The ratio of congenital heart disease and innocent murmur in children in Van city, the Eastern Turkey

Doğu Anadolu Bölgesi Van ilinde ilköğretim çağı çocuklarında konjenital kalp hastalığı ve masum üfürüm oranı

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ABSTRACT

Objective: We tried to determine the prevalence of and expose the significance of clinical evaluation of innocent and pathological murmurs due to underlying disorders and to determine the indication of echocardiographic examination in innocent murmurs' evaluation and the frequency of congenital heart diseases (CHD) in childhood.
Methods: This study was performed on 6035 children between 6-15 ages (3306 boys and 2729 girls) who attended six different elementary schools reflecting various economic groups in Van city in the Eastern of Turkey, which is a developing country.
Results: We detected murmurs of different intensities in 243 patients (4%). The results showed that 209 children's (3.5%) murmurs were accepted as innocent. The regurgitation was detected in single or two valves in 27% (56 cases) of cases with innocent murmurs. Additionally no valve insufficiency or regurgitation was determined in children who had innocent murmurs except these 56 cases. Of patients who had murmurs, 27 children (0.4%) had congenital heart disease and 7 (0.1%) had rheumatic heart disease. In patients who had CHD, mitral valve prolapsus and tricuspid valve prolapsus were found in 48% and 37% of the cases, respectively.
Conclusion: Congenital heart disease was found in similar frequency with the literature. Innocent murmurs were found lower than in the literature, but higher than in other studies done in our country. Our study showed that, especially valve prolapsus, other CHD and less frequently rheumatic carditis can be seen in children who look like otherwise healthy. We emphasize that all children especially attending primary education, should be examined by a cardiologist even they have no complaints. *(Anadolu Kardiyol Derg 2009; 9: 29-34)*
Key words: Childhood, murmurs, echocardiography

ÖZET

Amaç: Bu kitle taramasında amacımız çocukluk çağında masum ve patolojik üfürüm prevalansını tespit etmek, ayrıca masum veya patolojik üfürümlerde klinik değerlendirmenin önemini ortaya koyup sık olarak karşımıza çıkan masum üfürümlerin değerlendirilmesinde ekokardiyografi endikasyonlarının sınırlarının belirlenmesine katkıda bulunmak ve konjenital kalp hastalığı sıklığını belirlemektir.
Yöntemler: Bu çalışmada, gelişmekte olan Doğu Anadolu Bölgesi Van il merkezinde sosyo ekonomik düzeyi farklı 6 ilköğretim okulunda yaşları 6-15 arasında 3306'sı erkek, 2729'u kız, toplam 6035 öğrenci kalp üfürümleri yönünden incelendi.
Bulgular: Çalışmamızda, 243 (%4) öğrencide kalpte değişik şiddetlerde üfürüm duyuldu. İki yüz dokuz öğrencide (%3.5) duyulan üfürüm masum olarak kabul edildi. Masum üfürümlerin %78'i triküspid odakta, %22'si pulmoner odakta duyuldu. Masum üfürümler şiddetine göre değerlendirildiğinde %62 öğrencide I/VI, %37 öğrencide II/VI, %1 öğrencide III/VI şiddetinde idi. Anemiye bağlı üfürüm duyulmadı. Masum üfürüm olarak değerlendirilen olguların %27'sinde tek triküspid veya pulmoner yetersizliği ve/veya iki kapak yetersizliği saptandı. Masum üfürüm duyulan diğer olgularda herhangi bir kapak yetersizliği saptanmadı. Yirmi yedi öğrencide (%0.4) konjenital kalp hastalığı, 7 öğrencide (%0.1) romatizmal kalp hastalığı saptandı. Konjenital kalp defekti saptanan olguların 16 tanesinde (%59'inde) tek defekt, 11'inde (%41'inde) iki defekt bulundu. Konjenital kalp defekti saptanan hastaların %48'inde mitral kapak prolapsusu, %37'sinde triküspid kapak prolapsusu mevcuttu.
Sonuç: Çalışmamızda konjenital kalp hastalığı sıklığı literatürle uyumlu, masum üfürümlerin sıklığı literatüre göre daha düşük iken, yurdumuzda yapılan çalışmalara göre daha yüksek olarak bulunmuştur. Çalışmamız özellikle kapak prolapsusları olmak üzere diğer konjenital kalp defektleri ve daha az olarak da romatizmal karditlerin sağlıklı gibi görünen hiçbir problemi olmayan çocuklarda görülebileceğini göstermiştir. İlköğretim çağındaki tüm çocukların herhangi bir problemi olmasa dahi bir kardiyolog tarafından değerlendirilmesi gerektiğini vurgulamaktayız.
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Anahtar kelimeler: Çocukluk çağı, üfürümler, ekokardiyografi

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Introduction

The abnormalities in embryological development of cardiovascular system are different and responsible for significant clinical effects. Complex structural malformations may lead to fetal deaths or may be diagnosed within the first week or months of life, that was based on symptomatology of cardiovascular decompensation. When passing to postnatal life, placental circulation stops, as well as the dominance of right heart. In addition, pulmonary arterial resistance is modified and left heart circulation is established. In this period, malformations that are compensated in intrauterine life, becomes evident. However, some congenital cardiovascular malformations remain asymptomatic in this transition period and these can be clearly shown on later in clinic (1).

Determining the alterations in cardiac auscultation, especially the presence of murmurs, is the most common reason that patients resort to cardiologists. Additionally, chest pain and syncope are the second and the third most common reasons (2, 3). However, these alterations usually are the variations in normal interval or are innocent murmurs. Therefore, to make a more attentive pediatric evaluation by a pediatric cardiologist to avoid unnecessary detailed investigation and applications is important. Certainly, an evaluation by a cardiologist is a gold standard (2, 3).

In some studies, it has been shown that only a number of patients could be overlooked in evaluation of the pathological murmurs (2, 4). Pediatricians should have a systemic approach after certain clinical conditions and/or auscultation to determine difference between a possible cardiovascular disorder, which diagnosis and decision on its significance require a cardiologist opinion.

Echocardiography (ECHO), has been become quite informative technique providing additional knowledge concerning structure of cardiovascular system. It can be declared that this non-invasive technique is the substitute for cardiac catheterization in evaluation of many congenital malformations in newborns and children (5, 6).

Since 1981, some researchers have investigated the newborn and children with congenital heart disease (CHD) that underwent palliation and correction operations without cardiac catheterization, using only ECHO diagnosis (7).

In this study, our aim is to expose the significance of clinical evaluation of innocent and pathological murmurs due to underlying disorders and to determine the indication of ECHO examination in innocent murmurs' evaluation and the frequency of CHD in childhood.

Methods

Of 6035 children underwent clinical examination, 2729 (45%) were female and 3306 (55%) were male with the age range between 6 and 15 years, and mean age of 10 years. These subjects in six elementary schools, which were randomly selected between residential districts with different socioeconomic levels from December 2003 to March 2004 (8) in Van the Eastern of Turkey, were enrolled in the study (9, 10). This study was approved by our hospital ethical committee and Ministry of Education. All the parents of patients allowed us performing our study and gave their consent. .

The same person who was our hospital pediatric cardiologist performed all of the physical and ECHO examinations except first physical examination. The examinations were performed in a silent classroom by auscultation of mitral focus, pulmonary focus, aortic focus and tricuspid focus. All students' femoral pulses were examined. A history of acute rheumatic fever (ARF) was interrogated. In patients with murmurs, an electrocardiogram (ECG) and teleradiography were taken and complete blood counts (CBCs) were studied. The CBCs were studied in a coulter STKS complete blood device using scatter pac, lyse III and isoton-III solutions. An ECHO evaluation was performed in department of pediatric cardiology of our hospital, using 3.5 and 5 MHz probe by a device which has M-mode, 2-dimensional ECHO, colored, continuous wave (CW) and pulse wave (PW) Doppler modalities - Sonotron Vingmed CFM 725 (General Electric, USA). In patients who needed, a catheter angiography (CAG) was performed.

Characteristics of a pathological murmur were defined as below

- Holosystolic murmur
- Harsh murmur
- Abnormal heart sound
- Early or mid-systolic click
- Grade III murmur or greater
- Heard over the upper left sternal border and characteristics of an innocent murmur were defined as below;
- Systolic in nature
- Usually short in duration
- Usually soft
- May be either musical or low-pitched
- Usually heard along left sternal edge
- Intensity varies with phases of respiration and posture - usually louder when supine
- Intensity louder with exercise, anxiety, fever.

The intensity of a murmur is graded on a scale of 1-6 (or 1-5). Each grade was given in relation to the range used (e.g. grade 3/6). The grades are;

Grade 1: A quiet murmur that can be heard only after careful auscultation over a localized area.

Grade 2: A quiet murmur that is heard immediately once the stethoscope is placed over its localized PMI.

Grade 3: A moderately loud murmur

Grade 4: A loud murmur heard over a widespread area, with no thrill palpable

Grade 5: A loud murmur with an associated precordial thrill.

Grade 6: A murmur sufficiently loud that it can be heard with the stethoscope raised just off the chest surface

The patients who had a history of ARF or who had thickening and/or insufficiency of the mitral and/or an aortic valve, without unexplained reasons and determined by ECHO were accepted as rheumatic heart disease (RHD).

Statistical Analysis

The statistical analysis was performed using SPSS 11.5 for Windows software (Chicago, Il, USA). A Mann-Whitney U and Z

proportional test were used in the statistical analysis. In our study, Mann-Whitney U test was used to compare the nonparametric values and Z proportion tests were also used to compare the parametric values.

Results

Of total 6035 cases, 2729 (45%) were female and 3306 (55%) were male. A murmur was diagnosed in 243 of students (4%), of whom 34 (0.55%) had a pathological murmur.

Of the students who had a murmur, 27 students (0.4%) had a CHD, and 7 (0.1%) had a RHD. The murmurs determined in 209 students (3.5%) are evaluated as innocent murmurs (Fig. 1). Of the students who had a CHD, 16 (59%) had one defect, and 11 (41%) had two defects. Of the students who had one defect, one (3.7%) case had ventricular septal defect (VSD), two (7.4%) had pulmonary stenosis (PS), one (3.7%) had patent ductus arteriosus (PDA), one (3.7%) had aortic stenosis (AS), five (18.5%) had mitral valve prolapsus (MVP), five (18.5%) had tricuspid valve prolapsus (TVP), one (3.7%) had aortopulmonary (AP) window. On the other hand; of the students who had two defects, one case (3.7%) had atrial septal defect (ASD) and PS, one case (3.7%) had MVP and PS, one (3.7%) had PDA and PS, two (7.4%) had ASD and MVP, one (3.7%) had ASD and bicuspid aortic valve, five (18.5%) had MVP and TVP too. The MVP accompanied 8 cases (73%) among 11 students with two defects. Four (15%) students had a PS among the students with a CHD; of these, 3 (75%) had an additional defect (Table 1).

It was seen that auscultated innocent murmurs when were evaluated according to their age distribution, the murmurs showed an increase, which was correlated to age until 9 years old and a decrease after 9 years old. Despite we determined a frequency of innocent murmurs most common in 9 years, it was not statistically significant ($p>0.05$). The frequency of innocent murmurs was determined less in 13 years than other ages which was statistically significant ($p<0.05$). Cases with innocent murmurs when were evaluated according to their gender distribution, 80 cases (38%) were females and 129 (62%) were males. Cases with innocent murmurs when were evaluated according to their distribution of murmur auscultation region, 61 (29%) were at left sternal lower region, 46 (22%) were at pulmonary focus, and 102 (49%) were at tricuspid focus. An innocent murmur was not auscultated at aorta focus and apex (Fig. 2).

When innocent murmurs were evaluated according to their intensity, of all cases, 130 (62%) were of I/VI intensity, 78 (37.5%) were of II/VI intensity, and 1 (0.5%) was of III/VI intensity (Fig. 3).

Innocent murmurs when were evaluated regarding valvular insufficiency according to age, 10 cases (18%) between 6 and 8 years, 27 (48%) cases between 9 and 11 years, 16 (29%) between 12 and 14 years, 3 (5%) at 15 years old had either one valve insufficiency or two valves insufficiencies. When all valves insufficiencies were considered, it was found that valve insufficiencies in ages between 9 and 11 years were seen most frequently (Fig. 4).

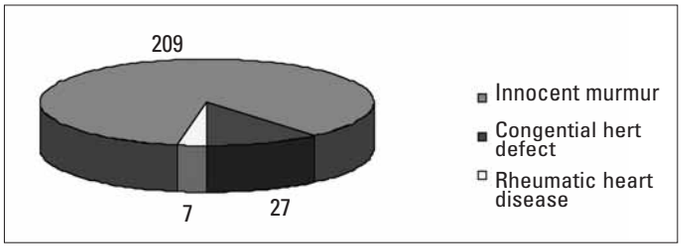

Figure 1. The distribution of all murmurs according to etiology

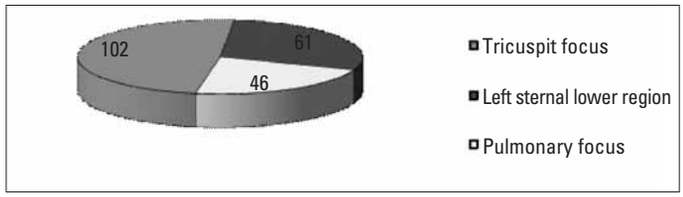

Figure 2. The distribution of innocent murmurs according to cardiac focus

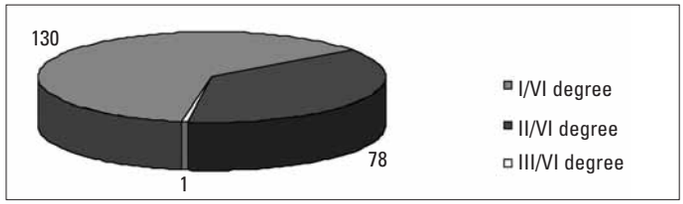

Figure 3. The distribution of innocent murmurs according to severity

Table 1. Congenital heart defect and its distribution according to gender

Congenital Heart Defect	Female	Male	Total	Prevalence, %
PS	1	1	2	0.033
VSD	-	1	1	0.016
ASD-PS	-	1	1	0.016
MVP-PS	-	1	1	0.016
PDA-PS	1	-	1	0.016
PDA	-	1	1	0.016
ASD-MVP	1	1	2	0.033
AS	-	1	1	0.016
AS-Bicuspid aortic valve	-	1	1	0.016
MVP	5	-	5	0.082
TVP	-	5	5	0.082
MVP-TVP	2	3	5	0.082
AP window	-	1	1	0.016
Total	10	17	27	0.440

AS- aortic stenosis, ASD- atrial septal defect, MVP- mitral valve prolapsus, PDA- patent ductus arteriosus, PS- pulmonary stenosis, TVP -tricuspid valve prolapsus, VSD- ventricular septal defect

Table 2. The distribution of patients with rheumatismal heart disease according to lesion localization and gender

Lesion	Female	Male	Total
MVI	3	1	4
AVI	1	-	1
AVI-MVI	1	1	2
Total	5	2	7

AVI - aortic valve insufficiency, MVI - mitral valve insufficiency

When valve insufficiency in cases with innocent murmurs was evaluated according to gender, of all cases, 20 (36%) were females and 36 (64%) were males.

Of 209 students who were evaluated as having innocent murmur, 56 (27%) students had either one valve insufficiency (tricuspid) or two valves insufficiencies (tricuspid-pulmonary). The tricuspid valve insufficiency (TVI) was determined in 48 (86%) students, the pulmonary valve insufficiency (PVI) in 4 (7%), and TVI plus PVI in 4 (7%) (Fig. 5). In cases with TVI, 75% of these cases had mild TVI, 22.8% of them had grade I° TVI, and 1.1% of them had grade II° TVI, 1.1% of them had grade III° TVI. In cases with PVI, ratios of mild, I°, II°, III° grades of PVI were 78%, 7.1%, 7.1%, 7.1% respectively. There was no difference in age distribution between in cases with valve insufficiency ($p > 0.05$).

Of all cases who had murmur, the number of cases that evaluated as RHD was seven (3%) and; of these, 5 (71%) were females and 2 (29%) were males. Of cases with RHD, 4 (57%) had mitral valve insufficiency (MVI), and 2 (29%) had an aortic valve insufficiency (AVI) plus the MVI, and one (14%) had AVI (Table 2).

Discussion

In our study, we heard murmurs with different intensities in 243 patients (4%). The results showed that 209 children's (3.5%) murmurs were accepted as innocent. These innocent murmurs were heard at tricuspid focus in 78% and pulmonary focus in 22%. When the innocent murmurs evaluated according to their intensities, I/IV degree murmur was detected in 62% of the cases, II/IV in 37%, III/IV in 1%. Murmur, related to anemia was not detected. Regurgitation was detected in single or two valves in 27% (56 cases) of cases with innocent murmurs. Additionally no valve insufficiency or regurgitation was determined in children who had innocent murmurs except these 56 cases. Of patients who had murmurs, 27 children (0.4%) had CHD and 7 (0.1%) had rheumatic heart disease. In children with CHD; 16 (59%) had single defect and 11(41%) had two defects. In patients who had CHD, MVP and TVP were found in 48% and 37% of cases respectively.

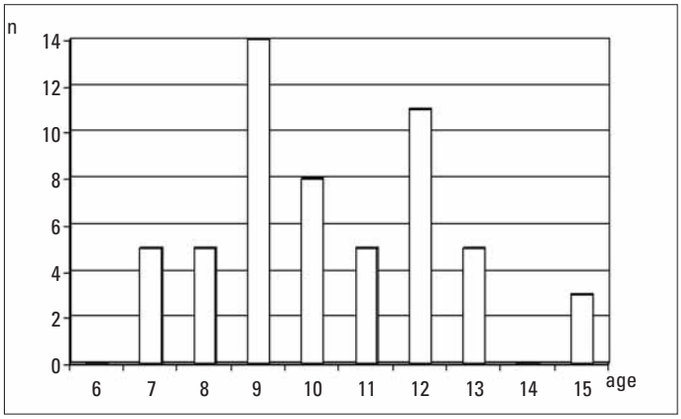

Figure 4. The distribution of valvular insufficiency in innocent murmurs according to age

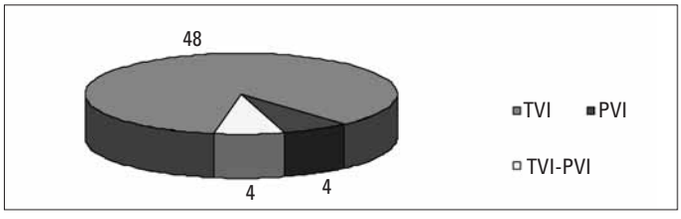

Figure 5. The distribution of valvular insufficiency according to valve involvement
PVI - pulmonary valve insufficiency, TVI - tricuspid valve insufficiency

While the auscultation was the unique method for many years to make a differential diagnosis between functional and organic murmurs, a transthoracic and Doppler ECHO have gained more importance today. The problem is that whether a transthoracic and Doppler ECHO is required, as routine investigation, in the presence of a cardiac murmur. An auscultation constitutes an important part of the examination in cardiac evaluation.

It has been reported that the prevalence of cardiac murmurs in childhood varies between 6 to 90% in the literature (11-14). Fagel (12) has reported the incidence of innocent murmurs in pediatric population that referred to cardiac evaluation to be 63% in 1960. There were many different studies in our native country on this issue. Koç et al. (15) reported rate of innocent murmurs as 1.07% in a study in Şanlıurfa; Aygün et al (16) reported this in Elazığ as 1.7%; Altıntaş et al. (17) in Adana-as 1.47%, Elevli et al (18) in Diyarbakır as 2.3%, and Yıldırım et al. (19) in Diyarbakır - as 1.4% (18-21 15-19). We found a value of 3.46%, which was lower than in other studies in the literature and higher than in the studies in our native country.

It has been reported that the frequency of congenital heart defect in cases of live births is 3.39 to 11.9 in 1000 (20-23). It is seen as approximately 1% in all live births. It has been reported that the ratio of CHDs in schoolchildren is between 0.27% and 0.51% in many studies (24-28). In studies performed in our country, Koç et al. (18) reported a frequency of CHD in elementary schoolchildren as 0.21% in Şanlıurfa; Aygün et al. (16) in Elazığ - as 1%; Yıldırım et al. (19) in Diyarbakır-as 0.2%; Elevli et al. (18) in Diyarbakır-as 0.44%; Altıntaş et al. (17) in Adana - as 0.14% (16-19). We found a ratio of CHD as 0.44% in our study.

Ventricular septal defect is the most common lesion seen in CHDs and constitutes at least 25% of all CHDs (28). In our cases, we found a VSD in 7.4% cases, which was less than in the literature. The reason of low occurrence in our study may be due to that 17% to 37% of VSDs closes at early ages (29).

According to their localizations ASDs are seen in many types; secundum type ASD as the most common lesion seen (62 to 78.7%), premium type ASD, sinus venosus type ASD (superior vena cava type-inferior vena cava type), and coronary sinus type ASD. Secundum type ASD constitutes 6 to 8% of all CHDs (28). In our study, we found secundum type ASD in 2 cases (7.4%).

Patent ductus arteriosus constitutes 6 to 8% of all CHDs (26). Two (7.4%) cases of PDA were determined in our study. This ratio was similar to the literature findings.

Pulmonary stenosis constitutes 5 to 7% of CHDs (28). We found this in 5 (18.5%) cases in our study and it was higher than in written sources. Because of the most patients with PS who were asymptomatic and referred to hospital late, cases, which may be diagnosed late may have increased the frequency in our study.

Aortic stenosis, constitutes 4 to 7% of CHDs (28). It has been reported that the ratio of AS is higher in males than in females and is frequently seen at 10 years old (17.63%). In our study, two (7.4%) cases of AS were 10 and 11 years old and were male too.

Mitral valve prolapsus is seen in a frequency of 4 to 21%, more in females (30, 31). In a study performed in our native country, an association of MVP and TVP, and of MVP and ASD has been determined as 11% and 7.3%, respectively (32). In our study, we found 5 (38%) isolated cases of MVP and 5 (38%) cases of MVP accompanied to TVP, and 2 (15%) cases of MVP accompanied to ASD and one (8%) cases of MVP accompanied to PS. Sixty-six percent of cases (66%) were females. However, 5 (50%) cases of TVP alone and 5 (50%) cases of TVP accompanied to MVP were determined. Eighty percent (80%) cases of TVP were males.

It has been reported that a ratio of RHD in schoolchildren is 0.03 to 0.71% in the literature (26, 33-38). In studies on this issue, Altıntaş et al. (17) reported a ratio of RHD as 0.03% in Adana; Eleveli et al. (18) in Diyarbakır-as 0.08%; Yıldırım et al. (39) in Diyarbakır-as 0.04% and Yüksel (40) et al. in Fatih county in Istanbul-as 0.41%. We determined a prevalence of RHD as 0.1%. In cases with RHD, in terms of valve involvement, mitral insufficiency was the most common lesion, followed by AVI-MVI and AVI. Our results were similar to the studies in the literature and in our country.

Several ECHO studies were performed to define frequency of valvular regurgitations in otherwise healthy children with constitutionally normal hearts. Ayabakan et al. (41) reported that a TVI frequency was 32.8%, a PVI - was 17.2%, a MVI - was 8.6%, and an AVI - was 1.1%. Brand et al. (42) reported a TVI as 6.3%, a PVI as 21.9%, and a MVI as 2.4%, but have not determined an AVI. Starek et al. (43) reported a TVI rate as 49.4%, a PVI - as 20%, a MVI - as 14.5%, and AVI - as 0.8%.

In our study of cases with innocent murmurs, we determined TVI rate as 25%, a PVI as 4%, but we did not determine an AVI and a MVI. There are no reports in literature on frequency of valvular insufficiencies that determined by an ECHO evaluation in healthy children with innocent murmurs.

Frequency of innocent murmurs when were evaluated according to their intensity in our study, was similar to those reported in the literature (14, 44).

Cost-Effectiveness

Yi MS et al. (45) designed a study to assess the cost-effectiveness of various strategies to evaluate heart murmurs in children. They modeled 6 strategies to follow the initial examination by the pediatrician: (1) refer suspected pathologic murmurs to a cardiologist, (2) obtain a chest radiography (CXR) and ECG and refer suspected pathologic murmurs to a cardiologist, (3) refer suspected pathologic murmurs for ECHO, (4) obtain a CXR and ECG and refer suspected pathologic murmurs for ECHO, (5) refer all patients with murmurs to a cardiologist, or (6) refer all patients with murmurs for ECHO. The least effective was strategy 1, which detects 82% of pathologic murmurs at $72 per patient evaluated. Strategy 5 detects 95% of pathologic murmurs at $38,000 per additional case detected over strategy 1. The most effective, strategy 6, detects 100% of pathologic murmurs at $158,000 per additional case detected over strategy 5. Strategies 2, 3, and 4 were not cost-effective. They finally emphasized that given the current cost constraints present in health care, whether the optimal strategy involves referring to a cardiologist or obtaining an ECHO for all patients with murmurs depends on how much society should allocate to diagnose pathologic murmurs. Finally, we know that our suggestion, which is about all children especially attending primary education should be examined by a cardiologist although they have no problem and look like healthy, is an expensive method. However, we also know that the patients in our study were examined many times by different pediatricians but were not diagnosed. Therefore, our suggestion is moderate expensive but very effective method to determine the pathological murmurs.

Conclusion

Our study showed that, especially valve prolapsus and other congenital heart defects and less frequently rheumatic carditis, can be seen in children who look like healthy. In our study, the first examination was performed by a pediatrician. Maybe, because of this, in our study the rate of murmurs was found lower than in the other studies in the literature (45). So, we emphasized that all children especially attending primary education should be examined by a cardiologist although they have no problem and look like healthy.

References

1. Martin JM, Neches WH, Wald ER. Infective endocarditis. 35 years of experience at a children's hospital. Clin Infect Dis 1997; 24: 669-75.
2. Pelech NA. The cardiac murmur. When to refer? Pediatr Clin North Am 1998; 45: 107-22.
3. Rajakumar K, Weisse M, Rosas A, Gunel E, Pyles E, Neal WA, et al. Comparative study of clinical evaluation of heart murmurs by general pediatricians and pediatric cardiologists. Clin Pediatr 1999; 38: 511-8.
4. Pelec NA. Evaluation of the pediatric patient with cardiac murmur. Pediatr Clin North Am 1999; 46: 167-88.
5. Allan LD, Leanage R, Wainwright R, Joseph MC, Tynan M. Balloon atrial septostomy under two dimensional echocardiographic control. Br Heart J 1982; 47: 41-3.
6. Hunta JC. Echocardiography, Two-Dimensional and M-Mode, In: Bricker G, McNamara DG editors. The Science and Pratice of Pediatric Cardiology. Phiadelphie: Lea and Febiger; 1990. p. 768-84.
7. Atalay S, Saraçlar M, Özkutlu S. Ductus arteriozus açıklığı vakasının iki boyutlu ve Doppler ekokardiyografi ile değerlendirilmesi. Türk Kardiyol Dern Arş 1991; 19: 67-70.
8. Arslan S, Arslan N, Soylu A, Akgün C, Tepebaşılı I, Türkmen M, et al. High altitude and blood pressure in children. Yale J Biol Med 2003; 76: 145-8.
9. Çaksen H, Odabaşı D. Keratomalacia and scurvy in a severely malnourished infant. Pediatr Dermatol 2002; 19: 93-5.
10. Anlar O, Tombul T, Arslan S, Akdeniz H, Çaksen H, Gündem A et al. Report of five children with Guillain-Barré syndrome following a nationwide oral polio vaccine campaign in Turkey. Neurol India 2003; 51: 544-5.
11. Barlow JB, Pocock WA. The significance of aortic ejection murmurs. Am Heart J 1962; 64: 149-58.
12. Fogel DH. The innocent systolic murmur in children: a clinical study of its incidence and characteristics. Am Heart J 1960; 59: 844-55.

13. Rosenthal A. How to distinguish between innocent and pathologic murmurs in childhood. Pediatr Clin North Am 1984; 31: 1229-40.
14. Van Oort A, Hopman J, De Boo T, Van Der Werf T, Rohmer J, Daniëls O. The vibratory innocent heart in schoolchildren: a case-control Doppler echocardiographic study. Pediatr Cardiol 1994; 15: 275-81.
15. Koç A, Kösecik M, Ataş A, Kılınç M. İlköğretim çağı çocuklarında kalp üfürümleri prevalans çalışması. Türk Pediatri Arşivi 1997; 32: 28-33.
16. Aygün D, Kocaman S, Akarsu S, Yaşar F, Türkbay D. İlkokul çocuklarında kalp üfürümlerinin sıklığı ve önemi. Türkiye Klinikleri Pediatri Dergisi 1998; 7: 133-7.
17. Altıntaş G, Acartürk E, Tokcan A, Dikmengil M. Adana ili ilkokul çocuklarında kalp üfürümleri taraması. Ç. Ü. Tıp Fakültesi Dergisi 1988; 3: 211-4.
18. Elevli M, Yakut İ, Devecioğlu C. Diyarbakır il merkezinde iki ilkokulda yapılan anemi ve kalp üfürümleri taraması. Dicle Tıp Bülteni 1991; 18: 145-53.
19. Yıldırım MS, Müftüoğlu E, Kepekçi Y. Diyarbakır ili belediye hudutları dahilinde 7-18 yaşları arasındaki ilk ve orta dereceli okul öğrencilerinde doğumsal kalp hastalığı oranı. Türk Kardiyoloji Derneği Arşivi 1986; 14: 21.
20. Hoffman JI. Congenital heart disease: incidence and inheritance. Pediatric Clinics of North America. 1990; 37: 25-43.
21. Hoffman JI, Christianson R. Congenital Heart Disease in a cohort of 19502 births with long-term follow up. Am J Cardiol 1978; 42: 461.
22. Gerlis LM. Cardiac malformations in spontaneous abortions. Int J Cardiol 1985; 7: 29.
23. Paladini D, Tartaglione A, Agangi A, Teodoro A, Forlego F, Borghese A, et al. The association between congenital heart disease and Down syndrome in prenatal life. Ultrasound Obstet Gynecol 2000; 15: 104-8.
24. Cayler GC, Warren MC. Benefits from mass evaluation of school children for heart disease. Chest 1970; 58: 349.
25. Durnin RE, Stanton RE, Gallaher ME, Golding RE, Gathman G, Fyler DC. Heart sound screening in children. JAMA 1968; 203: 1113-8.
26. Hassel TA, Renwick S, Stuart KL. Rheumatic fever and rheumatic heart disease in Barbados: detection and prophylaxis. Br Med J 1972; 3: 387.
27. Thakur JS, Negi PC, Ahluwalia SK, Sharma R, Bhardwaj. Congenital heart disease among school children in Shimla hills. Indian Heart J 1995; 47: 232-5.
28. Bassili A, Mokhtar SA, Dabous NI, Zaher SR, Mokhtar MM, Zaki A. Congenital heart disease among school children in Alexandria, Egypt: an overview on prevalence and relative frequencies. J Trop Pediatr 2000; 46: 357-62.
29. Bernstein D. Congenital heart disease. In: Behrman RE, Kliegman RM, Arvin AM, Nelson WE, editors. 15th edition. Nelson Textbook of Pediatrics. Phiadelphia; WB Saunders Co: 2004. p. 1499-554.
30. Lillian M, Valdes-Cruz L, Cayre RO. Echocardiographic diagnosis of congenital heart disease. An embryologic and anatomic approach. Philadelphia; Lippincott-Raven: 1999.
31. Levy D, Savage D. Prevalence of mitral valve prolapse. Am Heart J 1987. 113: 1281-90.
32. Naçar N, Atalay S, Tutar HE, Ekici F. Mitral valve prolapsuslu çocuklarda tanı kriterleri ve izlem. Ankara Üniversitesi Tıp Fakültesi Mecmuası 2002; 55: 283-90.
33. Yıldırım MS, Müftüoğlu E, Kepekçi Y. Diyarbakır ili belediye hudutları dahilinde 7-18 yaşları arasındaki ilk ve orta dereceli okul öğrencilerinde masum üfürüm oranı. Türk Kardiyoloji Derneği Arşivi 1986; 14: 19.
34. Demirağ B, İmamoğlu A, Yüksel M. Kalp ve damar sistemi. Sağlıkta ve hastada kalp ve dolaşımın değerlendirilmesi. Çocuk Sağlığı ve Hastalıkları, Cilt 2. Ankara; Feryal Matb: 1984. s. 49-54.
35. McLaren MJ, Hawkins DM, Koornhof HJ, Bloom KR, Bramwell-Jones DM, Cohen E et al. Epidemiology of rheumatic heart disease in black schoolchildren of Soweto, Johannesburg. Br Med J 1975; 23; 3: 474-8.
36. Morton WE, Huhn LA, Lichty JA. Rheumatic heart disease epidemiology. Observation in 17366 Denver school children. JAMA 1967; 199: 879-84.
37. Regmi PR, Pandey MR. Prevalence of rheumatic fever and rheumatic heart disease in school children of Katmandu city. Indian Heart J 1997; 49: 518-20.
38. Jose VJ, Gomathi M. Declining prevalence of rheumatic heart disease in rural schoolchildren in India. Indian Heart J 2003; 55: 158-60.
39. Yıldırım MS, Müftüoğlu E, Kepekçi Y. Diyarbakır ili belediye hudutları dahilinde 7-18 yaşları arasındaki ilk ve orta dereceli okul öğrencilerinde romatizmal kalp hastalığı oranı. Türk Kardiyoloji Derneği Arşivi 1986; 14: 20.
40. Yüksel H, Öztürk M, Öztürk E, Türkoğlu C, Bayrı G, Dalmak S et al. Fatih İlçesinde ilk ve orta öğrenim öğrencilerinde kalp hastalıkları prevalansı. Cerrahpaşa Tıp Fakültesi Dergisi 1986; 17: 49-55.
41. Ayabakan C, Özkutlu S, Kılıç A. The Doppler echocardiographic assessment of valvular regurgitation in normal children. Turk J Pediatr 2003; 45: 102-7.
42. Brand A, Dollberg S, Keren A. The prevalence of valvular regurgitation in children with structurally normal hearts: a color Doppler echocardiographic study. Am Heart J 1992; 123: 177-80.
43. Starek A, Niederle P, Spacek R, Suchan V, Feureisl R, Hes I et al. Regurgitation across an obviously normal valve orifice as a possible prerequisite for non-organic cardiac murmur. Cor Vasa 1989; 31: 186-94.
44. Aydın GB, Olguntürk R, Tunaoğlu FS. Ankara kent merkezinde masum üfürüm ve konjenital kalp hastalığı sıklığı. Türkiye Klinikleri Pediatri Dergisi 2001; 10: 121-4.
45. Yi MS, Kimball TR, Tsevat J, Mrus JM, Kotagal UR. Evaluation of heart murmurs in children: cost-effectiveness and practical implications. J Pediatr 2002; 141: 504-11.