Risk of Obstructive Sleep Apnea in Patients with Repaired or Palliated Congenital Heart Disease

Master of Public Health Integrating Experience Project

Utilizing Professional Publication Framework

by

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List of Abbreviations

AASM	American Academy of Sleep Medicine
AHI	Apnea-hypopnea index
BMI	Body mass index
BP	Blood pressure
CHD	Congenital heart disease
HLHS	Hypoplastic left heart syndrome
LV	Left ventricle
LVEF	Left ventricle ejection fraction
NMMC	Nork – Marash Medical Center
NYHA	New York Heart Association
OSA	Obstructive sleep apnea
PM	Portable monitor
PSG	Polysomnography
PSQ	Pediatric sleep questionnaire
SD	Standard deviation
SVC	Superior vena cava
TA	Tricuspid atresia
TOF	Tetralogy of Fallot
TR	Tricuspid Regurgitation

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To the Reader:

I Dedicate this Work to my Teacher:

Talented Cardiovascular Surgeon, Professional, Adviser and Person

Dr Hrair (Hagop) Hovaguimian

I would not be here without meeting you on my way.

Abstract

Background: Single ventricle (SV) defects and Tetralogy of Fallot (TOF) represent common cyanotic congenital heart defects (CHD). Obstructive sleep apnea (OSA) is a chronic breathing disorder linked to worse cardiovascular outcomes.

Aim: The aim of this study was to estimate the risk of OSA in patients with repaired congenital heart defects - patients with SV palliation and patients with repaired TOF, and compare it with matched controls with structurally normal hearts.

Methods: The study utilized cross-sectional design with three comparison groups: patients with Fontan palliation, patients with TOF repair and patients with structurally normal heart, treated at a single tertiary center, Nork-Marash Medical Center in Armenia. Patients were surveyed using standardized questionnaires for screening of OSA risk (Pediatric Sleep Questionnaire (PSQ) in children and STOP-Bang and Berlin questionnaires in adults). Medical charts were accessed to extract clinically relevant information. Conditional multivariable logistic regression analyses were performed for adjusted analyses.

Results: The study sample included 40 patients with Fontan palliation, 40 age and gender – matched patients with TOF repair and 80 age and gender-matched control patients with structurally normal heart. The mean age of participants was 16.9±6.1 years in Fontan, 16.7±5.9 in TOF and 17.2±6.2 in normal heart group (p=0.910). The risk of OSA based on PSQ was high in all three groups (31.8%, 39.1% and 34.1% in Fontan, Tetralogy and normal heart groups,

respectively, p=0.854). There were no differences in OSA risk measured by STOP-Bang and Berlin questionnaires. The prevalence of the high risk of OSA was 27.5% in the Fontan group and 22.5% in normal heart group (p=0.546). The New York Heart Association functional class was a significant predictor of OSA risk (odds ratio for functional class II/III versus 0/1 = 5.7 (95% CI 1.3 – 24.8), p = 0.020).

Conclusion: The risk of OSA was high in all study groups compared to reported prevalence in other countries, including pediatric patients. There was no difference in risk prevalence of OSA between patients with Fontan palliation and structurally normal heart. Future research is needed utilizing the reference standard for diagnostic testing of OSA using full-night, sleep laboratory polysomnography, to establish the true prevalence of OSA in patients with repaired congenital heart disease and in normal general population in Armenia.

1. Introduction

1.1 Burden of congenital heart defects

Congenital heart defects (CHD) include structural abnormalities of the heart or intrathoracic great vessels presenting at birth that have actual or potential functional significance(1). CHD is the most common congenital disease accounting for about one-third of all major congenital anomalies(2). The incidence of CHD ranged from 6.9 to 9.3 per 1000 live births in 2011 in the world with the lowest rate in North America and highest in Asia(3). The prevalence of CHD worldwide is estimated to be 5.78 per 1,000 in general population with the highest birth prevalence reported in Asia (3;4). There are estimated 2,800 adults per 1 million of population living with CHD worldwide(5). Given the current treatment successes and low surgical mortality rates the prevalence of CHD is projected to continue growing over time reaching to as high as 1 in 150 in the USA after a decade(4).

1.2 Types of CHD

CHDs can be grouped as left to right shunt lesions, obstructive and regurgitant valvular lesions, and cyanotic lesions(6). The period prevalence of different CHDs from 1978 to 2005 was estimated to be 68 per 10,000 live births in the US(7). The term “Univentricular heart” encompasses a summary of malformations where one of the pumping chambers of heart (left or right ventricle) is missing or hypoplastic and is not able to carry out the circulation (8). These malformations include: tricuspid atresia, hypoplastic right heart syndrome, hypoplastic left heart syndrome, double inlet ventricle, extreme forms of unbalanced atrioventricular septal defects, single ventricle with undefined morphology(4). The most prevalent type is hypoplastic left heart

syndrome (HLHS), reported in 2.5 per 10,000 live births during the same period in the USA followed by tricuspid atresia (TA) with a period prevalence of 0.6 per 10,000 live births. The crude median incidence of HLHS is reported as 2.3 per 10 000 live births (9;10). TA occurs less than once in every 10,000 live births and was present as 2.9% of CHD autopsy series(11). The prognosis of patients with unrepaired univentricular hearts is very poor(1;9). A series of 83 unrepaired patients showed that 70% of patients with single left ventricle died before 16 years of age(12). The prognosis is even poorer for those with single right ventricle whose survival was reported to be 50% at 4 years after diagnosis(12). Given the low survival rates for this diagnosis various surgical palliative options have been advanced. A surgical palliative intervention, otherwise known as Fontan procedure, is the current standard of care for patients with functionally univentricular heart disease who meet a set of clinical eligibility criteria(13).

Tetralogy of Fallot (TOF) represents the most common cyanotic congenital heart defect, affecting nearly 0.8 – 2.6 / 1,000 live births(14). It has four main components – pulmonary stenosis, large ventricular septal defect, right ventricular hypertrophy and an overriding of aorta(6). Most patients with TOF are symptomatic at birth with symptom severity dependent on the degree of cyanosis and magnitude of infundibular pulmonary stenosis(6). The prognosis of unrepaired TOF patients is also poor: Bertranou et al in 1978 reported that only 30% of TOF patients survive to 10 years of age(15).

1.3 **Fontan palliation**

Patients with univentricular heart malformations can present with two hemodynamic situations: heart defects with or without anatomic obstruction to pulmonary blood flow(5). The decision to

go to Fontan pathway is undertaken, when the anatomy and hemodynamics are favorable, namely, that the pulmonary arterial pressure is low (mean < 15mmHg), pulmonary vascular resistance (PVR) is low, ventricular function is preserved, the heart rhythm is normal and there is no significant atrioventricular valve regurgitation.

Fontan palliation represents a group of operations aimed at separating pulmonary and systemic circulations in the univentricular heart defects. It aims to direct the blood flow from systemic veins directly to the pulmonary artery, without passing to the ventricle. Described by Fontan and Baudet in 1971, it was initially applied to treat tricuspid atresia type of complex CHD but later was expanded to treat other defects(16). The Fontan procedure can be considered for patients with malformed hearts, who have single pumping chamber due to absence of the second chamber and/or cardiac valve(13). It is now considered as the final pathway for many anatomical and functional single ventricle physiologies (e.g. tricuspid atresia, pulmonary atresia with intact ventricular septum, hypoplastic left heart syndrome, double inlet ventricle etc.).

Prior to Fontan procedure the patient may need another palliative surgery to achieve moderation in pulmonary blood flow via either restricting the flow or putting aorta-pulmonary shunt to increase it(13). This component is very important, because pulmonary hypertension is an absolute contraindication for Fontan surgery (i.e., without a pumping chamber it is impossible to direct the blood into pulmonary circuit), and the presence of aorta-pulmonary shunts stimulates the growth of pulmonary vasculature(8).

The modern Fontan procedure connects the superior vena cava (SVC) and inferior vena cava (IVC) directly to the pulmonary artery (PA). In the current era the creation of total cavopulmonary Fontan circulation is achieved in two stages(13). It allows the patient's body to adapt to new hemodynamics easily and reduces surgical mortality and morbidity(13). The first stage is called Hemi-Fontan surgery, and is performed when the patient is 4 to 12 months old, and includes a construction of an end-to-site anastomosis between SVC and PA(13). The second stage is performed when the patient is 1 to 6 years old and completes the total cavopulmonary Fontan circuit by connecting the IVC to PA, using a conduit constructed from a foreign material or the lateral wall of the right atrium(13). Thus, the surgeries achieve a circulation which directs the blood flow from systemic veins to PA without using the mechanical contractile power of right ventricle.

Several types of Fontan operation have been used to connect systemic veins to pulmonary artery via bypassing the right heart, including classic atriopulmonary Fontan procedure, Bjork Modification, and modern total cavopulmonary connection(17;18). The latter has two types – extracardiac conduit and intracardiac lateral tunnel. These procedures direct blood more efficiently to the pulmonary arteries and are used more widely. A recent US study among 500 patients showed that following Fontan operation, actuarial freedom from death or transplantation at 20 years was 82.6% with no difference between lateral tunnel and extra-cardiac conduit types of Fontan(17;19). Major long-term complications after Fontan procedure include pulmonary hypertension, failure of the single ventricle, thromboembolic complications, arrhythmias, sudden death and complications linked to the lymphatic system, such as protein losing enteropathy or plastic bronchitis(18;20-22).

1.4 Repair of TOF

Patients with TOF undergo a radical repair which includes patch closure of the VSD and widening of right ventricular outflow tract and pulmonary valvotomy with or without cutting the annulus(6). The radical repair of TOF is being performed about 60 years and results are excellent in terms of survival(14). Patient survival is 90% at 30 years after surgery with most patients remaining asymptomatic during this period(14). The long-term morbidity of repair of TOF is mainly related to complications such as right ventricular functional deterioration, pulmonary insufficiency, ventricular arrhythmias and sudden death (23-25).

1.5. Obstructive sleep apnea

Obstructive sleep apnea (OSA) is a chronic, sleep-related breathing disorder characterized by symptoms of snoring, excessive daytime sleepiness and fatigue, nocturia, memory problems, and headaches(26). The prevalence of OSA in general adult population was reported to be 3-7% in adult men and 2-5% in adult women(27). In pediatric population the estimated prevalence of OSA according to different investigations varies between 1-5.7% (28;29).

Based on the 2009 American Academy of Sleep Medicine (AASM) guideline, OSA is diagnosed based on a comprehensive clinical evaluation by a qualified sleep specialist. The evaluation includes a detailed medical history, physical examination, and a sleep test(26). The sleep test can be done either in a sleep laboratory setting using polysomnography (PSG) or at home using portable sleep testing monitors (PM). Currently, PSG is the ‘gold standard’ test for OSA, and is used to record and calculate the frequency of obstructive events known as apnea-hypopnea index

(AHI). AHI is the average total number of apnea and hypopnea events per hour of recorded sleep. The AASM defines OSA as ‘‘occurrence of daytime sleepiness, loud snoring, witnessed breathing interruptions or awakenings due to gasping or choking in the presence of at least five obstructive respiratory events (apneas, hypopneas or respiratory effort related arousals) per hour of sleep’’ or 15 or more respiratory related events per hour of sleep in the absence of sleep related symptoms(26).

In the literature OSA severity has been defined as mild, moderate and severe by using AHI cut-offs of ≥5, 15, 30 events/hour respectively(30;31). These cut-offs however cannot be used to assess severity of OSA in children because of scarcity of data and population heterogeneity. Various levels of AHI cutoffs were used in past pediatric studies to diagnose OSA including AHI ≥1, >3, ≥5, or ≥10 events/hour(28).

The presence of OSA carries a significant morbidity and mortality burden. OSA is associated with an increased risk of developing heart failure, coronary heart disease, atrial fibrillation, pulmonary hypertension, stroke and motor vehicle accidents (32-36). There is an established mortality risk with untreated sleep disordered breathing, and the risk increases with the severity of OSA(37).

1.6 Screening for OSA

Several questionnaires have been developed in the past to screen and identify adults at high risk of OSA. A systematic review by Chung et al in 2009 compared the vast majority of available validated instruments for screening of OSA, and suggested the use of STOP or STOP-Bang

questionnaires for prediction of OSA risk in surgical patients because of their high methodological quality and easiness of use(38). Another review article by El-Sayed et al in 2012 compared the four most established questionnaires to assess their diagnostic accuracy including Berlin, STOP, STOP-Bang and Epworth Sleepiness Scale (ESS) tools(39). The STOP-Bang, STOP and Berlin questionnaires had the highest sensitivity to predict OSA (98%, 92% and 95% respectively), whereas the specificities were low (26%, 25% and 25%, respectively) for all, meaning a high probability of false positive results(39).

A number of questionnaires have been used to screen for sleep disordered breathing (SDB) in children. The review article by Lumeng et all (2008) identified the questionnaires used for pediatric population two of which have been validated against PSG(28). The first was the questionnaire by Bruilette et al which calculates a score to diagnose OSA; it had a reported high sensitivity and specificity but could not accurately differentiate between primary snoring and OSA; and its sensitivity and specificity in detection of OSA were significantly lower in subsequent studies(40;41). The Pediatric Sleep Questionnaire (PSQ) has been developed by Chervin et al and has two subscales: one for estimation of restless leg syndrome and the SRBD (sleep related breathing disorders) subscale for prediction of OSA risk(42). The SRBD uses 22 questions to calculate a summary score ranging from 0 to 1.0 with a cut-off point of 0.33 to define OSA. It has been reported that a positive response to at least one-third of 22 questions (which represents the cutoff = 0.33) was associated with 85% sensitivity and 87% specificity in detection of sleep related breathing disorders(42). Hence, while the sensitivity of this test is lower compared to that of the tests for adults reported above, it has higher specificity, i.e. more non-OSA patients are identified correctly as non-OSA. If the cutoff number 0.33 is lowered in

practice, it will increase the sensitivity of the test and vice versa – the number can be increased to ensure high specificity.

1.7. OSA and CHD

There is an established link between sleep disorders and occurrence of heart failure or pulmonary hypertension in patients (43;44). However, literature is scarce on OSA risk in patients with CHD. Perhaps, most cases of OSA go underdiagnosed in such patients because most of cardiac symptoms (heart failure, pulmonary hypertension, arrhythmias, etc) are being naturally linked to the underlying heart condition. On the other hand, the pressure in superior vena cava (SVC) is higher than normal in patients with Fontan repair, which can theoretically contribute to development of OSA in these patients(45).

To our knowledge, no study estimated the prevalence of OSA in patients with Fontan circulation. A 2009 case series report by Watson et al describes the management of four adult patients with Fontan palliation and obstructive sleep apnea(46;47). Theoretically, these patients might be predisposed to sleep apnea, due to venous stasis, which is usually present in their superior vena cava system. Sleep apnea could itself contribute to development of heart failure and dysrhythmias and worsen the quality of life of these patients. Another 2006 case report by Watson et al presented a woman with Fontan history and severe OSA, raising the question of appropriateness of CPAP therapy in these patients(48). Lastly, Sawada et al in 2008 described reversal of pulmonary hypertension in a Fontan candidate who underwent tonsillectomy and thus treatment of OSA(49).

Overall, there are only few studies that look at the prevalence of OSA in CHD patients. A study by Ykeda et al (2009) examined sleep patterns in 14 patients with CHD and discovered that 11 out of 14 infants with CHD had AHI > 1 compared to only one control group patient(50). The authors concluded that there is a need to further investigate the prevalence of OSA in population of patients with CHD. A study by Herold et al (2006) surveyed families of 37 pediatric patients with TOF using the Pediatric Sleep Questionnaire(51). They reported that the prevalence of obstructive sleep disordered breathing (SDB) was 38%, which was much higher than the described 1-5.7% prevalence in the general pediatric population (28;29).

1.8 Situation in Armenia

The Nork-Marash Medical Center (NMMC) is a tertiary cardiac hospital in Yerevan Armenia established in 1993. This is the only center in Armenia currently treating CHD patients. Over the period of 23 years since its establishment there were 60 patients in the center who underwent Fontan palliation. One of three types of Fontan operation were done in all of them – intracardiac lateral tunnel, extracardiac conduit Fontan and Kawashima operations, all of which represent the latest, most efficient modifications of Fontan surgery. Over the same period of time, 459 patients were diagnosed with Tetralogy of Fallot from which 420 underwent radical repair of the defect.

Evaluation of sleep disorders is an important area for both pediatric and adult patients with corrected CHD (52;53). No prior research has been done in Armenia on this topic. Research from other countries is also limited. Increasingly, investigation of sleep disorders is gaining more importance for patients with cardiac diseases(54). Therefore, the estimation of the risk of OSA in

different subgroups of patients with CHD is important as the early recognition and treatment of this condition may improve outcomes in these patients.

1.9 Study aim and objectives

The project aimed to estimate the risk of OSA in two subgroups of patients with repaired CHD - patients with Fontan palliation and patients with TOF repair, and compare this risk with age and gender matched controls with structurally normal hearts.

The study primary objective was to compare the risk of OSA between patients with CHD who underwent Fontan repair and the control group with structurally normal hearts, after matching for age and gender.

The study secondary objectives were:

1. Estimate the risk of OSA in patients who underwent Fontan palliation;
2. Estimate the risk of OSA in patients with TOF who underwent radical repair;
3. Compare the risk of OSA between patients with Fontan palliation and TOF repair;
4. Compare the risk of OSA between CHD patients (Fontan palliation and TOF repair) and patients with structurally normal hearts.

2. Methods

2.1 Study design

The study utilized a cross-sectional design with three comparison groups: i) patients with Fontan palliation, ii) TOF repair, and iii) those with structurally normal hearts. Justification for this

design was that the focus of the study was on the prevalence of risk of OSA, and not incidence or any long-term outcomes of surgeries or OSA. This study design was also appealing because of its relatively low resource requirements in terms of time and personnel.

2.2 Study setting and population

The study was conducted among patients in Nork-Marash Medical Center, Yerevan, Armenia. The study target population included patients with CHD in Armenia who underwent Fontan operation or radical repair of TOF. The study population consisted of the following three groups:

1. All patients who underwent Fontan operation and are currently under follow-up at Nork-Marash Medical Center of Armenia;
2. Age- and gender-matched controls (with Fontan patients) from the population of patients who underwent radical repair of TOF and are currently under follow-up at Nork-Marash Medical Center of Armenia;
3. Age- and gender-matched controls (with Fontan patients) with structurally normal heart patients referred to NMMC for screening of heart disease.

Study participants were both children/adolescents and young adults in the three groups identified above who met the following eligibility criteria:

- For Fontan repair group, we included patients with functionally univentricular heart circulation and history of Fontan repair any time between 1993 and 2016. Patients who dropped from the follow-up and patients who do not speak Armenian or English were excluded. We established the list of excluded patients via phone calls from the database list.

- For TOF group, we selected age- and gender-matched controls with diagnosis of TOF and a history of radical repair performed between 1993 and 2016. If there was more than one patient with repaired TOF who matched by age and gender with Fontan patients, we selected the patient with the nearest age at final surgery to the matching Fontan patient. For age, we considered the age of the Fontan patient at the time of study data collection. We excluded patients who were at the extreme spectrum of TOF diagnosis such as those with TOF-pulmonary atresia, TOF-atriovetricular canal defects, and TOF-absent pulmonic valve defects.
- We selected controls with structurally normal hearts matched by age and gender with Fontan patients who were referred to NMMC for evaluation of heart disease. The selection of controls was done consecutively, starting from January 2015 using NMMC's pediatric and adult clinical databases. Exclusion criteria for this group of patients was the presence of any major comorbid condition that increases the risk of OSA such as a history of chronic respiratory disease (e.g., asthma, chronic obstructive pulmonary disease, lung cancer, cystic fibrosis, occupational lung diseases), neuromuscular disease (e.g., multiple sclerosis, muscular dystrophy), congenital genetic syndromes(e.g. Down's; Turner's; Di-George's, William's; Velocardiofacial syndrome, Noonan's; etc.), congenital anomalies of upper airways, transient ischemic attack or stroke or an existing diagnosis of other sleep disorders.

2.3 Data collection strategies

2.3.1 Data collection instruments

Data collection consisted of two parts: a telephone survey of patients to screen for the risk of OSA and a clinical chart abstraction to extract clinically relevant information. During the telephone survey study participants who were less than 18 years old at the time of the call were screened for OSA using the Pediatric Sleep Questionnaire (Appendices 1A and 1B)(42) **Error! Bookmark not defined.**. We used a special subscale of the PSQ otherwise known as a Sleep Disordered Breathing Subscale (SRBD) which was introduced to one of the parents who acted as proxies for their children. PSQ has two subscales – SRDB is for screening for OSA and the other subscale is for diagnosing restless leg syndrome. PSQ uses 22 questions and a cut-off point of 0.33 to define OSA, which means if the patient provides positive answers to at least eight questions on PSQ, he/she is at high risk of having OSA.

For adult patients or those who were ≥18 years old at the time of the phone call, we used the STOP-Bang questionnaire to assess the risk of OSA (Appendices 2A and 2B). The STOP-Bang questionnaire uses 8 questions and defines low, medium, and high risk of OSA accordingly if the patient answers positively to 0-2, 3-4 and 5-8 questions(55). For our study, to define a patient at risk of OSA by combining the intermediate and high risk patients into the same group, meaning that the patient screened positive if he/she answered positively to more than two questions. In addition, we used the Berlin sleep questionnaire among study adult patients (Appendices 3A and 3B). It includes 10 questions related to three categories describing the risk of OSA(56). The patient was classified as having high risk of OSA, if he/she scored positively in at least 2 categories.

In addition to sleep questionnaires, we gathered information on social-demographic characteristics including current age, gender, weight and height of the patient, as well as questions concerning the clinical history and functional status of the patient including the history of any major comorbid conditions that were listed in the study exclusion criteria. The functional class of heart failure was assessed by using the New York Heart Association (NYHA) classification. We also asked participants to evaluate their academic performance compared to their peers using a 5-point grading scale from 'much worse' to 'much better'(57).

The study instruments were translated and pretested prior to their use among five pediatric and five adult patients who were not part of the study sample. The pretest was done using concurrent verbal probing cognitive interview method. As the STOP-Bang questionnaire contains a question on neck circumference, during the pretest the interviewer measured the neck circumference of the patient and afterwards asked the patient to measure it again to compare the results. Since the results were satisfactory, during the actual phone surveys, the interviewer described the exact technique of the measurement to the interviewee and then asked the patient/proxy/another family member to measure it twice to obtain an accurate estimate.

We developed a medical chart abstraction tool that collected information on social-demographic, anatomical, surgical, clinical, echocardiographic, and electrocardiographic characteristics of the patients (Appendix 3). The chart abstraction tool was pretested using charts of two adult and two pediatric patients who were not part of the study.

2.3.2 Data collection procedures

The list of phone numbers of study participants was obtained from the NMMC pediatric and adult clinical databases. All patients with diagnosis of CHD are currently in follow up care at NMMC pediatric clinic. Here we also obtained the list of control patients whose age was under 18 at the time of their visit to the clinic.

First, we identified Fontan patients from the pediatric clinical database and performed phone interviews after taking the informed consent either from the parent or the patient themselves. After surveying Fontan patients, we had the exact list of the respondents. Then the list of repaired TOF patients was obtained from the pediatric database and age- and gender-matched controls were selected and surveyed. The list of pediatric control patients was obtained from pediatric database and the list of remaining adult controls, whose age is more than 18 years, was obtained from NMMC's adult clinical database.

As part of the consent process for the phone surveys, we asked the participants if they would agree that we conduct abstraction of data from their medical charts. For those who agreed, we proceeded to paper chart abstraction after completion of the survey.

2.4 Sample size considerations

There have been 58 patients with functionally univentricular hearts who underwent Fontan repair in NMMC from 1993 to 2016. To our knowledge two of them passed away during the postoperative follow-up period. The remaining 56 patients comprised the exposed group. We contacted these patients to assess for eligibility and consent for the study. The comparison group

of TOF operated patients consisted of the same number of age- and gender-matched controls randomly selected using random digit generator from 420 patients with repaired TOF currently at follow-up in NMMC. The third comparison group consisted of 80 age- and gender- matched controls with structurally normal hearts, with twice larger sample size than the Fontan repair group in order to increase the statistical power of the study. We know that the OSA prevalence in pediatric population is estimated to be 1-5.7%(28). The study by Herold et al looked at the prevalence of OSA in patients with repaired TOF and estimated the risk of OSA as high as 38%(51). We created a power estimation curve (see Figure 1) to show the relationship between sample size and power of the study for various values of difference in proportion. Note that according to literature the expected difference in proportions between OSA in Fontan patients as compared with controls is 0.34. Based on this curve, we predicted that with a sample of nearly 40 Fontan patients, 40 TOF patients and 80 controls we should be able to detect a difference in OSA risk of 0.26 with 90% power at a significance level of 0.05.

2.5 Study variables

The study dependent (outcome) variable was the prevalence of risk of OSA in three main comparison groups. The study's main independent variable was the history of Fontan or TOF surgery or having a structurally normal heart. We considered the age (<18 years old versus ≥18 years old), BMI and functional class of heart failure assessed by NYHA classification as potential intervening variables.

2.6 Ethical considerations

The study protocol was approved by the Institutional Review Board of the American University of Armenia. Separate oral consent forms were developed for patients 18 years or older and for parents of patients who were less than 18 years old at the time of surveys (Appendices 4A and 4B). The data were fully de-identified before proceeding to the analysis phase by removal of patient names from the database.

2.7 Statistical analysis

Data entry, recoding and cleaning were performed using SPSS 17.0 software. Analysis was done using the STATA 13.0 software. In order to summarize different characteristics of patients, descriptive statistics were used such as averages and standard deviations for continuous variables and counts, percentages for categorical variables. Significance level of 0.05 was used to identify statistically significant differences. We first performed tests for confounding to identify the possible confounders to control for in our subsequent regression analyses. Conditional multivariable logistic regression analyses were performed to find possible associations between study independent and dependent variables while controlling for possible confounding.

3. Results

3.1 Administrative results

Out of 56 patients who underwent Fontan correction at NMMC, we were able to interview 40: two patients passed away during the follow-up period, six patients did not meet study eligibility criteria (one of them had severe neuromuscular disorder and the other five were patients from foreign countries not speaking Armenian or English), and the other eight patients changed

contact numbers and/or left Armenia. We were able to contact the remaining 40 patients who all agreed to participate and completed the interview.

Overall, there were 420 patients with TOF who underwent radical correction of the defect in NMMC. Of these, 234 had a follow-up visit in the center after January 2014. From the list of 234 patients we extracted 40 age- and gender-matching controls for Fontan patients. In cases where we had more than one control patient, we selected one who had the nearest date of radical surgery with the Fontan patient. We were able to do interval matching for age with plus or minus one year. The gender matching was exact. All contacted TOF patients agreed to participate and completed the interview.

The lists of control subjects with structurally normal hearts were obtained from NMMC pediatric and adult clinical databases. We went back from April 2017 and consecutively selected matching patients. Selected pediatric patients visited the clinic between January-April 2017 and adult patients visited between January 2016 – April 2017.

3.2 Descriptive statistics

Patient characteristics by main diagnosis groups (i.e., Fontan repair, TOF or structurally normal heart) are presented in Table 1. The groups were not different in BMI distribution as well as in heart rate and systolic and diastolic blood pressure at last clinic visit. Significant differences were observed in self-reported academic performance ($p=0.001$). NYHA functional class of heart failure was different between the groups with patients in structurally normal heart group reporting better functional status ($p<0.001$). Number of participants reporting tonsillitis or

adenoiditis was lower in Fontan group compared to TOF and normal heart groups (20.0% vs 42.5% and 42.5%, respectively, p<0.001). The reported prevalence of snoring in pediatric subgroups of patients did not differ (45.5% vs 21.7% and 40.9%, p=0.225). Also there was no difference between the reported prevalence of apnea in these subgroups (9.1% vs 4.4% and 6.8%, p=449). The findings were similar in adult subpopulation of patients with no significant differences in reported prevalence of snoring and apnea.

3.3 Risk of OSA

Comparison of the risk of OSA between three groups was performed according to study primary and secondary objectives. Table 2 compares OSA risk between Fontan group and normal heart group. The mean scores obtained from PSQ, STOP-BANG and Berlin questionnaires were not different between the groups (P>0.05). The prevalence of the high risk of OSA when combining the results from PSQ and STOP-Bang questionnaires was 27.5% in the Fontan group and 22.5% in normal heart group (p=0.546).

Table 3 shows the estimation of OSA risk between patients with Fontan palliation and TOF repair. The combined proportion of high risk participants was not different significantly between Fontan and TOF groups 27.5% vs 22.5% (p=0.606). Table 4 compares the risk of OSA between participants with CHD (Fontan plus TOF) and normal hearts. The prevalence of high risk of OSA was 25.0% in the CHD group and 22.5% in normal heart group (p=0.710).

3.4 Testing for confounding

Table 5a shows the comparison of age, BMI and NYHA functional class of heart failure as possible confounders in participants with Fontan palliation and structurally normal hearts. Age was tested both as a continuous and dichotomous variable and NYHA class was dichotomized into 0/I and II/III classes. Patient's age and BMI did not differ between groups with Fontan repair and normal hearts. Participants in Fontan group were more likely to be in higher NYHA functional class of heart failure compared to normal heart group ($p<0.001$). Table 5b shows the comparison of age, BMI and NYHA functional class of heart failure in participants with high and low probability of OSA. Both continuous and categorical variables were associated with the probability of OSA. The lower age was associated with higher probability of having OSA. BMI was not significantly different between groups, while the NYHA functional class was significantly different between disease groups – the participants who were in higher functional class of heart failure were more likely to be classified as high risk of OSA ($p<0.001$).

3.5 Conditional multivariable logistic regression analysis

A conditional multivariable logistic regression analysis was used to test for association between the probability of OSA and the following variables: diagnosis of Fontan vs Normal heart, age categorical (≥18y vs <18y) and NYHA functional class of heart failure (II/III vs 0/I). The results are shown in Table 6. Categorical age was removed from the conditional logistic regression analysis due to issues of model convergence. The odds of having OSA was 0.7 (95% CI 0.2 – 2.4) in Fontan group versus Normal heart group, $p=0.591$. In participants who were in II/III functional class of heart failure the odds of having OSA were 5.7 times higher (95% CI 1.3 – 24.8) compared to those who were in 0/I functional class $p=0.020$. Next, conditional

multivariable logistic regression model was run to test for association between participants from Fontan and TOF groups according to our secondary objective. Statistically significant associations were not identified between the probability of OSA and having diagnosis Fontan vs TOF repair (p=0.155) and having higher functional class of heart failure vs low (p=0.841). Adjusted logistic regression analysis tested for the risk of OSA and diagnosis of CHD (Fontan plus TOF) vs normal heart according to another study secondary objective. The analysis did not reveal significant link between the diagnosis of CHD versus normal heart and probability of OSA (p=0.192). The odds of having OSA were higher for participants in II/III functional class of heart failure compared to those in 0/I class (OR – 5.3, 95% CI 2.3 – 28.9, p=0.001).

4. Discussion

We evaluated the prevalence of OSA risk in different subpopulations of patients with repaired CHD – patients with Fontan palliation and patients with radical repair of TOF, and compared it to risk prevalence of OSA in general population. The assessment of OSA risk was done by using validated questionnaires for adults and children. We found that the OSA risk was high in all studies groups, and was not significantly different between the groups.

The literature is very scarce on the risk of OSA in patients with repaired CHD. In the study by Herold et al which was a cross-sectional survey of 37 pediatric patients with repaired TOF, the mean age of participants with low risk of OSA was 10.5 years and mean age of participants with high risk of OSA was 9.4 years (there was no statistically significant difference detected), the age range was from 2 to 18 years(51). In our sample, the overall mean age was 17 years and the range was higher (3-31years). The mean age of the pediatric (≤18 years old) population in our

study was 13.1 years. The academic performance of TOF patients in our study was lower than in Fontan group and patients with normal hearts. The literature indicates that patients with repaired cyanotic CHD have lower academic performance scores, so the finding with TOF group is not surprising(58). The high academic performance of Fontan patients can be probably explained by subjectivity of scale (they should evaluate themselves compared to peers).

The prevalence of OSA risk in adult population of our sample (using STOP-Bang and Berlin questionnaires) was within the range of 2-7% that was reported in other studies in general population(27). The prevalence of OSA risk, however, was surprisingly high all in pediatric subpopulations, and not different between these three groups. The highest proportion was identified in children with TOF repair (39.1% identified high risk of OSA based on PSQ) followed by those with structurally normal heart (34.1%) and Fontan procedure (31.8%). All these proportions are significantly higher from the reported 1-5.7% prevalence of OSA in the pediatric population (28;29). While it is expected that the true prevalence can be different from the screened prevalence, nevertheless this number is much higher than what we expected to find. Based on a study by Chervin et al, the PSQ has high sensitivity and specificity, 85% and 87%, respectively(42).

In a meta-analysis presented by Chervin and Lumeng the highest prevalence of OSA detected from diagnostic testing was 13% from an Italian study, which interviewed the parents of preschool-aged children and conducted home sleep studies using a Type IV (Mesam IV system) portable sleep diagnostic monitor, which is different from the gold standard PSG(28;59). Most of

the studies agreed on OSA prevalence of 0.2% to 4% using some type of diagnostic testing, which was performed after risk screening with different questionnaires(28).

The prevalence of habitual snoring in pediatric population was also higher in our sample (21.7% to 45.5%), than the reported prevalence in the literature that varied from 3.2% to 14.8%(28). This finding is however very much dependent on the definition of frequency of snoring, e. g. those studies using the term "always" for the snoring frequency reported the lowest prevalence compared to those not using it. In our study we did not question for snoring "always" while screening the pediatric population. We also revealed a high prevalence of reported apnea in children during sleep in all three subgroups (4.4% - 9.1%). Apnea was reported in 0.2% - 4.0% of children in other studies, and in 18.5% in the Italian study (28;59).

The detected risk prevalence of OSA in Fontan group was very significant – 27.5% which was even higher in the pediatric subgroup of patients with Fontan palliation (31%). There are no studies in literature addressing the risk of OSA in this specific subgroup of patients, so we cannot compare our results with other studies. However, it is still very high compared to the highest reported prevalence of OSA in general normal population (7%)(27). Further evaluation using the gold standard PSG is warranted to estimate the true prevalence of OSA in this population.

The risk of OSA was also high in the group of patients with repaired TOF. The combined risk prevalence was 22% in this group, but this was mostly driven by the high risk prevalence in the pediatric subgroup (39%). This finding is similar to what Herold and colleagues reported in 2006(51). The screened prevalence of OSA in Herold's study was 38%, while the age range was

similar to those in pediatric TOF subgroup of our study. The true prevalence of OSA still needs to be established in this population, using the current reference standard PSG.

The risk of OSA in structurally normal heart group in our study was also very high compared to literature. We detected 22.5 % combined risk prevalence in this group. The risk of OSA in pediatric subgroup was again higher than in adults (34.1% vs 8.3%). While the risk prevalence in adults approximated the reported highest prevalence in adult men (7%), the screened prevalence in children was much higher than reported 1-5.3% in the general pediatric population (27-29). Even after we apply the reported 87% sensitivity of the PSQ, the prevalence still remains quite high compared to available literature(42).

Our findings suggest that there is no difference in the prevalence of risk of OSA between patients with repaired univentricular heart, TOF and structurally normal heart. Nevertheless, we think that the differences could not be found due to surprisingly high risk prevalence of OSA in patients with structurally normal hearts compared with the prevalence reported in the literature. The reason for this high proportion of patients identified as high risk by the questionnaires could be the unusually high proportion of patients with tonsillitis in the subgroup of patients with structurally normal hearts (42.5% vs 20% in Fontan group). One of the possible explanations for this could be that until recently, the risk of rheumatic fever was high in the Armenian population, and pediatricians are prone to refer patients with tonsillitis for screening for heart disease. Tonsillitis itself is a cause of obstructive sleep apnea that is resolved after their removal. Thus we believe that patients with structurally normal heart referred to NMMC are different from the

general population with structurally normal heart, and therefore do not represent the true OSA risk for the latter group.

The only variable which was predictive of OSA risk was the functional class of heart failure measured by NYHA. This is similar to what was found by Herold et al that reported that increased exercise intolerance was positively correlated with higher screened probability of OSA in TOF patients(51). This finding is also very consistent with the available literature that established strong correlation between risk and severity of OSA and severity of heart failure measured by functional class(43;44;54;60).

A major limitation could be the selection bias introduced by high proportion of patients with adenotonsillitis in participants with structurally normal heart. Adenotonsillitis itself is associated with severity of OSA, so the presence of it could artificially increase the proportion of patients screened as high risk of OSA and change the results. The high proportion of adenotonsillitis in study pediatric population could also be a consequence of misclassification bias by parents. The season of interviewing was early spring and the parents could mistakenly classify some viral or bacterial illnesses (e.g. common flu) as adenotonsillitis. The study participants could also be subject to recall bias, as the questionnaire asked items about different habits of participants. Especially the pediatric questionnaires could introduce recall bias, because the parents of children were asked about their different habits during last two months. But, given the relatively short period of time and behavioral characteristics of Armenian parents (very focused on their children) the possibility of this bias is low. The major strength of our study was the sewing of validated questionnaires to establish the risk of OSA.

The detected high risk of OSA probability in patients with repaired CHD is very important for making suggestions of future implementations in practice. If the real OSA prevalence is so high, this could seriously compromise the outcomes of this special population. Pulmonary hypertension and heart failure caused by the presence of OSA could easily deteriorate the hemodynamic and functional status of these vulnerable patients, contributing to significant mortality and morbidity (34;43;44;54).

There was no difference in risk prevalence of OSA between patients with Fontan palliation, TOF repair and structurally normal heart. However, the risk of OSA was high in all these groups compared to reported prevalence in general normal population in other countries. Therefore, future research is needed utilizing the reference standard for diagnostic testing of OSA using full-night, sleep laboratory polysomnography, to establish the real prevalence of OSA in both populations of patients with repaired congenital heart disease and structurally normal heart in Armenia. If the diagnostic accuracy of the instruments will be approved, we will also recommend their application for screening of risk of OSA in patients with repaired or palliated congenital heart disease.

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6. Tables and Figures

Table1. Descriptive characteristics of study participants

Patient characteristics*	**Fontan group n = 40**	**TOF group n = 40**	**Normal heart group n = 80**	**P value**
Demographic characteristics				
Age (years), mean (SD)	16.9 (6.1)	16.7 (5.9)	17.2 (6.2)	0.910
Age<18 years, n (%)	22 (55.0)	23 (57.0)	44 (55.0)	0.990
Sex, n (%)				
Male	26(65)	26(65)	51(64)	0.987
Female	14(35)	14(35)	29(36)	
Weight (kg), mean(SD)	53.4 (18.5)	49.2(18.4)	54.7(17.8)	0.296
Height (cm), mean(SD)	158.4(19.3)	155.8(17.9)	158.3(18.0)	0.770
BMI (kg/m^2), mean (SD)	20.5 (4.0)	20.9 (4.7)	21.2 (3.8)	0.714
Rating of academic performance compared to peers, n (%)				
Much worse	0(0.0)	0(0.0)	1(1.3)	0.001
Worse	5(12.5)	8(20.0)	2 (2.5)	
Normal	21(52.5)	21(52.5)	41(52.5)	
Better	5(12.5)	10(25.0)	31(38.8)	
Much better	9(22.5)	1(2.5)	5(6.25)	
Clinical characteristics at last visit to clinic				
Heart Rate (beat/min), mean (SD)	83.0 (13.3)	79.5(13.2)	81.4(14.8)	0.545
Oxygen saturation (%), mean (SD)	90.1 (4.8)	95.9 (2.1)	96.4 (1.9)	< 0.001

Patient characteristics*	**Fontan group n = 40**	**TOF group n = 40**	**Normal heart group n = 80**	**P value**
Systolic BP (mmHg), mean (SD)	118.6 (15.8)	117.9 (13.2)	115.8 (15.8)	0.476
Diastolic BP (mmHg), mean (SD)	61.7 (8.8)	60.9 (7.6)	64.6 (10.0)	0.077
Duration of follow-up from first clinic visit (years), mean (SD)	16.5 (5.3)	15.5 (4.7)	na	<0.001
Follow-up after final surgery (y), mean (SD)	8.4 (5.5)	14.6 (4.8)	na	<0.001
NYHA functional class, n (%)				
0/I	6(15.0)	10 (25.0)	53 (66.2)	<0.001
II	29 (72.5)	27 (67.5)	26 (32.5)	
III	5 (12.5)	3 (7.5)	1 (1.2)	
Concomitant heart defects, n (%)	19(48.7)	1 (2.5)	none	<0.001
Other diseases / conditions, n (%)	8 (20.0)	3(7.5)	4 (5.0)	0.026
Palliative surgery (ies), n (%)	38 (97.4)	15.0 (41.7)	none	<0.001
Tonsillitis or adenoiditis, n (%)	8 (20.0)	17 (42.5)	34 (42.5)	<0.001
Reported prevalence of snoring in children, n%	10 (45.5)	5 (21.7)	18 (40.9)	0.225
Reported prevalence of apnea in children, n %	2(9.1)	1(4.4)	3 (6.8)	0.449
Reported prevalence of snoring in adults, n (%)	6 (33.3)	6 (35.3)	5 (13.9)	0.106
Reported prevalence of apnea in	1 (5.6)	1(6.25)	1(5.8)	0.810

Patient characteristics*	**Fontan group n = 40**	**TOF group n = 40**	**Normal heart group n = 80**	**P value**
adults, n (%)				
History of airway surgery, n (%)	3 (7.5)	1 (2.5)	14 (17.5)	0.034
Prescribed medications, n (%)				
Aspirin	34 (85.0)	1 (2.6)	0 (0.0)	<0.001
Anticoagulant	5 (12.5)	0 (0.0)	0 (0.0)	0.019
B-blocker	10 (25.0)	3 (7.5)	0 (0.0)	0.030
ACEI/ARB	21 (52.5)	0 (0.0)	0 (0.0)	<0.001
Diuretic	7 (17.5)	0 (0.0)	0 (0.0)	0.005
Antiarrhythmic	5 (12.5)	0 (0.0)	0 (0.0)	0.019
Sildenafil	1 (2.6)	0 (0.0)	0 (0.0)	0.314

* P-values from ANOVA, T-test, Chi-square test or Fisher's Exact test.

ACEI = Angiotensin converting enzyme inhibitor; ARB = Angiotensin receptor blocker; BMI = body mass index; BP = blood pressure; na = not applicable; NYHA = New York Heart Association; SD=standard deviation; TOF = Tetralogy of Fallot

Table 2. Risk of OSA in participants with Fontan palliation and structurally normal heart

	Fontan group	**Normal heart group**	**P-value***
Pediatric Sleep Questionnaire (PSQ)			
	n = 22	n = 44	
Mean (SD) score	5.2(3.5)	5.8(4.1)	0.548
High risk (score > 33%), n (%)	7 (31.8)	15 (34.1)	0.854
Low risk, n (%)	15 (68.2)	29 (65.9)	
STOP-Bang Questionnaire			
	n = 18	n = 36	
Mean (SD) score	1.2(1.4)	0.7 (0.9)	0.077
Intermediate/high risk (≥3 (+) answers, n(%)	4 (22.2)	3(8.3)	0.205
Low risk, n(%)	14(77.8)	33(91.7)	
Berlin Questionnaire			
	n = 18	n = 36	
Mean (SD) score	0.9(0.9)	0.8 (1.1)	0.857
High risk (≥2 (+) categories), n(%)	1 (5.6)	2(5.6)	1.000
Low risk, n(%)	17(94.4)	34(94.4)	
Risk of OSA (using PSQ and STOP-Bang)			

	n = 40	n = 80	
High risk, n(%)	11 (27.5)	18 (22.5)	0.546
Low risk, n(%)	29 (72.5)	62 (77.5)	

* P-values from T-test, Chi-square test or Fisher's Exact test.

OSA = obstructive sleep apnea; PSQ = Pediatric sleep questionnaire; SD = standard deviation

Table 3. Risk of OSA in participants with Fontan palliation and TOF repair

	Fontan group	**TOF group**	**P-value***
Pediatric Sleep Questionnaire (PSQ)			
	n = 22	n = 23	
Mean (SD) score	5.2 (3.5)	5.8 (4.0)	0.586
High risk (score > 33%), n (%)	7 (31.8)	9 (39.1)	0.608
Low risk, n(%)	15 (68.2)	14 (60.9)	
STOP-Bang Questionnaire			
	n = 18	n = 17	
Mean (SD) score	1.2 (1.4)	0.6 (0.8)	0.146
Intermediate/high risk (≥3 (+) answers, n(%)	4 (22.2)	0(0)	0.104
Low risk, n(%)	14(77.8)	17(100.0)	
Berlin Questionnaire			
	n = 18	n = 17	
Mean (SD) score	0.9 (0.9)	0.6(0.6)	0.423
High risk (≥2 (+) categories), n (%)	1 (5.6)	0(0)	1.000
Low risk, n (%)	17(94.4)	17(100.0)	
Risk of OSA (using PSQ and STOP-Bang)			

	n = 40	n = 40	
High risk, n (%)	11 (27.5)	9 (22.5)	0.606
Low risk, n (%)	29 (72.5)	31 (77.5)	

* P-values from T-test, Chi-square test or Fisher's Exact test.

OSA = obstructive sleep apnea; PSQ = Pediatric sleep questionnaire; SD = standard deviation;

TOF = tetralogy of Fallot

Table 4.Risk of OSA in participants with CHD repair and structurally normal heart

	CHD group	Normal heart group	P-value*
Pediatric Sleep Questionnaire (PSQ)			
	n = 45	n = 44	
Mean (SD) score	5.5(3.7)	5.8(4.1)	0.721
High risk (score > 33%), n (%)	16 (35.6)	15 (34.1)	0.885
Low risk, n (%)	29(64.4)	29 (65.9)	
STOP-Bang Questionnaire			
	n = 35	n = 36	
Mean (SD) score	0.9(1.2)	0.7(0.9)	0.258
Intermediate/high risk (≥3 (+) answers, n (%)	4 (11.4)	3(8.3)	0.710
Low risk, n (%)	31(88.6)	33(91.7)	
Berlin Questionnaire			
	n = 35	n = 36	
Mean (SD) score	0.8(0.9)	0.8(1.1)	0.798
High risk (≥2 (+) categories), n(%)	1 (2.9)	2 (5.6)	0.319
Low risk, n (%)	34 (97.1)	34 (94.4)	
Risk of OSA (using PSQ and STOP-Bang)			
	n = 80	n = 80	

High risk, n (%)	20 (25.0)	18 (22.5)	0.710
Low risk, n (%)	60 (75.0)	62 (77.5)	

* P-values from T-test, Chi-square test or Fisher's Exact test.

**CHD = congenital heart disease; PSQ = Pediatric sleep questionnaire, SD = standard deviation*

Table 5a. Comparison of age, BMI and NYHA functional class in participants with Fontan palliation and structurally normal heart

Variable*	Fontan group n=40	Normal heart group n=80	P value
Age, mean (SD)	16.9 (6.1)	17.1(6.2)	0.818
Age, categorical, n (%)			
<18	22 (55.0)	44 (55.0)	1.000
≥18	18 (45.0)	36 (45.0)	
BMI, mean (SD)	20.5 (4.0)	21.2(3.8)	0.395
NYHA class, n (%)			
0/I class	6 (15)	53 (66.3)	<0.001
II + III classes	34 (85.0)	27 (33.7)	

*P-values from T-test, Chi-square test or Fisher's Exact test.

BMI = body mass index; NYHA = New York Heart Association; OSA = obstructive sleep apnea; SD = standard deviation

Table 5b. Comparison of age, BMI and NYHA functional class in participants with high and low risk of OSA

Variable*	OSA low risk N=122	OSA high risk N= 38	P value
Age, mean (SD)	17.6 (6.1)	14.9 (5.7)	0.017
Age, categorical, n (%)			
<18	58 (47.5)	31 (81.6)	<0.001
≥18	64 (52.5)	7 (18.4)	
BMI, mean (SD)	21.1 (3.7)	20.4 (5.1)	0.449
NYHA class, n (%)			
0/I class	63 (51.6)	6 (15.8)	<0.001
II/III class	59 (48.4)	32 (84.2)	

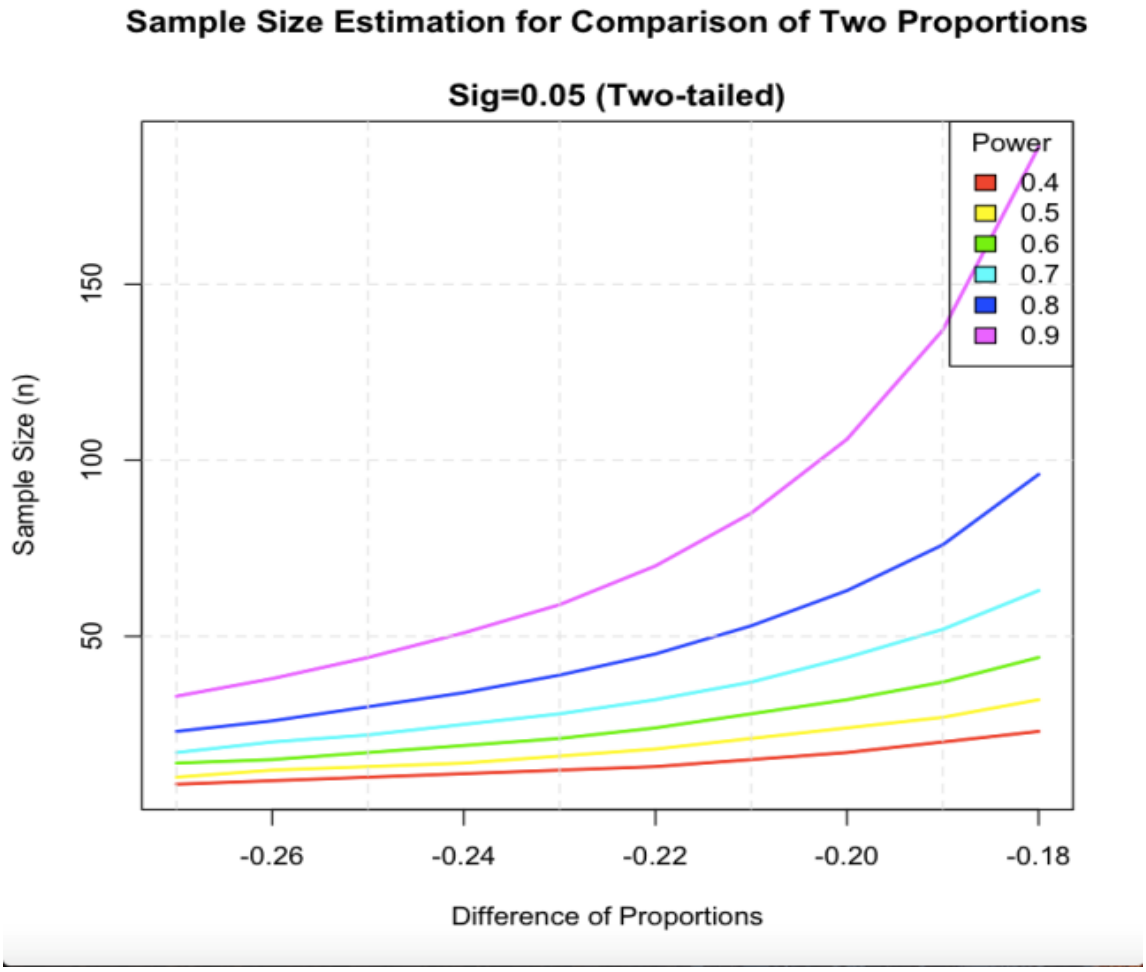
*P-values from T-test, Chi-square test or Fisher's Exact test.

BMI = body mass index; NYHA = New York Heart Association; OSA = obstructive sleep apnea; SD = standard deviation

Table 6. Multivariable logistic regression of the probability of OSA

Variable	Odds Ratio (CI 95%)	p-value
Participants with Fontan palliation and structural normal heart		
Diagnosis Fontan vs Normal Heart	0.7 (0.2 – 2.4)	0.591
NYHA (II/III vs 0/I)	5.7 (1.3 – 24.8)	0.020
Participants with Fontan palliation and TOF		
Diagnosis Fontan vs TOF	0.9 (0.3 – 2.9)	0.155
NYHA (II/III vs 0/I)	4.8 (0.6 – 42.3)	0.841
Participants with CHD and structural normal heart		
Diagnosis CHD vs Normal heart	2.0 (0.7 – 6.0)	0.192
NYHA (II/III vs 0/I)	5.3 (2.3– 28.9)	0.001

Figure 1. Sample size estimation for comparison of two proportions



7. Appendices

Appendix 1A. Questionnaire for pediatric patients (English version)

Questionnaire for pediatric patients

Child's ID _____

Date of Interview ___ / ___ / ___

A. Screening questions

1. Does the child have any of these conditions?

1. Chronic respiratory disease (e.g., asthma, chronic obstructive pulmonary disease, lung cancer, cystic fibrosis, occupational lung disease)……....Y_1 N_2
2. Neuromuscular disease (e.g., multiple sclerosis, muscular dystrophy)…Y_1 N_2
3. Congenital syndrome (e.g. Down's; Turner's; Di-George's, William's; Velocardiofacial syndrome, Noonan's; etc.).....**.**Y_1 N_2
4. Congenital anomaly of upper airways…….. Y_1 N_2
5. Existing sleep disorder…….. Y_1 N_2

If the answer to any of above mentioned questions is "Yes", thank the participant and finish the interview.

B. Social – demographic characteristics

2. Date of Birth (dd/mm/yyyy) __/__/__

3. Gender *(just mark)*

1. Male
2. Female

4. What is the current weight of the child (kg)? _____

5. What is the current height of the child (cm)? _____

6. What is the current age of the child (years)? _____

7. How do you rate your child's academic performance in comparison with his/her fellow children?

1. Much worse
2. Worse
3. Same
4. Better
5. Much better

C. Clinical history/cardiac symptoms

8. What was the child's weight at birth (kg)? _____

9. Does the child have tonsillitis/adenoiditis?..... …….Y_1 N_2

10. Did the child have tonsillectomy/adenoidectomy in the past?

1. Yes_1
2. No

11. Does the child have exercise intolerance?

1. Yes_1
2. No

12. Does your child:

1. Perform all physical activity without getting short of breath or tired, or having palpitations?
2. Get short of breath or tired, or have palpitations when performing more strenuous activities? For example, walking on steep inclines or walking up several flights of steps.

3. Get short of breath or tired, or have palpitations when performing day to day activities. For example, walking on the flat.
4. Feel breathless at rest, and is mostly housebound or unable to carry out any physical activity without getting short of breath or tired, or having palpitations?

D. SRBD subscale *(SRBD is the subscale of PSQ designed for screening of OSA)*

Please answer these questions regarding the behavior of your child during sleep and wakefulness. The questions apply to how your child acts in general during the past month, not necessarily during the past few days since these may not have been typical if your child has not been well.

13. **While sleeping, does your child**:

1. Snore more than half the time? ……..Y_1 N_2 DK_{88}
2. Always snore? …….. Y1 N2 DK88
3. Snore loudly? …….. Y1 N2 DK88
4. Have "heavy" or loud breathing? …….. Y1 N2 DK88
5. Have trouble breathing, or struggle to breathe? …… Y1 N2 DK88

14. Have you ever seen your child stop breathing during the night?

……. Y_1 N_2 DK_{88}

15. Does your child:

1. Tend to breathe through the mouth during the day?……Y_1 N_2 DK_{88}
2. Have a dry mouth on waking up in the morning? …….Y_1 N_2 DK_{88}
3. Occasionally wet the bed? ……..…. Y_1 N_2 DK_{88}

16. Does your child:

1. Wake up feeling unrefreshed in the morning? …… Y_1 N_2 DK_{88}
2. Have a problem with sleepiness during the day? …… Y_1 N_2 DK_{88}

17. Has a teacher or other supervisor commented that your child appears sleepy during the day? ……..… Y_1 N_2 DK_{88}

18. Is it hard to wake your child up in the morning? Y_1 N_2 DK_{88}

19. Does your child wake up with headaches in the morning? Y_1 N_2 DK_{88}

20. Did your child stop growing at a normal rate at any time since birth?

……..……..Y_1 N_2 DK_{88}

21. Is your child overweight? …… Y_1 N_2 DK_{88}

22. This child often:

1. Does not seem to listen when spoken to directly……. Y_1 N_2 DK_{88}
2. Has difficulty organizing tasks and activities. …….. Y_1 N_2 DK_{88}
3. Is easily distracted by extraneous stimuli…… Y_1 N_2 DK_{88}
4. Fidgets with hands or feet or squirms in seat. …… Y_1 N_2 DK_{88}
5. Is “on the go” or often acts as if “driven by a motor”……. Y_1 N_2 DK_{88}
6. Interrupts or intrudes on others (e.g., butts into conversations or games) Y_1 N_2 DK_{88}

Thank you!

Scoring the SRBD Scale

The 22 items of the SRBD Scale are each answered yes = 1, no = 0, or don't know = missing. The number of symptom-items endorsed positively ("yes") is divided by the number of items answered positively or negatively; the denominator therefore excludes items with missing responses and items answered as don't know. The result is a number, a proportion that ranges from 0.0 to 1.0. Scores > 0.33 are considered positive and suggestive of high risk for a pediatric sleep-related breathing disorder. This threshold is based on a validity study that suggested optimal sensitivity and specificity at the 0.33 cut-off, but this number could be lowered in practice if increased sensitivity is a priority, or raised if increased specificity is a priority.

Appendix 1B. Questionnaire for pediatric patients (Armenian version)

Մանկական հարցաշար

Երեխայի ID _____

Ամսաթիվ ___ / ___ / ___

A.Սկրինինգ հարցեր

1. Ունի՞ արդյոք ձեր երեխան հետևյալ կարգավիճակներից

որևիցէ մեկը

1. Քրոնիկ շնչառական հիվանդություն (օր.՝ աստմա, քրոնիկ բրոնխիտ, թոքի քաղցկեղ,մուկովիսցիդոզ, պրոֆեսիոնալ թոքային հիվանդություն). . . . . .

. . . .Y_1 N_2

2. Նյարդամկանային հիվանդություն (օր.՝ տարածուն սկլերոզ, մկանային դիստրոֆիա). . . . . .

. . . .Y_1 N_2

3. Բնածին սինդրոմ. (օր.՝ Դաունի, Թըրների, Դի-Ջեորջի, Ուիլյամսի, Նունանի, Վելոկարդիոֆացիալ համախտանիշ, և այլն.)…. Y_1 N_2

4. Վերին շնչուղիների բնածին անոմալիա. ..... Y_1 N_2

5. Ախտորոշված քնի խանգարում . ..... Y_1 N_2

Եթե վերոնշյալ հարցերից մեկի պատասխանը դրական է, շնորհակալություն ենք տանք մասնակցին և դադարեցրեք հարցազրույցը:

B. Սոցիալ-դեմոգրաֆիկ բնութագրեր

2. Ծննդյան ամսաթիվ (օօ/աա/տտտտ) __/__/__

3. Սեռը *(միայն նշել)*

1. Արական
2. Իգական

4. Որքա՞ն է երեխայի ներկայիս քաշը (կգ): _____

5. Որքա՞ն է երեխայի ներկայիս հասակը (սմ): _____

6. Որքա՞ն է երեխայի ներկայիս տարիքը (տարի): _____

7. Ինչպե՞ս կգնահատեք Ձեր երեխայի ակադեմիական կարողականությունը (սովորելու ունակությունները), համեմատած իր ընկերների հետ:

1. Շատ ավելի վատ
2. Վատ
3. Նույնը
4. Ավելի լավ

5. Շատ ավելի լավ

C. Կլինիկական անամնեզ/սրտայինախտանիշեր

8. Որքա՞ն է եղել երեխայի քաշը ծնվելիս (կգ)՝ _____

9. Ունի՞ արդյոք երեխան տոնզիլիտկամ

ադենոիդիտ..... .....Y1 N2

10. Երեխան երբևիցե վիրահատվե՞լ է տոնզիլիտի կամ

ադենոիդիտի կապակցությամբ՝

1. Այո
2. Ոչ

11.Հոգնու՞մ է արդյոք երեխան ֆիզ. ծանրաբեռնվածության ժամանակ՝

1. Այո 1
2. Ոչ 2

12. Ձեր երեխան՝

1. Կատարում է բոլոր ֆիզիկական ակտիվությունները առանց հևալու, հոգնելու կամ սրտխփոցների՝
2. Հնում է, հոգնում է կամ սրտխփոցներ է ունենում, երբ կատարում է միջինից բարձր ֆիզիկական ակտիվություններ, օրինակ՝ կտրուկ թեքությունկամ մի քանի հարկ աստիճաններով բարձրանալիս՝

3. Հնում է, հոգնում է կամ սրտխփոցներ է unենում, երբ կատարում է առօրյա ֆիզիկական ակտիվություններ, օրինակ՝ հարթ տարածքում քայլելիս:
4. Հնում է հանգստի ժամանակ, հիմնականում գտնվում է տանը և անկարող է կատարել որևէ ֆիզ. ակտիվություն առանց հևալու, հոգնելու կամ սրտխփոցների:

D. SRBD subscale

Խնդրում ենք պատասխանել հետևյալ հարցերին, որոնք վերաբերվում են Ձեր երեխայի վարքին քնած կամարթուն ժամանակ: Հարցերը վերաբերվում են Ձեր երեխայի պահվածքին վերջին ամսվա ընթացքում, ոչ անպայման վերջին մի քանի օրվա, քանի որ եթե երեխան լավ չի եղել այդ ընթացքում, նրա վարքը կարող է տիպիկ չլինել:

13. Քնած վիճակում արդյո՞ք Ձեր երեխան:

1. Խռոցնում է ժամանակի կեսից ավելին .....Y_1 N_2 DK_{88}
2. Միշտ է խռոցնում . . . . Y_1 N_2 DK_{88}
3. Բարձր է խռոցնում ..... Y_1 N_2 DK_{88}
4. Շնչում է «ծանր» կամ աղմկոտ. . . . . .
. . . . Y_1 N_2 DK_{88}

5. Դժվարանում է շնչել կամ տանջվում է շնչելու

   նպատակով ... Y_1 N_2 DK_{88}

14.Երբևիցե նկատե՞լ եք, որ երեխան շունչը պահի գիշերվա

ընթացքում ..... Y_1 N_2 DK_{88}

15. Արդյո՞ք Ձեր երեխան:

1. Շնչում է բերանով օրվա

   ընթացքում . . . . Y_1 N_2 DK_{88}

2. Առավոտյան արթնանում է չորացած

   բերանով . . . . Y_1 N_2 DK_{88}

3. Երբեմն թրջում է անկողինը ..... Y_1

   N_2 DK_{88}

16. Արդյո՞ք Ձեր երեխան:

1. Առավոտյան արթնանում է չթարմացած ..... Y_1

   N_2 DK_{88}

2. Ունենում է քնկոտություն օրվաընթացքում

   ..... Y_1 N_2 DK_{88}

17. Երբևիցէ եղե՞լ է, որ ուսուցիչը կամայլ խնամակալ նշեն, որ երեխան քնկոտէթվում օրվաընթացքում ..... Y_1 N_2 DK_{88}

18. Դժվա՞րէ արդյոք առավոտյան արթնացնել Ձեր երեխային..

Y_1 N_2 DK_{88}

19. Արդյո՞ք Ձեր երեխան առավոտյան արթնանում է գլխացավով.... Y_1 N_2 DK_{88}

20. Ծնվելուց հետո պատահե՞լ է, որ երեխան դադարի նորմալ աճել.....

.....Y_1 N_2 DK_{88}

21. Ձեր երեխայի քաշը նորմայից ավե՞լ է..... Y_1 N_2 DK_{88}

22. Երեխան հաճախ.

1. Թվում է, թե չի լսում, երբ ուղիղ իր հետեն խոսում ..... Y_1 N_2 DK_{88}
2. Դժվարանում է կազմակերպել անելիքներն ու ակտիվությունները. Y_1 N_2 DK_{88}
3. Հեշտությամբ շեղվում է արտաքին ազդակներից..... Y_1 N_2 DK_{88}

4. Ձեռքերն ու ոտքերն անհանգիստ են կամ գալարվում է նստած տեղում. Y_1 N_2 DK_{88}
5. Անընդհատ «շարժման մեջ է» կամ իրեն պահում է կարծես շարժիչ ունի. Y_1 N_2 DK_{88}
6. Ընդհատում կամ ներխուժում է այլ մարդկանց մեջ (օր.՝ խոսակցությունների կամ խաղերի մեջ). . . . . Y_1 N_2 DK_{88}

Շնորհակալություն!

Appendix 2A. Questionnaire for adult patients (English version)

Questionnaire for adult patients

Patient's ID _____

Date of Interview (dd/mm/yyyy) __/__/__

A. Screening questions

1. Do you have any of these conditions?

1. Chronic respiratory disease (e.g., asthma, chronic obstructive pulmonary disease, lung cancer, cystic fibrosis, occupational lung disease)……....Y_1 N_2
2. Neuromuscular disease (e.g., multiple sclerosis, muscular dystrophy)…Y_1 N_2
3. Congenital syndrome (e.g. Down's; Turner's; Di-George's, William's; Velocardiofacial syndrome, Noonan's; etc.)……..... .Y_1 N_2
4. Congenital anomaly of upper airways…….. Y_1 N_2
5. Existing sleep disorder…….. Y_1 N_2

If the answer to any of the above mentioned questions is "Yes", thank the participant and finish the interview.

B. Social –demographic characteristics

2. Date of Birth (dd/mm/yyyy) __/__/__
3. Male$_1$ / Female$_2$ _____
4. Weight (kg)_____

5. Height (cm) _____

6. Age(y) _____

7. How do you rate your academic performance in comparison with your fellow students?

1. Much worse
2. Worse
3. Same
4. Better
5. Much better

C. Clinical history/cardiac symptoms

8. What was your weight at birth (kg)? _____

9. Do you have tonsillitis/adenoiditis?.....…Y_1 N_2

10. Did you have tonsillectomy/adenoidectomy in the past?

1. Yes_1
2. No_2

11. Do you have exercise intolerance?

1. Yes_1
2. No_2

12. Do you:

1. Perform all physical activity without getting short of breath or tired, or having palpitations?

2. Get short of breath or tired, or have palpitations when performing more strenuous activities? For example, walking on steep inclines or walking up several flights of steps.

3. Get short of breath or tired, or have palpitations when performing day to day activities, for example, walking on the flat.

4. Feel breathless at rest, and are mostly housebound or unable to carry out any physical activity without getting short of breath or tired, or having palpitations?

D. STOP-BANG Sleep Apnea Questionnaire

23. Neck Circumference(cm) _____ _____*find a flexible measuring tape marked with centimeters, in a standing position locate the widest part of your neck called larynx or Adam's apple and zero in on it. Wrap the tape around the widest part of your neck, so there is no slack, but don't squeeze your neck with the tape. Now repeat it again.*

STOP

24. Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?

Yes$_1$ No$_2$

25. Do you often feel tired, fatigued, or sleepy during daytime?

Yes1 No2

26. Has anyone observed you stop breathing during your sleep?

Yes1 No2

27. Do you have or are you being treated for high blood pressure?

Yes1 No2

BANG

28. BMI more than 35kg/m2? Yes$_1$ No$_2$

29. AGE over 50 years old? Yes$_1$ No$_2$

30. NECK circumference > 40cm? Yes$_1$ No$_2$

31. GENDER: Male? Yes$_1$ No$_2$

Scoring: High risk of OSA: Yes 5 – 8; Intermediate risk of OSA: Yes 3 – 4; Low risk of OSA: Yes 0 – 2

E. Berlin Sleep Apnea Questionnaire

Category 1

32. Do you snore?[1]

    1. Yes$_1$
    2. No$_2$
    3. DK$_{88}$

If you answered "Yes":

33. Your snoring is:[2]

    1. Slightly louder than breathing
    2. As loud as talking
    3. Louder than talking

34. How often do you snore?[3]

    1. Almost every day
    2. 3-4 times per week

3. 1-2 times per week
4. 1-2 times per month
5. Rarely or never

35. Has your snoring ever bothered other people?[4]

1. Yes$_{1}$
2. No$_{2}$
3. DK$_{88}$

36. Has anyone noticed that you stop breathing during your sleep?[5]

1. Almost every day
2. 3-4 times per week
3. 1-2 times per week
4. 1-2 times per month
5. Rarely or never

37. How often do you feel tired or fatigued after your sleep?[6]

1. Almost every day
2. 3-4 times per week
3. 1-2 times per week
4. 1-2 times per month
5. Rarely or never

Category 2

38. During your waking time, do you feel tired, fatigued or not up to par?[7]

1. Almost every day
2. 3-4 times per week

3. 1-2 times per week
4. 1-2 times per month
5. Rarely or never

39. Have you ever nodded off or fallen asleep while driving a vehicle?[8]

1. Yes$_1$
2. No$_2$

If you answered "Yes":

40. How often does this occur?[9]

1. Almost every day
2. 3-4 times per week
3. 1-2 times per week
4. 1-2 times per month
5. Rarely or never

Category 3

41. Do you have high BP?[10]

1. Yes$_1$
2. No$_2$
3. DK$_{88}$

Categories and Scoring:

Category 1: items 1, 2, 3, 4, and 5;

Item 1: if 'Yes', assign 1 point

Item 2: if 'c' or 'd' is the response, assign 1 point

Item 3: if 'a' or 'b' is the response, assign 1 point

Item 4: if ‘a’ is the response, assign 1 point

Item 5: if ‘a’ or ‘b’ is the response, assign 2 points

Add points. Category 1 is positive if the total score is 2 or more points.

Category 2: items 6, 7, 8 (item 9 should be noted separately).

Item 6: if ‘a’ or ‘b’ is the response, assign 1 point

Item 7: if ‘a’ or ‘b’ is the response, assign 1 point

Item 8: if ‘a’ is the response, assign 1 point

Add points. Category 2 is positive if the total score is 2 or more points.

Category 3 is positive if the answer to item 10 is ‘Yes’ or if the BMI of the patient is greater than 30kg/m2.

(BMI is defined as weight (kg) divided by height (m) squared, i.e.., kg/m2).

High Risk: if there are 2 or more categories where the score is positive.

Low Risk: if there is only 1 or no categories where the score is positive.

Additional Question: item 9 should be noted separately

Appendix 2B. Questionnaire for adult patients (Armenian version)

Մե ծ ահ աս ակ ն ե ր ի հ ար ց աշ ար

Պաց ի ե ն տի ID _____

Հարցազրույցի ամսաթիվ (օօ/աա/տտտտ)__/__/__

A. Սկրինինգ հարցեր

1. Ունե՞ք արդյոք հետևյալ հիվանդություններից մեկը.

1. Քրոնիկ շնչառական հիվանդություն (օր.՝ աստմա, քրոնիկ բրոնխիտ, թոքի քաղցկեղ,մուկովիսցիդոզ, պրոֆեսիոնալ թոքային հիվանդություն). . . . . .
. . . .Y1 N2
2. Նյարդամկանային հիվանդություն (օր.՝ տարածուն սկլերոզ, մկանային դիստրոֆիա). . . . . .
. . . .Y1 N2
3. Բնածին սինդրոմ. (օր.՝ Դաունի, Թըրների, Դի-Ջեորջի, Ուիլյամսի, Նունանի, Վելոկարդիոֆացիալ համախտանիշ, և այլն.)..... Y1 N2
4. Վերին շնչուղիների բնածին անոմալիա. Y1 N2
5. Ախտրոշված քնի խանգարում. Y1 N2

Եթե վերոնշյալ հարցերից մեկի պատասխանը դրական է, շնորհակալություն հայտնեք մասնակցին և դադարեցրեք հարցազրույցը:

B. Սոցիալ-դեմոգրաֆիկ բնութագրեր

2. Ծննդյան ամսաթիվ (օօ/աա/տտտտ)__/__/__

3. Արական [1] / Իգական [2] _____

4. Քաշ (կգ) _____

5. Հասակ (սմ) _____

6. Տարիք (տ) _____

7. Ինչպե՞ս կգնահատեք Ձեր ակադեմիական

կարողականությունը (սովորելու ունակությունները),

համեմատած Ձեր ընկերների հետ:

1. Շատ ավելի վատ
2. Վատ
3. Նույնը
4. Ավելի լավ
5. Շատ ավելի լավ

C. Կլինիկական անամնեզ/սրտայինախտանիշեր

8. Որքա՞ն է եղել Ձեր քաշը ծնվելիս (կգ): _____

9. Ունե՞ք արդյոք Դուք տոնզիլիտկամ

ադենոիդիտ.....Այո [1] Ոչ [2]

10. Վիրահատվե՞լ եք տոնզիլիտի կամ ադենոիդիտի

կապակցությամբ:

1. Այո

2. Ոչ

11. Հոգնու՞մ եք արդյոք ֆիզ. ծանրաբեռնվածության ժամանակ:

1. Այո
2. Ոչ

12. Դուք.

1. Կատարում եք բոլոր ֆիզիկական ակտիվությունները առանց հևալու, հոգնելու կամ սրտխփոցների:
2. Հևում եք, հոգնում կամ սրտխփոցներ ունենում, երբ կատարում եք միջինից բարձր ֆիզիկական ակտիվություններ, օրինակ՝ կտրուկ թեքություն կամ մի քանի հարկ աստիճաններով բարձրանալիս:
3. Հևում եք, հոգնում կամ սրտխփոցներ ունենում, երբ կատարում եք առօրյա ֆիզիկական ակտիվություններ,օրինակ՝ հարթ տարածքում քայլելիս:
4. Հևում եք հանգստի ժամանակ, հիմնականում գտնվում եք տանը և անկարող եք կատարել որևէ ֆիզ. ակտիվություն առանց հևալու, հոգնելու կամ սրտխփոցների:

D. STOP-BANG հարցաշար

23. Պարանոցի շրջագիծը (սմ)_____ _____ *Գտեք ճկուն չափիչ ժապավեն՝ սանտիմետր, կանգնած վիճակում շոշափեք Ձեր*

պարանոցի ամենալայն հատվածը, որը կոչվում է կոկորդկամ աղամախնձոր, պտտեք սանտիմետրը պարանոցի շուրջն այդ հատվածում այնպես, որ ոչշատսեղմի, ոչէլթույլլինի: Կրկնեք այդգործողությունըևս մեկանգամ:

STOP

24. Դուք բարձրխոռոցնու՞մեք (խոսելուցավելիբարձրկամայնքանբարձր, որլսվիփակդռներիհետևում):

Yes1 No2

25. Հաճա՞խեք Ձեզզգումհոգնած, ուժասպառկամքնկոտցերեկայինժամին:

Yes1 No2

26. Որևէմեկընկատե՞լէ, որԴուքշունչըպահեքքնածժամանակ:

Yes1 No2

27. Ունե՞քկամբուժվու՞մեքարդյոքբարձրարյանճնշմանկապակցությամբ:

Yes1 No2

BANG

28. Մարմնիզանգվածիինդեքս > 35կգ/մ^2? Yes1 No2

29. Տարիք > 50տ? Yes1 No2

30. Պարանոցիշրջագիծը > 40սմ? Yes1 No2

31. Սեռը՝ արակա՞ն Yes1 No2

E. Բեռլինյան Հարցաշար

Կատեգորիա 1

32. Խոմփացնու՞մեք արդյոք [1]

1. Այո 1
2. Ոչ 2
3. Չգիտեմ 88

Երեայո,

33. Ձեր խոմփոցը [2]

1. Շնչառությունից մի փոքր բարձր է
2. Բարձր է, ինչպես խոսքը
3. Խոսքից բարձր է
4. Այնքան բարձր է, որ կարողէլսվելհարևան սենյակում

34. Որքա՞նհաճախեքխոմփացնում [3]

1. Համարյաամենօր
2. Շաբաթականից 3-4 անգամ
3. Շաբաթականից 1-2 անգամ
4. Ամսեկան 1-2 անգամ
5. Երբեքկամգրեթեերբեք

35. Ձեր խոմփոցըերբևէանհանգստացրե՞լէայլմարդկանց [4]

1. Այո 1

2. Ոչ 2

36. Որևէ մեկը նկատե՞լ է, որ դուք դադարում եք շնչել քնած ժամանակ [5]

1. Համարյաամեն օր
2. Շաբաթական 3-4 անգամ
3. Շաբաթական 1-2 անգամ
4. Ամսեկան 1-2 անգամ
5. Երբեք կամ գրեթե երբեք

Կատեգորիա 2

37. Որքա՞ն հաճախ եք զգում Ձեզ հոգնած կամ թուլացած քնից հետո [6]

1. Համարյա ամեն օր
2. Շաբաթական 3-4 անգամ
3. Շաբաթական 1-2 անգամ
4. Ամսեկան 1-2 անգամ
5. Երբեք կամ գրեթե երբեք

38. Որքա՞ն հաճախ եք արթուն ժամանակ զգում Ձեզ հոգնած, թուլացած կամ սովորականից վատ[7]

1. Համարյա ամեն օր
2. Շաբաթական 3-4 անգամ
3. Շաբաթական 1-2 անգամ

4. Ամսեկան 1-2 անգամ
5. Երբեք կամ գրեթե երբեք

39. Երբևէ ննջել կամքնե՞լ եք մեքենայի ղեկին [8]

1. Այո 1
2. Ոչ 2

40. Եթե այո, որքա՞ն հաճախէ դա կատարվում [9]

1. Համարյաամեն օր
2. Շաբաթական 3-4 անգամ
3. Շաբաթական 1-2 անգամ
4. Ամսեկան 1-2 անգամ
5. Երբեք կամ գրեթե երբեք

Կատեգորիա 3

41. Ունե՞ք բարձրարյան ճնշում [10]

1. Այո 1
2. Ոչ 2
3. Չգիտեմ 88

Appendix 3. Medical Record Review Form

Medical Record Review Form

Social – demographic characteristics	
42.Patient ID_____	43. Date of chart abstraction___/___/__ dd/mm/yyyy
	3. Birth Date___/___/_____ dd/mm/yyyy
44. Date of first visit __/__/____ Dd/mm/yyyy	45. Residency 0.Armenia 1.Other
46. Main diagnosis	
1. Functionally univentricular heart 2. Tetralogy of Fallot 3.Structurally normal heart	
47. Subtype of univentricular heart	
1. Tricuspid atresia	2. Double inlet ventricle
3. Double outlet ventricle	4. Complete AV canal
5. Transposition of great arteries with ventricular septal defect (TGA-VSD)	6. Mitral atresia
7. Pulmonary atresia – ventricular septal defect (PA- VSD)	8. Pulmonary atresia – intact ventricular septum (PA-IVS)
48. Concomitant heart defects 1. Yes 2. No *If yes, specify* _____	**49.Concomitant disease/syndrome** 1. Yes 2. No *If yes, specify*_____

50. Palliative surgery 1.Yes 2.No	
51. Bidirectional Glenn 1.Yes 2.No	52. Hemifontan classic 1.Yes 2.No
53. Hemifontan turbo 1.Yes 2.No	54. Aorta-pulmonary shunt 1.Yes 2.No
55. Pulmonary artery banding 1.Yes 2.No	56. Atrioseptectomy 1.Yes 2.No
57. Damus - Kaye - Stansel procedure (DKS) 1.Yes 2.No	58. Other 1.Yes 2.No *If yes, specify* _____
Date of surgeries dd/mm/yyyy 59. 1st palliation___/___/___	60. 2nd palliation __/__/___
61. 3rd palliation__/__/___	62. 4th palliation __/__/___
63. Date of final repair/palliation (dd/mm/yyyy)	___/___/____

64. Type of final repair

1. Extracardiac Fontan	2. Intracardiac lateral tunnel	3. Kawashima surgery	4. TOF repair

65. Date of last hemodynamic catheterization(dd/mm/yyyy) ___/___/____

66. Total pulmonary resistance(TPR)_____ 67. Arteriolar pulmonary resistance (APR)_____	68. Mean PA pressure_____
69.Mean SVC pressure(mmHg)_____	70. Mean pressure in aorta(mmHg)_____
71. SV end – diastolic pressure (SVEDP)_____	72. Transpulmonary gradient_____
73. Index of McGoon _____	74. Index of Nakata _____
75. Presence of significant collateral vessels a. Yes b. No	

76. Morphology of single ventricle

1. Left ventricle 2. Right ventricle 3. Undefined

Echocardiographic data at last visit

77. Last echo date (dd/mm/yyyy) ___/___/____

Fontan	**TOF**
78. Single ventricle end-diastolic diameter (SVEDD)(mm)_____ 79. Single ventricle end-systolic diameter (SVESD)_____ 80. Single ventricle ejection fraction	87. Right ventricle dimension (M-mode)(mm)____ 88. Right ventricular end-diastolic area index (RVEDAI)_____ 89. Residual pulmonary stenosis (PS)

(SVEF)____ 81. SVC peak velocity_____ 82.Presence of fenestration 1. Yes 2. No 83. Fenestration velocity (m/sec)_____ 84. Atrioventricular valve regurgitation (AVR) 1.No 2.Mild 3.Moderate 4.Severe 85. Presence of reverse flow on hepatic veins 1. Yes 2. No 86. SVEF (%) _____	1.No 2.Mild 3.Moderate 4.Severe 90. Residual pulmonary regurgitation (PR) 1.No 2.Mild 3.Moderate 4.Severe 91. Tricuspid regurgitation (TR) 1.No 2.Mild 3.Moderate 4.Severe 92. TR peak systolic pressure gradient(mmHg)_____ 93. Aortic regurgitation (AR) 1.No 2.Mild 3.Moderate 4.Severe 94. LVEDD _____ 95. LVEF (%) _____

Clinical Characteristics at last visit		
96. Last visit weight (kg) _____	97.Last visit height(cm) _____	98.Last visit heart rate(bpm) _____
99. Last visit BP (systolic/diastolic)_____/_____	100. Last visit oxygen saturation(%) _____	

Medications prescribed at last visit	
101. Aspirin 1.Yes 2.No	102. Coumadin/phenilin 1.Yes 2.No
103. B-blockers 1.Yes 2.No	104. ACEI/ARB 1.Yes 2.No
105. Antiarrhythmic	106. Diuretics

<table>
<tr><td>1.Yes 2.No</td><td>1.Yes 2.No</td></tr>
<tr><td>107. Sildenafil

1.Yes 2.No</td><td>107. Other

1.Yes 2.No, If yes-

specify_____</td></tr>
<tr><td>108. Arrhythmia history

1. Yes 2.No

109. Type of arrhythmia

1. Atrial 2. Ventricular 3. Both</td><td>110. QRS duration (msec)_____

111. Implanted device

1. Stent 2. PMK/ICD 3.

Fenestration device</td></tr>
</table>

Appendix 4A. Oral Consent form (Englsih version)

American University of Armenia

Institutional Review Board #1

Oral Consent form for Congenital Heart Disease Patients

Title of research project: Risk of Obstructive Sleep Apnea in Patients with Repaired or Palliated Congenital Heart Disease

Hello, my name is _____. I am a pediatric cardiologist / pediatric cardiologist and second year graduate student at School of Public Health at the American University of Armenia. As part of my thesis project, and with the support of the faculty members and in collaboration with Nork-Marash Medical Center, I am conducting a study to investigate the risk of sleep disorders in patients with repaired congenital heart disease. Proper identification and treatment of this disorder can contribute to improvement of heart health.

You have been contacted because based on NMMC records you or your child have been diagnosed with congenital heart disease (either Tetralogy of Fallot or Univentricular heart) and underwent surgical repair of that anomaly / you have been selected randomly, because based on NMMC records you have structurally normal heart, underwent heart study for some reason. You will be one of 200 people who will participate in this study. If you are willing to participate in this study I will review your personal medical chart in NMMC. I will also ask you questions about your heart health and sleep habits. This is safe procedure and there are no risks linked to its' performance. Your participation in the study is voluntary. You may skip any question you think is inappropriate and stop the further investigation at any moment you want with no further negative consequences. The interview will take place when it's convenient to you and take no more than 15 minutes.

There will be no monetary benefits for you if you participate in this project. The information provided by you will be very helpful for understanding the mechanisms of worsening heart health status in patients with repaired CHD.

There is no penalty for refusing to participate. Whether or not you are in the study will not affect your future treatment at the NMMC. The information provided by you is fully confidential and will be used only for the study. Only aggregate data will be reported. Contact information will be destroyed upon completion of the research.

If you have more questions about this study you can contact to dean of School of Public Health Varduhi Petrosyan via following number (+37460 61 25 92). If you feel you have not been treated fairly or think you have been hurt by joining this study, please contact Dr. Kristina Akopyan, AUA Human Subject Protection Administrator at the American University of Armenia (+374 60) 61 25 61.

If you agree to be involved in this study, could we continue?

Appendix 4B. Oral Consent form (Armenian version)

Հայ աստանի Ամերիկյան Համալսարան

Գիտահետազոտական էթիկայի թիվ 1 հանձնաժողով

Իրազեկ համաձայնության ձև

Հետազոտության անվանումը՝ Քնի օբստրուկտիվ ապնոէի ռիսկը շտկված սրտի բնածին արատով պացիենտների շրջանում

Բարև Ձեզ, իմ անունը _____ է: Ես մանկական սրտաբան եմ /մանկական սրտաբան եմ և Հայ աստանի Ամերիկյան համալսարանի Հանրային Առողջապահության բաժնի մագիստրատուրայի ավարտական կուրսի ուսանող եմ: Եվ, որպես իմ ավարտական գիտական աշխատանքի մի մաս, հետազոտական խմբի անդամ դասախոսների աջակցությամբ և Նորք-Մարաշ բժշկական կենտրոնի հետհամատեղ, իրականացնում եմ հետազոտություն ուսումնասիրելու քնի խանգարումների ռիսկը շտկված բնածին սրտի հիվանդություններով պացիենտների մոտ: Այս հիվանդության ժամանակին հայտնաբերումը և բուժումը կարող են նպաստել սրտի առողջության բարելավմանը: Դուք ընտրվել եք, որովհետև Նորք-Մարաշ բժշկական կենտրոնում գրանցված տվյալների համաձայն Ձեզ կամ Ձեր երեխայի առկա է սրտի բնածին հիվանդություն (Ֆալլոյի տետրադակամ ֆունկցիոնալ միափորոք սիրտ) և կրել եք շտկման վիրահատություն նրա կապակցությամբ /Դուք ընտրվել եք պատահականության կարգով, որովհետև Նորք-Մարաշ բժշկական կենտրոնում գրանցված տվյալների համաձայն ունեք կառուցվածքով նորմալ սիրտ և

ինչ-որ պատճառով անցել եք սրտի հետազոտությունը այդ կենտրոնում: Դուք կլինեք այս հետազոտության երկու հարյուր մասնակիցներից մեկը:

Եթե դուք պատրաստեք մասնակցելու, ապահովում եմ ՆՄԲԿ-ի ձեր անձնական բժշկական քարտը: Նաև կտամ հարցեր ձեր սրտի առողջության և քնի սովորությունների վերաբերյալ: Սա ապահով գործընթաց է և նրա իրականացման հետ կապված որևէ ռիսկեր չկան: Ձեր մասնակցությունը հետազոտության կամավոր է: Դուք իրավունք ունեք չպատասխանել այն հարցերին, որոնք Ձեզ կարող են տհաճություն պատճառել և կարող եք դադարեցնել հարցազրույցը ցանկացած պահի՝ առանց որևէ հետագա բացասական հետևանքների: Հարցազրույցը տեղի կունենա մեկ անգամ, Ձեզ առավելը հարմար ժամանակ, և կտևի ոչ ավելի քան 15 րոպե: Այս հետազոտությանը Ձեր մասնակցության դեպքում որևէ դրամական խրախուսանք նախատեսված չէ: Ձեր կողմից տրամադրված տվյալները շատ օգտակար կլինեն հասկանալու համար սրտի բնածին արատով վիրահատված պացիենտների սրտի կարգավիճակի վատացման մեխանիզմները: Հետազոտությանը չմասնակցելը չունի որևէ բացասական հետևանք: Անկախ նրանից Դուք կմասնակցեք այս հետազոտությանը թե ոչ, ոչինչ չի ազդի Ձեր ՆՄԲԿ հետագա այցելությունների վրա: Ձեր կողմից տրամադրված ողջ տեղեկությունները գաղտնի կպահվեն և կօգտագործվեն միայն

հետազոտության համար: Միայն ընդհանրացված արդյունքները կներկայացվեն զեկույցում: Ձեր անձնական տվյալները անմիջապես կոչնչացվեն հետազոտության ավարտից հետո:

Հետազոտության հետ կապված հետագա հարցերի համար կարող եք զանգահարել Հանրային առողջապահության ֆակուլտետի դեկան Վարդուհի Պետրոսյանին հետևյալ հեռախոսահամարով (+37460 61 25 92): Եթե կարծում եք, որ հետազոտության ընթացքում Ձեզ հետ լավ չեն վերաբերվել և/կամ հետազոտությունը Ձեզ վնաս է հասցրել, կարող եք զանգահարել ՀԱՀ-ի Էթիկայի հանձնաժողովի ադմինիստրատոր Քրիստինա Հակոբյանին, հետևյալ հեռախոսահամարով (+374 60) 61 25 61:

Եթե Դուք համաձայնեք մասնակցել հետազոտությանը, կարո՞ղ ենք շարունակել: