Protocol Title: GO^2 PEEP Study: The Use of a Bidirectional Oxygenation Valve in the Prevention and Management of Postoperative Atelectasis

Protocol Short Title: GO^2 PEEP Study

Protocol version 5.0, dated November 20, 2020

NCT Number: NCT04253834

Principal Investigator: Jeffrey S. Miller, MD
Division of Cardiothoracic Surgery
Emory University School of Medicine
Emory Saint Joseph's Hospital

Sponsor: PEEP Medical, LLC

Protocol Author: Sean G. Boutros, M.D.
Houston Plastic Craniofacial and Sinus Surgery

Study Objective

The objective of this pilot study is to determine the feasibility and safety of a bidirectional oxygenation mouthpiece compared to incentive spirometry in the prevention and management of postoperative atelectasis.

Hypothesis:

We hypothesize that the bidirectional oxygenation mouthpiece is a safe and effective respiratory therapy, will reduce or prevent postoperative atelectasis, improve oxygenation (PaO2), improve pulmonary function tests, and reduce postoperative pulmonary complications in cardiac surgical patients compared to conventional incentive spirometry therapy.

Background and Significance

Postoperative pulmonary complications (PPCs) are the principal cause of morbidity, mortality and prolonged hospitalizations in surgical patients, [1-3] which results in a 50% increase in healthcare costs compared to postoperative cardiac complications. [4-5] This is especially evident following cardiovascular surgery. Pneumonia, unplanned re-intubation and prolonged postoperative mechanical ventilation (>48 hours) remain the most concerning adverse events, with a reported incidence between 2-5%. [4-5] One of the most common PPCs is atelectasis, resulting in dyspnea, tachypnea and hypoxemia. A number of identified risk factors associated with the development of PPCs are listed in Table 1. [6-14]

Postoperative atelectasis is a predictable consequence of anesthesia, surgical trauma, and pain associated with breathing.[15] This often results in hypoxemia and pulmonary complications. Methods aimed at increasing lung volume and treating atelectasis, commonly known as *postoperative physiotherapy*, play an important role in preventing PPCs. These methods include cough and deep breathing, continuous positive airway pressure (CPAP), postural drainage, incentive spirometry and positive end expiratory pressure (PEEP).

Introduced by Bartlett *et al* [2,16] over 40 years ago, incentive spirometry has served as a convenient approach for the postoperative patient to sustain maximal inflations and encourage deep breathing. Minschaert and colleagues found faster recoveries of tidal volumes following conventional protocols of incentive spirometry when compared to conventional physical therapy. [17]

Although incentive spirometry is used commonly by post-operative patients, evidence fails to support its benefit. [18-23] One systematic review stated, "Presently, the evidence does not support the use of incentive spirometry for decreasing the incidence of PPCs." [19] Another meta-analysis found no evidence of benefit from incentive spirometry after coronary artery bypass surgery. [22] In addition, a recent study on the financial impact of incentive spirometry demonstrated that for the 9.7 million inpatient surgeries performed annually in the United States, the total annual cost of implementing postoperative incentive spirometry is estimated to be $1.04 billion.[24] Most importantly, incentive spirometry is not the ideal treatment for atelectasis or hypoxemia. Incentive spirometry does not provide PEEP.

PEEP is a well-known pulmonary physiologic principle. There are on average 600 million alveoli in the lung. Each alveolus has surfactant to resist the natural propensity for these small air sacs to collapse during exhalation. Despite this surfactant, some alveoli will collapse and not be available for gas exchange. This atelectasis results in a ventilation/perfusion mismatch where alveolar units are perfused but not adequately ventilated. This is referred to as shunting and results in hypoxemia (decreased PaO2).

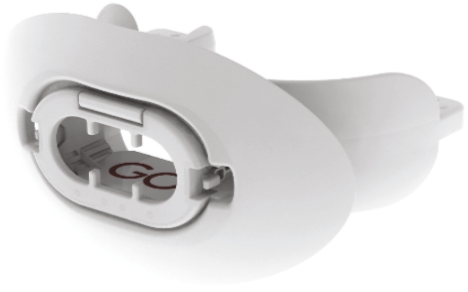
Atelectasis, shunting, and hypoxemia are very common complications of surgery and result in significant morbidity and mortality in surgical patients.

PEEP decreases the propensity for the alveoli to collapse by increasing the air pressure in the lungs. This residual pressure in the lungs at the end of exhalation decreases shunting and allows for more complete gas exchange and improved oxygenation. In patients, PEEP is one of the safest ways to increase PaO2 and is used on almost all modern ventilator settings.

We have developed a simple, comfortable, and straightforward silicone-injected, bidirectional oxygenation mouthpiece that effectively delivers PEEP with every breath (image 1). The purpose of this pilot study is to demonstrate the safety and feasibility of the bidirectional oxygenation mouthpiece in cardiac surgical patients, compare this novel device to conventional incentive spirometry, and identify any potential benefits to respiratory dynamics.

Image 1. Bidirectional oxygenation mouthpiece

1a – PEEP Mouthpiece valve closed during expiration.



1b – PEEP Mouthpiece valve open during inhalation.

Initial testing using the bidirectional oxygenation mouthpiece on healthy subjects has been encouraging. Crouse et al. studied nine subjects during exercise and reported that the "Wearable Positive End-Expiratory Pressure Valve Increases Aerobic Capacity and Performance." [25] Subjects were assigned at random to the novel bidirectional oxygenation mouthpiece, a standard oxygenation mouthpiece, or nothing at all. Subjects wearing the bidirectional oxygenation mouthpiece showed an improvement in VO2 max of 6.1% compared to the standard mouthpiece and 4.0% compared to no mouthpiece. The endurance test showed an improvement of 6.5% compared to the standard mouthpiece and 6.0% compared to no mouthpiece. All results had p-values < 0.05. No adverse events were reported during the testing. Furthermore, the consumer version of this device, which is being used by athletes during vigorous exercise, has sold over 2000 units to date with no reported adverse events.

Research Design and Methods

Design

This pilot study will utilize a single center, prospective, randomized controlled study design.

Target Study Population
Patients undergoing coronary bypass and/or valve replacement will be evaluated for study eligibility, and will be preoperatively selected according to the below criteria:

Inclusion Criteria
1. Undergoing CABG and/or valve replacement surgery
2. Able to provide written informed consent
3. Maintenance of an arterial line postoperatively

Exclusion Criteria
1. Active smoking, within three months of surgery
2. FEV1 <75% predicted
3. Relative risk to develop pulmonary barotrauma as evident by history of pneumothorax or emphysema
4. Unable or unwilling to provide informed consent, cognitive impairment

Study Endpoints

Primary Endpoint
1. Pa02 level at 1, 6, 12 and 24 hours post-extubation.

Secondary Endpoints
1. Atelectasis on CXR (Atelectasis Severity Score) immediately post-op and on postoperative days 1-4
2. Oxygen requirement 1, 6, 12 and 24 hours post-extubation and daily each morning
3. CO^2 level at 1, 6, 12 and 24 hours post-extubation
4. FEV1 and FVC measurements pre-op and on postoperative day 3
5. Respiratory rate 1, 6, 12 and 24 hours post-extubation then daily each morning
6. Peak body temperature every 24 hours (as a marker of atelectasis)

Study Procedures

After an eligible patient has provided written informed consent, he/she will be randomly assigned to one of two study cohorts: incentive spirometer (Control Arm) or Bidirectional Oxygenation Valve (G02 Mouthpiece).

Permuted block randomization will be employed to ensure balance between groups when the number of recruited patients reaches a multiple of the block size. All patients will undergo additional postoperative respiratory therapy, including: deep breathing exercises, directed cough, early mobilization and optimal analgesia per routine care. Mouthpieces for each study arm will be provided to a patient throughout the hospitalization.

Both cohorts will use the assigned device following similar protocols:
1. Proper positioning of the patient in bed.
2. Proper positioning of the incentive spirometer or Go2 mouthpiece.
3. A breath cycle will consist of 10 breaths every hour while awake. See instructions in Appendix A.
4. The research assistant will provide adequate training for both devices and will supervise their use.

Arterial blood gases (ABGs) will be collected on 2L/NC (x 5 min) at 1, 6, 12 and 24 post-extubation (+/- 1 hour). Pt. will be asked to use assigned device (incentive spirometer or GO2 mouthpiece) before each ABG is collected. Blood samples will be tested locally at the Emory St. Joseph's Hospital Laboratory.

A chest radiograph will be obtained immediately post-op and daily on post-op days 1-4 to assess the presence of atelectasis using the atelectasis severity score. X-rays will be read by a single radiologist in a blinded fashion.

Respiratory rate will be measured 1, 6, 12 and 24 hours post-extubation then daily each morning.

Body temperature will be measured per nursing routine (as a marker of atelectasis). Temperature max will be recorded each 24 hours.

Schedule of Assessments

Study Procedures	**Baseline (up to 30 days before surgery)**	**Post-Op**	**POD 1**	**POD2**	**POD3**	**POD4**
Consent	**X**					
Pulmonary function test (PFT)	**X**				**X**[2]	
Randomization	**X**					
Treatment: breathing exercises with mouthpieces		**X**	**X**	**X**	**X**	**X**
Arterial blood gas (ABGs)			**X**[1]	**X**[1]		
Chest x-ray with Atelectasis Severity Score	**X**	**X**	**X**	**X**	**X**	**X**
RR and body temp		**X**	**X**	**X**	**X**	**X**
Peak Body Temp			**X**	**X**	**X**	**X**
Adverse Events		**X**	**X**	**X**	**X**	**X**
Use of Device Questionnaire						**X**[3]

[1]ABGs 1, 6, 12 and 24 post extubation.

[2]Peformed for research purposes only

[3]Can be done from POD4 up until discharge from hospital

Statistical Analysis Plan

As a pilot study, our goal is to examine the feasibility and safety of conducting this pilot study on a larger scale. We evaluate the feasibility of recruitment, retention, assessment and implementation of the proposed interventions. We wish to identify any potential flaws in the study design and potential challenges in the subsequent large-scale study. Moreover, the pilot data will give us a first impression of the variability and effect sizes of Pa02 in the patient population of interest and thus assist in the sample

size and power calculation of the subsequent larger study. Finally, the data that we collect from this pilot will help identify modifications needed in the planning and design of the subsequent study.

We will also assess safety of the new mouthpiece with close monitoring of patient symptoms, physical exam, PaO2, PCO2, CXR results, vital signs, and temperature. At the conclusion of the study, we will attempt to assess between-group differences, but given that low power is characteristic of pilot studies, statistical significance is not the focus of the analysis. However, we plan to provide statistical summaries that would be useful in the subsequent study and to other researchers, such as number of patients screened per month, number of patients enrolled per month, proportion of screen eligible who enrolled, lost-to-follow rate, study costs.

We will also summarize patient characteristics at baseline and during follow-up using mean ± standard deviation (or median and interquartile range, as appropriate) for quantitative variables and frequency (percentage) for categorical variables. Summary statistics on Pa02 will be reported at each measurement occasion for each group. We will also attempt to fit a mixed effects model to examine between-group differences in Pa02 at each study visit. An error covariance structure most appropriate to the data will be chosen. Every effort will be made to ensure complete follow-up, and to handle missed visits, missingness at random will be assumed. Finally, a qualitative review will also be provided, and this will include, among others, an evaluation of the representativeness of the patient volunteers, a discussion on how to refine the data collection tools, how to improve the database, how to track patients better as well how to improve implementation of the proposed intervention.

Sample Size and Accrual

The sample size for this pilot study will include 20 patients undergoing coronary bypass and/or valve replacement surgery, however, we anticipate that approximately 40 patients may be consented to account for patients that may be ineligible, screen fail, or withdraw from study. This is the number of anticipated eligible patients that may be recruited over a period of 2 months. This number is deemed sufficient to demonstrate the feasibility and safety of the bidirectional oxygenation mouthpiece.

General Design Limitations

Possible pitfalls may include unsupervised use of the assigned mouthpiece or unexpected non-pulmonary complications secondary to the surgery which may affect the results of the analysis. Also, subjects opting out of the study may represent a potential drawback, secondary to pain or fatigue, or evidence of hyperventilation and/or respiratory alkalosis.

Protection of Human Subjects

Institutional Review Board (IRB) Review and Informed Consent

Screening and enrollment will not begin until the Emory University IRB has approved the study protocol and informed consent form.

A physician investigator or study team designee(s) will obtain the informed consent document and verify the date of consent document is within the IRB approval period.

A physician-investigator or study team member designee(s) will begin the informed consent process with the subject ≥24 hours in advance of surgery and/or study procedures when possible. This will allow the subject sufficient opportunity to consider whether or not to participate in a study. The informed consent process may begin either in-person with the patient or by telephone.

The person obtaining informed consent will meet the subject in a private area to present the consent document to the subject, provide a description of the study purpose, procedures, risks/benefits, alternative treatment options, and follow-up schedule. The subject will be given adequate time to fully understand the study, including risks and benefits and study-required follow up visits, and time to ask questions.

If the subject volunteers to participate in a study, he/she must verbalize understanding of the consent before he/she signs. The person obtaining informed consent will obtain all required signatures on the informed consent and HIPAA documents. The subject's consent will be obtained before any research related procedures are performed.

e-Consent

The consent process begins when a patient is screened, identified and verified as eligible for study participation. During the Zoom teleconference call, a member from the study team will discuss the consent form in its entirety with the potential participant. The patient will be offered ample time to discuss the consent form with family and or friends, and have questions answered. In DocuSign, potential subjects have the ability to review the consent document as freely as they would if they were consenting in person. They also have the opportunity to exit the document without signing.

The process for obtaining e-consent is outlined below:

1. First, the IRB approved, stamped consent forms are added to an envelope in DocuSign.
2. Recipients (subject/coordinators) are then added to the envelope and signature and initial fields are assigned to them on the IRB approved consent form.
3. The consent is then sent to the patient via email.
4. Once the consent document is completed by all parties, a signed copy is forwarded to the subject via email. The completed document is also saved on the research team's secure, internal shared drive.

Subject Confidentiality

Subject confidentiality will be guaranteed by storing all data collected in a password-protected database with no associated PHI or patient identifier information included. Patients in this database will only be identified via a unique study ID number. This study ID number will link the electronic data set of each patient to their PHI that will be stored separately in the research study binder.

Subject Safety

Subject safety is of utmost importance throughout this study. The use of oxygenation devices such as the incentive spirometer has not been associated with pulmonary complications or other adverse events. Nonetheless, patients with history of chronic obstructive pulmonary disease or those at risk of developing barotrauma will be excluded from this study.

Adverse Events

Patients will be assessed for the following adverse events:

1. Hypoxia (O2 saturation <85%)
2. CO rise 20% over baseline
3. Increasing O2 requirement (non-rebreather mask, biflow, BIPAP requirement)
4. Reintubation

5. Pneumothorax

All serious adverse events will be assessed and reported per the Emory IRB Policies and Procedures.

Data Collection and Monitoring

Study data will be collected from the patient's electronic medical records and from the local Society of Thoracic Surgeons (STS) clinical outcomes database. All information will be entered in a de-identified fashion into a password protected Microsoft Excel spreadsheet created for the study. All study data will be coded using indirect identifiers consisting of a unique numeric study ID code linked to each study participant's name to enable verification of study data against source data, as needed.

Study data, including Protected Health Information (PHI), will be obtained with the patient's direct authorization through the consent form in accordance with HIPAA policy. PHI will be obtained via patient medical records and the STS database as noted above. Permission for use or evaluation of PHI will be limited to the principal investigator, and research study staff. The PHI will be a part of the clinic record and patient study binder. The binders will be kept in a secure location when not being used by the research staff. The PHI collected will be used by the PI and research staff for study tracking purposes, to link and confirm study data with the information located in the patient's clinical record, and if patient safety necessitates, to communicate relevant findings with the patient's healthcare providers. The PHI will be destroyed using the institution's official recycling system once the study is completed. The PI and staff will maintain the records of the study including all correspondence, the study protocol with any/all amendments, all correspondence with and approval from the Emory IRB, and signed informed consent forms in the Regulatory Binder. All these materials, along with individual patient files, data collection forms and source data will be stored and maintained, along with a record of the location of storage, for up to 1 year after the completion of the study. Records will be destroyed using the official institutional recycling system.

Data Management

Upon study completion the final data set will be provided to Sponsor and stored within the secure server in the Houston Plastic Craniofacial and Sinus Surgery office (9230 Katy Freeway, Houston, TX 77055). All non-identifiable patient data collected will be stored on a password encrypted Microsoft Excel document on the same server. No information will be transmitted electronically outside of the server nor will any data be stored off of the server on any portable type media storage device. All study participant PHI and personal contact information will be securely stored in a study binder at Emory Saint Joseph's research office.

A data safety monitoring plan is not necessary for this minimal risk study.

Facilities

The surgical procedure and postoperative care will take place at Emory Saint Joseph's Hospital, Atlanta, Georgia.

Funding Source

Funding for the study will be provided by PEEP Medical, LLC. Bidirectional oxygenation mouthpieces will be provided by the Sponsor. Incentive spirometers will be provided by the hospital as part of the routine postoperative respiratory therapy.

Appendix A

Instructions for Patients Assigned to the Incentive Spirometer

Thank you for participating in the GO^2 PEEP research study. You have been assigned to the study group using the incentive spirometer.

1. To use the incentive spirometer, sit up as far as you can in bed and hold the incentive spirometer
2. Take a deep breath in and then blow out all the way through your mouth with pursed lips.
3. Put the mouthpiece in your mouth. Seal your lips tightly around it.
4. **Breathe in slowly through your mouth as deep as possible.** The blue disc will rise toward the top of the column.
5. Keep the blue indicator on the right side between the arrows.
6. Open your mouth and then breathe out, allowing the blue disc to fall to the bottom of the column.
7. Rest for a few seconds and repeat steps above at least 10 times every hour while you are awake. If you feel dizzy, slow your breathing down.
8. Move the arrow on the left side of the spirometer to show the highest number you reached.
9. After each set of 10 deep breaths, practice coughing to be sure your lungs are clear. You may use the device additionally if desired.
10. Place a pillow firmly against incision area to ease any discomfort while coughing.

Practice this 4-6 times each day before your surgery.

If there are any issues or problems contact Dr. Jeffery Miller or the research coordinator at 678-843-6092 as soon as possible.

Instructions for Patients Assigned to the Bidirectional Oxygenation Mouthpiece

Thank you for participating in the GO^2 PEEP research study. You have been assigned to the study group using the bidirectional oxygenation mouthpiece.

1. To use mouth piece, place the device inside the mouth, loosely biting down on the bite plate. Allow your lips to surround the lip flange.

2. Breathe in as deeply as you can in a steady manner. Exhale through the device as completely and forcibly as possible.

3. Repeat the process, breathing as deeply as possible and exhaling for 2.5 minutes, rest for 10 minutes and then repeat another 2.5 minutes. Complete this every hour while awake.

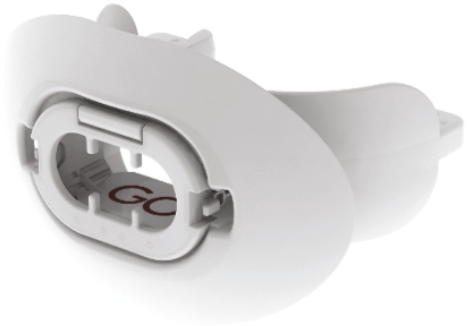
4. After using mouth piece each hour, practice coughing to be sure your lungs are clear. You may use the device additionally if desired.

5. Place a pillow firmly against incision area to ease any discomfort while coughing.

Practice this 4-6 times each day before your surgery.

If there are any issues or problems contact Dr. Jeffery Miller or the research coordinator at 678-843-6092 as soon as possible.

1a – PEEP Mouthpiece valve closed during expiration.



1b – PEEP Mouthpiece valve open during inhalation.

Table 1

Table 1. Risk Factors for PPCs

Preoperative	Postoperative
Age > 50	Type of surgery*
Congestive heart failure	Neuromuscular blocking agents
Cigarette and/or alcohol abuse	Perioperative blood transfusions
COPD	Operative time longer than 3 hours
Corticosteroids use	General anesthesia
	Emergency surgery

*Thoracic, upper abdominal, head and neck, neurosurgery, open aortic resection

References

1. Lawrence VA, Dhanda R, Hilsenbeck SG, *et al*. Risk of pulmonary complications after elective abdominal surgery. Chest 1996; 110(3):744-750
2. Bartlett RH, Brennan ML, Gazzaniga AB, *et al*. Studies on the pathogenesis and prevention of postoperative pulmonary complications. Surg Gynecol Obstet 1973;137(6):925-933.
3. Lawrence VA, Hilsenbeck SG, Mulrow CD, *et al*. Incidence and hospital stay for cardiac and pulmonary complications after abdominal surgery. J Gen Intern Med 1995;10(12):671- 678
4. Smetana GW. Postoperative pulmonary complications: an update on risk assessment and reduction. Cleve Clin J Med 2009;76(Suppl 4):S60-S65.
5. Dimick JB, Chen SL, Taheri PA, *et al*. Hospital costs associated with surgical complications: a report from the private-sector National Surgical Quality Improvement Program. J Am Coll Surg 2004;199(4):531-537.
6. Johnson RG, Arozullah AM, Neumayer L, *et al*. Multivariable predictors of postoperative respiratory failure after general and vascular surgery: results from the patient safety in surgery study. J Am Coll Surg 2007;204(6):1188- 1198.
7. Qaseem A, Snow V, Fitterman N, *et al*. Risk assessment for and strategies to reduce perioperative pulmonary complications for patients undergoing noncardiothoracic surgery: a guideline from the American College of Physicians. Ann Intern Med 2006;144(8):575-580.
8. Smetana GW, Lawrence VA, Cornell JE; American College of Physicians. Preoperative pulmonary risk stratification for noncardiothoracic surgery: systematic review for the American College of Physicians. Ann Intern Med 2006;144(8):581-595.
9. Brueckmann B, Villa-Uribe JL, Bateman BT, *et al*. Development and validation of a score for prediction of postoperative respiratory complications. Anesthesiology 2013;118(6):1276-1285.
10. Lawrence VA, Cornell JE, Smetana GW; American College of Physicians. Strategies to reduce postoperative pulmonary complications after noncardiothoracic surgery: systematic review for the American College of Physicians. Ann Intern Med 2006;144(8):596-608.
11. Licker M, Diaper J, Villiger Y, *et al*. Impact of intraoperative lung-protective interventions in patients undergoing lung cancer surgery. Crit Care 2009;13(2): R41.
12. Arozullah AM, Daley J, Henderson WG, Khuri SF. Multifactorial risk index for predicting postoperative respiratory failure in men after major noncardiac surgery. The National Veterans Administration Surgical Quality Improvement Program. Ann Surg 2000;232(3): 242-253.
13. Hwang D, Shakir N, Limann B, *et al*. Association of sleep-disordered breathing with postoperative complications. Chest 2008;133(10):1128-1134.
14. Fernandez-Perez ER, Sprung J, Afessa B, *et al*. Intraoperative ventilator settings and acute lung injury after elective surgery: a nested case control study. Thorax 2009;64(2):121-127.
15. Saski N, Meyer MJ, Eikermann M. Postoperative respiratory muscle dysfunction. Anesthesiology 2013;118(4):961-978.
16. Bartlett RH, Gazzaniga AB, Geraghty TR. Respiratory maneuvers to prevent postoperative pulmonary complications. A critical review. JAMA 1973;224(7):1017-1021.
17. Minschaert M, Vincent JL, Ros AM, Kahn RJ. Influence of incentive spirometry on pulmonary volumes after laparotomy. Acta Anaesthesiol Belg 1982;33(3):203-209.
18. Agostini P, Calvert R, Subramanian H, Naidu B. Is incentive spirometry effective following thoracic surgery? Interact Cardiovasc Thorac Surg 2008;7(2):297-300.
19. Overend TJ, Anderson CM, Lucy SD, Bhatia C, Jonsson BI, Timmermans C. The effect of incentive spirometry on postoperative pulmonary complications: a systematic review. Chest 2001;120(3): 971-978.

20. Pasquina P, Tramer MR, Walder B. Prophylactic respiratory physiotherapy after cardiac surgery: systematic review. BMJ 2003; 327(7428):1379.
21. Pasquina P, Tramer MR, Granier JM, Walder B. Respiratory physiotherapy to prevent pulmonary complications after abdominal surgery: a systematic review. Chest 2006 Dec;130(6):1887-1899.
22. Freitas ER, Soares BG, Cardoso JR, Atallah A´ N. Incentive spirometry for preventing pulmonary complications after coronary artery bypass graft. Cochrane Database Syst Rev 2012;(9):CD004466.
23. Guimaraes MM, El Dib R, Smith AF, Matos D. Incentive spirometry for prevention of postoperative pulmonary complications in upper abdominal surgery. Cochrane Database Syst Rev 2009;(3):CD006058.
24. Eltorai AE, Baird GL, Pangborn J, Eltorai AS, Antoci V, Paquette K, Connors K, Barbaria J, Smeals KJ, Riley B, Patel SA, Agarwai S, Healey TT, Ventetuolo CE, Sellke FW, Daniels AH. Financial impact of incentive spirometry. Journal of Health Care Organization, Provision, and Financing. 2018.
25. Crouse SF, Lytle JR, Martin SE, Green JS, Moreno M, McCulloch P, Boutros S, Benton W, Lambert BS. Wearable positive end-expiratory pressure valve increases aerobic capacity and performance. Poster presentation. Applied Exercise Science Lab. 2018.