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Cardiovascular Function Following Surgical Repair of Pectus Excavatum*

A Metaanalysis

Moh H. Malek, MS; Dale E. Berger, PhD; Terry J. Housh, PhD; William D. Marelich, PhD; Jared W. Coburn, PhD; and Travis W. Beck, MPE

Background: **Despite numerous published reports, there is no consensus in the literature as to whether the surgical repair of the pectus excavatum improves cardiovascular function. As a result, it has been suggested that correction should be considered a cosmetic procedure, and therefore, many health insurance companies have questioned whether the repair of the pectus excavatum improves cardiovascular function and thus are reluctant to authorize the procedure. The purpose of this study was to apply metaanalysis methodology to generate a quantitative synthesis of the effects of surgical repair on cardiovascular function and to test the hypothesis that surgical repair of the pectus excavatum results in significant improvements in cardiovascular function.**

Methods: **Studies were retrieved via computerized literature searches, cross-referencing from original and review articles, and a review of the reference list by a recognized authority in the area of pectus excavatum repair. The inclusion criteria were as follows: (1) reporting quantitative measures of preoperative and postoperative cardiovascular function; (2) published in the English language; (3) indexed between January 1960 and May 2005; (4) reporting the duration between which preoperative and postoperative assessments were conducted; and (5) describing the cardiovascular assessment procedures.**

Results: **A comprehensive search of the literature identified eight studies that met all of the inclusion criteria. These studies, representing 169 pectus excavatum patients, were used for the metaanalysis. Random-effects modeling yielded a mean weighted effect size (ES) for cardiovascular function that was statistically significant (ES, 0.59; 95% confidence interval, 0.25 to 0.92; p = 0.0006).**

Conclusions: **The findings of the present study indicated that surgical repair of the pectus excavatum significantly improves cardiovascular function and contradicts arguments that surgical repair is primarily cosmetic yielding minimal physiologic improvement.**

(CHEST 2006; 130:506–516)

Key words: cardiac anatomy; cardiopulmonary function; chest wall deformity; oxygen uptake; physiology; surgery

Abbreviations: CI = confidence interval; ES = effect size; $\dot{V}O_2max$ = maximal oxygen uptake; τ-$\dot{V}O_2$ = oxygen uptake kinetics

Pectus excavatum (Fig 1) is a relatively common congenital deformity of the chest wall with an incidence of approximately 1 in every 300 to 400 white male births.[1] Although the pathogenesis of pectus excavatum remains unclear, investigators have hypothesized that the deformity results from unbalanced overgrowth in the costochondral regions. As a result, the chest appears concave, and a displaced heart is often palpable on the left mid-axillary line slightly below the armpit. Pectus excavatum occurs more often in male patients than female patients (6:1) and accounts for 90% of congenital chest wall deformities.[2,3] Approximately 40% of pectus excavatum patients are aware of one or more members of their family who have pectus deformities; however, a genetic link has not been established.[3] Despite numerous published reports, there is no consensus in the literature as to whether surgical repair improves cardiovascular function.[1,4–11]

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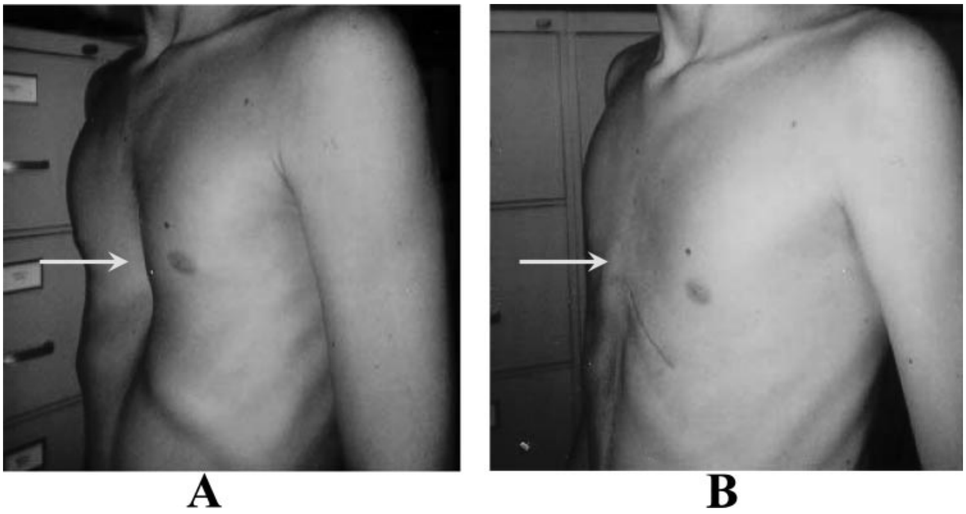

FIGURE 1. Chest of a 25 year-old male with a pectus severity index of 6.0 before (*left*, *A*) and 6 months after (*right*, *B*) surgical repair using the modified Ravitch Repair procedure.[1,3]

Thus, it has been suggested by some researchers that the correction of pectus excavatum should be considered a cosmetic procedure.[12–14] Therefore, many health insurance companies are of the opinion that surgical repair of pectus excavatum may not improve cardiovascular function and are thus reluctant to authorize the procedure.

The symptoms associated with pectus excavatum include fatigue, dyspnea with mild exertion, chest discomfort, and tachycardia. A systolic cardiac murmur along the upper left sternal border is occasionally present although intrinsic structural abnormalities of the heart, other than mitral valve prolapse, are rarely found.[1] Early pathological studies demonstrated compression of the heart between the vertebral column and the depressed sternum.[15] Sigalet et al[11] examined the preoperative and postoperative cardiovascular response to exercise in 11 pectus excavatum patients who had a mean pectus severity index of 4.1. The Nuss procedure was used to correct the pectus deformity. The investigators found that maximal oxygen uptake ($\dot{V}O_2$max) and anaerobic threshold had decreased by $> 15\%$ 3 months after surgical repair. These decreases in cardiorespiratory function, however, may have been due, in part, to a combination of the Nuss procedure and the reduction in the patient's level of physical activity following the surgical repair.[16] Nevertheless, stroke volume and cardiac output at rest increased by 26% and 31%, respectively, after surgical repair.[11] These findings were inconsistent with Borowitz et al[17] who found no change in $\dot{V}O_2$max and anaerobic threshold after surgical repair using the Nuss procedure in 10 pectus excavatum patients. Quigley et al[18] examined cardiovascular function in 15 pectus excavatum patients before and after surgical repair using the Ravitch technique. These investigators found no changes in $\dot{V}O_2$max and anaerobic threshold following surgical repair, but did find that oxygen pulse, which is an indirect measure of stroke volume, increased by 12%.[18]

Reviews of the literature regarding the surgical repair of pectus excavatum have resulted in subjective qualitative summaries in which a researcher provides a narrative of previous findings in chronologic order.[19–21] A potential pitfall of this approach is that statistical significance alone does not provide sufficient information to support qualitative distinctions between studies.[22] Because studies using ≤ 15 cases are common in this research area, tests of statistical significance in many individual studies have low statistical power for detecting meaningful effects. In this context, there is a critical need to develop comprehensive analytical data regarding the effectiveness of surgical repair for pectus excavatum

*From the Human Performance Laboratory (Mr. Malek, Dr. Housh, and Mr. Beck), Department of Nutrition and Health Sciences, University of Nebraska-Lincoln, Lincoln, NE; the Department of Psychology (Dr. Berger), Claremont Graduate University, Claremont, CA; and the Departments of Psychology (Dr. Marelich) and Kinesiology (Dr. Coburn), California State University-Fullerton, Fullerton, CA.
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Correspondence to: Moh H. Malek, MS, CSCS, Human Performance Laboratory, Department of Nutrition and Health Sciences, University of Nebraska-Lincoln, 110 Ruth Leverton Hall, Lincoln, NE 68583-0806; e-mail: mmalek@unlserve.unl.edu
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on cardiovascular function. Metaanalysis is a state-of-the-art statistical technique for literature synthesis in which quantifiable results from individual studies addressing a common problem are statistically combined to arrive at conclusions about a body of research.[22] In the present study, metaanalysis allows one to do the following: (1) aggregate and compare findings on the effectiveness of surgical repair on cardiovascular function; (2) summarize and draw reliable conclusions on a body of literature in which there is a lack of consensus; and (3) improve estimates of treatment effectiveness.[22–25] Metaanalysis represents the findings of each study in terms of an effect size (ES). Briefly, the ES statistic is a statistically standardized measure of the study findings such that the resulting numerical values are interpretable in a consistent fashion across all variables and measures.[22] Therefore, the ES provides information related to the magnitude and direction of an intervention, which depend heavily on sample size, rather than merely on its statistical significance.[22]

The inconsistent findings in the pectus excavatum literature may be explained, in part, by the relatively small sample sizes and the large variances within each study. As a result, the ability to detect statistically meaningful differences in individual studies is often limited, increasing the risk of incorrectly concluding that surgical repair for pectus excavatum is ineffective. No previous studies have used the metaanalysis approach to examine the efficacy of surgical repair on cardiovascular function in pectus excavatum patients. The purpose of this study was to apply metaanalysis methodology to generate a quantitative synthesis of the effects of surgical repair on cardiovascular function and to test the hypothesis that the surgical repair of pectus excavatum results in significant improvements in cardiovascular function.

Materials and Methods

Data Sources

Computerized literature searches were performed using Current Contents, EMBASE, Health Periodicals Database, Medline, Nursing and Allied Health, and SPORTDiscus. In addition, references from retrieved review articles and original investigations were examined. The year 1960 was chosen as the starting date because it is highly unlikely that relevant studies that assessed preoperative and postoperative cardiovascular function in pectus excavatum patients were published prior to this time. The earliest relevant study that we located was published in 1984. The following key words were used either alone or in various combinations for computer searches: "aerobic fitness"; "cardiac"; "cardiac compression"; "cardiac output"; "cardiorespiratory function"; "cardiovascular function"; "cardiovascular testing"; "chest wall deformity"; "funnel chest"; "oxygen uptake"; "pectus excavatum"; "pectus severity index"; "stroke volume"; and "ventricular function". The titles and abstracts of studies that were identified in the computerized searches were examined to exclude any articles that were clearly irrelevant. The full text of the remaining articles was retrieved, and each article was read to determine whether it contained information on the topic of interest. Because computer searches have been shown to yield less than two thirds of relevant articles in some research areas,[26] reference lists from original and review articles were reviewed to identify any studies that had not been previously identified and appeared to contain information on the topic of interest. Hand searches of selected journals related to general medicine and surgery were also performed. In addition, a recognized authority in the area of pectus repair scrutinized our reference list for thoroughness and completeness (Eric W. Fonkalsrud, MD; personal communication; June 2005).

Study Selection

Inclusion criteria for this metaanalysis included the following: (1) reporting quantitative measures of preoperative and postoperative cardiovascular function; (2) published in the English language; (3) indexed between January 1960 and May 2005; (4) reporting the duration between which preoperative and postoperative assessments were conducted; and (5) describing the cardiovascular assessment procedures. Studies published in foreign language journals were not included because of the potential error in the translation and interpretation of findings. Abstracts from conference proceedings, doctoral dissertations, and Master's theses were also not included because those sources are unlikely to report substantive research findings that have not been published elsewhere. Studies meeting the inclusion criteria were examined to ensure that the same patients were not included in more than one study.[27]

Data Extraction

A coding sheet was developed to record the information from each article. To avoid intercoder and intracoder bias, all data were independently extracted by two of the coauthors. The major categories of variables that were coded include (1) study characteristics (*ie*, author, year, and number of subjects), (2) the physical characteristics of subjects (*ie*, gender and age), (3) the type of surgical repair performed, (4) the duration between preoperative and postoperative assessment, and (5) primary outcomes (cardiovascular indexes) [Tables 1, 2].

Statistical Analysis

Cardiovascular Indexes: Due to the fact that not all studies reported the same index for cardiovascular function, we elected to place the indexes reported in each study into a global category, cardiovascular function. This was done (1) to maximize the number of studies that could be used in the metaanalysis, (2) to have the best representation of the current findings in this body of literature, and (3) to better answer the question, "Does surgical repair of pectus excavatum improve cardiovascular function?" The indexes included in the present metaanalysis represent components that individually or collectively determine cardiovascular function (*eg*, cardiac output, ejection fraction, end-diastolic volume, end-systolic volume, heart rate, $\dot{V}O_2$max, oxygen pulse, and stroke volume). Table 3 includes the separate dependent variables from each of the eight studies selected for inclusion in the present metaanalysis. These variables were combined into a single index that we have termed *cardiovascular function* in the present study.

Standardized Mean Gain: The primary outcome of interest was possible changes in cardiovascular function following surgical repair.

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Table 1—*Characteristics of Studies Used in the Metaanalysis**

Study	Pectus Excavatum Patients, No.: Patients Assessed in Each Study	Male	Female	Reported Mean Age of Entire Sample, yr	Method of Assessing Pectus Severity Index
Cahill et al[34]	14	NR	NR	10.9	NR
Peterson et al[36]	13	NR	NR	13.0	Chest radiograph
Wynn et al[14]	7	11	2	13.6	Calipers (chest width and depth)
Morshuis et al[42]	35	28	7	17.9	Lateral chest radiograph
Quigley et al[18]	15	NR	NR	16.0	Chest CT scan
Kowalewski et al[8]					
Moderate group	22	24	10	13.4	Chest radiograph
Severe group	12				Chest radiograph
Hu et al[35]	40	137	34	4.6	NR
Sigalet et al[11]	11	10	1	13.5	Chest CT scan

*NR = not reported. Note: The reported number of male and female patients does not necessarily reflect the number of men and women who were assessed preoperatively and postoperatively.

The standardized mean gain[22] was calculated using the following formula: ESsg = [(Mean-postoperative − Mean-preoperative)/S-preoperative], where (Mean-postoperative − Mean-preoperative) equals the amount of change in the mean on a variable of interest for a sample measured preoperatively and then, later, postoperatively, whereas the S-preoperative equals the SD for the preoperative time point. The S-preoperative was used instead of the pooled SD, because, theoretically, the S-preoperative is unaffected by the treatment.[28,29] Because each study in the present metaanalysis produced multiple ESs from separate dependent variables, we followed the recommendation of Lipsey and Wilson[22] that an average ES for each study should be calculated to maintain statistical independence.

The standard error (SEsg) and inverse variance (wsg) for the average ES of each study was calculated using the following equations[22]:

Table 2—*Characteristics of Studies Used in the Metaanalysis Related to Cardiovascular Function, Surgical Repair, and Duration Between Preoperative and Postoperative Assessment**

Study	Cardiovascular Indices	Surgical Repair Technique	Duration Between Preoperative and Postoperative Assessment
Cahill et al[34]	Total exercise time, $\dot{V}O_2$max	NR	3–9 mo
Peterson et al[36]	LVEF-r, LVEDV-r, LVSDV-r, SVI-r, CI-r, RVEF-r, RVEDV-r, LVEF-e, LVEDV-e, LVSDV-e, SVI-e, CI-e, RVEF-e, RVEDV-e	NR	≥ 6 mo after repair
Wynn et al[14]	Total exercise time, $\dot{V}O_2$max, power output, maximal heart rate, CO-r, % of work performed, CO-e, SV-r, SV-e	Ravitch	Reported mean of 11 mo
Morshuis et al[42]	$\dot{V}O_2$max, maximal heart rate, oxygen pulse, maximal power output	Daniel	1 yr
Quigley et al[18]	Total exercise time, maximal heart rate, oxygen pulse, grade† (%), speed‡ (km per hour), $\dot{V}O_2$max, anaerobic threshold	Ravitch	8.5 mo
Kowalewski et al[8]			
Moderate group	LVEDVI, LVESVI, SVILV, RVEDVI, RVESVI, SVIRV	Ravitch	1 yr
Severe group	LVEDVI, LVESVI, SVILV, RVEDVI, RVESVI, SVIRV	Ravitch	
Hu et al[35]	SV, EF, FS, MVCF	Ravitch	4.2 yr
Sigalet et al[11]	Maximal heart rate, CO-r, SV-r, $\dot{V}O_2$max, anaerobic threshold, cardiac index	Nuss	3 mo

*r = rest; e = exercise; EF = ejection fraction; CO = cardiac output; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVEDVI = left ventricle end-diastolic volume index; LVESVI = left ventricle end-systolic volume index; LVSDV = left ventricular systolic volume; MVCF = mean ventricular circumference fraction; RVEDV = right ventricular end-diastolic volume; RVEDVI = right ventricular end-diastolic volume index; RVEF = right ventricular ejection fraction; RVESVI = right ventricular end-systolic volume index; SV = stroke volume; SVI = stroke volume index; SVILV = stroke volume index of left ventricle; SVIRV = stroke volume index of right ventricle; FS = fractional shortening of the minor-semiaxis.

†Refers to the final incline the patient achieved at the end of an incremental treadmill test.

‡Refers to the final velocity the patient achieved at the end of an incremental treadmill test.

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Table 3—*Percentage Change and ES for Each Cardiovascular Index Per Study**

Study	Cardiovascular Index	Change, %	ES, Cohen's d
Cahill et al[34]	Total exercise time	18	0.51
	$\dot{V}O_2$max	16	0.45
Peterson et al[36]	LVEF-r	− 3	− 0.25
	LVEF-e	− 1	− 0.20
	LVEDV-r	21	0.71
	LVEDV-e	− 4	− 0.13
	LVSDV-r	24	0.50
	LVSDV-e	− 17	− 0.31
	SVI-r	19	0.82
	SVI-e	− 3	− 0.14
	Cardiac index-r	14	0.50
	Cardiac index-e	− 1	− 0.04
	RVEF-r	− 15	− 1.00
	RVEF-e	− 7	− 0.44
	RVEDV-r	40	1.35
	RVEDV-e	7	0.29
Wynn et al[14]	Total exercise time	11	0.36
	$\dot{V}O_2$max	6	0.52
	Power output	8	0.14
	Maximal heart rate	1	0.27
	CO-r	11	0.45
	% of work performed	39	0.98
	CO-e	6	0.16
	SV-r	13	0.47
	SV-e	7	0.20
Morshius et al[42]	$\dot{V}O_2$max	9	1.45
	Maximal heart rate	2	0.26
	Oxygen pulse	10	0.31
	Maximal power output	0	0.01
Quigley et al[18]	Total exercise time	8	0.33
	Oxygen pulse	12	0.38
	Grade† (%)	12	0.40
	Speed‡ (km per hour)	14	1.00
	Oxygen pulse/BSA	7	0.31
	Maximal heart rate	0	0.00
	$\dot{V}O_2$max	0	0.00
	Anaerobic threshold	0	0.00
Kowalewski et al[8]			
Moderate group	LVEDVI	11	0.51
	LVESVI	6	0.12
	SVILV	7	0.50
	RVEDVI	49	1.16
	RVESVI	19	0.54
	SVIRV	45	2.33
Severe group	LVEDVI	26	0.81
	LVESVI	4	0.09
	SVILV	43	1.33
	RVEDVI	118	6.88
	RVESVI	103	2.86
	SVIRV	122	5.00
Hu et al[35]	SV	23	0.83
	EF	11	0.70
	FS	8	0.45
	MVCF	7	0.53
Sigalet et al[11]	Maximal heart rate	− 1	− 0.07
	CO-r	31	1.08
	SV-r	26	0.66
	$\dot{V}O_2$max	− 18	− 4.33
	Anaerobic threshold	− 26	− 0.59
	Cardiac index	16	0.50

*BSA = body surface area. See Table 2 for abbreviations not used in the text.

†Refers to the final incline the patient achieved at the end of an incremental treadmill test.

‡Refers to the final velocity the patient achieved at the end of an incremental treadmill test.

$$\mathrm{SEsg} = \sqrt{\frac{2(1-r)}{n} + \frac{\mathrm{ESsg}^2}{2n}}$$

and

$$\mathrm{wsg} = \frac{2n}{4(1-r) + \mathrm{ESsg}^2}.$$

No studies reported the correlation (r value) between the preoperative and postoperative scores. Lipsey and Wilson[22] noted that the computed weighted ESs are not very sensitive to the r value and suggested that an r value of 0.80 can be substituted in the above formulas when the correlation between the preoperative and postoperative scores are not reported.[22] Based on this recommendation, SEsg and wsg were calculated using a conservative r value of 0.80. With a less conservative value of $r = 0.40$, the average ES estimate would be about 5% larger.

Homogeneity Analysis: To determine whether each ES in a set of ESs can be viewed as a measure of a common population ES (*ie*, whether there is consistency across the studies), the homogeneity statistic Q was calculated. The Q statistic has an approximate χ^2 distribution with $k - 1$ degree of freedom, where k is the number of ESs.[22] If Q exceeds the critical value for χ^2 with $k - 1$ degree of freedom ($p < 0.05$), then a random-effects model (*ie*, error arises from patient-level variability and study-level variability) should be used, whereas if Q does not exceed the critical value for χ^2 with $k - 1$ degree of freedom ($p > 0.05$), then a fixed-effects model could be used (*ie*, the error arises from only patient-level variability).[22] It has been suggested by Higgins and colleagues[30,31] that, in metaanalyses with a small number of studies, the Q statistic may have low statistical power. Therefore, these investigators developed the I^2 statistic which ". . . describes the percentage of total variation across studies due to heterogeneity rather than chance."[31(p 558)] The I^2 statistic, in the present study, was calculated by using the following equation[31]: $I^2 = 100\% \times (Q - df)/Q$. The value for I^2 ranges from 0 to 100%, with a larger number indicating greater heterogeneity.[31]

Publication Bias Analysis and Fail Safe N: Publication bias, the tendency for journals to publish only studies that yield statistically significant results, was examined in the present study. Publication bias was not anticipated to be a substantive factor in the pectus excavatum literature because the literature included a high proportion of studies that did not attain statistical significance. The approach used to determine publication bias was to examine a funnel plot of the sample size by plotting sample size on the vertical axis and the ES measure on the horizontal axis for all studies.[22,24,32] Ordinarily, smaller studies show a larger range of ESs than larger studies. Thus, the plot generally resembles an inverted funnel, wide on the bottom and narrow at the top. A gap at the bottom of the funnel on the left side in the range of nonsignificant test results would indicate that small studies with null results may be missing from the published literature.[22]

The fail-safe N (*ie*, the file drawer number), which is a measure of possible publication bias, was also calculated. The concern was that even if the pooled ES from the published literature shows an overall significant effect, there may be many unpublished studies that do not show an effect and therefore remain in a file drawer. The fail safe N is the number of studies with zero effect that would need to be unpublished (in file drawers) if there really is no effect in the population, given the effects reported in the published literature. The following formula[22] was used to determine the fail safe N:

$$k_0 = k\left[\frac{\overline{\mathrm{ES}}_k}{\overline{\mathrm{ES}}_c} - 1\right]$$

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where $k_0 = N$ = the number of studies with ES = 0 that would be needed to produce an overall statistically nonsignificant result if they were included in the metaanalysis, k is the number of studies in the metaanalysis, $\overline{ES}k$ is the observed weighted mean ES, and $\overline{ES}c$ is the maximum value of an ES that would be considered trivial. The $\overline{ES}c$ value was set at 0.20, which represents a small ES, based on the benchmark of Cohen[33] and also the upper limit of a clinically trivial ES, based on the judgment of an expert on pectus excavatum.

Moderator Analysis: To examine the relationship between continuous variables (*ie*, sample size, age, and duration between preoperative and postoperative assessment) and changes in cardiovascular indexes, simple, generalized least squares regression models (*ie*, random effects and method-of-moments approach) were calculated with each ES weighted by the reciprocal of its variance, as described by Lipsey and Wilson.[22]

Statistical analysis was performed by using a statistical software package (SPSS, version 13.0; SPSS Inc; Chicago, IL). The results were considered to be significant if $p < 0.05$. Also, confidence intervals (CIs) were reported in all cases at the 95% level.

Results

Study Characteristics

The initial computerized searches identified 190 potentially relevant articles using the search terms "pectus excavatum" and "cardiac." A careful review of the abstracts resulted in 13 studies[4,7–9,11,14,18,34–39] that could potentially meet the inclusion criteria for the metaanalysis. The reference lists from these 13 articles as well as from review articles[19–21] were examined to identify any additional potentially relevant studies that had not been previously identified. Hand searches of selected journals related to general medicine and surgery were also performed. The result of these searches yielded four additional articles.[17,40–42]

Of the 17 studies, 4 studies[4,17,39,40] were excluded because sufficient statistics were not reported to calculate an ES, whereas a fifth study[37] was excluded because the pectus excavatum patients in the study also had congenital heart disease (*eg*, ventricular septal defect or tetralogy of Fallot). The studies by Quigley et al[18] and Haller and Loughlin[7] appeared to use the same sample of pectus excavatum patients based on identical means and SDs for cardiovascular indexes presented in both articles. Thus, this information from these two studies were combined and analyzed as one study. Also, Kowalewski and colleagues[8,9] published two studies in 1998 and 1999, respectively, using samples that overlapped. Hence, only the initial study published in 1998 by Kowalewski et al,[8] which included groups with moderate and severe pectus excavatum, was included in the metaanalysis. Similarly, Sigalet et al[11] and Bawazir et al[38] used overlapping patients; therefore, the initial study by Sigalet et al[11] was used in the metaanalysis. In addition, Morshuis and colleagues presented two studies in 1994 that examined cardiorespiratory function[42] and pulmonary function.[41] Therefore, the former study[42] was used for the metaanalysis. A total of eight studies was analyzed for the metaanalysis. Three of the studies were conducted in the United States,[14,18,34] while the remaining studies were conducted in Canada,[11] Poland,[8] the Netherlands,[36,42] and China.[35] A total of 169 pectus excavatum patients were assessed in the metaanalysis. Two studies[34,35] did not report a pectus severity index, and the remaining studies[8,11,14,18,36,42] used various techniques for estimating a pectus severity index. It was not possible to compute a consistent index of pectus severity, so the relationship between pectus severity and the average ES for each study could not be examined in the present study. The number of subjects in each study ranged between 7 and 40 (mean [± SD], 19.3 ± 12.2 subjects). The time between the preoperative and postoperative cardiovascular assessments ranged from 0.25 to 4.2 years. Four of the eight studies used the Ravitch repair surgical procedure, one used the Daniel procedure, one used the Nuss procedure, and two did not report the type of procedure (Table 2).

The mean age across all eight studies was 12.9 years (SD, 3.9 years). Only four studies[8,11,14,42] reported the gender of their subjects. Thus, the male/female ratio calculated from these four studies was 3:1. All eight of the studies reported that subjects were healthy and/or physically active; however, this information was not quantified in terms of duration, frequency, or mode of exercise performed.

Standardized Mean Gain (Cardiovascular Function)

Measures of ES were computed for each dependent measure in each study. A total of 59 ESs for cardiovascular outcomes was calculated from the eight studies. Of these, 56% were reported as being statistically nonsignificant, whereas 44% were reported as being statistically significant. Furthermore, of the 59 ESs, 19% (n = 11) were in a negative direction, 5% (n = 3) equaled zero, and 76% (n = 45) were in a positive direction (Table 3). The Q statistic was significant ($Q = 25.676$; $p = 0.0012$), indicating heterogeneity. This was further supported by the I^2 statistic (68.9%). Thus, a random-effects model (for technical details see Lipsey and Wilson[22]) was used to estimate the pooled ES and error for the eight studies. The average ES for each study and the mean weighted ES for all studies combined are shown in Figure 2, along with CIs. The mean weighted ES for cardiovascular function was statistically significant (ES, 0.59; 95% CI = 0.25 to 0.92; $p = 0.0006$). The ES of 0.59 indicates that the

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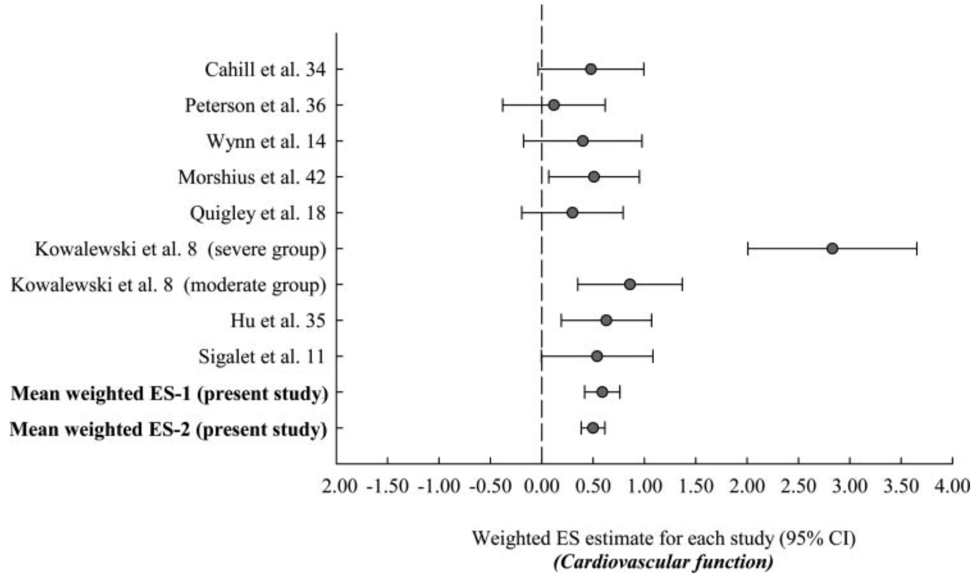

Figure 2. Weighted ES and 95% CIs of each study analyzed in the metaanalysis with (ES-1) and without (ES-2) the severe group from the Kowalewski et al[8] study. Note: The investigation by Kowalewski et al[8] was a single study which examined the cardiovascular function preoperatively and postoperatively in patients with moderate or severe pectus excavatum.

average patient improved by 0.59 SDs on the measures of cardiovascular functioning.

To ensure that the present mean weighted ES was not inflated or biased, we conducted two *post hoc* analyses. First, we wanted to be confident that the mean weighted ES of 0.59 was not due to the relatively high average ES value for the group with severe pectus excavatum from the study of Kowalewski et al[8] (ES, 2.83) [Fig 2]. Therefore, we removed this ES and then reanalyzed the data. The mean weighted ES for cardiovascular function remained statistically significant (ES, 0.50; 95% CI, 0.38 to 0.61; $p < 0.001$). Thus, the ES for the group with severe pectus excavatum from the study of Kowalewski et al[8] was included in all further analyses.

In the second *post hoc* analysis, we added the ES value for $\dot{V}O_2$max and anaerobic threshold indexes from Sigalet et al[11] (Table 3). These two variables were withheld from the initial analyses, because they introduced a confounding variable (*ie*, deconditioning; see the "Discussion" section for details). However, in the interest of minimizing experimenter bias, the ES values for $\dot{V}O_2$max (ES, −4.33) and anaerobic threshold (ES, −0.59) were added to the other ES values from the study by Sigalet et al,[11] and then a new average value (ES, −0.46) was calculated. The data were then reanalyzed with this new average ES value. The results indicated that the mean weighted ES for cardiovascular function was statistically significant (ES, 0.50; 95% CI, 0.11 to 0.88; $p = 0.0112$).

Publication Bias and Fail Safe N

There was no quantitative evidence supporting publication bias, as indicated by the correlation between ES and sample size ($r = -0.11$; $p = 0.79$). A funnel plot analysis showed no evidence of missing studies with small or negative effects. Additionally, the fail-safe N indicated that approximately 17 unpublished null-result studies would be required to reduce the mean weighted ES to a clinically trivial level of 0.20.

Moderator Analysis

No statistically significant relationships with ES were found when changes in cardiovascular function were regressed on study sample size, mean patient age, or duration between preoperative and postoperative assessment using inverse variance weights, as recommended by Lipsey and Wilson[22] (all two-tailed p values were > 0.40). Because of the small number of studies (Tables 1, 2), these analyses have quite limited power.

Discussion

The principal finding of the present study was that average cardiovascular function increased by greater than one half SD following the surgical repair of pectus excavatum. This result, which was consistent with our hypothesis, is a meaningful effect that can

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be characterized as moderately large by statistical benchmarks.[33] In addition, the test for the fail-safe N suggested that a large number of unpublished studies examining cardiovascular function preoperatively and postoperatively in pectus excavatum patients would need to exist to significantly reduce this magnitude of improvement. The primary purpose of metaanalysis is to make optimal use of the quantitative information in a body of literature and to synthesize multiple findings into a clear summary. Currently, decisions regarding the surgical repair of pectus excavatum are made on the basis of limited and inconsistent information from many small studies. Consequently, many patients are advised by well-intentioned physicians that (1) the deformity will improve with age; (2) surgical repair is dangerous, minimally effective, and unnecessary; and (3) the malformation produces few symptoms and is primarily a cosmetic problem. Because of the inconsistent findings in the research literature and the high cost of surgery, health insurance companies are reluctant to authorize corrective surgery for pectus excavatum. The total medical cost of surgical repair for pectus excavatum may be > \$30,000, and many patients cannot afford this procedure without assistance from their health-care insurance.

The cardiovascular limitations experienced by pectus excavatum patients may be explained, in part, by the configuration of the chest wall deformity, which may compromise the cardiac chambers. Recently, Fonkalsrud and Reemtsen[43] found that the force required to elevate the depressed sternum was associated with the pectus severity index. Specifically, the investigators reported that approximately 12.2, 13.4, or 18.6 kg of force was required to lift the sternum for individuals with pectus severity indexes < 4.0, 4.1 to 5.0, or > 5.0, respectively.[43] Therefore, this amount of pressure on the heart may hinder normal cardiac function. Pectus excavatum patients often exhibit tachycardia at rest and abnormally high heart rate responses during submaximal physical activity.[1,44,45] The salient component of cardiac output, stroke volume, may explain the symptoms of fatigue that most pectus excavatum patients experience while performing activities of daily living. Cardiac stroke volume is calculated from the difference between the end-diastolic volume and the end-systolic volume, and patients with pectus excavatum represent a unique opportunity to examine this hemodynamic relationship during cardiac compression. In pectus excavatum patients, the pressure exerted by the sternum may attenuate the filling of the right atrium and therefore cause a reduction in the ejection fraction of the ventricles.[1,44,45] During physical activity, the heart of the pectus excavatum patient is positioned ventrally by the hyperventilated lungs, while the right atrium is compressed because it is directly posterior to the sternum.[8,9] Studies[36,46] have found that the right ventricle is less concentric, more anterior relative to the sternum, and more distensible than the left ventricle. Additionally, it has been reported[2,36,47] that the sternum impinges the right side of the heart. Malek et al[45] reported that oxygen pulse, which is a surrogate measure of cardiac stroke volume, was significantly lower in 21 pectus excavatum patients when compared to normative data during incremental cycle ergometry. As shown in Table 3, the percentage change for cardiac output, stroke volume, and oxygen pulse ranged between 6% and 31%, which corresponded to an ES between 0.16 and 1.08. In addition, the average ES value for each study was in a positive direction (Fig 2). The exceptionally large ES found in the study by Kowalewski et al[8] following surgical repair of patients categorized with severe pectus excavatum (Fig 2), however, provides further support regarding the closely linked relationship between cardiac compression and cardiovascular function.

Previous studies have shown that oxygen supply to the working muscles is critical for sustaining a physical activity such as running, cycling, or swimming. Additionally, studies restricting blood flow to the working muscles have further supported the importance of oxygen supply.[49] Related to pectus excavatum, Malek and Fonkalsrud[44] reported a 7.9% increase in $\dot{V}O_2$max following the surgical repair of pectus excavatum, which was consistent with the results of previous studies[14,34,42] that reported a 6 to 16% increase in $\dot{V}O_2$max postoperatively. In the current investigation, indexes of cardiovascular function measured during physical activity had an ES ranging from 0 to 1.45, with the majority of the values distributed around an ES approximating 0.40. It should be noted that none of the studies provided a quantifiable measure of the subject's level of physical activity. Therefore, we were unable to examine the relationship between the subject's level of fitness activity and cardiovascular function preoperatively and postoperatively.

It is well-established in the exercise physiology literature that deconditioning attenuates the cardiac dimensions and cellular adaptations inherent with aerobic exercise.[16,50–52] Previous well-controlled studies have reported reductions in $\dot{V}O_2$max and anaerobic threshold indexes > 17% after 12 weeks of detraining.[16,50–52] In the study by Sigalet et al,[11] the changes for $\dot{V}O_2$max and anaerobic threshold 12 weeks following surgical repair were −18% and −26%, respectively. Thus, these results are consistent with the data from the literature related to deconditioning. Furthermore, Sigalet et al[11(p 383)] stated, ". . . these patients have had a period of

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restricted activity induced both by specific instruction from the surgical team, to allow for healing and stabilization of the bar. . . there may have been a significant loss of conditioning induced by these changes in activities. . . . " Thus, Sigalet et al[11] unintentionally introduced a confounding variable (*ie*, deconditioning), which may potentially explain why individual studies[11,36] report decreased cardiopulmonary responses to exercise following surgical repair. In our experience,[44,45] we have observed patients who have either significantly reduced their habitual exercise activity or have adopted a sedentary lifestyle for fear of displacing the Adkins strut. Malek and Fonkalsrud,[44] however, found that if the patient maintains a similar preoperative level of physical activity in the months following surgical repair, there are clinically significant increases in cardiopulmonary responses to maximal and submaximal exercise testing (see Table 2 in the study by Malek and Fonkalsrud[44]).

An important component in assessing the cardiovascular limitation resulting from pectus excavatum is the determination of the onset of blood lactate accumulation (*ie*, anaerobic metabolism) relative to the individual's predicted $\dot{V}O_2$max during an incremental exercise test. Briefly, during the onset of incremental exercise the energy required to sustain the workout is supplied via aerobic metabolism. As the intensity of the exercise increases, the energy demands required to maintain the level of exercise during the workout are not sufficiently met by aerobic metabolism alone.[53–55] Therefore, the combination of anaerobic and aerobic metabolism supplies the energy required to sustain the exercise workout until the patient reaches fatigue. The onset of anaerobic metabolism, as measured by gas exchange parameters (*ie*, ventilatory threshold) during incremental exercise testing in healthy individuals, normally occurs at 50 to 60% of $\dot{V}O_2$max, whereas this value increases to 60 to 85% of $\dot{V}O_2$max for individuals who have undergone endurance training.[56] Malek et al,[45] however, reported that the ventilatory threshold occurred at 41% of the predicted $\dot{V}O_2$max in 21 pectus excavatum patients who maintained a regular exercise regimen (see Table 1 in the study by Malek et al[45]). Furthermore, Malek and Fonkalsrud[44] found that the ventilatory threshold occurred at 50% of the predicted $\dot{V}O_2$max postoperatively, which was a clinically significant improvement from 39% of the predicted $\dot{V}O_2$max preoperatively. The reduced values observed preoperatively for the ventilatory threshold are the result of decreased cardiac output due to cardiac compression and, therefore may potentially be explained by a lack of sufficient oxygen delivery to the working muscles.[44]

It should be noted that the cardiovascular impairment of pectus excavatum can also be manifested during submaximal, low intensity (*ie*, subthreshold) exercise workouts. Malek et al[45] and Malek and Fonkalsrud[44] examined the time constant for oxygen uptake kinetics ($\tau\dot{V}O_2$) during submaximal workouts in pectus excavatum patients prior to and following surgical repair. Briefly, oxygen uptake kinetics is the rate at which oxygen uptake increases in response to an exercise stimulus.[51] Typically, the on-$\tau\dot{V}O_2$ (on-transient) and off-$\tau\dot{V}O_2$ (off-transient) value in young, healthy individuals is 35 s (SD, 5 s) for workouts conducted below the ventilatory threshold. However, this value can either decrease (*ie*, faster kinetics) with endurance training or increase (*ie*, slower kinetics) as a result of cardiovascular impairment. For example, Phillips et al[57] reported that the mean on-$\tau\dot{V}O_2$ and off-$\tau\dot{V}O_2$ during submaximal exercise decreased significantly from 38.1 s (SD, 2.6 s) and 38.0 s (SD, 1.0 s), respectively, to 28.3 s (SD, 1.0 s) and 30.6 s (SD, 0.9 s), respectively, after only 30 days of endurance training. Malek et al[45] examined 21 physically active pectus excavatum patients (mean severity index, 5.1; SD, 1.2) and reported mean values for on-$\tau\dot{V}O_2$ (37.4 s; SD, 10.1 s) and off-$\tau\dot{V}O_2$ (41.6 s; SD, 13.1 s) that were substantially longer than the expected values for aerobically trained individuals. Interestingly enough, however, Malek and Fonkalsrud[44] found that the on-$\tau\dot{V}O_2$ (preoperatively, 46.8 s; postoperatively, 33.6 s) and off-$\tau\dot{V}O_2$ (preoperatively, 46.5; postoperatively, 30.3 s) dramatically improved following surgical repair of pectus excavatum in a 30-year-old man (severity index, 3.7). These findings, along with the results of the present investigation, further indicate that pectus excavatum results in clinically significant cardiovascular impairment.

The application of quantitative metaanalysis in the present study offers advantages compared to previous comprehensive reviews of pectus excavatum because to date such reviews of the literature have resulted in subjective qualitative summaries based on descriptions of chronologically arranged studies.[19–21] Individual studies have as few as three patients[4] with large variances and thus have very low statistical power (high type II error rates). As a result, the failure to attain statistical significance is easily misinterpreted by some researchers and many health insurance companies that surgical repair of pectus excavatum is not physiologically beneficial. Rhea[58(p 921)] stated, ". . . a single study. . . contributes to the body of knowledge only when it is examined in relation to the related body of literature." In the present investigation, metaanalysis provides a quantitative synthesis of the entire body of literature on pectus excavatum, resulting in a larger effective

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sample size. Thus, the ES estimates and the statistical conclusions resulting from a metaanalysis are more robust and accurate than those provided from single studies or narrative reviews.[22,24]

In conclusion, a metaanalytic approach was used in a detailed and analytically rigorous fashion to generate quantitative summaries of the magnitude of effects as well as the relationships among variables associated with cardiovascular function. Suita et al[59(p 347)] stated, ". . . the indications for surgery are mainly based on cosmetic and psychological factors." The findings of the present study indicated that the surgical repair of pectus excavatum significantly improved cardiovascular function (ES, 0.59; $p = 0.0006$). These results contradict arguments that surgical repair is primarily cosmetic and that the postoperative cardiovascular improvements are minimal.

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Cardiovascular Function Following Surgical Repair of Pectus Excavatum: A Metaanalysis
Moh H. Malek, Dale E. Berger, Terry J. Housh, William D. Marelich, Jared W. Coburn and Travis W. Beck
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