi HJ, et al. Premature narrowing or closure of the foramen ovale. *Am Heart J* 1963;65:638–47.
13. Hanslik A, Pospisil U, Salzer-Muhar U, et al. Predictors of spontaneous closure of isolated secundum atrial septal defect in children: a longitudinal study. *Pediatrics* 2006; 118:1560–5.
14. Wang N-K, Shen C-T, Lin M-S. Results of echocardiographic screening in 10,000 newborns. *Acta Paediatr Tw* 2007;48: 7–9.
15. Fisher DC, Fisher EA, Budd JH, et al. The incidence of patent foramen ovale in 1,000 consecutive patients: a contrast transesophageal echocardiography study. *Chest* 1995; 107:1504–9.
16. Meier B, Lock JE. Contemporary management of patent foramen ovale. *Circulation* 2003;107:5–9.
17. El Said HG, McMahon CJ, Mullins CE, et al. Patent foramen ovale morphology and impact on percutaneous device closure. *Pediatr Cardiol* 2005;26:62–5.
18. 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.
19. Cayler GG. Spontaneous functional closure of symptomatic atrial septal defects. *N Engl J Med* 1967;276:65–73.
20. Cockerham JT, Martin TC, Gutierrez FR, et al. Spontaneous closure of secundum atrial septal defect in infants and young children. *Am J Cardiol* 1983;52:1267–71.
21. Sherman FS, Sahn DJ, Valdes-Cruz LM, et al. Two-dimensional Doppler color flow mapping for detecting atrial and ventricular septal defects: studies in an animal model and in the clinical setting. *Herz* 1987;12:212–6.
22. Oberhoffer R, Lang D. Diagnostic criteria of interatrial defects: a single gate pulsed Doppler echocardiographic study. *Int J Cardiol* 1989;25:167–71.
23. Riggs T, Sharp SE, Batton D, et al. Spontaneous closure of atrial septal defects in premature vs. full-term neonates. *Pediatr Cardiol* 2000;21:129–34.