Natural Aortic Valve Complications of Ventricular Septal Defect: A Prospective Cohort Study

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Objective: *To study the incidence and onset of aortic valve prolapse (AVP) and aortic regurgitation (AR) in the ventricular septal defect (VSD).*
Study design: *A prospective cohort study.*
Population: *The less than one-year old children with diagnosis of isolated VSD were studied from October 2000 to September 2006 at Queen Sirikit National Institute of Child Health. Clinical follow-up and echocardiographic studies were scheduled every 2-3 months in the first year of age and then every 6 months to evaluate the size, location, flow across VSD, aortic valve morphology and aortic regurgitation.*
Results: *Three hundred and twenty-one cases of VSD were followed up. One was excluded due to associated hypoplastic RV. An overall of 2,644 echocardiograms were performed. The percentage of perimembranous, subpulmonic, muscular, inlet and multiple types were 70.3%, 19.4%, 5.6%, 3.1% and 1.6%, respectively. Size of the VSD was diagnosed to be small, moderate, and large VSD in 62.5%, 15.9% and 21.6% respectively. At the end of the study, the incidence of AVP in subpulmonic VSD was 87.1% compared to 16.4% in perimembranous VSD, with a relative risk of 5.30 and the incidence of AR in subpulmonic VSD was 37.1% compared to 5.3% in perimembranous VSD, with a relative risk of 6.95. From the survival analysis, the patient with subpulmonic VSD developed AVP at 46%, 77%, 90% and 94% compare to 8%, 13%, 20% and 23% of perimembranous VSD at 12, 24, 36 and 48 months of age respectively ($p < 0.001$). The patient with subpulmonic VSD developed AR at 8%, 17%, 35% and 38% compare to 2%, 4%, 5% and 7% of perimembranous VSD at 12, 24, 36 and 48 months of age respectively ($p < 0.001$). At the end of the study, ninety-six cases (30%) underwent cardiac operation with the indication of heart failure or the occurrence of AR. Sixty one cases (19.1%), including two cases of subpulmonic type had spontaneous closure of VSD. Seven cases (2.2%) had lost to follow up and five cases (1.6%) died during the follow up period.*
Conclusion: *The incidence of AVP and AR are high in subpulmonic VSD being much higher than perimembranous VSD with a relative risk of 5.30 and 6.95 respectively. These complications are significantly from infancy period and are an indication for early cardiac surgery.*

Keywords: *Ventricular septal defect, Aortic valve prolapse, Aortic regurgitation, Subpulmonic, Perimembranous, Natural complications, Relative risk*

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Aortic valve prolapse (AVP) and aortic regurgitation (AR) are the natural aortic valve complications of ventricular septal defect (VSD)[1-11]. These complications can occur in both perimembranous and subpulmonic type VSD[1-3,5,8-10,12]. The prevalence rate of AVP and AR reported in the literature are much higher in subpulmonic than perimembranous VSD[1,5,10]. Perimembranous VSD is the most common type of VSD reported worldwide. Subpulmonic VSD although less

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commonly found, has been reported more frequently in the eastern than the western countries. From our retrospective study of 312 cases of subpulmonic VSD, the incidence of AVP and AR were 49% and 26.9% and the mean age were 5.5 and 6.3 year respectively[3]. AVP was also reported in both types of VSD in the children under one year of age[1,6,7,10]. There are usually no clinical symptoms and signs of AVP or AVP with trivial to mild AR. They are detected only by echocardiogram. The clinical symptoms will develop when AR progresses to moderately severe degree. The natural history of AR in VSD is a progressive one and cardiac intervention is needed[1,3,5,6]. The onset time of AVP and AR in VSD is a critical point for making decision when the patients with VSD need an intervention. The recommendation for patients who develop AR from AVP in VSD patients are generally accepted for surgery but there are some debates in management of the VSD patient with AVP without AR or even subpulmonic VSD without AVP. In our institute, patients with large VSD and uncontrolled congestive heart failure, pulmonary hypertension or who developed AR from AVP are referred for cardiac surgery. The main objective of this present study is to find out the time of onset of AVP and AR in perimembranous and subpulmonic VSD during early childhood period.

Material and Method

This prospective cohort study was conducted at the cardiology unit, Queen Sirikit National Institute of Child Health. The patients who had initial diagnosis of isolated VSD, by using color flow Doppler echocardiogram, during the first year of life were enrolled after signing an informed consent. The exclusion criteria included the patients who had associated major cardiac abnormalities or who had other systemic diseases such as systemic hypertension or renal diseases which might affect hemodynamics. The patients were enrolled from January 2001 to December 2002. All patients had a scheduled echocardiogram every 2-3 months during the first year of life and then every 6 months. The authors followed the patients for a period of 5 years until September 2006. The endpoints of the study were cardiac operation, spontaneous closure of VSD, development of AR from AVP, infective endocarditis or death. The echo machine used before the year 2003 was "Toshiba (Power Vision)" and then changed to "Aloka (Prosound 5500)". A 5-10 MHz transducer probe was used in infant and a 3.5-5 MHz transducer probe was used in childhood period. The echocardiogram was performed by the pediatric cardiologists and recorded into either VDO tape (super VHS) or digital files for review. Some patients needed sedation with 50-75 mg/kg of chloral hydrate to complete echocardiographic study. Types of VSD were diagnosed according to classification by Soto[13]. The diagnosis of AVP needed systematic echocardiographic study with a frame by frame evaluation of the aortic cusps and theirs relationship to VSD rim[14]. Doppler gradient and color flow jet across the VSD under aortic valve were carefully evaluated in each view for diagnosis of AR. The AR was diagnosed only when persistently detection of early diastolic jet flow, usually central jet under the aortic valve from any views. The severity of AR was evaluated by using color flow Doppler in cross-sectional view at subaortic area measuring the ratio of AR jet area and left ventricular outflow area. Type and size of VSD, aortic valve complications and hemodynamics abnormalities in each study were reported. Management of the patient depended on the cardiologist who took care of the patient and surgery was done according to the guideline of our institute. Statistical analysis of data was done and reported as the percentage, relative risks and Kaplan-Meier survival analysis.

Results

Demographic data

During the two-years period of enrollment, there were a total 366 cases of VSD; 45 cases were did not come back again after the diagnosis and/or refused enrollment, another case was excluded after the second echo due to associated hypoplastic RV. A total of 320 cases were finally included in the study; 166 were male and 154 were female. The median registration age (the first echo) was 3 months (range 1-12 months) and mode was 1 month of age. Overall 2,644 echocar-diograms were performed during the study period, with the median and mode number of echo per case being 9 (range 1-14) and 10 respectively.

Types and size of VSD

Perimembranous VSD was found in 225 cases (70.3%), subpulmonic VSD 62 cases (19.4%), muscular VSD 18 cases (5.6%), inlet VSD 10 cases (3.1%) and multiple VSD 5 cases (1.6%). Small VSD were found in 200 cases (62.5%), moderate VSD in 51 cases (15.9%) and large VSD was found in 69 cases (21.6%) (Table 1).

Associated anomalies

Subsequent echocardiogram showed associated minor cardiac anomalies in 44 cases (13.8%)

Table 1. Types and size of VSD

Type	Size of VSD			Total cases (%)
	Small	Moderate	Large	
Perimembranous type	136	37	52	225 (70.3)
Subpulmonic type	41	14	7	62 (19.4)
Muscular type	17	0	1	18 (5.6)
Inlet type	4	0	6	10 (3.1)
Multiple type	2	0	3	5 (1.6)
Total cases	200 (62.5%)	51 (15.9%)	69 (21.6%)	320 (100%)

Table 2. Prevalence of AVP and AR in perimembranous and subpulmonic VSD

	Perimembranous VSD n = 225 cases	Subpulmonic VSD n = 62 cases	Relative risk (95%CI)
AVP (%)	37 (16.4%)	54 (87.1%)	5.30 (3.88-7.22)
AVP with AR (%)	12 (5.3%)	23 (37.1%)	6.95 (3.67-13.17)

including small PDA 11 cases (3.4%), bilateral SVC 10 cases (3.1%), mild PS 10 cases (3.1%), right sided aortic arch 5 cases (1.6%) including aberrant left subclavian artery 3 cases, left sided aortic arch with aberrant right subclavian artery 2 cases (0.6%) and others 6 cases (1.9%). There was progressive subpulmonic stenosis, needing for surgical correction in 6 of 10 cases of VSD with PS. There were 5 cases who had associated systemic disease including Trisomy 21 (4 cases), Trisomy18 (1 case) and HIV exposed (1 case).

Prevalence of AVP and AR in perimembranous and subpulmonic VSD

At the end of 5 years follow-up period, in cases with perimembranous VSD, AVP was found in 37 of 225 cases (16.4%) and AR was found in 12 of 37 of the AVP cases (32.4%) or 5.3% of all perimembranous VSD. In cases of subpulmonic VSD, AVP was found 54 of 62 cases (87.1%) and AR was found in 23 of 54 of the AVP cases (42.6%) or 37.1% of all subpulmonic VSD. Relative risk of AVP and AR in subpulmonic type VSD compared to perimembranous was 5.30 and 6.95 respectively (Table 2). The mean age of occurrence of AVP in perimembranous VSD was 32.4 months (1-74 months) compared to 16.7months (1-60 months) in the subpulmonic VSD group. The mean age of occurrence of AR in perimembranous VSD was 35.9 months (3-76 months) compared to 37.6 months (5-80 months) of the subpulmonic VSD group. All AR cases had trivial AR (AR jet area less than 2-3% of LVOT jet area) at the time of diagnosis.

Kaplan-Meier survival analysis of AVP and AR

From survival curves of AVP in perimembranous type and subpulmonic type VSD with time, the patients with subpulmonic type VSD developed AVP at 46%, 77%, 90% and 94% compared to 8%, 13%, 20% and 23% of perimembranous type VSD at 12, 24, 36 and 48 months of age respectively. (Fig. 1) The occurrence rate of AVP in subpulmonic type is significantly higher than that in perimembranous type VSD ($p < 0.001$), beginning within the first year of life and continue further difference until at 4 years of age, then seem to be stable after that.

From survival curves of AR in perimembranous type and subpulmonic type VSD with time, at 12, 24, 36 and 48 months of age, AR developed 8%,17%, 35% and 38% in patients with subpulmonic type VSD while in patient with perimembranous type VSD developed in 2%, 4%, 5% and 7% at the same age period (Fig. 2). There were also differences in the two survival curves of AR in perimembranous and subpulmonic type VSD which the occurrence rate of AR in subpulmonic type VSD was significantly higher than perimembranous type VSD ($p < 0.001$). These differences continued until about four and a half years of age.

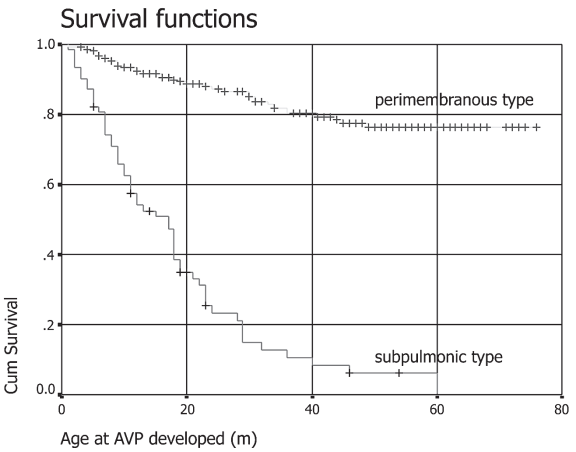

Fig. 1 Kaplan-Meier survival curves of AVP developed in perimembranous and subpulmonic type VSD

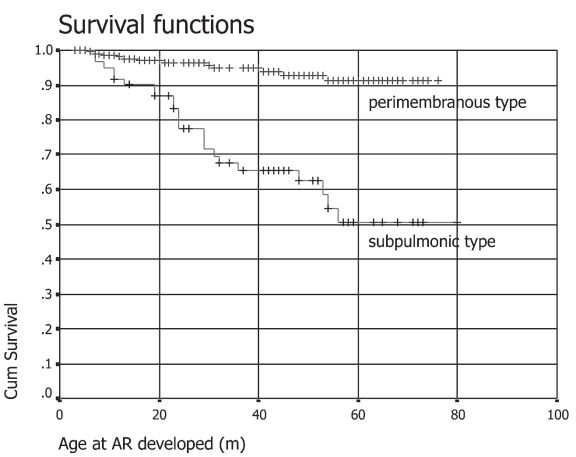

Fig. 2 Kaplan-Meier survival curve of AR developed in perimembranous type and subpulmonic type VSD

Timing of AR occurrence after AVP

There were 23 cases that developed AR following AVP in subpulmonic VSD of which 7 cases occurred simultaneously with AVP. The mean time of occurrence of AR after AVP was 12.9 months (0-50 months).

Cardiac surgery

During the study period, 96 cases had cardiac surgery performed. All had VSD closure, except for one case of PA banding due to cardiac failure in an 8-months Jehovah's Witness baby. The indications for cardiac surgery were large VSD with cardiac failure (68 cases) and aortic valve complication (28 cases). There were 9 cases waiting for surgery.

There were 7 cases (2.2%) that failed to follow-up before complications of the study. Five cases (1.6%) died during the follow-up period including one case each of trisomy 18 and 21, two cases with residual VSD and pulmonary hypertension post cardiac surgery for multiple muscular VSD and one case had cardiomyopathy post op VSD closure. Most of the survival cases had functional class I at the last follow-up, only a few cases had functional class II.

Discussion

The prevalence rate of perimembranous (70.3%) and subpulmonic VSD (19.4%) in this present are about the same as the previous retrospective study from our institute (74.8%, 17.5%)[3]. There was no difference in types of VSD in the 45 cases of isolated VSD who were not enrolled in this cohort study during the enrollment period. This finding confirmed the high prevalence rate of subpulmonic VSD in Thailand, similar to the reports from the eastern countries (17.5%-30.9%) compared to the reports from the western countries (3.3%-6.9%)[10,15-19].

The overall incidence rate of AVP (87.1%) and AR (37.1%) in our subpulmonic VSD patients are higher than most of the previous reported 20.8%-57.2% of AVP and 14%-37.4% of AR[3,5,6,10,20] except from Tohyama[21], who found the high prevalence rate of AVP (80%) and AR (42%) at 5 year of age of the patients which is similar to our findings. AVP and AR can be diagnosed in infants less than one year of age as some previous reports[7,21,22]. The overall incidence rate of AVP (16.4%) and AR (5.3%) in perimembranous VSD is not higher than the previous reports (8.8%-14% of AVP and 6-6.8% of AR)[1,5]. The survival analysis of natural aortic valve complications and the relative risk of AVP in subpulmonic compared to perimembranous VSD was 5.30 and those for AR was 6.95 in this present study and is quite useful as it has never been reported before.

The present prospective cohort study with scheduled echo follow-up can detect the onset time of AVP and AR. Concerning diagnosis of AVP, some physicians might feel that it is quite subjective. To make the diagnosis of AVP, there must be careful evaluation from many views, by rotating the transducer from cross-sectional to long-axis view and frame by frame evaluation of the right coronary and non-coronary cusps of the aortic valve at the VSD rim. A small part of the cusp may be prolapsed toward the small defect rim

of the septum. Ballooning or thickening of the affected cusp may be seen in some long-standing prolapsed cusp. Close follow-up with echocardiogram may be needed in some highly suspicious cases. From our experience, the color flow Doppler of VSD jet may be helpful screening to detect AVP, if there is a high flow velocity of VSD jet at just right under the aortic valve, that cusp should be carefully evaluated for anatomical prolapsed cusp. If there is some distance between the aortic valve and the VSD rim, or the color flow Doppler of VSD jet has some distance from the aortic cusp, it should not have much venturi effect on the aortic cusp. Aortic regurgitation jet is easily detected by color flow Doppler, but it may need many views to evaluate because some trivial AR jets may only be detected by only one view, but not the others.

In general, small to moderate sized VSD had been thought to be benign lesions due to no cardiac symptoms. However, annual clinical follow-up has been recommended in some cardiac units. From past experiences, the authors have seen many small VSD patients developing cardiac failure from severe AR that occurred in late childhood and adolescent, which had many surgical problems. Hence our finding of high relative risk of AVP and AR in the subpulmonic type VSD compare with perimembranous type during early childhood showed that not only size of the VSD but also its location related to the aortic cusps is important for recommendation of proper management. Scheduled follow-up with echocardiogram every 6 month as performed in study for early detection of aortic valve complications in VSD has been shown to be an additional option in the management of these patients instead of clinical follow-up only[1]. Development of AR from AVP is generally accepted as an indication for surgical closure of the VSD and/or aortic valvuloplasty[23]. Ross's operation was performed instead of aortic valve replacement in some centers for severe deformities of aortic valve with severe AR[24,25]. There are some controversies about surgical management of subpulmonic VSD patients who have AVP without AR or have no AVP/AR[26-28]. Many papers have suggested early operation for subpulmonic VSD in order to prevent aortic valve complications[28-30], but so far there have been no recommendations for perimembranous type VSD[31]. The decision to operate on the patient depends on the acceptable low risk of VSD closure in the patient age groups in each institute. This present study gave no evidence regarding surgical decisions but has shown occurrence of the higher prevalence rate and early age of aortic valve complications.

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ภาวะแทรกซ้อนของลิ้นหัวใจเอออร์ติกตามธรรมชาติในโครงรั่วที่ผนังหัวใจห้องล่างภารศึกษาวิจัยเชิงวิเคราะห์เก็บข้อมูลไปข้างหน้า

ธนะรัตน์ ลยางกูร, ธวัชชัย กิระวิทยา, ชัยสิทธิ์ แสงทวีสิน, วิเชาว์ กอจรัญจิตต์, พีรพัฒน์ มกรพงษ์, อมรรัตน์ เพชรดำรงค์สกุล, ญาณิศา อินทศร, พุทรา น้อยแสง

วัตถุประสงค์: *เพื่อศึกษาอุบัติการณ์และอายุที่เกิดการโป่งยื่นและการรั่วของลิ้นหัวใจเอออร์ติกตามธรรมชาติของโครงรั่วที่ผนังหัวใจห้องล่าง*

รูปแบบการศึกษา: *การศึกษาแบบสังเกตอาการติดตามไปข้างหน้า*

วัสดุและวิธีการ: *ผู้ป่วยเด็กที่มีอายุต่ำกว่า 1 ปีซึ่งได้รับการวินิจฉัยว่าเป็นรูรั่วที่ผนังหัวใจห้องล่างที่สถาบันสุขภาพเด็กแห่งชาติมหาราชินี ระยะเวลาของการศึกษาเริ่มตั้งแต่เดือนตุลาคม พ.ศ. 2545 จนถึงเดือนกันยายน พ.ศ. 2549 เด็กจะได้รับการตรวจติดตามดูอาการและตรวจด้วยเครื่องคลื่นเสียงสะท้อนหัวใจเป็นระยะทุก 2-3 เดือนในช่วงขวบปีแรก และทุก 6 เดือนหลังอายุ 1 ปี เพื่อตรวจหาขนาด ตำแหน่ง การไหลเวียน และความเร็วของเลือดที่ไหลผ่านรูรั่วที่ผนังหัวใจห้องล่าง ลักษณะรูปร่างการโป่งยื่น และการรั่วของลิ้นหัวใจเอออร์ติก ที่เป็นภาวะแทรกซ้อน*

ผลการศึกษา: *เด็กที่ได้รับการวินิจฉัยว่าเป็นรูรั่วที่ผนังหัวใจห้องล่างที่ได้รับการติดตามจำนวน 321 ราย ตัดออกจากการศึกษา1 รายเนื่องจากพบว่ามีหัวใจด้านขวาล่างฝ่อร่วมด้วย เด็กทั้งหมดได้รับการตรวจด้วยคลื่นเสียงสะท้อนหัวใจทั้งสิ้น 2,644 ครั้ง พบว่าตำแหน่งของรูรั่วชนิด perimembranous, subpulmonic, muscular, inlet และ multiple มีจำนวนเท่ากับ 70.3%, 19.4%, 5.6%, 3.1% และ 1.6% ตามลำดับ โดยรูรั่วมีขนาดเล็ก กลาง และใหญ่ เท่ากับ 62.5%, 15.9% และ 21.6% ตามลำดับ เมื่อสิ้นสุดการศึกษา พบอุบัติการณ์การโป่งยื่นของลิ้นหัวใจเอออร์ติกใน subpulmonic VSD เท่ากับ 87.1% และ perimembranous VSD เท่ากับ 16.4% คำนวณ relative risk ได้เท่ากับ 5.30 พบอุบัติการณ์การรั่วของลิ้นหัวใจเอออร์ติกใน subpulmonic VSD เท่ากับ 37.1% และ perimembranous VSD เท่ากับ 5.3% คำนวณ relative risk ได้เท่ากับ 6.95 จากการวิเคราะห์อัตราการรอดชีพพบว่าเด็กที่เป็น subpulmonic VSD พบการโป่งยื่นของลิ้นหัวใจเอออร์ติกที่อายุ 12, 24, 48 และ 60 เดือน เท่ากับ 46%, 77%, 90% และ 94% แตกต่างกันอย่างมีนัยสำคัญ ($p < 0.001$) กับที่เวลาเดียวกันของชนิด perimembranous VSD คือพบได้ 8%, 13%, 20% และ 23% ตามลำดับ พบว่าเด็กที่เป็น subpulmonic VSD มีการรั่วของลิ้นหัวใจเอออร์ติกที่อายุ 12, 24, 48 และ 60 เดือน เท่ากับ 8%, 17%, 35% และ 38% แตกต่างกันอย่างมีนัยสำคัญ ($p < 0.001$) กับที่เวลาเดียวกันของชนิด perimembranous VSD คือพบได้ 2%, 4%, 5% และ 7% ตามลำดับ เมื่อสิ้นสุดการศึกษาเด็กจำนวน 96 ราย (30%) ได้รับการผ่าตัด ข้อบ่งชี้ในการผ่าตัดคือเกิดภาวะหัวใจวายที่ไม่ดีขึ้นหลังได้รับการรักษาทางยา หรือ เกิดภาวะลิ้นหัวใจเอออร์ติกรั่ว มีเด็กจำนวน 61 ราย(19.1%) ที่รูรั่วสามารถปิดได้เองตามธรรมชาติ ในจำนวนนี้ 2 รายเป็น subpulmonic VSD ในช่วงที่ทำการศึกษานี้พบว่าเด็ก 7ราย (2.2%) ขาดการติดตาม และมีเด็กเสียชีวิตจำนวน 5 ราย (1.6%)*

สรุป: *อุบัติการณ์ของการโป่งยื่นและการรั่วของลิ้นหัวใจเอออร์ติกพบได้สูงใน subpulmonic VSD มากกว่า perimembranous VSD โดยมี relative risk 5.30 และ 6.95 ตามลำดับ ภาวะแทรกซ้อนตามธรรมชาติที่ลิ้นหัวใจเอออร์ติกนี้ สามารถเกิดได้เร็วตั้งแต่ในช่วงเด็กเล็กซึ่งเป็นสาเหตุของการที่ต้องได้รับการรักษาด้วยการผ่าตัด*