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Title: Custom 3-D Printed Noninvasive Ventilation Mask

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Title of Study: Custom 3-D Printed Noninvasive Ventilation Mask

Principle Investigator: Narong Simakajornboon, MD
Co-investigators/advisors: Geoffrey Rulong, MD, John van Aalst MD, Stacy Gruber BS,

1. ABSTRACT

Studies have shown that even though noninvasive ventilation (NIV) with positive airway pressure (PAP) is successful at treating obstructive sleep apnea and hypoventilation, individuals have poor compliance with therapy[1-2]. The reasons for poor compliance are numerous, but one significant and continually reported reason is poor mask fit. A poor mask fit is not only uncomfortable, but frequently causes side effects such as dry eyes, congestion, skin irritation and breakdown, and ineffective ventilation from inadequate pressures due to air leaking around the mask. Pediatric patients tend to be especially difficult to fit with conventional masks because of their smaller facial features and the lack of masks developed for pediatric use. This difficulty is increased significantly for pediatric patients, who more commonly require positive pressure ventilation, due to craniofacial abnormalities and neuromuscular disease.

In this study, patients will be fitted with a custom made NIV mask following facial imaging with a three dimensional (3D) camera (Artec 3-D scanner). The facial image will be used to construct a NIV mask model using computer design software (Blender) that will then be created by using a 3D printer (Stratasys Objet).

Patients enrolled in the study will be recruited from the pediatric sleep clinic at Cincinnati Children's Hospital Medical Center who have been stable on their current noninvasive ventilation settings, with the same mask, for a minimum of 2 months. Study visits will be conducted during regularly scheduled clinic visits and data will be collected on their compliance by downloading the information from their home ventilation equipment. Three questionnaires that are routinely given at every clinic visit: Pediatric Quality of Life Inventory (PEDS QOL), Epworth Sleepiness Scale (ESS) and the Pediatric Sleep Questionnaire (PSQ), as well as an additional questionnaire developed at CCHMC asking quality of life and subjective compliance data will also be collected at each visit. Patients will be followed for 6 – 9 months following their mask change to determine if the custom made mask decreased side effects while increasing ventilation and compliance.

2. PURPOSE OF STUDY

The aim of this study is to improve adherence and effectiveness of noninvasive ventilation by decreasing the side effects commonly seen with noninvasive ventilation. To our knowledge, there have been no prospective studies to determine if three dimensional imaging of a subject's face can be analyzed to create a personalized 3D printed noninvasive ventilation mask.

It is hypothesized that a better fitting customized mask, using 3-dimensional imaging technology, will lead to increased comfort and better ventilation by decreasing the air leak and residual apnea-hypopnea index. The improved ventilation, increased comfort and fewer side effects will, in return, lead to improved adherence in our subjects. To study this question, we will recruit patients seen in the CCHMC Sleep Center Clinic. Side effects, patients' quality of life and adherence will be measured by having participants complete questionnaires and downloading ventilator data, respectively, during study visits.

If the use of three dimensional technologies to create a noninvasive ventilation mask is found to improve residual leak, residual AHI and patient adherence, this study has the potential to benefit countless other patients.

3. BACKGROUND

Noninvasive ventilation (NIV) methods such as continuous positive airway pressure (CPAP) and Bi-level positive airway pressure (BiPAP) are beneficial therapies for obstruction sleep apnea (OSA) and nocturnal hypoventilation respectively[3-5]. If untreated or undertreated, OSA and nocturnal hypoventilation can lead to negative effects on patients' overall health and quality of life ([6-7]). Following diagnosis and initiation of NIV, adherence to therapy, defined as using NIV for greater than 4 hours per night, varies from 50% to 80%[1]. At Cincinnati Children's Medical Center adherence to NIV is approximately 50%. Prior studies have shown that there is no difference in the mode of therapy and adherence[1-2]. A common reason reported for poor adherence is related to mask fit: comfort, skin breakdown and leaks. Additional complaints that are frequently reported with NIV include nasal congestion or dryness, abdominal discomfort and burping[1-2]. However, studies have shown that individuals, who have better ventilation with an increased reduction in their residual number of apneas and hypopneas, following NIV initiation, are more compliant[1].

4. STUDY DESIGN

This will be a prospective pilot study to determine if the use of 3D technologies to create a customized computer designed NIV mask will improve ventilation and comfort, resulting in improved adherence in patients requiring PAP. Patients, who have been stable on noninvasive ventilation for at least 2 months will be recruited from Cincinnati Children's Medical Center sleep clinic.

All study visits will be incorporated into regularly scheduled clinic visits. On their first study visit, the clinical conventional mask fitting, done in a standardized fashion by a professionally trained,

experienced respiratory therapist, nurse or physician will be reviewed. During this visit, 3D facial imaging will be obtained using an Artec 3D Scanner (Artec Group, San Diego, Ca, USA). The clinically obtained baseline self-assessment data of the participants' sleep related breathing disorders (SRBD) and symptom complexes, such as hyperactivity, sleepiness, and inattention will be reviewed through the Michigan Pediatric Sleep Questionnaire (PSQ), Epworth Sleepiness Scale (ESS), Pediatric Quality of life Inventory (PedsQL) and CPAP follow up questionnaire when available. It is standard practice to have patients complete such questionnaires at all CCHMC Sleep Disorders Center follow up visits. Objective, compliance and ventilation data will also be collected clinically and reviewed during the initial visit by evaluating the meter readings on the patient's home assisted ventilation machines, which is standard practice at follow-up visits in the CCHMC CPAP clinic.

Facial images obtained using the Artec 3D scanner will be examined with Blender software to analyze the subject's facial contours in order to create a 3D printed customized mask. A Stratasys Objet 3D printer, using the PolyJet method with bio-compatible material (Polylactic acid (PLA) filament) , will then be used to create the rigid portion of the mask. Smooth-on EcoFlex material will then be attachment to the rigid portion of the mask in order to interface with the subject. At the second clinic visit, which will be a regularly scheduled visit, the participants will be provided with the mask created using the imaging software and this mask will be sent home to be worn by the participant while asleep. The clinically acquired self-assessment data such as PSQ, ESS, PedsQL and CPAP questionnaires and clinically obtained compliance data from the PAP machine will be reviewed.

The third and subsequent visits will also be regularly scheduled follow up visits, which occur approximately every 3 months. As part of the clinical care at each of these visits, participants routinely complete the PSQ, ESS, PedsQL and CPAP follow up questionnaires and objective, compliance and ventilation data is downloaded from the meter readings of the PAP machine. These data will be reviewed.

5. DURATION

This study will last about 18 months with patient recruitment being in the first 3 - 6 months. Subject participation will last about 9 months with first two visits and the remainder of the visits to allow for approximately 6 months of using the test mask.

6. SELECTION AND RECRUITMENT OF PARTICIPANTS

A. Number of patients:
We plan to enroll about 15**-**20 subjects

B. Inclusion / Exclusion criteria
Inclusion – patients aged 5 – 25 years of any race or socioeconomic background who have been stable on NIV settings for a minimum of 2 months for any reason.
Exclusion – new diagnosis or not on stable NIV settings.

C. Recruitment

Participants will be recruited from Cincinnati Children's Medical Center Sleep Disorders Clinic. Potential study participants will be identified by study physicians at the time of their clinic visit to discuss the trial and possible enrollment. Interested, eligible candidates, who are willing to be enrolled and give informed consent, will then be enrolled in the study during the clinic visit.
Any recruitment materials used will be submitted to the IRB for approval prior to use.

D. Vulnerable Populations

For subjects under 18 years of age, additional efforts will be made to protect this vulnerable population. Assent will be obtained after age appropriate explanation of the study is completed. The child will be informed that participation in this clinical trial is voluntary and that they may decline or withdraw at any time, for any reason, independent of their parent or legal guardian. Assent will be reaffirmed before any study procedures are performed. Participants will be informed that participation in this trial will not affect their clinical care in the Sleep Disorders Center.

7. PROCESS OF OBTAINING CONSENT

The participant or the participant and his or her parent/legal guardian will be given the consent form for the study. The form will be reviewed with the participant and his or her parent/legal guardian with time given for questions. The subject will sign assent, as determined by the IRB, and their parent or legal guardian will sign consent after all questions have been answered. If participants are 18 years of age or older they will sign the consent form themselves after all questions have been answered. A signed copy of the consent form will be given to the subject and their legal guardian to keep. The participant will be informed that this research trial is voluntary and that they are free to withdraw at any time. All participants who are of age to assent for this study, as determined by the IRB, and those consenting will sign after all questions are answered. No study related procedures will be done prior to the assent and consent forms being signed.

To provide a consent form in understandable language, the CCHMC approved consent form template will be used. Any non-English speaking participants, enrolled in the study, will be consented using a short form consent process as per CCHMC SOP 41-1.8. The approved long consent form will serve as the summary of the research.

8. STUDY PROCEDURES

Review of medical records: a review for inclusion/exclusion criteria will be completed by a member of the research team prior to enrollment in the study. Review of medical records will continue throughout the study to document changes in health during subject's participation.

Informed Consent: informed consent will be obtained by a member of the research team at a regularly scheduled clinic visit. Participants and their parent/legal guardian will be informed at their clinic visit that approximately 30 to 45 minutes, beyond the routine clinical care, will be required during this visit. The additional time will be used to review the procedures and goals of the study, review the informed consent and/or assent forms, answer questions the participants or their legal guardians have regarding the study.

Imaging: facial imaging will be obtained using a 3D camera (Artec 3-D scanner) for three-dimensional re-creation of facial contours. This will take about 10 minutes and will occur in the pre-determined imaging room within the clinic space.

Questionnaires: participants will complete as part of their clinical visits the Michigan PSQ, ESS, and PedsQL questionnaires, which is standard clinical practice for all patients seen in the sleep center. In addition to the standard questionnaires, participants will be asked to complete a CPAP follow up questionnaire (CFU) that will be used to measure comfort and side-effects of NIV at each visit as well. The results of the clinical questionnaires will be used for this research. If a questionnaire is not collected during the clinical visit, it will be recorded as missing in the research record.

Ventilation machine download: a review of the participants NIV machine data, which is standard practice at each clinical visit, by a professionally trained respiratory therapist, nurse or physician will be completed. The data obtained will be used to evaluate compliance, mask leak and residual apnea-hypopnea index will occur at each visit. If the participant does not bring their PAP machine to their clinical visit, the downloaded data will be recorded as missing in the research record.

Mask creation: facial images of the participants, using the Artec three dimensional surface scanner will be examined using Blender software, to analyze their facial contours described below, located in the surgery clinic at CCHMC and in Dr. Chia-Ying Lin's laboratory at the University of Cincinnati Bioengineering Department. A NIV mask will then be created at the University of Cincinnati using a Stratasys Objet machine's PolyJet method out of bio-compatible material (Polylactic acid (PLA) filament Smooth-On's Ecoflex silicone will then be attached to the ridged portion of the mask to interface with the subject.

Participants will then be provided, without charge, their customized mask to wear exclusively throughout the duration of the study. All masks will be compatible for use with the participant's home health supplied equipment and fitted by a professionally trained respiratory therapist, nurse or physician during the visit. The mask will be created to be compatible with the tubing and elbow used for the Respironics Wisp mask, which has built in, FDA approved exhalation ports to allow for continuous airflow out of the mask.

The number of study visits will vary and be determined by each subject's scheduled clinic visits. It is planned that subjects will be followed, during regularly scheduled follow up visits, for approximately 12 months after mask selection. At these subsequent visits, subjects will complete the Michigan PSQ, ESS, PedsQL and CFU questionnaires. Objective, compliance data will be reviewed by downloading their home ventilation machine's meter readings and they will be refitted with their mask by a professionally trained respiratory therapist, nurse or physician (all of which are standard practice for clinic follow up visits besides the CFU questionnaire).

	Visit 1	Visit 2	Visit 3	Visit X (regularly scheduled clinic visitis up to 18 months post V1)
Sign informed consent	R			
Given Customized mask		R		
Conventional mask fitting process	C	C	C	
3D Imaging photos	R	R	R	R
Questionnaires: *Michigan PSQ, Epworth ESS, PedsQL, CPAP follow-up questions*	C	C	C	C
Download CPAP machine use readings	C	C	C	C
Review of medical records	C	C	C	C
Adverse Events assessment		R	R	R

C = clinical R = Research

Custom Noninvasive Ventilation Masks:

We feel the use of this custom mask may fall under the FDA regulations 21CFR812.3(b) Custom Devices because we feel it meets the following requirements. If the IRB determines, we will submit this as a device without significant risk under the FDA regulations 21CFR812.2(b)1 abbreviated requirements.

> *Custom device defined by FDA:*
> *(1) Necessarily deviates from devices generally available or from an applicable performance standard or premarket approval requirement in order to comply with the order of an individual physician or dentist;*
> *(2) Is not generally available to, or generally used by, other physicians or dentists;*
> *(3) Is not generally available in finished form for purchase or for dispensing upon prescription;*
> *(4) Is not offered for commercial distribution through labeling or advertising; and*
> *(5) Is intended for use by an individual patient named in the order of a physician or dentist, and is to be made in a specific form for that patient, or is intended to meet the special needs of the physician or dentist in the course of professional practice.*

NIV masks created for use during this study will be similar to those that are commercially available and clinically used at the CCHMC Sleep Center. At the time of study initiation, participants will have already been using a CCHMC provided NIV mask, with stable settings, for a minimum of 2 months.

The goal of the 3-dimensionally created custom mask is to increase patient comfort, and decrease common side effects such as air leaks, skin irritation, dry mouth, congestion, rhinorrhea, sneezing, nosebleeds and stomach discomfort. As a result of decreasing side effects, we hypothesize that adherence will be improved.

The mask will be 3D printed using the PolyJet method (see below) of a Stratasys Objet printer using the bio-compatible material MED610 (see below). A silicone gel attachment (Smooth-on

Ecoflex), which is standard on commercially produced NIV masks, will then be placed on the mask to directly interface with the subject.

The personalized mask will be compatible with the FDA approved Respironics Wisp mask tubing and elbow that can be connected to the subjects NIV machine. The choice of the Wisp mask tubing and elbow was made because it has built in exhalation ports that allow for a continuous flow of air out of the mask.

Hardware for Creating a Customized NIV Mask:

- **3-Dimensional Surface Imaging:** three dimensional surface scans of participant's faces will be obtained using an Artec 3D Scanner (Artec Group, San Diego, CA, USA). The Artec 3D Scanner uses fringe projection, light based imaging technology to obtain 360 degree images. The resolution is up to 0.5 mm with point accuracy of 0.1 mm. Exposure times are 0.2 milliseconds. The scanner's software produces images that will be analyzed with standard software described below. The speed and location of this scanner will allow investigators to collect images in the clinical setting quickly and will eliminate the limitations of a two dimensional imaging system.
- **Software for Creating a Customized NIV Mask:** the Artec 3D Scanner images will be analyzed with Blender software (Amsterdam, Netherlands) as follows. The subject's facial scan will be aligned in the anterior and profile views. Points along the contour of the subjects face will then be selected and the distance between the selected points will be measured, in millimeters, to create the outline for an appropriate mask mold using 3D printing.
- **Objet 3D printer (Stratasys, Eden Prairie, MN, USA):** uses PolyJet technology to layer and cure, using UV light, liquid photopolymer to create an accurate 3D mask.
- **Bio-compatible PolyJet photopolymer (Polylactic acid (PLA) filament:** a rigid medical rapid prototyping material. A biocompatible material that is used in many medical devices[1]. It will be used in the three-dimensional printing process to create the rigid portion of the mask. [12].
- **Ecoflex® (Smooth-on, Macungie, PA, USA):** platinum-catalyzed silicone that is versatile and easy to use. Cured material is certified by an independent laboratory to ISO 10993-10, Biological evaluation of medical devices, Part 10: Tests for irritation and skin sensitization.[13]

Questionnaires:

- **Pediatric sleep questionnaire (PSQ)** – 22 question screen, completed by the patient's parent, for sleep-disordered breathing, snoring, sleepiness and behavioral problems in subjects 2 – 18 years of age that was developed by researchers at the University of Michigan. It was shown to be valid and reliable in identifying sleep related breathing disorders by Chervin et al in 2000[11].
- **Epworth Sleepiness Scale (ESS) –** scale used to measure daytime sleepiness using 8 questions. It has shown reliability and been validated in the diagnosis of obstructive sleep apnea in adult patients and a modified version has been used frequently in

pediatric patients, but has yet to be validated. It is used frequently during follow up visits after initiating NIV to evaluate for improvement of symptoms[14].

- **Pediatric Quality of life Inventory (PedsQ) –** used to measure health related quality of life in children and adolescents aged 2 – 18 years. It has been shown to be reliable and valid in a study published by Varni et al in 2001[15].
- **CPAP Follow Up Questionnaire (CFU):** The items included in this questionnaire are often reviewed with patients during their sleep clinic visits regarding side-effects, comfort, problems encountered with CPAP use and their adherence to treatment. It has not been validated but is solely being used to collect information in a standardized format.

9. DATA ANALYSIS/METHODS

Descriptive analyses will include calculation of mean (SD), median and range for each continuous variable and n (%) for each categorical variable. Primary outcomes include adherence rates, as measured by machine-based compliance. We will compare self-reported adherence to machine-reported adherence using Bland-Altman analyses and correlation coefficients (Pearson's r). This comparison will be performed on paired data at each visit and on the overall average for each subject across multiple visits. Data will be transformed to achieve normality as needed. Appropriate linear mixed models will be used to assess change in outcome over time, with adjustment for within-subject correlation and any multiple comparisons made across visits. Analyses will be performed using SAS 9.3.

Power analysis – For this pilot study, planned enrollment is between 15-20 subjects, and we assume the potential for 10% attrition from baseline to the first follow-up assessment. We have sufficient power (80-92%) to detect a 10% increase in compliance, given a level of 50% compliance at baseline and the aforementioned enrollment and attrition. Our analysis is based upon percentage of time mask is used as directed for each subject, as recorded by the machine. Actual data acquired on this percentage outcome will be transformed to achieve normality. For the power analysis, we assume SD is 0.12 from baseline to follow-up visit, using a paired t-test with two-sided alternative and alpha=0.05.

10. FACILITIES AND PERFORMANCE SITES

All participants will be recruited from and followed up in the CCHMC Sleep Disorders Center Clinic, located in Building C.
Dr. Chia-Ying Lin's laboratory at the University of Cincinnati Bioengineering Department will be used to manufacture the custom mask.
3D Imaging will be done in the Surgery Clinic on C2.

11. POTENTIAL BENEFITS

We feel this study offers the potential of direct benefit to participants. It is hypothesized that participants will have improved adherence with their NIV which can be attributed to a more

comfortable and better fitting mask. Secondary goals would be improving the patient's quality of sleep, decreasing daytime sleepiness, increasing energy levels and an overall improvement in their quality of life. If this personalized 3 dimensional creation of a NIV mask does improve patient adherence and comfort levels, this study will likely benefit countless other patients by providing them with an optimal mask that more appropriately fits their face.

12. POTENTIAL RISKS, DISCOMFORTS, INCONVENIENCES AND PRECAUTIONS

We anticipate there is no difference between a custom mask and a commercial mask other than better fit and greater comfort. We recognize that there may be other risks that we do not know about yet. One potential risk could be the rebreathing of exhaled air. To address this possible risk, we will use the FDA approved elbow and tubing from the Respironics Wisp mask that has exhalation ports built into the elbow, which directly connects with the mask. Additionally for this study, only nasal masks will be created; allowing for subjects to exhale through their mouths as well. Patients will also trial the mask in a supervised clinical setting prior to going home to monitor for any difficulties they have tolerating the mask. We will monitor for adverse events that include report of increase in headaches, particularly on waking; increase restlessness or awakenings during sleep; difficulty breathing with the mask; and increased tiredness.

The risk to participant privacy would be accidental release of protected health information. To limit this risk, we will remove all patient identifiers at the time of data entry into a secure, password protected database maintained by the PI. Any accidental disclosure of patient health information will be conveyed to the CCHMC IRB as a reportable event.

Patients enrolled in this study will only be seen during regularly scheduled clinic visits. Extra time spent during the initial visit for this study will be approximately 5 to 10 minutes to obtain imaging and an additional 30 to 60 minutes for the fitting and trial of custom mask on Visit 2.

13. RISK/BENEFIT ANALYSIS

This study has minimal risk with potential direct benefit to the participants and to future patients.

14. DATA SAFETY AND MONITORING

The primary investigator will review all adverse events and determine causality. This study defines expected adverse events in the risk section and these will be reported at time of continuing review in table format. Reportable events (RE) will be defined for this study as any adverse event (injury or unexpected outcome) **related** to study procedures or use of interventional masks that are **not listed in the risks above**. RE and accidental release of protected health information will be reported to the IRB in a timely manner.

15. PRIVACY AND CONFIDENTIALITY

All participants enrolled in this study will be assigned a unique study number. Protected health information other than dates of visits, dates of tests and dates of birth will not be entered into the database. Images taken for 3D scans will be maintained on the proprietary software of the Artec 3D Scanner. Hard copies of images captured as part of this study will be labeled and stored with the following information: study ID, date and visit number. The images will be shared with UC bioengineering team who are involved in this study and part of Dr. Lin's laboratory but will be identified by Study ID number, visit number and date. A Data Use agreement will be obtained if the IRB determines it is needed.

The code linking medical record number to study number will be kept in a secure manner and access restricted to the research team. All computerized records will be kept on the password protected CCHMC secure network.

Future Research:

Data and images may be used for future research studies by the PI and Co-Investigators for subjects who give consent for future research.

The results of this study may be published and presented to the public for educational purposes. No information that could identify a subject will be used in any publication or presentation.

16. COST OF PARTICIPATION

No participants or third party payers will be billed for time spent or imaging related to their study visits. Participants and third party payers will not be billed for the mask selected by 3D imaging. There will be no cost incurred to the patient's and their families for this study in relation to travel (fuel and time off work) and parking because participants will be seen during regularly scheduled follow up visits in the sleep clinic.

17. PAYMENT FOR PARTICIPATION

No payments will be provided for participation

18. INVESTIGATOR RESPONSIBILITIES

The investigators will comply will all relevant requirements of 21 CFR 820.30 as determined in document FDA Device Advice: Investigational Device Exemption (IDE)
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourD

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