

REVIEW ARTICLE

CLINICAL SCREENING OF CONGENITAL HEART DISEASE IN
NEONATES: A LITERATURE REVIEW ON FIVE STUDIES

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ABSTRACT

Background : Diagnosing Congenital Heart Disease (CHD), particularly critical CHD in newborns, could be difficult but crucial, since the field of congenital heart surgery has shifted from initial palliation followed by final correction at a later age to stressing early repair even in the youngest individuals. Although echocardiography remains the gold standard for diagnosing CHD, simple clinical examination may be helpful in screening neonates who require further investigation and treatment. In this study, we searched and reviewed the literature on clinical screening for CHD using a simple, affordable tool that is readily available in primary health care facilities, to prove that early simple clinical examination would help physician to screen for asymptomatic CHD.

Methods : We searched articles on google scholars that discuss clinical screening of CHD in neonates. Inclusion criteria is articles published within five years and exclusion

criteria is articles published older than five years.

Results : We found five articles eligible and pick consecutively. We found that pulse oximetry sensitivity and specificity ranged from 21.54%-77.3% and 82.65%-99.9%, respectively. Cardiac auscultation with murmur of grade ≥ 2 as count as positive, having high range of sensitivity and specificity, with sensitivity ranged from 17.3%-89.58% and specificity ranged from 47.36%-99.69%. When pulse oximetry and cardiac auscultation combined, three studies found that the sensitivity and specificity increased dramatically, 89.9%-95.5%, 94.7%-99.37%, respectively.

Conclusion: Both cardiac auscultation and pulse oximetry was an easy, feasible method with readily available basic tools at all hospital with acceptable sensitivity and specificity to screening CHD before suspected neonates undergo echocardiography, therefore making CHD diagnosed more effective and efficient.

Keywords: CHD, diagnose, neonates, pulse oximetry, cardiac auscultation

INTRODUCTION

Congenital heart disease (CHD) is a disease in the form of anatomical structural defect of the heart or large vessels around the heart that occurs during fetal development, leading to physiological disorder and malfunctional, causing various symptoms and signs. CHD varies many, but broadly and widely used classification were cyanotic and acyanotic (blue and not blue)¹⁻³, where cyanotic CHD is also called critical CHD. "Right heart obstructive lesions, left heart obstructive lesions, and mixed lesions are the three forms of critical CHD lesions."³ There are other less popular perspectives classification (from point of view of a congenital heart surgeon): "disorders whose best option is total correction, disorders requiring palliative care (only), and disorders that can be treated either palliatively or total correction."⁴

Considering it's a disorder of heart formation process during pregnancy, CHD is very likely to occur in fetus with genetic and chromosomal abnormalities (e.g., trisomy 21,

13, 18, turner syndrome, etc)^{3,5}, although definitive etiology is still unknown.³ "CHD also occurs in 40%-50% of children with down syndrome and is common in other chromosomal disorders."⁵ The most frequent type of birth defect is congenital heart disease (CHD), which is the major cause of death in infants with congenital malformations.³

The incidence worldwide about 8 out of every 1000 baby births^{1,2}, but another literature mentions 9 out of 1000 live births, making it's incidence around 8-9 out of every 1000 live birth.³ Meanwhile, birth rate in Indonesia: November 2020-Feb 2021 there are around 501,319 births⁶, which statistically counted that should be additional 4511 additional cases in less than a year.

Diagnosing CHD is quite challenging, especially in the early days after birth. The majority of children diagnosed with CHD have a chief complaint that isn't related to the heart, such as a reduced amount of formula per feed, a history of longer time between breastfeeds, poor weight gain, slow growth compared to their age or failure to thrive, rapid breathing, and fast and/or irregular breathing.^{3,5} Baby might

looked blue if suffer from cyanotic lesion which indicate big right to left shunt and might need early proper treatment, intervention, or even surgery.³ Meanwhile, if defect is small enough, CHD may not be diagnosed until the patient is fully adult and found by accident. Echocardiography is the gold standard for diagnosing CHD, but performing echocardiography on neonates is quite challenging, and not all physicians would be ready to perform echocardiography on neonates, for its tiny form and unable to obey the instruction.

Congenital cardiac surgery is an ever-changing and dynamic discipline. In the field of congenital cardiac surgery, there has been a paradigm change. The traditional strategy of initial palliation followed by definitive correction later in life, which had dominated most surgeons' minds, began to give way to one emphasizing early repair possible, even in the youngest patients.⁴

Therefore, we conducted a review on the studies and journals that discuss and focus on clinical screening for asymptomatic neonates with CHD, including examination with simple, affordable instrument that is readily available in primary health care facilities instruments: pulse oximetry. The aim of this study is to prove that whether early simple clinical examination, mainly cardiac auscultation and pulse oximetry would be useful for physician to screen asymptomatic CHD. Clinical screening is the easiest and most feasible, non-invasive method to screen CHD before suspected neonates undergo echocardiography, therefore high-quality clinical screening would be useful to patients and physicians. Physical examination such cardiac auscultation is also taken into account, even though it is very operator dependent and finding may subjectively vary from one clinician and others.

METHODS

This is a literature review study. We searched articles on google scholars that discuss clinical screening CHD on neonates. The clinical screening would be focused on cardiac auscultation and pulse oximetry. Articles older than five years would be excluded, and article published within five years are picked consecutively. Keywords as "cardiac auscultation and neonates with CHD", and "pulse oximetry neonates CHD" are used to search article. The search conducted between 23 February 2022 22:00 (Indonesian Western Time zone/Greenwich Mean Time +7) to 27 February 2022 17:17. Studies found are then summarized and presented in a narrative review.

RESULTS

As our criteria, we found five articles eligible (study published within 5 years). All five studies found came from China. As for five studies found, three studies emphasize clinical screening such as pulse oximetry, cardiac

auscultation, and combined to diagnose CHD, one comparing cardiac auscultation with murmur degree to diagnosing CHD.⁷⁻¹⁰ Another one literature comparing cardiac auscultation, pulse oximetry, tachypnea, extracardiac malformation and combined.¹¹ All studies established echocardiography as the gold standard for diagnosing CHD.⁷⁻¹¹

"From July 1, 2012, to December 31, 2014, Xiao-Jing et al conducted a multicenter study at 15 hospitals in Shanghai, China, reporting that out of 167190 newborns without CHD symptoms, 1326 babies were identified with CHD (0.79 percent incidence), with 203 neonates having major CHD (44 critical and 159 serious). Of the 167190 infants examined by pulse oximeter and cardiac auscultation, 1170 were positive at screening, of which 42 were classified as critical CHD and 145 serious. Then, Xiao-Jing et al re-screened CHD within 6 weeks of follow-up from 165143 infants who were declared normal by cardiac auscultation and oximeter examination before, and 156 of them were found positive for CHD, which 2 of them categorized as critical and 14 cases serious CHD. The oximeter was found to have a sensitivity of 95.5% (95% confidence interval 84.9-98.7%) for critical CHD and 92.1% (95% confidence interval 87.7%-95.1%) for major CHD when used in conjunction with cardiac auscultation. The false positive rate for detecting critical CHD was reported to be 1.2%, and 1.1% for detecting serious CHD. The Wilson method was used to calculate the 95% confidence interval of sensitivity and specificity for the statistic. To examine differences in sensitivity and specificity, the McNemar test was utilized. The trend of FPRs was tested using a logistic regression model throughout seven time intervals during which screening took place. The difference in FPRs between time intervals was determined using a χ^2 decomposition analysis. Only 90 of 203 (44.3%) instances of major CHD were found during the pulse oximeter evaluation, while 34 of 44 (77.3%) cases of critical CHD were found. 33 of 44 (75%) cases of critical CHD and 137 of 203 (67.48%) cases of significant CHD were discovered via cardiac auscultation alone. Within the positive screening criteria, the oximeter examination is considered positive if: 1. Pulse oximetry screening considered abnormal if saturation <90% is found on the right hand or in both feet, and 2. Infants who have initial saturation of 90-95% will be re-measured after 4 hours, and screening results were considered abnormal if saturation was <95%. Neonates should be kept calm during measurement to avoid detection errors. As for the auscultatory of the heart, any murmur that is grade II or beyond is considered abnormal."⁷ This study did not mention gestational age. This study is also more focused on screening for major and critical CHD than screening for non-critical or non-major CHD. "From this study, it was found that the first highest incidence of CHD was PDA (377 cases), followed by VSD (320 cases), and ASD (153 cases)."⁷

“In Study conducted by Qu-ming Zhao, Conway Niu, Fang Liu, Lin Wu, Xiao-jing Ma, and Guo-ying Huang on 6750 of 6785 asymptomatic neonates (screening rate 99.48%) in three hospitals (Songjiang Maternity Hospital, Minhang Maternity Hospital, and Songjiang District Central Hospital) in China, found that total of 180 neonates were diagnosed CHD (incident rate 26.7%), of which 48 (0.71%) were classified as major CHD and 10 cases (0.14%) cyanotic CHD.”⁸ Authors focused mainly on cardiac auscultation (by general pediatrician) in detection CHD by general pediatricians. “The study compare between murmur grade ≥ 1 , grade ≥ 2 , and grade ≥ 3 for CHD screening. Before taking data, five pediatricians simultaneously underwent simple cardiac auscultation simulation training at Children's Hospital of Fudan University (CHFUFU). The sensitivity of a grade 2 murmur used as a reference general standard for major CHD was found to be 89.58%, with the false positive rate being significantly lower related time of auscultation, with 84.4% of false positives requiring follow-up for non-major CHD cardiac issues, while the specificity was 97.3% and the odd ratio was 309.8. Auscultation after 27 hours of life reduced the false positive rate of significant CHD from 2.7% to 0.9%, according to the authors. At the time of auscultation, the median age was 43 hours (2-97 hours). Most common type of CHD was ventricular septal defect (113 cases/62.77%), atrial septal defect (40 cases/22.22%), and patent ductus arteriosus (11/6.11%).”⁸

“Song et al screened 3327 neonates with pulse oximetry alone, cardiac auscultation alone, and both together in a study done at Wenzhou Medical University Hospital from July 2019 to January 2020, with all positive screening results being verified by echocardiography. They reported a total of 139 cases of verified CHD (confirmed by echocardiography), resulting in a CHD incidence of 4.2 percent. The sensitivity, specificity, and diagnostic odds ratio of using cardiac auscultation with a pulse oximeter to identify CHD were 89.9%, 94.7%, and 169.0, respectively. To compare differences between two groups, this study utilized the Student's t-test or the χ^2 test, with a P value of 0.05 considered statistically significant. Song et al established echocardiography as confirmatory diagnostic for these newborns. In this study, newborns were examined 6-72 hours after birth, with positive screening infants having echocardiography within 1 week. In their study, they compared the accuracy of cardiac auscultation, oximetry, and the combination of cardiac auscultation with oximetry for the diagnosis of CHD. Pulse oximeter examination was performed immediately after auscultation of the heart was performed. The positive screening criteria in this study are exactly the same as those conducted by Xiao-Jing et al: An oximeter examination was considered positive if: 1. The measurement was found to be abnormal after $< 90\%$ saturation was found on the right hand or on both feet, and 2. The infant had initial saturation. 90-95%, will be re-measured after 4 hours. Screening results were declared

abnormal when the detected saturation was $< 95\%$. To reduce detection errors, neonates should be kept quiet throughout measurements. In terms of heart auscultatory measurements, five points were checked (pulmonic area, aortic lobe area, erbs point, tricuspid area, and mitral area), and heart murmurs of grade II or higher were classified as abnormal. Echocardiography will be used to check all aberrant outcomes. As a result, 24 of 139 (17.3%) CHD cases were detected solely by cardiac auscultation, and 90 of 139 (64.7%) CHD cases were detected solely by oximeter, but the number increased dramatically, with 125 of 139 (89.9%) CHD cases being diagnostically echocardiography confirmed with a combination of oximeter and cardiac auscultation (both $P < 0.01$). In this study, Jiajia et al attached data of the list on type CHD screened, the most common CHD was patent ductus arteriosus (86 out of 139), 42 of which were atrial septal defects, 6 ventricular septal defects, 2 atrioventricular septal defects, 1 tetralogy of fallot, 1 pulmonary atresia, 1 ventricular septal defect combined with double outlet of the right ventricle.”⁹ In this study, Authors included only asymptomatic patients, and patients diagnosed with prenatal CHD were excluded. This study did not mention gestational age (preterm, term, postterm). “One of the study's limitations was that 2082 babies were lost due to errors in the clinical recording system, decreasing the CHD screening rate to just 61.5 percent, which is lower than the study conducted by Xiao-Jing et al in Shanghai (94.0-99.8%).”⁹

“Between January 2016 and December 2018, Yu-Lin Zhang and Hai-Tao Bai found 65 cases of CHD with a total incidence of 7.82% in a study conducted on 8305 of 8425 live neonates in Jinjiang City, China (120 of them were transferred to the neonatal intensive care unit or another hospital within 24 hours of birth, making the study's screening rate 98.5%). From 8305 neonates screened, there were 22 cases positive for pulse oximeter examination alone (of which six cases were confirmed by echocardiography), 83 cases positive for cardiac auscultation alone (47 cases confirmed by echocardiography), and eight cases positive for combined cardiac auscultation and oximeter examination (of which all eight cases were confirmed by echocardiography). During the phone follow-up, four more cases were discovered. Screening by oximeter and cardiac auscultation combined had sensitivity, specificity, and positive and negative predictive values of 93.85%, 99.37 percent, 53.98 percent, and 99.95 percent, respectively. The intergroup comparison of counting data was done statistically using the Chi-square test and presented as a percentage (%), with a P-value of 0.05 regarded statistically significant. Author established echocardiography as confirmatory CHD diagnostic for these neonates. Negatively screened newborns who reported symptoms such as cyanosis, shortness of breath, and feeding difficulties would be followed up by phone at six weeks for symptoms of CHD, such as cyanosis, ecphysepsis, and feeding difficulties. Any

neonates that developed symptoms would then undergo echocardiography to confirmed CHD diagnosis. Positive screening indicators for pulse oximetry were: the percutaneous oxygen saturation of the right hand and either foot was between 90% and 94 %, or the difference in this index between the right hand and either foot was >3%, and the result remained unchanged in a recheck four hours later under the same conditions, or the percutaneous blood oxygen saturation of the right hand or either foot was less than 90%. A stethoscope placed in the heart valve auscultation area, and auscultation performed in the mitral valve area, the pulmonary valve area, the aortic valve area, the tricuspid valve area, and the first to fifth intercostal space on the left edge of the sternum are standards point for cardiac auscultation. The strength of cardiac murmurs was assessed using the Levine classification system, with cardiac murmurs referring mostly to systolic murmurs. Those with a grade 2 or higher heart murmur auscultation were considered positive. Ventricular septal defect, atrial septal defect, and patent ductus arteriosus (including other various heart abnormalities) were the most prevalent CHDs discovered by the author, accounting for 41.5%, 18.4%, and 12.3%, respectively. Two of the four false negatives showed an atrial septal defect (>5mm), whereas the other two had a patent ductus arteriosus (which was not closed at three months after birth). CHD exclusion criteria as follows: Children with patent ductus arteriosus were re-examined by echocardiography three months after birth, and if the arterial duct could be closed, they were not included in the statistics, as were patients with a septal defect of less than 5 mm, a patent foramen ovale, or mild to moderate tricuspid valve regurgitation. Authors mentioned as many as 582 from 8305 neonates are premature (7%). The accuracy of cardiac auscultation should be increased with training, according to the authors of the study. After that, echocardiography should be performed for children suspected of having CHD at a later stage, based on follow-up data and feedback from parents. Furthermore, missing diagnoses are unavoidable in large sample sizes, so enhancing health education and post-discharge follow-up is the only practicable method to reduce diagnostic errors.”¹⁰

“From January 2019 to January 2020, Kai Chen Jiao Wang Huihui Zhou and Xiang Huang conducted a study on 4500 neonates (with a 100% screening rate) at Ningbo Yinzhou No. 2 Hospital in Zhejiang, China. They discovered 65 children with CHD (CHD rate 1.4%). Heart murmurs, SpO₂ abnormalities, tachypnea, and extracardiac deformity are all used in this study to screen for neonatal CHD. When murmur, tachypnea, abnormal SpO₂, and extracardiac malformation were used to diagnose CHD independently, the sensitivity ranged from 30.68% (extracardiac malformation group) to 51.26% (abnormal SpO₂ group), with specificity ranging from 47.36% (murmur group) to 82.65% (abnormal SpO₂ group) and Youden's Index ranging from 0.13 (Extracardiac malformation group) to 0.36

(abnormal SpO₂ group). Murmur, tachypnea, abnormal SpO₂, and extracardiac malformation were found to have 91.23 percent sensitivity, 95.26 percent specificity, and 0.91 YI when used combined to diagnosis CHD. The counting data were statistically expressed as a ratio or percentage, and the chi-square test was used to analyze them. The diagnostic value was assessed using the area under the receiver operating characteristic (ROC) curve (AUC), with a level of P<0.05 regarded statistically significant. Authors established color echocardiography confirmatory CHD diagnostic for each neonates, which done within 3-7 days after birth. Neonates were separated into four groups in this study based on the presence of heart murmurs, tachypnea, transdermal SPO₂ of 95%, and extracardiac abnormality alone or in combination (≥3). Patients with a murmur, tachypnea, and abnormal SpO₂ were placed in group A, those with a murmur, tachypnea, and extracardiac malformation were placed in group B, those with murmurs, SpO₂, and extracardiac malformation were placed in group C, those with SpO₂, tachypnea, and extracardiac malformation were placed in group D, and those with all four were placed in group E. A heart murmur was considered present in neonates with a grade II murmur at cardiac auscultation. Tachypnea was considered present in neonates with a breathing rate of more than 60 times per minute, deep breathing, and an irregular rhythm. A value of less than 95% on a transcutaneous SpO₂ measurement at the right hand or any foot was considered abnormal. Within 3-7 days of delivery, all newborns will have a color echocardiogram to check for extracardiac anomalies such as Central nervous system malformations, urinary system malformations, digestive system malformations, craniofacial abnormalities, and visceral inversion, fetal edema, limb abnormality, respiratory system malformation, and abdominal wall abnormality. The following were the inclusion criteria in this study: born at the authors' obstetric department, no death before discharge, birth weight greater than 1000 g or gestational age greater than 28 weeks, and age ranging from 0.5 to 12 months. Exclusion criteria included having a CHD diagnosed prenatally, having a guardian who was unwilling to have a neonate undergo color doppler echocardiography, and needing oxygen treatment.”¹¹ Authors did not mention the time between birth and screening. “Ventricular septal defect (18 cases/27.7%), atrial septal defect with diameter >5mm (12 cases/18.5%), and patent ductus arteriosus (8 cases/12.3%) were the most prevalent CHDs observed. Authors also did 3 months follow up to those echocardiography screened positive for CHD before, to assess whether previously lesion could naturally self-healed or not. They discovered that out of 65 positive cases and 18 patients with ventricular septal defect, 4 cases with perimembranous ventricular septal defects with a defect diameter of less than 5 mm, self-healed after 3 months, with a self-healing rate of 22.2 %. In three of the twelve cases with atrial septal defect, the shunt bundle was not detected again,

indicating that the septal defect closed spontaneously, with a self-healing rate of 25.0%. Eight patients with patent ductus arteriosus were found, three of them were self-healing, with a cure rate of 37.5%, while the other types self-healing rate

was 22.2%. Preterm to term neonates ratio was 1.94: 1 (2970 to 1530, respectively), with average gestational age at birth of 39.21±1.23 weeks and average birth weight of 3236±324g, according to the authors.”¹¹

Table 1. Studies, number of subject, indicators, and result.

No	Author	n	Indicator	Sensitivity (%)	Specitivity (%)	Youden Index	Diagnostic Odd Ratio	
1	Xiao-Jing et al	167190	Critical CHD	Pulse Oximetry	77.3	99.8	N/A*	N/A*
				Cardiac Auscultation	75.0	99.0	N/A*	N/A*
				Combined	95.5	98.8	N/A*	N/A*
			Major CHD	Pulse Oximetry	44.3	99.9	N/A*	N/A*
				Cardiac Auscultation	83.7	99.0	N/A*	N/A*
			Combined	92.1	98.9	N/A*	N/A*	
2	Qu-ming Zhao et al	6750	Murmur Grade ≥ 1	89.58	94.00	N/A*	134.8	
			Murmur Grade ≥ 2	89.58	97.3	N/A*	309.8	
			Murmur Grade ≥ 3	83.33	99.69	N/A*	1591	
3	Jiajia Song et al	3327	Pulse Oximetry	64.7	95.0	N/A*	35.0	
			Cardiac Auscultation	17.3	99.7	N/A*	65.9	
			Combined	89.9	94.7	N/A*	169.0	
4	Yu-Lin Zhang and Hai-Tao Bai	8305	Pulse oximetry	21.54	99.8	0.21	N/A*	
			Cardiac Auscultation	84.62	99.56	0.84	N/A*	
			Combined	93.85	99.37	0.93	N/A*	
5	Kai Chen Jiao et al	4500	Murmur Group	40.32	47.36	0.21	N/A*	
			Tachypnea group	31.25	78.98	0.15	N/A*	
			Abnormal SpO2 Group	51.26	82.65	0.36	N/A*	
			Extracardiac Malformation Group	30.68	54.23	0.13	N/A*	
			Group A	71.6	89.65	0.57	N/A*	
			Group B	55.6	91.23	0.71	N/A*	
			Group C	62.39	89.65	0.75	N/A*	
Group D	68.65	94.68	0.65	N/A*				
			Group E	91.23	95.26	0.91	N/A*	

*N/A = Not Available, not mentioned by the authors.

DISCUSSION

Clinical screening studied in this review is the most easy, feasible method with readily available basic tools with acceptable sensitivity and specificity to screening CHD before suspected neonates undergo echocardiography, therefore making CHD diagnosed effective and efficient. This finding is important as there are shifting paradigm in treating CHD surgically, which newer paradigm emphasizes intervention as early as possible, palliatively or total correction, making early CHD diagnosing important.

From the study, we found out that pulse oximetry sensitivity and specificity ranging from 21.54%-77.3% and 82.65%-99.9%, respectively.^{7,9-11} Cardiac auscultation (with standard murmur of grade ≥2 count as suspected CHD) having high range of sensitivity and specificity, with sensitivity ranging from 17.3%-89.58% and specificity ranging from 47.36%-99.69%.⁷⁻¹¹ When pulse oximetry and cardiac auscultation combined, three studies found that the sensitivity and specificity increased dramatically, 89.9%-

95.5%, 94.7%-99.37%, respectively.^{7,9,10} In study conducted by Kai Chen Jiao et al, neonates divide into four groups, which explained before.¹¹ We highlighted that in the group A, group C, and group E, there were cardiac auscultation and pulse oximetry indicator included with others, having sensitivity and specificity ranging from 62.39%-91.23% and 89.65%-95.26%, respectively.¹¹ In study conducted by Qu-ming Zhao et al found that cardiac auscultation alone with varying degree of murmur having high sensitivity and specificity, with grade ≥1 murmur having 89.58% sensitivity and 94.00% specificity, grade ≥2 murmur having 89.58% sensitivity and 97.3% specificity, and grade ≥3 murmur having 83.33% sensitivity and 99.69%.⁸ This outstanding result might come from cardiac auscultation simulation training before obtain data, therefore making standardized murmur and increasing clinician sensitivity to detect murmur, even in low grade murmur.⁸

As found in those data, we know that pulse oximetry and cardiac auscultation are sufficient to screen CHD, therefore both methods could and should be used to screen CHD in neonates throughout Indonesia. Neonates screened

as positive should undergo echocardiography and appropriate treatment, conservatively or surgically, as early as possible, to reduce further complication, morbidity, and mortality.

CONCLUSION

Congenital heart disease could be screened in neonates as early as days age using standard clinical assessment and simple widely available tools with acceptable sensitivity and specificity. This study found that pulse oximetry and cardiac auscultation by general paediatrician could detect CHD in neonates, though cardiac auscultation simulation training might increase the sensitivity clinician to the murmur. In those neonates screened positive CHD should undergo echocardiography as soon as possible to detect structural defect that may affect baby's growth and development if left untreated, conservatively or surgically. Given the results of this review, we suggest that: 1. The next study should propose a scoring system to detect CHD in neonates from an early age, in which the scoring involves mainly pulse oximetry and cardiac auscultation. 2. Improving the auditory sensitivity of medical students throughout Indonesia to murmurs and their grading, and routinely cardiac auscultation simulation training (which could be attended virtually) for all doctors who have graduated and work in the neonatal department, especially those in remote area. 3. To invent electronic stethoscope that is integrated with software and algorithm that can detect murmurs and their degree, as well as a built in loud speaker so that the sound captured by the stethoscope can be amplified and heard around the room, so that the murmur can be heard more clearly by other clinicians who may be present in the room.

CONFLICT OF INTEREST

None declared.

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