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The physiologic impact of pectus excavatum repair

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ABSTRACT

The adverse physiologic effects of pectus excavatum and subsequent resolution following correction have been a subject of controversy. There are numerous accounts of patients reporting subjective improvement in exercise tolerance after surgery, but studies showing clear and consistent objective data to corroborate this phenomenon physiologically have been elusive. This is partially due to a lack of consistent study methodologies but even more so due to a mere paucity of data. As experts in the repair of pectus excavatum, it is not uncommon for pediatric surgeons to operate on adult patients. For this reason, this review evaluates the contemporary literature to provide an understanding of the physiologic impact of repairing pectus excavatum on pediatric and adult patients separately.

Pediatric patients

Introduction

Pectus excavatum affects patients at different ages and is the most common congenital chest wall deformity (88%).[1] While some patients are born with the deformity, most do not develop the deformity until their prepubescent and early teenage years.[2] Preteen children are typically asymptomatic, but as they become more active in their teenage years they start to report symptoms. These symptoms include exercise intolerance, lack of endurance and shortness of breath with exercise.[3] Over 400 years ago in Spain, Bauhinus described a patient with severe pectus excavatum that suffered from exercise intolerance and since then there have been multiple similar reports in the literature.[4] More recent data supports this historic description with pectus patients reporting symptoms of shortness of breath and exercise intolerance ranging from 68 to 86%.[5,6] After repair, using validated questionnaires (i.e. Pectus Excavatum Evaluation Questionnaire (PEEQ), Child Health Questionnaire (CHQ)), a statistically significant perceived improvement in exercise tolerance has been reported by both patients and their parents.[5,7] A recent query of our database at Children's Hospital of The King's Daughters in Norfolk, Virginia from 1985 to 2018 which included 1270 patients demonstrated a similar finding. Approximately 95% of these patients no longer reported exercise intolerance with the bar in place. While these subjective reports are encouraging, it is important to investigate the anatomic and physiologic explanation for this perceived improvement after pectus excavatum repair.

In the previous decade there were several small studies that found evidence to support improved cardiovascular function after the Ravitch procedure.[8] The focus of this review is on data obtained from contemporary literature on pediatric pectus patients undergoing minimally invasive repair of pectus excavatum (MIRPE). The current literature frequently demonstrates improvements in pulmonary function,[9] chest wall mechanics,[10,11] cardiac function,[12] and cardiopulmonary exercise tolerance[13] after surgical correction of pectus excavatum. The dominant physiologic explanation is difficult to identify due to the complex interrelated function of respiratory mechanics and cardiac function, particularly during exercise. The current literature also has several limitations: short-term versus long-term results, rest versus exercise studies, inconsistent measure of pectus excavatum severity and outcomes, lack of control groups (i.e., normal patients or pectus patients forgoing treatment), inconsistent aerobic exercise capacity testing methods, and failure to control for conditioning of subjects. Finally, while a statistically significant change in exercise tolerance is difficult to demonstrate in even a well-designed study, the clinical improvement in exercise tolerance reported by the overwhelming majority of pectus patients after repair cannot be discounted.

Resting pulmonary function testing

The majority of pectus patients do not have pulmonary parenchymal or airway disease, therefore any improvement in pulmonary function after pectus excavatum correction is likely

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Table 1
Percent predicted FVC before repair and after bar removal.*

Author	Year	Patients	Pre-operative	Post bar removal	*p-value*
Lawson**	2005	25	84 ± 8	90 ± 11	**0.0015**
Castellani	2010	46	91 ± 14	88 ± 13	0.117
O'Keefe	2013	67	91 ± 19	99 ± 23	**<0.001**
Maagaard	2013	44	92 ± 14	92 ± 13	n.s.

* Values rounded to whole numbers for clarification and ranges estimated based on available data.
** Includes only patients over 11 years of age.

Table 2
Percent predicted FEV1 before repair and after bar removal.*

Author	Year	Patients	Pre-operative	Post bar removal	*p-value*
Lawson	2005	25	81 ± 8	90 ± 9	**0.0052**
O'Keefe	2013	67	81 ± 17	90 ± 21	**<0.001**
Maagaard	2013	44	86 ± 13	93 ± 13	**<0.001**

* Values rounded to whole numbers for clarification and ranges estimated based on available data.

attributable to an improvement in respiratory mechanics.[10] At rest the diaphragm initiates most of the inspiratory effort. During exercise, more thoracic excursion is required to generate higher lung volumes, at which time the sternum and costochondral cartilage become more important for efficient respiration.[14] Although resting pulmonary function tests (PFTs) may not be the optimal way to evaluate patients complaining of symptoms during exercise, they have the inherent strength of being reported against a normal distribution.[15]

Siglet et al. from Calgary produced one of the first comprehensive reports in 2003 which looked at results 3 months after repair in 11 patients.[16] This investigation helped pave the way for future studies by including an assessment of exercise tolerance, pulmonary effects, and cardiac function. Their patients universally reported modest to marked improvement in exercise tolerance, but interestingly their PFTs worsened. This result was likely secondary to patient deconditioning as reported by the authors. One month later, Borowitz and the group from Buffalo performed similar testing on 10 patients, for whom the deleterious effects on PFTs resolved at 6 –12 months after repair.[17] Many authors have even made the argument that PFTs may be suboptimal while the bar is still in place due to its restrictive effects. For this reason, the literature reviewed here includes only long-term studies where PFTs were compared before repair and after bar removal. The first study to compare PFT outcomes at these two time points was reported by Lawson et al. in 2005. This study included 45 patients with an FVC and FEV1 measured anywhere from 0.1 to 3.8 years (average 1.2) after bar removal. Patients less than 11 years of age did not appreciate a significant increase in PFTs, however those over 11 years of age had a 6% increase in FVC and a 9% increase in FEV1, both reaching statistical significance.[18] Five years later, Castellani et al. completed a cardiovascular performance study in Austria which was similar to Sigalet's study in 2003. Only the long term outcome of FVC was reported, which decreased but did not reach statistical significance.[21] Almost a decade after his first report, Sigalet collaborated with O'Keefe et al. to publish the follow-up study "Longer term effects".[12] This study also detailed the effects of MIRPE on PFTs and demonstrated a significant improvement in both FVC and FEV1 after bar removal.[12] In the same year, Maagaard et al. found no significant change in FVC but a statistically significant increase in FEV1 after MIRPE[13] (Tables 1 and 2). Maagaard et al. was the only group to examine PFTs in pectus patients versus matched controls. A statistically lower FEV1 in preoperative pectus patients (48) versus controls (25) (86% vs 94%; p=0.008) was noted, but this normalized 3 years later after pectus bar removal (93% vs 97%; p=0.268). There was no statistically significant change in FVC before repair (92% vs 98%; p=0.060) or 3 years later (92% vs 98%; p=0.076).[13]

It is worth noting that changes in PFTs after the Ravitch procedure have been less favorable than after MIRPE, potentially due to the disruption and subsequent calcification of the costochondral cartilage.[20,21] This concept combined with the greater improvement appreciated in FEV1 over FVC in all of these studies (Tables 1 and 2) may help provide some explanation for improved exercise tolerance. One theory to explain this is that the total volume of air that can be exchanged during maximal inspiration and expiration (i.e., FVC) is not significantly affected by predominantly reshaping the middle of the chest wall. However, the remodeling of the costochondral cartilage by MIRPE may improve respiratory mechanics such that patients are able to expel air faster in one second (i.e., FEV1) and thus inhale oxygen-rich air faster during exercise. In summary, resting PFT studies evaluating FVC and FEV1 show an expected initial decline shortly after MIRPE that improves to slightly above baseline after bar removal in most studies.

Chest wall motion analysis

In 2011, Redlinger et al. employed Optoelectronic Plethysmography (OEP), a form of motion analysis, to demonstrate regional chest and abdominal wall motion dysfunction in pectus excavatum patients. During deep breathing, the movement of the upper and lower sternum was decreased by 28–51%, and the abdominal wall motion was increased by 147% in pectus patients compared to matched controls. The significant increase in abdominal wall motion was hypothesized to be a compensatory reaction to a relatively fixed sternum during forceful breathing.[10] The following year, 42 patients underwent repeat testing 6 months postoperatively with the Nuss bar in place. There was a resolution of aberrant paradoxical movement of the sternum and abdominal wall during forceful respiration. These studies demonstrate an increase in sternal motion after pectus excavatum correction, which may provide a biomechanical explanation for the noted increase in FEV1. The improvement in respiratory mechanics as demonstrated by OEP analysis and PFT studies may help explain patient reported improvement in exercise tolerance after MIRPE.[12,22]

Resting cardiac function testing

Right ventricle

Analogous to resting PFTs, cardiac studies performed during rest may not provide a clear physiologic cardiac explanation for improved exercise tolerance. Jeong et al. demonstrated a statistically significant resolution of cardiac compression, namely the right ventricle, on computed tomography after pectus excavatum repair. However, it is important to recognize that supine imaging may underestimate the severity of this compression when the patient is in the upright position during exercise.[11] This cardiac compression was further characterized by Coln et al. in 2006. They reported the largest pediatric series of preoperative and postoperative resting echocardiograms in 123 pediatric patients with pectus excavatum and demonstrated that 117 pectus patients had resolution of chamber compression after Nuss repair. Valve abnormalities, most commonly mitral valve prolapse and regurgitation, also resolved in almost all patients.[6] These anatomic changes produce a relief of cardiac compression that has been postulated by several authors to improve right heart filling and function.[6,11,23] In 2016, Topper et al. proved this effect using Cardiovascular Magnetic Resonance (CMR) imaging. CMR has evolved to be the accepted standard to evaluate the right ventricular function due to its complex crescent shape that makes it difficult to model with

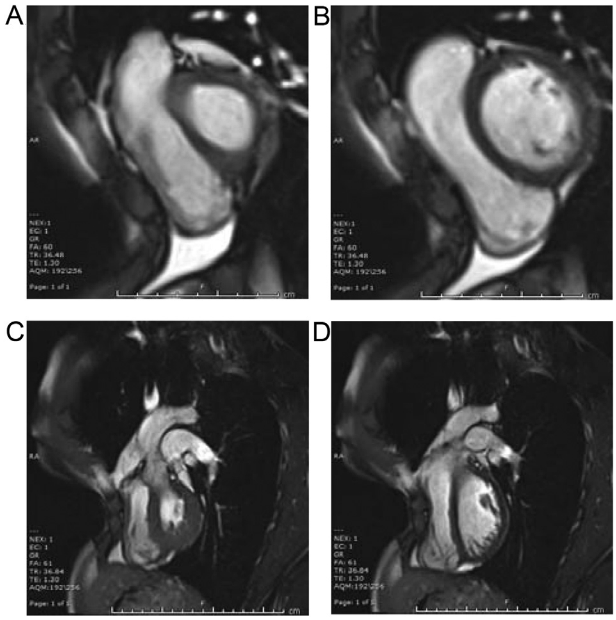

Fig. 1. CMR images showing deformation of the crescentric shaped right ventricle obtained in the same plan during systole and diastole (A & B: left and right ventricle view; C & D: left ventricular outflow tract view).

standard echocardiography (Fig. 1). Their study included a mixed-age population (mean age 21 ± 8.3 years) of 38 pectus excavatum patients repaired with titanium bars. They performed CMR imaging preoperatively and demonstrated an increase in right ventricular ejection fraction (RVEF, %) as soon as 2 weeks post-repair with an effect that persisted over 1 year after repair [45.7 ± 1.7 to 48.3 ± 1.3 ($p = 0.0004$)]. In this study they also demonstrated that the Haller index, and several other radiographic indices, could not predict the adverse physiologic effect of the pectus deformity on RVEF. The only finding that predicted improvement in RVEF after pectus excavatum repair was a low RVEF preoperatively.[24] These studies demonstrate that MIRPE resolves compression of the right ventricle and in some patients improves right ventricular function at rest.

Left ventricle

The most frequent measure used to quantify heart function is cardiac output. Cardiac output (CO) is calculated using the equation:

$$CO = HR \times SV$$

(HR = heart rate and SV = stroke volume)

Cardiac index is a more useful measure when comparing cardiac function in pediatric patients because it controls cardiac output as it relates to the patient's body surface area (BSA).

$$CI = CO/BSA$$

(BSA = Body Surface Area)

Even after correcting for BSA, several other variables not represented in this equation, particularly those affecting SV, can affect cardiac output including hydration, position, contractility, afterload, and preload. In the 2013 study by O'Keefe et al., there was no significant change in resting cardiac index before pectus excavatum repair and after Nuss bar removal in 67 pediatric patients: 3.23 + 1.09 to 2.98 + 0.79 L/min/m^2 (p=0.10).[12] Similarly, in the study by Topper et al. they did not demonstrate a significant change in SV normalized for BSA in a mixed-age population over a year after pectus excavatum repair: 48.2 + 2.8 to 49.7 + 1.9 mL/m^2 (p=0.0591).[24] Compared to the right ventricle, the left ventricle is located more posteriorly and is a thicker muscular structure. This combination makes the left ventricle comparatively protected from the compressive effects of the sternum. These reasons likely explain the diminutive changes in resting cardiac output/index demonstrated after MIRPE.

Cardiopulmonary exercise testing

Background

Exercise tolerance is difficult to measure, but cardiopulmonary exercise testing (CPET) is generally accepted as one of the most reliable methods to measure functional aerobic exercise capacity.[16,25,26] During CPET exercise capacity is quantified using peak oxygen uptake (vO_2max, mL/min/kg) calculated by applying Fick's equation:

$$vO_2max = (SVmax \times HRmax) \times (CaO_2\,max - CvO_2\,max)$$

(SVmax = max stroke volume; HRmax = max heart rate; CaO_2max = max arterial oxygen content; CvO_2max = mixed venous oxygen content)

This represents the maximum ability of a patient to inspire, transport, and consume oxygen in the peripheral tissue. CPET allows for an integrative assessment of the interplay between the cardiac, pulmonary, musculoskeletal, hematopoietic, and neuropsychological systems.[26] There are multiple other variables that affect vO_2max: conditioning, lean body mass, diet, rest, mitochondrial efficiency, motivation, and ergometric testing methods. Conditioning is important when measuring vO_2max and since a consistent level of training in all study subjects and controls would be a herculean task, it is an obvious limitation of all studies to date. Cardiac function during exercise, which is only one part of Fick's equation, has also been studied to help investigate the effects of pectus excavatum on cardiac physiology. Oxygen pulse (O_2 pulse, mL O_2/beat) is a commonly accepted method to estimate stroke volume during exercise.[27,28] Measuring the actual peak stroke volume (mL/beat), peak stroke index (mL/beat/m^2), and peak cardiac index (L/min/m^2) is much more difficult and has been utilized in only one study on pediatric pectus patients.[13]

vO_2max

The three largest long-term studies evaluating vO_2max in pediatric patients before pectus excavatum repair and after Nuss bar removal include the following: Castellani (59 patients), O'Keefe (67 patients), and Maagaard (44 patients including 26 controls). It is worth noting that all three studies used different ergometric testing methods but the differences are beyond the scope of this discussion. Castellani's study demonstrated a small yet statistically significant decrease in vO_2max after bar removal from 43.8 ± 6.5 to 42.2± 7.2 (p=0.027). However, they noted a significant increase in BMI [18.9 +/−2.6 kg/m^2 to 21.0 +/−2.3 kg/m^2 (p<0.001)] and body fat content from the Pre-op to Post-op group [12.5 +/−5% to 15.2 +/−5.4% (p<0.001)]. Since lean muscle mass is the main tissue bed responsible for oxygen consumption during exercise, they presented their data in terms of lean body mass to calculate their vO_2max. After correcting for lean muscle mass they demonstrated no significant difference in vO_2 max between pectus excavatum patients before repair and after bar removal.[19] O'Keefe showed a trend toward improved vO_2max in patients after MIRPE that did not reach statistical significance.[12] Maagaard et al. conducted the only study to compare pectus patients to matched controls. They demonstrated a statistically lower vO_2max in preoperative pectus patients versus controls. The vO_2max was no longer statistically different between pectus patients after Nuss bar removal versus

Table 3
vO_2max (peak oxygen uptake; mL/min/kg).

Author	Subjects	Age (years)[a]	Type of repair	Preoperative	Post bar removal	*p-value*
Castellani et al. (2010)[b]	$N=59$	16 ± 5	MIRPE	49.8 ± 5.5	49.8 ± 7.3	0.941
O'Keefe et al. (2013)	$N=67$	14 ± 2	MIRPE	33.2 ± 7.5	34.2 ± 7.5	0.09
Maagaard et al. (2013)	$N=44$[c]	16 ± 2	MIRPE	26.0 ± 7.1[d]	29.0 ± 5.9[e]	**<0.05**[f]
	$N=26$[c]	15 ± 2	Controls	30 ± 7.7[d]	31 ± 8.0[e]	

[a] Mean age range rounded to closest whole year.
[b] Corrected for lean body mass.
[c] Body mass index not statistically different.
[d] $p=0.043$; pectus patients' vO_2 max statistically lower than controls.
[e] $p=0.430$; pectus patients' vO_2 max approaches controls and is no longer statistically significant.
[f] Pectus patients demonstrated a significant increase in vO_2max after MIRPE.

controls.[13] Additionally, the pectus patients demonstrated a significant increase in their vO_2max after MIRPE[23] (Table 3).

Peak stroke volume and peak cardiac index

O'Keefe and Maagaard evaluated peak stroke volume (i.e., stroke volume during peak exercise) before and after MIRPE in pediatric patients. Both demonstrated a statistically significant improvement but used different techniques. O'Keefe used O_2 pulse as a surrogate for stroke volume and found an improvement from 75.8 ± 14.4 to 80.5 ± 18.3 mL O_2/beat ($p=0.01$). Maagaard measured the actual peak stroke index and demonstrated a statistically significant increase from 42.0 ± 9.0 up to 50.0 ± 10.0 mL/beat /m^2 ($p=0.0002$).[12,13] Furthermore, Maagaard et al. is the only study to evaluate peak cardiac index in pectus excavatum patients compared to healthy, age-matched controls. They demonstrated a statistically significant lower cardiac index in the pectus patients. [6.6 ± 1.2 vs. 8.1 ± 1.0 L/min/m² ($p=0.0001$)]. Three years after MIRPE and after removal of the Nuss bar, they found no statistical difference in cardiac index between the pectus patients and controls. [8.1 ± 1.2 compared to 8.3 ± 1.6 L/min/m² ($p=0.572$)].[13] In a review article, Maagaard also calculated that the pectus patients as a group had a statistically significant increase in peak cardiac index during this same time period. [6.6 ± 1.2 L/min/m² to 8.1 ± 1.2 L/min/m² ($p<0.05$)]. Compression of the right ventricle in a relatively fixed pericardium shifts the interventricular septum leftward and decreases left ventricular filling during diastole, a phenomenon known as ventricular interaction.[13,29–32] In pectus excavatum patients, the compression on the right ventricle is even more pronounced during forceful breathing. These two physiologic effects may explain why there is more significant improvement in cardiac output during exercise than rest after MIRPE.[10,12,33,34]

Adult patients

A number of pectus excavatum patients may not experience cardiopulmonary symptoms until their later adult years or note progression of symptoms with aging.[35,36] This is more likely secondary to the increasing rigidity of the anterior chest wall structures versus worsening of the defect[37]. Adult pectus repair is more difficult and has higher complication rates reported.[38–43] Although symptoms are subjectively improved with surgical correction, there are only a few studies on the postoperative cardiopulmonary benefits of repair in adults. This limits the ability to fully validate benefits versus risks of repair in this population. It is also possible that cardiopulmonary recovery in the older patient may require additional time after operation and normalization may be less complete than what has been seen in pediatrics and adolescents.

Resting pulmonary function testing

Only one study has been published assessing post MIRPE pulmonary outcomes in adults.[44] Acosta et al reported no significant changes in either FEV1 or FVC at 6 months post repair, but there is no long term data which would be the appropriate measure of outcomes as previously discussed.

Resting cardiac function testing

Right and left ventricle

A number of studies utilizing cardiac MRI for assessment of right and left ventricular dimensions/function have included adult patients however the information is not separated out from the younger population to allow further analysis by age group.[24,45–48] The majority of information available for the adult population on right ventricular (RV) and left ventricular (LV) function and volumes has come from intraoperative transesophageal echocardiogram (TEE).[39,49–53] All but one study document significant improvement in RV dimensions and function[52] A single center has reported their cohort of 168 patients of intraoperative TEE before and after a modified MIRPE.[39,49,50] Significant increases in right heart chamber dimensions were seen after surgery. In a subset of 42 patients, RV stroke volume increased by 34% and RV cardiac output by 38% post repair.[49] An even greater increase in RV ejection fraction (65%) was reported in a subset of 101 patients who were 30 years and older.[39] Chao et al. subsequently evaluated speckle-tracing of RV and LV strain in 165 of the patients.[50] Speckle tracking strain is a method for direct evaluation of myocardial contractile function which does not require parallel alignment of the ultrasound beam to the area being evaluated (as occurs in Doppler echocardiogram).[49] They noted an immediate, significant improvement after repair in both RV and LV strain rates. Kruger et al. 2010 also evaluated by intraoperative TEE 17 patients undergoing open repair.[51] A significant increase in end diastolic RV dimensions and LV ejection fraction (estimated mean increase of the end-diastolic RV area and volume after surgical correction were 47% and 88%, respectively; mean LV EF +14%) occurred after repair.

There have been only 2 studies in adults (Gurkan included patients ≥16 years) assessing RV and LV parameters utilizing standard supine transthoracic echocardiogram.[52,53] Neviere et al. looked at 70 adult patients at baseline preoperative and subsequently at 6–12 months post modified Ravitch. They noted cardiac function at rest to be within the normal range preoperative with a mean Haller index of 4.5 ±1. At postsurgical evaluation, left ventricular ejection fraction (%) increased insignificantly from 63 ± 7 to 65 ± 7 postoperative (P values were not provided). Gurkan et al. investigated 16 patients with preoperative evidence of RV compression as defined by an RV diastolic diameter less than 20 mm. An increase in RV end-diastolic diameter of 47% was reported at

Table 4
vO_2max (peak oxygen uptake; mL/min/kg).

Author	Subjects	Age (years)	Type of repair	Pre-operative	Postoperative1-year after surgery	*p-value*
Neviere et al. (2011)	*N* = 70	27 ± 11	Open	34.9 ± 5	37.6 ± 7.1	**0.0001**
Neviere et al. (2013)	*N* = 20	32 ± 11	Open	30.8 ± 6.9	34.4 ± 8.6	<0.1
Udholm et al. (2015)	*N* = 12	32 ± NR	MIRPE	30.4 ± 6	33.3 ± 5	0.09

one-month follow-up. No significant changes were observed in LV ejection fraction.[53]

Cardiopulmonary exercise testing

Assessment of the effects of surgical repair in adults by CPET has been reported in only 3 major studies, and only one after MIRPE. Follow up has been limited to the first year after operation. Neviere et al. 2011 evaluated 70 adult patients before and after an open modified Ravitch procedure.[52] The significant findings in this study were that the adult PE patients had a reduced peak VO_2 (77% of predicted) which increased after surgery. PE patients were able to achieve a higher aerobic exercise tolerance secondary to an increased peak VO_2, maximal VE and O_2 pulse. In a subsequent report in 2013,[55] Neviere again noted in 20 patients reduced peak VO_2 and peak oxygen pulse. Significant improvements occurred in the anaerobic threshold, peak VO_2, and peak oxygen pulse after repair. A recent report by Udholm et al. 2016 noted findings in their adult cohort that were in contrast to the significant improvements that were seen in their prior reports for children and adolescents.[13,54,56] Only 12 adults completed the cardiac function testing at baseline and again 1-year post repair, however, making the study significantly underpowered to detect a difference. The authors theorized that adult patients might need longer to recover and improve exercise capacity[55,56] (Table 4).

Summary

Pediatric and adult patients experience subjective clinical improvement in exercise tolerance after pectus excavatum repair in the majority of cases. The benefits are likely multifactorial as suggested by studies demonstrating improved respiratory mechanics and increased stroke volume due to relief of right ventricular compression. The culmination of these physiologic effects is difficult to assess objectively, but cardiopulmonary exercise testing (CPET) currently represents the best non-invasive method to evaluate exercise capacity. The available CPET studies are limited but are beginning to demonstrate a physiologic explanation for perceived improved exercise tolerance after MIRPE. Future studies should focus on cardiopulmonary exercise testing with consistent methodologies using control groups to provide a more objective evaluation of the physiologic effects after pectus excavatum repair.

Disclosure statement

Obermeyer and Jaroszewski are product development consultants for Zimmer-Biomet, Inc., manufacturers of the bar used in the Nuss procedure.

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