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Atrial septal defect. A diagnostic approach

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Abstract

A simple objective screening method for diagnosis of the atrial septal defect (ASD) is needed. Acoustic signals were collected from 61 children with ASD and 60 with a physiological murmur. The second heart sound (S_2) and the spectrum of systolic murmur were analysed. A statistical model was designed using stepwise logistic regression analysis. Significant variables distinguishing pathological form normal findings were the interval between the first heart sound and the beginning of systolic murmur or the respiratory variation of S_2, and the frequency of the murmur at its maximum intensity. The area under the ROC curve was 0.922; indicating very good fit of the model and the confidence interval was 0.872-0.971. The sensitivity of the model was 91% and the specificity 73%. The analysis of acoustic findings from the heart is a valuable tool in diagnosing ASD. The next step will be automating this process.

1. Introduction

Secundum atrial septal defect (ASD) represents 6-10% of congenital cardiac anomalies (1). Many children with this defect are asymptomatic, and so referral to treatment can be significantly delayed. Because clinical diagnosis is based on a widely and consistently split second heart sound rather than the murmur, many patients are missed in the screening process (2, 3). Late diagnosis and delayed management of significant defects may lead to impaired exercise tolerance, an increased incidence of pneumonia, cardiac arrhythmia later in life, and, in some cases, pulmonary hypertension and shortened life expectancy (4).

Children with ASD are often referred to a cardiac specialist because of a systolic murmur. Associated physical findings can usually be used to distinguish a pathological murmur from the soft ejection systolic murmur that arises in the right ventricular outflow tract due to a high

right ventricular output, which is physiological in character (5). However, even given a pathological second heart sound (S_2), the physical examination, ECG, and chest x-ray could be inconclusive. Echocardiography is usually diagnostic, but is also quite expensive when the costs of the equipment, the procedure, and the parent's time are all taken into account. Thus, there is a need for a simple, in-office instrument that can be used for primary screening to determine which patients should be sent for further cardiologic consultation. This study highlights the most important auscultation findings in patients with ASD and the use of time interval measurements and signal processing as screening tools for the diagnosis of ASD.

2. METHODS

2.1 Patients and data collection

Acoustic signals from the heart with a simultaneous registration of electrocardiography (ECG) and phases of respiration were collected from 61 children with ASD and 60 healthy children with a physiological murmur. Diagnosis of ASD was based on echocardiographic examination of the heart. The recordings were made by a PC-based device developed at Helsinki University of Technology (6).

The median age of the patients with ASD was 4 years (range 8 months–17 years) and that of the healthy children 5.5 years (range 1 month–13 years). The recordings took place in ordinary outpatient clinic rooms without special sound insulation, and were made at intercostal spaces 2, 3, and 4 at the left parasternal border, and at the cardiac apex. The examination, including the 45-second recording, took 10-12 minutes per child.

Data concerning weight, length, gender, body mass index (BMI), and ECG were collected. All children were examined with echocardiography by the same experienced cardiologist

(M.E.S.) with either an Acuson Sequoia or a 128 XP echocardiographic system. Heart volume was calculated from chest x-rays and adjusted to body surface area (7). The ratio of pulmonary flow to systemic flow (Qp:Qs) was measured according to Fick's principle in 34 patients during heart catheterisation to evaluate the clinical significance of the ASD.

The study was approved by the Ethics Committee of Lund University Hospital, and informed consent to participate was given by either the children or their parents.

2.2 Time interval measurements

The first heart sound (S_1) was defined as the first signal peak after the QRS complex, and the second heart sound (S_2) as the signal peak after the T-wave in the ECGs. Measurements were taken of the following: (a) the width of S_2 splitting, i.e. the interval between aortic (A_2) and pulmonary (P_2) valve closing sounds, (b) the interval between the end of S_1 and the beginning of the systolic murmur (S_1SM), and (c) the interval from the end of S_1 to the maximum intensity in the spectrum of the murmur (Timax). Measurements were taken during both inspiration and expiration. The respiratory variation of the width of S_2 (ΔS_2) and the relative variation (the ratio of ΔS_2 to the maximal duration of S_2) were calculated. Time interval measurements are presented in Figure 1.

2.3 Signal analysis

Sound signals were band-pass filtered using a fourth-order Butterworth filter (cut-off frequencies of 40 Hz and 1100 Hz) and processed using the short-time Fourier transform (STFT) (8). The lower filtration limit was set to 40 Hz in order to avoid filtration of S_1 and S_2. The frequency range for S_1 and S_2 usually ranged from 40 to100 Hz (8-10). The systolic murmur was analysed in regard to its (a) maximum intensity (Imax), (b) mean spectral power

(mean sound intensity, MSp), (c) frequency at its maximum intensity in the spectrum (Fimax), (d) mean frequency (the mean of the frequencies measured per unit time, Fmean), (e) highest frequency (HF) of the sound signal above the intensity of 0.1 dB and 40 Hz, and (f) frequency range (FR) (8). Table 1 presents definitions of all parameters derived from time interval measurement and signal analysis, along with their abbreviations.

2.4 Statistical analyses

The data set was divided into two parts; 11 observations from each group (ASD and physiological murmurs) were selected at random and used as the prediction set. The remaining 99 observations (50 ASD and 49 physiological murmurs) were used for the model-building set.

A stepwise logistic regression analysis was performed on the model-building set, using the SAS software package (version 6.12) and taking ASD or physiological murmurs as the dependent variable. The independent variables were those derived from signal processing of the murmur, measurement of time intervals, and the standard deviations (SD) of Imax, MSp, Timax, Fimax, Fmean, HF, and FR. Sex, age, weight, length, BMI, and proportional heart volume were also included as independent variables in the statistical analyses. Because some patients with ASD have a systolic murmur starting late in systole, like healthy children with physiological murmur, S_1SM and ΔS_2 were combined into one independent variable. S_1SM was used as a separate independent variable if its value was 0 (in the presence of systolic murmur signal early in systole), while if its value was > 0 then ΔS_2 was used instead. In the results and discussion, this variable will be referred to as the “designed variable”. Alpha to enter and alpha to remove were both set to 0.05.

The appropriateness of the fitted model suggested by the stepwise procedure was then examined for adequacy. P-values > 0.05 in the Pearson, deviance, and Hosmer-Lemeshow goodness-of-fit tests were required for the fitted model to be considered adequate (11, 12). Goodness-of-fit tests were performed using the Minitab software package (version 13.2).

In addition, a model with no multicollinearity was to be preferred over a model with multicollinearity. The stepwise procedure can exclude variables that might be theoretically relevant, due to multicollinearity. If the pairwise correlation among independent variables was significant ($p<0.05$) we inferred multicollinearity. However, multicollinearity could still exist even without significant pairwise correlation. To ensure that multicollinearity was not present, we manually added and deleted variables to see the effect on the regression coefficients, and inferred multicollinearity in the cases where these coefficients were significantly altered (13).

The percentages of concordant, discordant, and tie pairs were calculated as a measure of association between the observed response and the predicted response. A pair (one respondent with ASD and one with physiological murmurs) was considered concordant if the fitted value for the respondent with ASD was higher than the fitted value for the respondent with physiological murmurs. A pair was considered discordant if the opposite was true, and a tie if the two fitted values were equal.

An ROC curve was plotted (using SPSS version 11.0.1) to show the prediction power of the model graphically. The area under the curve (AUC) was measured by the non-parametric method, and the 95% confidence interval (CI) was calculated. AUC measures discrimination, or the ability to classify patients correctly. AUC is defined as the number of concordant pairs plus half the number of tied pairs divided by all the pairs (the number of pairs equals the

number of ASD patients multiplied by the number of non-ASD patients). An AUC of 0.5 (represented by the 45 degree line in the ROC curve) indicates that the model's ability to correctly classify patients is 50%. An AUC of 0.7-0.8 is considered fair, 0.8-0.9 is considered good, and a value above 0.9 is considered excellent (14, 15).

Graphical and visual analysis was performed to evaluate the possible outliers in the model; Delta Chi-2 was plotted against the fitted values and Delta Chi-2 was plotted against the leverage values. A high delta Chi-2 can result from a high leverage, a high Pearson residual, or both. Observations with delta chi-2 greater than 3.84 were considered as a sign of bad fit by the model (12).

For prediction purposes, we wanted to minimize the risk of missing patients with ASD, and therefore sought to achieve a sensitivity of around 95% at the expense of a lower specificity, while still trying to avoid losing too much specificity. To find the best threshold for classifying patients with ASD, various cut-off points (ranging from 0.01 to 0.99 in steps of 0.01) were used to calculate the sensitivity and specificity. A patient was considered to have an ASD if the fitted value was greater than the cut-off point. The cut-off point that maximized specificity and had sensitivity around 95% was then chosen as the threshold for prediction purposes.

We applied this threshold to the prediction set and calculated the sensitivity and specificity. The sensitivities and specificities were then compared between the model-building set and the prediction set.

3. RESULTS

3.1 Time interval measurements

The width of S_2 could be measured in all records. The calculated ΔS_2 was small, ≤ 14 ms, in all records when Qp:Qs was more than 1.5:1 and in 25 of 60 records from healthy children. Only 57% (35 of 61) of patients with ASD had a systolic murmur. The S_1SM interval could always be measured in association with a systolic murmur, and ranged from 0 ms to 55 ms (median = 0 ms, mean = 13 ms). The relative spectral frequency of the murmur was low in children with a physiological murmur. Hence, 43% (26 of 60) of the physiological murmurs were filtered out by a 40 Hz high-pass filter. In the 34 remaining records, S_1SM could be measured, and ranged from 0 ms to 108 ms (median = 48 ms, mean = 46 ms).

3.2 The statistical model and the ROC curve

The stepwise logistic regression procedure suggested a model with the designed variable (S_1SM or ΔS_2) and Fimax ($p<0.001$ for both variables). The goodness-of-fit tests for this model showed p-values greater than 0.05, indicating an adequate fit (Table 2).

The correlation between the two selected independent variables was not significant ($P>0.05$), indicating no sign of multicollinearity (Pearson correlation between the designed variable and Fimax = 0.032, p = 0.752). Manual investigation of different possible models did not reveal any sign that the final model presented by the stepwise logistic regression procedure was a result of multicollinearity.

The percentages of concordant, discordant, and tie pairs are shown in Table 3, and the ROC curve and the area under the curve (AUC=0.922) are shown in Figure 2. The confidence interval for the AUC was 0.872-0.971.

The graphical analysis did reveal seven observations with a high delta Chi-Square (3 of 50 cases with ASD and 4 of 49 cases with physiological murmur). The cases with ASD were the ones which were misclassified by our model. Two of the three cases had a measured small and clinically insignificant shunt, Qp:Qs 1.5:1 and 1.1:1. The third false negative had long S_1SM (31 ms); atypical for ASD, the Qp:Qs was not measured, but according to echocardiography the right ventricle was not enlarged, which indicates a small shunt. The children that were misclassified as having ASD had either a small absolute ΔS_2 (0, 4, and 7 ms in three children) or a short S_1SM (0 ms in one child). The relative ΔS_2, the ratio of ΔS_2 to the maximal duration of S_2, was small (0.06, 0.24, and 0.31), but within lower normal range (normal range 0.06 – 1, mean 0.4).

The cut-off point that gave sensitivity close to 95% and maximized the specificity was found to be 0.27. At this cut-off point, the sensitivity was 94% and the specificity was 71%. The cut-off points and the resulting pairs of sensitivities and specificities close to a sensitivity of 95% are presented in Table 4. Sensitivity and specificity for all cut-off points are presented in Figure 3. When applying the chosen cut-off point, 0.27, to the prediction set, we achieved 91% sensitivity and 73% specificity.

4 DISCUSSION

Our statistical model distinguishes very well between patients with ASD and healthy children with physiological murmur, and can thus serve as a good backup for the clinical diagnosis of ASD. Three patients in the model-building set were misclassified as healthy; however, they had a small shunt, for which treatment is not indicated. The small additional burden of the false positives is more than offset by the accrued benefits of simplified screening, automated

diagnostic approach, and reduction in total referrals. The sensitivity (91%) and specificity (73%) for the prediction set was about the same as for the model-building set, supporting the conclusion that the model has an excellent predictive power.

Numerous methods can be applied when classifying data. One of our criteria was that the model must give a probability of class membership. Models that do not give a probability (for example, support vector machines) were therefore not considered. Logistic regression, k-nearest neighbours, and decision trees are examples of methods that can be applied (10). The probability for a given observation is calculated as the ratio of members of class y among the k nearest neighbours of the given observation. The value k takes can greatly affect the result. Another difficulty with k-nearest neighbour arises when many variables are included. If the relative importance of variables is not weighted, then data from irrelevant variables have an equal impact to data from an important variable (16). Since no prior knowledge existed about which variables to include or how different weights should be created, this method was not applied. However, this approach could be considered in future analysis when more knowledge exists about which variables should be included for prediction of patients with ASD (17).

The decision tree is built up of nodes, where the main node is the dependent variable. Data is split into groups with the goal of maximizing the separation of the data. Some prior knowledge regarding best and second best variables to include in the tree is necessary to apply this method. Additionally, when working with continuous variables, a definition of how to split them into groups is needed in order to obtain the nodes. Since this was an explorative study, we did not have any prior knowledge of which variables to include or how the independent variables should be split, and so chose not to apply this method. (18).

The reason for selecting the logistic regression model was that it gave us not only a probability of class membership but also a chance to study the impact of different variables through its coefficients. The stepwise procedure is also convenient when it comes to choosing variables to include in an explorative study. Additionally, there exist several known tests for evaluation of models.

Patients with ASD do not always have a systolic murmur; only 57% of our patients had it. A large flow through a normal pulmonary valve may cause a murmur with physiological quality. The frequency of the systolic murmur at the point of maximum intensity in the spectrum (Fimax) was spectrally higher in patients with ASD than in healthy children, due to a higher blood flow velocity. The intensity of the murmur was also greater, apparently for the same reason. Analysis of the signal spectrum and its intensity will make it possible to differentiate the ejection systolic murmur in patients with ASD from other physiological murmurs.

The model given by the stepwise logistic regression analysis showed an adequate fit. There was no significant correlation between the two independent variables (the designed variable and Fimax), and the predictive ability of the model was excellent (AUC=0.922). However, future studies with a larger prediction set could help further to investigate the predictive power of this suggested model. Yet another interesting aspect for further analysis would be to test how stable the regression coefficients are when the sample size increases.

5. CONCLUSIONS

The combination of time interval measurements and signal processing provides a diagnostic method for a haemodynamically significant ASD, differentiating pathological from normal

findings. When encapsulated in a tool for primary care physicians, referral of children to heart specialists can be minimized without endangering the safety of the patients. This would result in significant savings for the health care system, decreasing patient and family anxiety and expense.

This study has demonstrated the potential power of automated analysis as a tool for ASD diagnostic screening. Nevertheless, further studies are required to develop a fully automated system.

6. Acknowledgement

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Figure legends

Figure 1: Measurements of time intervals.

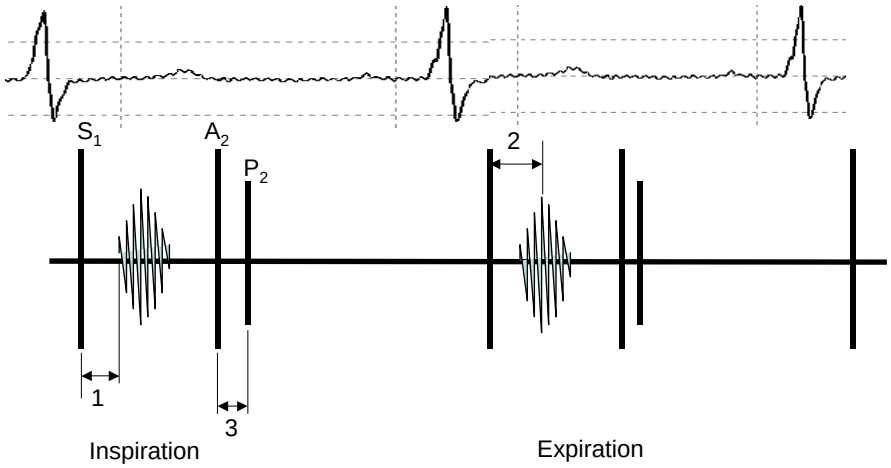
Figure 2:

Receiver-operating characteristic (ROC) curve. The area under the curve is 0.922, standard error is 0.025 under the non-parametric assumption. The 95% confidence interval is 0.872-0.971. Null hypothesis: true area = 0.5 ($p \leq 0.01$).

Figure 3

The sensitivity and specificity at different cut-off points. The figure illustrates the trade-off between sensitivity and specificity for various cut-off points.

Figure 1



1 = Intervals from the end of S_1 to the beginning of the systolic murmur (S_1Ms)
2 = Intervals from the end of S_1 to the murmur at its maximum intensity (Timax)
3 = S_2 duration

Figure 2

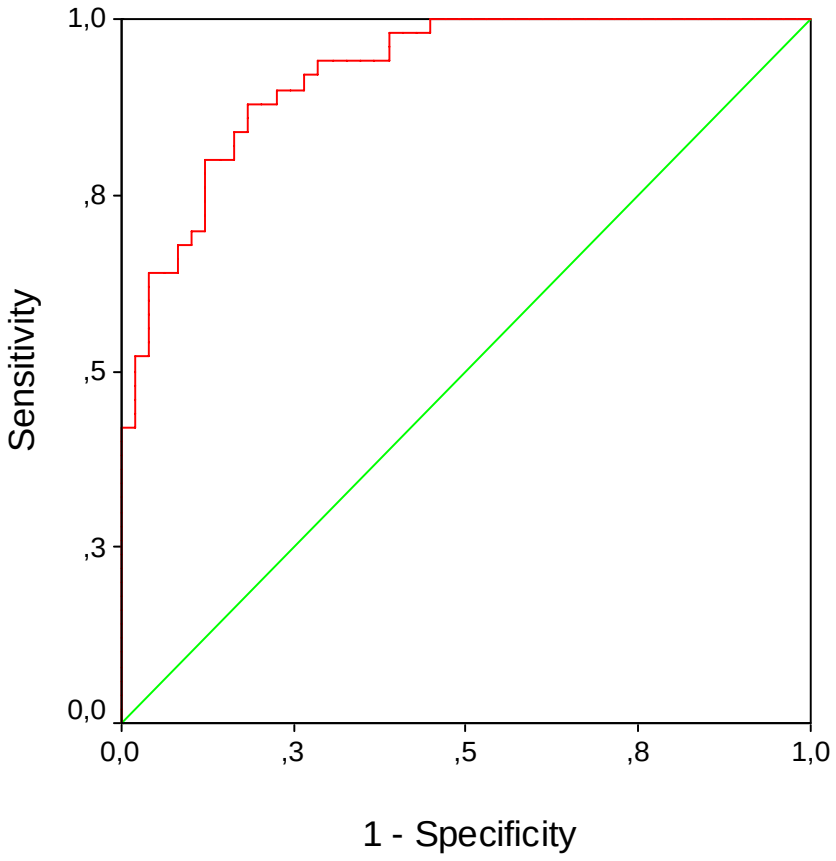


Figure 3

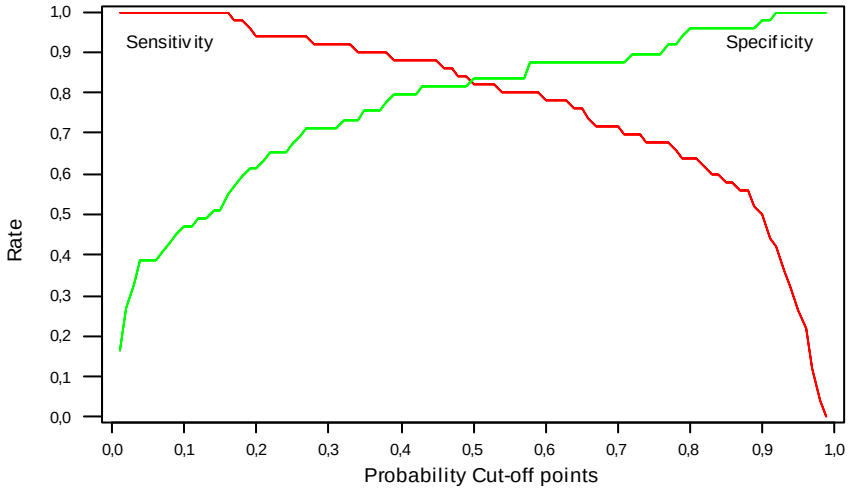

Sensitivity
Specificity
Rate
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0,0
0,0
0,1
0,2
0,3
0,4
0,5
0,6
0,7
0,8
0,9
1,0
Probability Cut-off points

Table 1. Parameters used in statistical comparisons, and their abbreviations.

Variable definition	Variable abbreviation and units
The interval between the end of S_1 and the beginning of the systolic murmur	S_1SM, ms
The respiratory variation of the splitting of S_2	ΔS_2
Combination of S_1SM and ΔS_2	The designed variable*
Mean spectral power or mean sound intensity	Sp, dB
Mean frequency, the mean of the frequencies measured per unit time	Fmean, Hz
The interval from S_1 to the point of maximum intensity in the spectrum	Timax, ms
The frequency at the point of maximum intensity in the spectrum	Fimax, Hz*
The maximum intensity of the systolic murmur	Imax, dB
Highest frequency	HF
Frequency range	FR

***** Significant variables in the logistic regression analysis.

Table 2

Results of goodness-of-fit tests.

Method	Chi-Square	Degrees of freedom	p-value
Pearson	72.099	96	0.967
Deviance	70.002	96	0.979
Hosmer-Lemeshow	3.634	8	0.889

Table 3
Number of concordant and discordant variables and ties.

Pairs	Number	Percentage
Concordant	2258	92.2%
Discordant	190	7.8%
Ties	2	0.1%
Total	2450	100%

Table 4:

The cut-off points, sensitivities, and specificities around a sensitivity value of 95%.

* indicates the best cut-off point according to our restriction of maximizing specificity while at the same time achieving a sensitivity of around 95%.

Potential cut-off point	Sensitivity	Specificity
0.18	0.98	0.59184
0.19	0.96	0.61224
0.2	0.94	0.61224
0.21	0.94	0.63265
0.22	0.94	0.65306
0.23	0.94	0.65306
0.24	0.94	0.65306
0.25	0.94	0.67347
0.26	0.94	0.69388
0.27*	0.94	0.71429
0.28	0.92	0.71429
0.29	0.92	0.71429
0.3	0.92	0.71429