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High Prevalence of Muscular Ventricular Septal Defect in Neonates

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Objectives. **This study sought to use echocardiography to evaluate the prevalence of muscular ventricular septal defect in neonates.**

Background. **Ventricular septal defect is usually asymptomatic and closes spontaneously. An increase in its prevalence has been noted recently. One reason is the improved detection of small defects, especially with the increased use of echocardiography. Therefore, one would expect a higher prevalence in neonates on the basis of echocardiographic screening.**

Methods. **Color Doppler echocardiography was performed in 1,053 consecutive neonates 6 to 170 h old at Western Galilee Hospital, Israel. Data on the neonates, parents and family were obtained to analyze the influencing factors. The identified patients were followed up for 1 to 10 months or until ventricular septal defect closure.**

Results. **Muscular ventricular septal defect was found in 56 (25 male, 31 female) of the 1,053 neonates, a prevalence of 53.2/1,000 live births. All neonates were asymptomatic. Six had a systolic murmur. Electrocardiographic findings were normal in 44 (97.8%) of 45 neonates followed up, and left ventricular hypertrophy occurred in 1 (2.2%). By echocardiography, 50 ventricular septal defects (89.3%) were single and 6 (10.7%) were multiple. The defects (range 1 to 5 mm in diameter, mean [±SD] 2.3 ± 0.8) occurred anywhere along the muscular septum; 43 (76.8%) were detectable only on color Doppler imaging. The left atrium and left ventricle were mildly dilated. Of 45 neonates who were followed up for 6 to 10 months or until closure of the defects, 40 (88.9%) had defects that closed spontaneously. The risk of ventricular septal defect was not significantly associated with gestational age, birth weight, birth order, maternal age, diabetes, smoking, exposure to drugs or infection, paternal age, familial congenital heart disease, religion or consanguinity.**

Conclusions. **There is a prevalence of muscular ventricular septal defect in neonates of 53.2/1,000 live births. The patients were asymptomatic, and 88.9% had defects that closed spontaneously within 1 to 10 months. These defects may be caused by environmental factors. In many cases, muscular ventricular septal defect may also result from delayed physiologic development.**

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Ventricular septal defect is usually asymptomatic and often closes spontaneously (1). The reported rates of spontaneous closure vary between 50% and 75% in small defects (2–4). Therefore, the prevalence of ventricular septal defect should be higher in neonates. An increase in its prevalence, especially that of muscular ventricular septal defect, has been reported in some recent studies (5–7). The reason was ascribed to improved detection of small isolated defects, especially with the increased use of echocardiography (1,5,7). Color Doppler echocardiography has proved to be a sensitive and reliable method for identifying ventricular septal defect (8–12). We therefore examined 1,053 consecutive neonates with color Doppler echocardiography to evaluate the prevalence of isolated muscular ventricular septal defect at birth and to analyze its clinical and prognostic characteristics and influencing factors.

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Methods

Subjects and protocol. Color Doppler echocardiography was performed in 1,053 consecutive neonates in the Western Galilee Hospital-Nahariya, Israel, from April to September 1994. Data on the neonates, parents and family were obtained by interviewing the parents on the day of examination. Maternal exposure to medicines or infections meant that the mother took medicines or had infection during the first trimester of pregnancy. Consanguineous marriages among Arabs living in the Galilee in northern Israel have been found to be high (13,14). To analyze whether consanguinity contributes to the prevalence of ventricular septal defect, family relationships were assessed. The couples were defined as consanguineous if they had a common grandparent or great-grandparent (i.e., first or second cousins) (14). At the first examination the neonates were 6 to 170 h old (mean 37 h). Parental consent was obtained for each neonate. The study had the approval of the Hospital Human Investigation Committee.

The neonates with muscular ventricular septal defect were followed up at intervals of 2 to 3 months or until spontaneous closure of the ventricular septal defect was confirmed. At each follow-up visit, clinical history, physical examination, 12-lead

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electrocardiography and color Doppler echocardiography were performed.

Echocardiography. The echocardiographic examination was performed with either an Aloka Color Doppler SSD-870 System (Aloka Co.) or a Hewlett-Packard Sonos 1000 Flow-Mapping System with a 5-MHz transducer at the lowest available pulse repetition frequency and moderately high flow gains. The muscular portion of the ventricular septum was visualized using the parasternal left ventricular long-axis, parasternal four-chamber, apical four-chamber, apical five-chamber, parasternal aortic root and left ventricular short-axis views. Careful modulation of the transducer was needed to scan every part of the muscular septum and show the largest flow mapping of the ventricular septal defect diameter (10). Classification of defects was according to Soto et al. (15). The diagnosis of muscular ventricular septal defect was established on the basis of two criteria: 1) the presence of a mosaic image passing through the muscular ventricular septum from the left to the right ventricle; 2) and a turbulent systolic flow jet recorded on the right surface of the ventricular septal defect by pulsed or continuous wave Doppler (8,16). Care was taken to avoid misdiagnosing the accelerated flow in the right ventricular trabeculae or coronary artery as a ventricular septal defect. The diameter of the ventricular septal defect on color flow mapping was measured. All examinations were recorded on videotape and reviewed by at least two pediatric cardiologists. Ventricular septal defect was identified only when the diagnoses of the two pediatric cardiologists concurred.

Statistics. To analyze the factors during pregnancy influencing the occurrence of ventricular septal defect and the dimensional changes of the heart in neonates with muscular ventricular septal defect, 975 neonates without any structural cardiovascular disease served as the control group. The prevalence of ventricular septal defect was based on the number of live births with ventricular septal defect divided by all 1,053 neonates. The chi-square test or Fisher exact test was used to compare differences between the rates, and the Student *t* test was used to compare the differences between the means at a significance level of 5%.

Results

Prevalence of ventricular septal defect and influencing factors. There were 56 isolated muscular ventricular septal defects in 1,053 consecutive neonates, a prevalence of 53.2/1,000 live births (25 male [44.6%], prevalence 45.2/1,000 live births; 31 female [55.4%], prevalence 62/1,000 live births). Although muscular ventricular septal defect seemed to be present more frequently in female neonates, the difference between prevalence in male and female neonates was not significant ($p > 0.05$). Gestational age ranged from 36 to 42 weeks and birth weight from 2.42 to 4.42 kg. Apgar scores at the first minute were 7, 8 and 9 in 1, 2 and 53 neonates, respectively, and all were normal at the fifth minute. The birth order was as follows: first born in 19 neonates (33.9%), second in 14 (25%), third in 11 (19.6%), fourth in 7 (12.5%), and fifth or later in 5 (8.9%). Compared with the control group, there were no significant differences in gestational age, birth weight, type of delivery, Apgar score or birth order (all $p > 0.05$) (Table 1).

Table 1. Data for Neonates and Their Families

	VSD (n = 56)	Control Group (n = 975)	p Value
Gestational age (wk)	39.1 ± 1.2	39.3 ± 1.6	0.84*
Cesarean delivery	9 (16.1%)	142 (14.6%)	>0.1†
Birth weight (kg)	3.40 ± 0.47	3.32 ± 0.49	0.12*
Maternal age (yr)	26.9 ± 5.6	27.0 ± 5.4	0.81*
Diabetes	1 (1.8%)	5 (0.5%)	0.25§
Hypothyroidism	1 (1.8%)	6 (0.6%)	0.24§
Exposure to antibiotics‡	3 (5.4%)	81 (8.3%)	0.31§
Exposure to methyldopa‡	1 (1.8%)	4 (0.4%)	0.22§
Exposure to thyroxine‡	1 (1.8%)	6 (0.6%)	0.24§
Respiratory infection‡	1 (1.8%)	38 (3.9%)	0.25§
Urinary tract infection‡	2 (3.6%)	43 (4.4%)	0.28§
Hypertension	1 (1.8%)	5 (0.5%)	0.25§
Paternal age (yr)	30.8 ± 4.8	31.1 ± 5.9	0.47*
Siblings with CHD	2 (3.6%)	14 (1.4%)	0.16§
Family with CHD	2 (3.6%)	17 (1.7%)	0.20§
Family with diabetes	15 (26.8%)	251 (25.7%)	>0.1†
Family with G-6-PD	1 (1.8%)	4 (0.4%)	0.22§
Consanguinity			
1st degree	9 (16.1%)	137 (14.1%)	>0.1†
2nd degree	5 (8.9%)	68 (6.9%)	>0.1†

*Student *t* tests. †Chi-square test. ‡Mothers took medicines or had an infection during the first trimester. §Fisher exact tests. Data presented are mean value ± SD. CHD = congenital heart disease; G-6-PD = glucose-6 phosphate dehydrogenase deficiency.

The ages of the parents of neonates with muscular ventricular septal defect were 19 to 39 years for mothers and 23 to 42 years for fathers and were not significantly different from parents of the control group (Table 1). Maternal diabetes, hypothyroidism, hypertension, maternal exposures to medicines (antibiotic agents, methyldopa, thyroxine) or infection (respiratory or urinary tract infection), familial congenital heart disease, familial diabetes and other genetic diseases were not significantly more prevalent among the neonates with ventricular septal defect. The risk of ventricular septal defect was also not associated with consanguinity (Table 1). There was no maternal alcohol consumption or exposure to chemicals at the workplace during the first trimester of gestation in the neonates with ventricular septal defect.

The neonates were the offspring of four religious denominations living in this area: Jews, Moslems, Druze and Christians. Of the 1,053 neonates, there were 316 Jews (30.0%), 441 Moslems (41.9%), 218 Druze (20.7%) and 78 Christians (7.4%). Of the 56 neonates with muscular ventricular septal defect, 13 were Jews, 26 Moslems, 15 Druze and 2 Christians. The prevalence of muscular ventricular septal defect was 41.4, 59, 68.8 and 25.6/1,000 live births in Jews, Moslems, Druze and Christians, respectively. There were no significant differences among the four religious groups ($p > 0.05$).

Clinical features. All the neonates appeared healthy at the first examination. No neonate had cyanosis or tachypnea. By

Table 2. Left Ventricular and Atrial Changes in Neonates With Ventricular Septal Defects

Index	VSD (n = 56)	Control Group (n = 975)	p Value
LVEDD	18.3 ± 1.7	16.4 ± 1.8	<0.001
LA	13.3 ± 1.7	11.2 ± 1.7	<0.001
LA/AO ratio	1.39 ± 0.21	1.17 ± 0.20	<0.001

Data presented are mean value ± SD. AO = aortic diameter; LA = left atrial diameter; LVEDD = left ventricular end-diastolic diameter.

palpation, one had increased precordial activity, and none had a palpable thrill. On auscultation, S_1 and S_2 were normal in all the neonates; one neonate had a grade 3/6 harsh holosystolic murmur heard in the third and fourth intercostal spaces, and five had a grade 1 to 2/6 early short systolic murmur.

Echocardiographic features. Of 56 neonates with muscular ventricular septal defect, 50 had a single ventricular septal defect (89.3%), and 6 had multiple ventricular septal defects (10.7%) (5 with two, 1 with at least three); 59 defects with measurable data were detected. The ventricular septal defect diameter measured 1 to 1.9, 2 to 2.9, 3 to 3.9 and to 4 to 5 mm in 9 (15.3%), 29 (49.2%), 18 (30.5%) and 3 (5.1%) neonates, respectively (mean [±SD] 2.3 ± 0.8). Ventricular septal defects occurred anywhere along the muscular septum, with most in the midtrabecular septum. The jet direction on color flow mapping varied greatly, and there were no particular characteristics.

Of 59 muscular ventricular septal defects with measurable data, 13 (22%) were detectable by two-dimensional echocardiography with small dropouts in the muscular septum. The left ventricle and left atrium were dilated mildly compared with that in the control group ($p < 0.001$) (Table 2).

Follow-up of neonates with muscular ventricular septal defect. Of 56 neonates with muscular ventricular septal defect, 45 (80.4%) were followed up for 6 to 10 months or until the closure of the defect, 3 for 1 month; 8 (14.3%) did not return for examination. The rates of spontaneous closure for different ages were calculated on the basis of the 45 neonates who were followed up for 6 to 10 months. Of these neonates, the ventricular septal defect closed in 7 (25%) of 28 who returned for examination within 1 month, 15 (37.5%) of 40 within 2 months, 19 (44.2%) of 43 within 3 months, 28 (62.2%) of 45 within 4 months, 32 (71.1%) of 45 within 5 months, 34 (75.6%) of 45 within 6 months, 37 (82.2%) of 45 within 7 months and 40 (88.9%) of 45 within 8 to 10 months. In the 9, 20, 15 and 2 neonates with ventricular septal defect diameters 1 to 1.9, 2 to 2.9, 3 to 3.9 and 4 to 5 mm, 8 (88.9%), 17 (85%), 9 (60%) and 1 (50%) defect closed within 6 to 10 months, respectively. There were no significant differences in the rates of closure in ventricular septal defects of different sizes ($p > 0.05$). After spontaneous closure of the ventricular septal defect, the atrial and ventricular dimensions and ventricular function were all normal on echocardiography.

All infants who were followed up had normal growth and development. None had any clinical or echocardiographic signs of infectious endocarditis. In three of six neonates with a systolic murmur heard at the initial examination, the murmur disappeared at defect closure within 4, 4.5 and 8 months, respectively. No pericordial overactivity or thrill was found. The ECG findings were completely normal in 37 infants (82.2%) and showed a polyphasic rsr' pattern in lead V_1 in 7 (15.6%); that is essentially a normal variant. Left ventricular hypertrophy was seen in one (2.2%) infant who had a defect 4 mm in diameter that did not close until she was 7.5 months old. Infants with and without rsr' patterns in lead V_1 did not differ in prognosis ($p > 0.05$). No neonate had left deviation of the QRS axis in the frontal plane.

Discussion

Prevalence of ventricular septal defect. In the present study, the prevalence (53.2/1,000 live births) greatly exceeded the expected rates. The reported prevalence of ventricular septal defect in previous studies varied from 0.3 to 3.3/1,000 live births (17–20). Although an increase in its prevalence has been noted in some recent reports, it has never exceeded 5/1,000 live births (2). Thus, prevalence in our study is >10 times greater than that in the previous reports.

Possible reasons for high prevalence of ventricular septal defect. Two possibilities may account for these results.

1. *Screening method.* We used color Doppler echocardiographic screening to identify neonates with muscular ventricular septal defects. Most of the neonates in this study were clinically healthy. When a murmur was heard by the pediatrician, it was usually an early short systolic murmur, difficult to differentiate from an "innocent murmur." In addition, most of the ventricular septal defects closed spontaneously within 6 to 10 months. Therefore, neonates with small muscular ventricular septal defects were most easily missed without echocardiographic screening. Even when our patients were examined by echocardiography, those with small muscular ventricular septal defects could also be missed if color Doppler flow mapping was not used or if the muscular septum was not completely scanned. Most of the ventricular septal defects were undetectable with two-dimensional echocardiography and occurred at any point along the muscular septum. In previous studies (17–19), the diagnosis of ventricular septal defect was made on the basis of clinical diagnosis by a pediatric cardiologist in patients usually referred by their pediatricians. To our knowledge, no previous reports on the prevalence of ventricular septal defect used echocardiographic screening in consecutive neonates. Therefore, most of our cases would have been missed in previous studies, which may explain the unusually high prevalence in the present work.

2. *Teratogens.* There might have been some potential teratogens that caused an epidemic of small muscular ventricular septal defects in our region during the period from April to September 1989. Of 56 neonates, 50 had no signs of ventricular septal defect on physical examination. If these "silent" cases were excluded, then the prevalence would be 5.7/1,000 live births, which is still greater than that in previous reports

(2,17–20). Although the present work could not establish any relation between the high prevalence of muscular ventricular septal defect and known teratogens, we could not exclude the possibility that there were some environmental factors or unknown teratogens that resulted in this high prevalence of muscular ventricular septal defect.

Postnatal closure of the muscular septum. On the basis of fact that there are an excess number of isolated ventricular septal defects among premature infants, a lack of any abnormal autopsy findings in patients with spontaneously closed ventricular septal defects and a disproportionate lack of ventricular septal defect among the autopsied adult population compared with the living pediatric clinical population, Mitchell et al. (21) proposed that the normal time of ventricular septal closure may not be limited to the fourth and fifth postconceptive weeks; rather, it may extend, in a minority of infants, throughout pregnancy and into the postpartum period. The high prevalence in our work may also be explained by the postnatal closure of the muscular septum. Thus, in many cases, these ventricular septal defects may result from a delayed normal process rather than from disease. Therefore, to avoid unnecessary anxiety, the parents should be informed of this benign muscular ventricular septal defect whether it is identified by echocardiography intentionally or accidentally. It is not necessary to look for this ventricular septal defect in asymptomatic neonates.

Conclusions. There is a high prevalence (53.2/1,000 live births) of muscular ventricular septal defect in neonates. All the neonates were asymptomatic; 10.7% had a systolic murmur on physical examination. The ECG findings were normal in 97.8% of neonates and showed left ventricular hypertrophy in 2.2%. Spontaneous closure occurred in 88.9% of neonates within 1 to 10 months. These ventricular septal defects may be caused by some environmental factors, and in many cases, they may represent delayed physiologic development.

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