ORIGINAL ARTICLE

Computerized Automatic Diagnosis of Innocent and Pathologic Murmurs in Pediatrics: A Pilot Study

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A B S T R A C T

Objective. Computer-aided auscultation in the differentiation of pathologic (AHA class I) from no or innocent murmurs (AHA class III) would be of great value to the general practitioner. This would allow objective screening for structural heart disease, standardized documentation of auscultation findings, and may avoid unnecessary referrals to pediatric cardiologists. Our goal was to assess the quality of a novel computerized algorithm that automatically classifies murmurs in phonocardiograms (PCGs) acquired in a pediatric population.

Design. This is a pilot study testing the ability of a novel computerized algorithm to accurately diagnose PCGs compared with interpreted echocardiograms as a gold standard.

Setting. This study was performed in pediatric cardiology clinics at a tertiary care hospital.

Patients. All incoming patients were recruited, including patients with no murmurs, innocent murmurs, and pathologic murmurs (106 patients).

Intervention. Using an electronic stethoscope, PCGs were acquired by the pediatric cardiologist from each patient. The PCGs were analyzed by the algorithm and diagnoses were compared with findings by echocardiograms interpreted by pediatric cardiologists which were used as the gold standard.

Outcome Measures. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated.

Results. When compared with echocardiography as a gold standard in diagnosing murmurs, the computerized algorithm tested on N=34 PCGs, yielded a sensitivity of 87% and specificity of 100%, a positive predictive value of 100%, negative predictive value of 90% and an accuracy of 94%.

Conclusion. With echocardiogram as a gold standard, this computerized algorithm can detect pathologic murmurs with high sensitivity, specificity and accuracy, comparable to if not better than published results of pediatric cardiologists and neonatologists. This study confirms the high quality and "real-world" robustness of a novel computational algorithm in the assessment of pediatric murmurs.

*Key Words.* Murmur; Pediatric; Cardiology; Computerized Assisted Auscultation; Automatic Detection; Consultation; Elective; Echocardiogram; Auscultation; Medical Software

Introduction

Up to 90% of children will have a heart murmur at some point during their infancy or childhood.[1–4] The majority of murmurs detected in children are clinically insignificant.[5,6] However, clinicians are most worried over missing the small incidence of congenital heart disease which is less than 1% across all pediatric age groups.[7–10] Specifi-cally in the neonatal population, a higher incidence has been reported, where in one study 42.5% of babies with heart murmurs where found to have structural cardiac malformations requiring clinical attention.[11,12] Auscultation remains the standard screening method used worldwide to assess premature babies, newborns, and children during routine
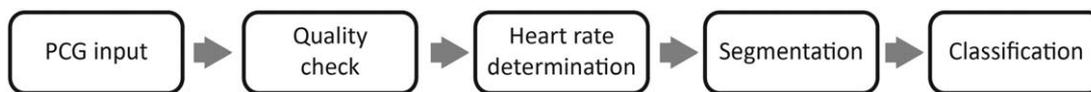
Figure 1. Major components of the algorithm performing automated heart murmur detection solely based on recorded phonocardiograms.

examinations. However, auscultation can be especially challenging in babies and younger children due to unsettled, agitated behavior and high heart rates, which limits the accuracy of diagnosis. Even when these factors are excluded, the sensitivity and specificity of auscultation is strongly dependent on the physician's experience and expertise. Consequently, the majority of elective referrals made to pediatric cardiac specialists result from the inability of the generalist to distinguish between innocent and pathologic murmurs.[8,10,13–17]

CSD Labs has developed a computer automated mathematical algorithm[18] that can analyze digitally recorded heart sounds using an electronic stethoscope. The automatic, accurate detection and distinction of pathologic from innocent murmurs, by a computing device, would be of great diagnostic value to the general practitioner. This potentially would allow more timely diagnosis of structural heart disease requiring treatment, while accurate differentiation of an innocent murmur may avoid costly and disruptive referral for unnecessary assessment by pediatric cardiologists. Several studies have shown that heart murmurs can be detected by analyzing digitally recorded phonocardiograms (PCGs) obtained using an electronic stethoscope.[19–24] They have demonstrated promising results, but these were not tested in a clinical environment or were tested in artificially controlled conditions for the best sound acquisition.

This pilot project was performed to further develop and preliminarily test the computerized algorithm's ability to automatically classify PCGs as either a class I murmur: "pathologic murmur requiring an echocardiogram" or a class III murmur: "innocent murmur or no murmur that does not require an echocardiogram" as per the ACC/AHA guidelines 2008.[25]

Patients and Methods

Patient Recruitment
Ethics approval for the study protocol was obtained from the Children's Hospital of Eastern Ontario Research Ethics Board. Patients attending the general pediatric cardiology clinic for routine assessment were subsequently recruited over a 6 week period between November 2013 and December 2013.

Basic Algorithm Scheme
The computational algorithm used in this study was based on a functioning prototype which underwent a successful clinical proof-of-concept study in 2012 on 40 premature babies and newborns at the University Clinic of the Medical University Graz, Austria.[18] Figure 1 illustrates the major components of the algorithm utilized in this study. This study focuses on analysis of the subset of recorded heart sounds acquired during a study performed to further develop, refine and validate the computer algorithm; the protocol is described below. Details of the algorithm are protected under proprietary regulations, however, specifics of the validation study can be found in Appendix A. The PCGs tested for the purposes of this study were not used in the development of the algorithm to remove any bias.

Study Protocol
Each participating patient was assigned a consecutive patient number. Patient demographics recorded included: examination date, gender, date of birth, weight, height, heart rate, reason for visit, and anatomical cardiac diagnosis, presence and type of the murmur diagnosed by the pediatric cardiologist and echo confirmation of murmur.

Four pediatric cardiologists participated in the auscultation and acquisition of the digital recordings. Each pediatric cardiologist had practiced 6–10 years and all passed the Canadian Royal College qualifying exams for pediatric cardiology.

The 3M Littmann Electronic Stethoscope Model 3200 (3M Littmann, St. Paul, MN, USA) was used. If there was a murmur present, the murmur was recorded at the loudest location. For each PCG acquisition, the pediatric cardiologist held the electronic stethoscope onto the patient's chest, simultaneously listening and recording the heart sounds for a maximum of 30 seconds. Two PCGs per patient were recorded. During the first acquisition the patients were asked to breathe normally.

Table 1. Reasons for Follow-up Visits

Reasons	Total = 81
Repaired CHD*	23
Unrepaired CHD†	19
BAV	10
Arrhythmia	13
Normal heart	3
Other‡	5
Palpitations	7
Syncope	1

*Twenty-three repaired CHD (congenital heart disease): 9 tetralogy of Fallot (TOF), 3 atrial septal defect (ASD), 2 ventricular septal defect (VSD), 2 Total anomalous pulmonary venous drainage (TAPVD), 2 coarctation, and one of each of the following: aortic atresia/ventricular septal defect (AA/VSD) (s/p Yasui), congenitally corrected transposition of the great arteries (CCTGA), double outlet right ventricle (DORV), transposition of the great arteries (TGA), supravalvar pulmonary stenosis (PS)/aortic stenosis (AS).
†Nineteen CHD: 6 VSD, 6 PS, 2 patent ductus arteriosus (PDA), 1 coarctation, 1 Ebstein's, 1 left pulmonary artery (LPA) stenosis, 1 mitral regurgitation (MR)/mitral valve prolapse (MVP), 1 polyvalvar disease (with Hurler's syndrome).
‡Five other: left ventricular diverticulum, hypertrophic cardiomyopathy, rule out rheumatic fever, surveillance for mitochondrial disease, pulmonary hypertension.

In the second acquisition, they were asked to hold their breath for as long as possible. For children unable to follow such orders a free breathing recording was performed for both assessments.

The PCGs were downloaded via a Bluetooth connection onto the StethAssist software (3M Littmann, USA) installed on a laptop, from where the PCGs could be exported as a standard .wav audio file. Each PCG was given a consecutive number linking it to the corresponding assigned patient number and no personal patient data (such as name or a patient identification number) were recorded, ensuring patient anonymity and blinding.

Results

Demographic Data

In total, 106 patients between the ages of 1 day–18 years (60 males [57%], 46 females [43%]) were included, the mean age was 8 years. On assessment of ability to hold ones breath by age, we divided the total number of patients into 3 groups. In group 1 none of the 34 patients aged (0–3.5 years) could hold their breath as directed, compared with 24 of 38 (63%) in group 2 (3.5–12 years) and 28 out of 34 (82%) in age group 3 (12–18 years).

Seventy-six percent (n = 81) were seen for follow up visits for known congenital heart disease or reassessment of other cardiac conditions (e.g., arrhythmia, palpitations) (Table 1), while 24% (n = 25) were new referrals, of which 56% (14/25) were for assessment of murmur.

Ninety out of one hundred six (85%) of the patients had echo confirmation of their diagnosis.

Of these 41/90 (46%) had pathologic murmurs, 16/90 (18%) had innocent murmurs and 33/90 (37%) had no audible murmur.

Of the patients referred for assessment of a murmur 12/14 (86%) were not pathologic. Ten of the 12 murmurs (83%) were diagnosed as innocent by the pediatric cardiologist of which 1/10 was confirmed by echo. The remaining 2/12 (17%) patients had no audible murmurs at the time of auscultation. The 2/14 murmurs deemed pathologic were confirmed as pulmonary valve stenosis and a perimembranous ventricular septal defect by echocardiogram.

Phonocardiograms

We acquired two datasets of PCGs for the 106 patients. Dataset 1 was comprised of PCGs acquired while free breathing (N = 106) and these were used in further development of the algorithm (see Appendix A). Dataset 2 was comprised of PCGs where the patients held their breath (N = 52) and were NOT used in further developing the algorithm. Nine PCGs from each set were excluded from further analysis by the algorithm due to poor quality.

We tested the algorithm's ability to accurately diagnose PCGs either as class I: "echocardiography is recommended because the patient's PCG contains a potentially pathologic murmur," or as class III: "echocardiography is not recommended because the patient's PCG contains an 'innocent murmur' or 'no murmur,'" based on the American College of Cardiology/American Heart Association guidelines (ACC/AHA guidelines 2008).[25] Of the 52 PCGs tested, only 34 PCGs were acquired from patients who also had an echocardiogram. Table 2 shows results of the algorithm vs. interpreted echocardiogram as a gold standard on the 34 PCGs not used in the development of the system and which were completely new to the algorithm.

Discussion

In this pilot project, we successfully show that a novel computational algorithm can diagnose electronic PCGs accurately in children with a sensitivity of 87%, a specificity of 100%, a positive predictive value of 100% and a negative predictive value of 90% using echocardiography as the gold standard (Table 2). These results are at least comparable if not better than published performance of pediatric cardiologists and neonatologists: sensitivity 78–83%, specificity 25–98%.[26–28]

Table 2. Algorithm vs. Echocardiogram as the Gold Standard in the Diagnosis of PCGs not used in Development of the Algorithm (N = 34)

		Echo		
		AHA class I: Pathologic murmur	AHA class III: No or innocent murmur	
Algorithm	AHA class I: Pathologic murmur	True positive 13	False positive 0	**Pos. predictive value 1.00**
	AHA class III: No or innocent murmur	False negative 2	True negative 19	**Neg. predictive value 0.90**
		Sensitivity 0.87	**Specificity 1.00**	**Accuracy 0.94**

Most importantly, we show that this high level of accuracy in diagnosis is maintained across all pediatric age groups where the superimposition of loud breathing and ambient noise can be a challenge to clinical assessment. Only 9/106 PCGs were rejected for poor quality. By way of digital analysis, the algorithm can very simply differentiate between noise and the repetitive signal created by a cardiac murmur. The signals created by environmental noise and breathing are not rhythmic, are not consistently associated to the S1 and S2 cycles and are, therefore, automatically filtered out of the interpretation. The signal created by a murmur is rhythmic and is consistently associated with S1 and S2. In our validation analysis, where we tested PCGs that were used in the development of the algorithm (see Appendix Table A2), we were able to show an average sensitivity and specificity of 94.9% and 94.8%, respectively, despite expected breathing and ambient noise in this patient population when compared with the pediatric cardiologist interpretation as a gold standard.

Existing computer assisted auscultation systems have also reported very promising results. Using proprietary software, (Zargis Cardioscan 3M Littman, Princeton, NJ, USA),[29] the sensitivity of identifying pathologic murmurs in children and young adults by a primary care physician increased from 82% to 90%, the specificity increased from 75% to 89%, and there was also a decrease in the percentage of innocent murmurs referred from 19% to 13%.[30] However, this study was performed on prerecorded heart sounds from a database[31] that was created for teaching purposes and thus would consist of heart sounds of optimal sound quality. Additionally, use of this software requires that "the patient should be instructed to remain still, and breath in a normal and quiet manner" and that the user has to "make sure that there are no background conversations being conducted during recording."[29] This is not feasible in the assessment of a newborn baby or active neonate or toddler.

Our results are also comparable to another computer assisted auscultation system aimed at the pediatric population[32] which reports a sensitivity 91% and specificity 94% for the detection of murmurs associated with structural heart disease.[33–35] However, this system (as well as the Cardioscan as discussed above) requires acquisitions at 4 different sites for 20–30 seconds at each site, something that again, may not be feasible in uncooperative babies or infants. Furthermore the reported results are based on testing where a three lead electrocardiogram (ECG) system was placed on the patient at the time of the heart sound acquisition, but yet in the actual use of the product no such instruction is given. The importance of the ECG at the time of acquisition lies in pinpointing the R-wave peaks on the ECG to find the positions of individual heart beats in the PCG, a process called segmentation. The segmentation process in our novel algorithm

is done without the need of an ECG. While the SensiCardiac system can also be used without ECG data input, corresponding clinical performance measures including sensitivity and specificity have not been reported in this context.

There are several compelling reasons for developing automated systems for the accurate diagnosis or exclusion of significant heart disease. Access to specialist care in third world countries is limited[36] and as a result, a system that can safely replace the need for any level of physician input could be highly advantageous. Indeed, several studies on this topic have originated from developing countries where access to tertiary level medical care is limited[33,37–41] and it is feasible that such a tool could be used by the less trained medical staff in the field, with subsequent referral only of those patients with pathologic murmurs. A study with a much larger study population would be warranted if we are to assess our algorithm as a screening tool. Although there is potential for use in this manner, at present, our algorithm is meant to be an aid to a trained personnel who can at the very least distinguish a murmur on auscultation.

It is not only in developing countries where the diagnosis of heart murmurs is a challenge however. The majority of elective referrals made to cardiac specialists result from the inability of general practitioners to distinguish between innocent and pathologic murmurs, resulting in an unnecessary high number of patients undergoing heart testing without any clinical purpose.[8,10,13–15] Several studies have documented declining clinical and auscultation skills of medical students, residents, and family physicians compared with the pediatric cardiac specialist.[42–47] It has also been suggested that the majority of pediatric echoes are ordered due to these declining auscultation skills.[48] In the United States, approximately $1.1 billion was spent by Medicare in 2010 to pay for echocardiograms.[49] It has been suggested that the most cost efficient method is referral to the pediatric cardiologist, who would decide whether a costly echocardiogram would be worthwhile, but given the large numbers of children with murmurs who would need assessment, this may not be feasible.[13,15,50–52] The algorithm validated in this study for automated, user-independent heart murmur classification could improve cost-efficiency in the health care system by offering a tool with similar sensitivity and higher specificity compared with primary care physicians, to filter patients who are being considered for referral to a specialist or directly for echocardiography.

That said, our study does have limitations. First, our sample size is small but as a pilot project the results are promising and a more formal study is planned with a larger sample size. Second, this study was not designed to test the algorithm as a screening tool for the presence of a murmur, but rather necessitates that the user at bare minimum should be able to distinguish a cardiac murmur on auscultation. Third, the dataset formally tested against interpreted echocardiograms were acquired on patients who were able to hold their breath. We suspect that our algorithm will hold strong even in PCGs acquired in free breathing patients, as our validation analysis which used free breathing PCGs, was promising. It showed a sensitivity and specificity of 94.9% and 94.8%, respectively. But these PCGs were already used previously in the development of the algorithm, and this may have introduced some bias. Fourth, not every patient had an echocardiogram to verify the presence of an anatomical abnormality that would explain the murmur. In our institution, it is the pediatric cardiologist who is the gate keeper to the use of the echocardiogram for verification and may not be ordered based on the pediatric cardiologist's confidence in recognizing the characteristics of an innocent murmur. A further study is planned where every patient will be required to have an echocardiogram with interpretation by the pediatric cardiologist to verify the cause of the murmur heard.

Conclusions

In summary, the outcome of this pilot study confirms the high quality and "real-world" robustness of a novel computational algorithm that yields high sensitivity, specificity, and predictive values in the assessment of pediatric murmurs.

Author Contributions

Lillian Lai, Michael J. Unterberger, Andreas J. Reinisch, Andreas J. Schriefl, designed the study and data collection instruments, coordinated, and supervised data collection, carried out the analyses, wrote, critically reviewed, and revised the manuscript, and approved the final manuscript as submitted. Andrew N. Redington: reviewed and revised the manuscript, and approved the final manuscript as submitted. Dr. Letizia Gardin, Dr. Robert Gow, Dr. Suzie Lee, and Dr. Derek Wong participated in the assessment of patients and acquisition of data and agree to be listed in the Acknowledgements section.

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Appendix A

Basic Algorithm Scheme

The computational algorithm used in this study was based on a functioning prototype which successfully underwent a clinical proof-of-concept study in 2012 on 40 premature babies and newborns at the University Clinic of the Medical University Graz, Austria, during which its ability to automatically detect systolic heart murmurs was demonstrated.[18] Figure 1 illustrates the major components of the algorithm utilized in this study.

The algorithm requires a recorded PCG of a length between 15 and 30 seconds (depending on the quality of the PCG) as input data. No additional external input by the user or input through an additional device is required (e.g., electrocardiogram (ECG) data). Next, the algorithm automatically performs a signal quality check. Insufficient PCG quality caused by excessive noise, for example, screaming sounds from toddlers, background noise from the environment, or loud friction noises from moving the stethoscope's head during the recording led to
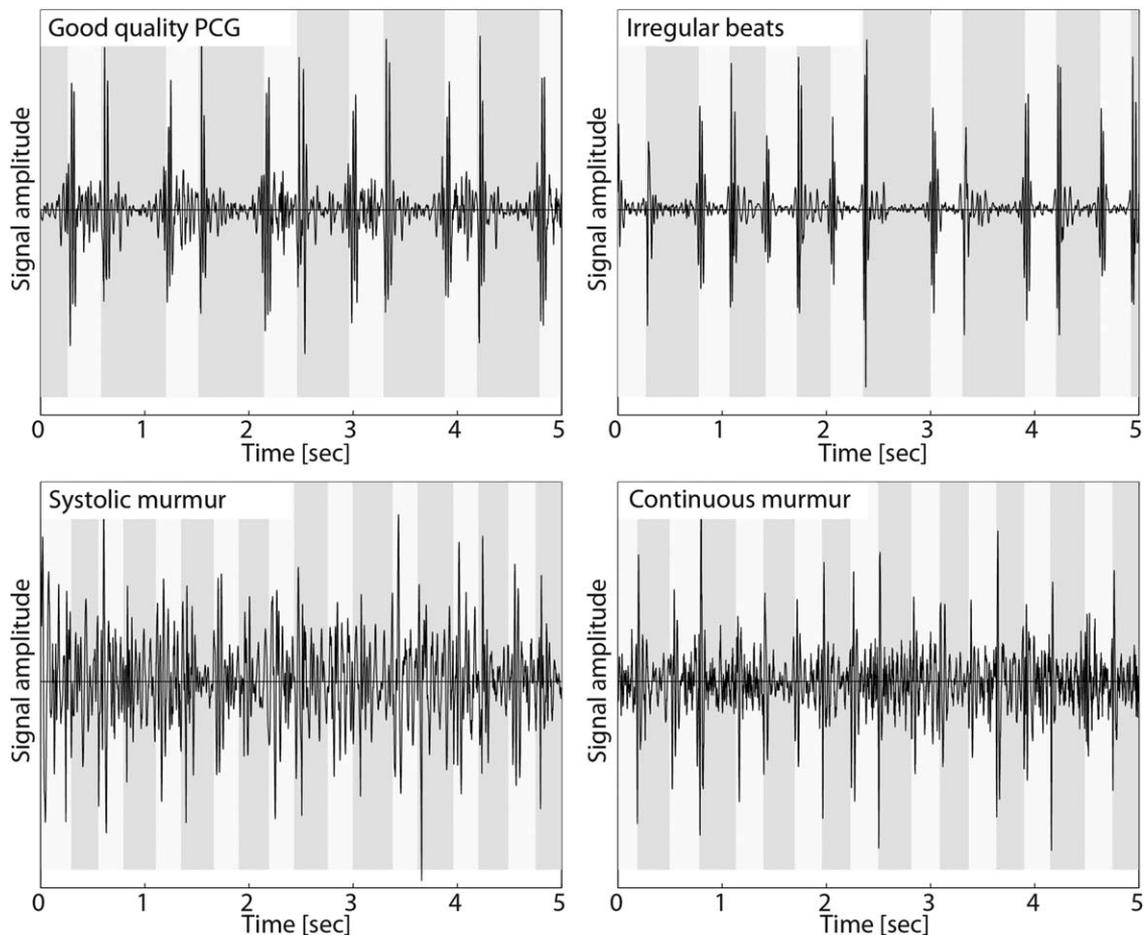
Figure A1. Four examples of recorded PCGs, illustrating the natural variability in signal form in both time and amplitude domain. The shaded light and dark gray areas behind the signal curves correspond to the systolic and diastolic phases of the PCGs, as automatically determined by the algorithm.

Table A1. Sensitivities and Specificities (Including Standard Deviations for 200 Repetitions) of the k-fold CV and the Leave-one-out* Method to Distinguish Pathologic from Nonpathologic Murmurs. The CV Results Converge With Increasing k values (i.e., Number of Recordings Used) With those of the Leave-one-out Method (k = 97), Proving that the Algorithm Yields Stable Outcomes

k value	Average Sensitivity	Average Specificity
97*	94.9%	94.8%
20	94.5% (±2.0%)	94.3% (±1.7%)
10	94.2% (±2.6%)	93.9% (±1.8%)
5	92.8% (±2.9%)	93.1% (±1.9%)
3	90.5% (±4.2%)	92.0% (±1.9%)
2	87.7% (±4.6%)	90.6% (±2.0%)

the recording being rejected for analysis. Similarly, if the useable part of the PCG was too short for a meaningful analysis, the PCG was not further analyzed. For signals with sufficient signal quality the heart rate was automatically determined, followed by a segmentation stage during which systole and diastole was identified. This was followed by a classification stage during which the final diagnosis was generated. Further details of the algorithm are protected under proprietary regulations.

Validation Analysis

PCG Recordings

We acquired PCGs with breathing noises (N = 106) from 106 patients (Dataset 1). Nine PCGs were excluded from further analysis by the algorithm due to poor quality. Figure A1 illustrates the variability in form and quality among PCG recordings. Note the difference between the four signals in both time and amplitude. The vertical light and dark gray areas in the signal background indicate the systolic and diastolic parts of the PCGs, respectively, as automatically determined by the algorithm.

Algorithm Validation

The algorithm was further developed using the PCGs from Dataset 1 and validated using k-fold cross-validation (CV). CV is well suited to detect underfitting and overfitting, that is, assessing the robustness of the algorithm. Underfitting occurs when too few training samples are presented to the classifier. Overfitting happens when the classifier is too specialized to the presented training data. In both cases, the classifier is insufficiently generalized and leads to poor predictions on the

Table A2. Algorithm vs. Physician as the Gold Standard in the Diagnosis of PCGs Acquired from Free Breathing Patients and which Were Used in the Development of the Algorithm, Using the Cross-validation Leave-one-out Method (N = 97). Accuracy Calculated by Number of Correctly Diagnosed PCGs Divided by Total Number of PCGs

		Physician		
		Class I: Pathologic murmur	Class III: No & innocent murmur	
Algorithm	Class I: Pathologic murmur	True positive 37	False positive 3	**Pos. predictive value 0.93**
	Class III: No or innocent murmur	False negative 2	True negative 55	**Neg. predictive value 0.96**
		Sensitivity 0.95	**Specificity 0.95**	**Accuracy 0.95**

Table A3. Algorithm vs. Physician as the Gold Standard in the Diagnosis of PCGs Acquired from Free Breathing Patients and which Were Used in the Development of the Algorithm (Excluding PCGs with No Murmurs), Using the Cross-validation Leave-one-out Method (N = 66). Accuracy Calculated by Number of Correctly Diagnosed PCGs Divided by Total Number of PCGs

		Physician		
		Pathologic murmur	Innocent murmur	
Algorithm	Pathologic murmur	True positive 37	False positive 1	**Pos. predictive value 0.97**
	Innocent murmur	False negative 2	True negative 26	**Neg. predictive value 0.93**
		Sensitivity 0.95	**Specificity 0.96**	**Accuracy 0.95**

validation data set. We used CV to determine the stability and performance of the algorithm.[53] By means of k-fold CV, Dataset 1 of the recorded PCGs was randomly divided into equally sized groups. For example, if the size of the dataset were 100 and k = 5, then each group would contain 20 randomly chosen PCGs. The classification stage was trained to k-1 of the available groups, and then validated on the one group not included in the training. This yielded an outcome for the one unseen group based only on the data of the other k-1 groups. This process was repeated k times, each time using a different validation group chosen from the k available groups, until all possible choices for the validation group were exhausted. The k outcomes were then averaged, yielding sensitivity, and specificity for such a run.

The outcomes depended on two factors. First, on the specific datasets comprising the k groups. To eliminate the effect of random sampling, we repeat each run 200 times, each time randomly assigning different datasets to k groups. Second, the outcome depends on the group size; for instance larger groups, that is, smaller k values, lead to fewer samples in the training set and more samples in the validation set (e.g., k = 2 means 50% of the samples are in the validation set). We performed runs for k = 2,3,5,10, and 20. The leave-one-out method was also used, where k was set to the total number of PCGs in the dataset, leaving only one sample for validation.

Resulting sensitivities and specificities including standard deviations (in parentheses) of the k-fold CV for different values of k plus the leave-one-out method are shown Table A1. The average sensitivity and specificity for k = 2 (strongest case, 50% of the data is treated as unseen) was $87.7 \pm 4.6\%$ and $90.6 \pm 2.0\%$, respectively. For increasing k values, both sensitivity and specificity consistently increased as well.

The leave-one-out method yielded an average sensitivity and specificity of 94.9% and 94.8%, respectively when tested on 97 PCGs used in the development of the algorithm and which were acquired from free breathing patients (Table A2). Testing was also performed on a set of PCGs that excluded ones in which no murmurs were identified by the physician (Table A3).

The convergence of the results of the k-fold CV for increasing k values with the results of the leave-one-out method proves that the algorithm is stable, utilizes meaningful input parameters and is neither overfitted nor underfitted.