Recovery after Abdominal Wall Reconstruction

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THE 4 ORIGINAL PAPERS ARE

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2. Jensen KK, Brøndum TL, Harling H, Kehlet H, Jørgensen LN. Enhanced recovery after giant ventral hernia repair. Hernia 2016;20:249-256.
3. Jensen KK, Backer V, Jørgensen LN. Abdominal wall reconstruction for large incisional hernia restores expiratory lung function. Surgery 2017;161:517-524.
4. Jensen KK, Munim K, Kjær M, Jørgensen LN. Abdominal wall reconstruction for incisional hernia optimizes truncal function and quality of life. Ann Surg 2016 [Epub ahead of print].

INTRODUCTION

The term 'Hernia' originates from Latin and means 'rupture' [1]. An abdominal wall hernia is defined as the protrusion of intra-abdominal content through a defect in the abdominal wall and the pathology can be divided into primary (umbilical, epigastric, Spigelian, and lumbar) and incisional hernias [2].

An incisional hernia is defined by the European Hernia Society as 'any abdominal wall gap with or without a bulge in the area of a postoperative scar perceptible or palpable by clinical examination or imaging' [2]. It is thus per definition a consequence of previous surgery and a complication to surgery. Patients who suffer from incisional hernia are often men [3, 4], obese and smokers [4, 5]. Further, insufficient closure of the abdomen, postoperative wound infection, and fascial dehiscence are factors that contribute significantly to the risk of developing an incisional hernia [3, 5, 6]. Incisional hernia is common, reflected by an estimated annual number of 300,000 incisional hernia repairs in Europe [7].

Incisional hernias vary from small, unnoticeable defects to giant bulges severely affecting the cosmetic appearance of a patient. While risk factors for developing an incisional hernia seem well-defined, knowledge about which patients develop giant incisional hernias is lacking. From a clinical perspective it seems that patients who suffered from an abdominal catastrophe and were left with an open abdomen, along with patients with fascial dehiscence are more prone to develop giant incisional hernias.

The definition of a giant incisional hernia varies to some extent. It has been suggested that a horizontal fascial defect of 10 cm defines the cutoff for the largest group of incisional hernias [2, 8, 9], whereas others propose the presence of 'loss of domain' or hernia volume > 30% of abdominal volume as necessary for a hernia to be defined as giant [10]. In the current thesis, a giant hernia is defined as a hernia with a horizontal fascial defect > 10 cm measured on preoperative computed tomography (CT) scan.

The impact of giant incisional hernia on the patient

Incisional hernia affects patients' everyday life in many ways. Several studies on patients with incisional hernias of different sizes have been performed [11-13]. However, few papers have directly compared patients who developed incisional hernia to those who did not [14, 15]. One study found that overall physical quality of life (QOL) was decreased in patients with incisional hernia, whereas mental QOL was comparable to that of patients without incisional hernia, suggesting that the physical impairment associated with incisional hernia is more pronounced than the mental impact [14]. Curiously, the same study reported a significantly decreased self-perceived body-image in patients with incisional hernia compared to patients with no incisional hernia, perhaps indicating that the mental component is indeed affected by incisional hernia. Another study reporting follow-up on patients treated with open abdomen found no differences in QOL in patients with and without incisional hernia [15]. It can thus be concluded that incisional hernia may affect some aspects of QOL negatively, however the evidence is sparse. It may be tempting to conclude that large incisional hernias impact greater on the QOL than smaller incisional hernias; however this has never been examined. Whereas large incisional hernias may intuitively lead to greater bother, smaller incisional hernias may be more prone to incarceration, intestinal obstruction and strangulation, even intermittently, and thus cause severe daily problems for the patient.

The impact of incisional hernia on the physiological function of the patient is virtually unknown. Theoretically, incisional hernia results in impaired function of the diaphragm due to the disruption of the 'cylinder' composed by the truncus and diaphragm

[16]. Clinically, this should present as platypnea (shortness of breath that worsens when standing) as well as reduced vital capacity of the lungs and decreased maximal inspiratory pressure – however, no studies have been conducted to support this hypothesis. Reduced diaphragmatic and pulmonary function severely affects patients' health, as it is associated with development of atrial fibrillation [17], impaired left ventricular filling [18] and coronary heart disease [19]. Therefore, identification of factors impairing the pulmonary function is important in order to reduce morbidity.

No studies directly comparing the abdominal wall function of patients with incisional hernia to individuals with an intact abdominal wall have been published [20]. One small reliability study from our group compared weight-adjusted truncal flexion and extension in patients with and without incisional hernia. We found a tendency towards reduced function in patients with incisional hernia [21]. However, age, gender and comorbidities were not adjusted for and thus, it is still unknown if incisional hernia indeed impacts negatively on the muscular function of the abdominal wall.

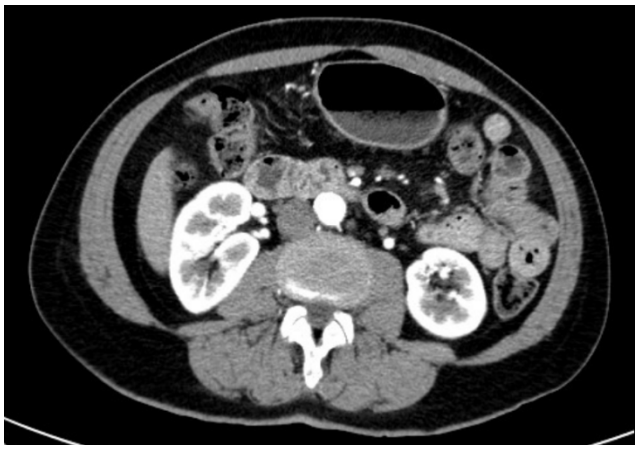
One small study has reported that the average abdominal pressure was increased after inguinal hernia repair, although not to a level of clinical importance [22]. Even though the size of the hernias in this study was not reported, it may be assumed that they were relatively small. Hernia related impaired ability to raise the intra-abdominal pressure, perhaps due to a reduced function of the abdominal wall muscles, thus may impact on the ability to urinate and defecate [23].

Treatment options for giant incisional hernia

Traditionally, giant incisional hernias were considered untreatable. Luckily, this is no longer the case. Several options for the treatment of giant incisional hernia exist today: The open surgical approach, minimally invasive surgery, and non-operative, conservative treatment [24-26].

Laparoscopic hernia repair generally leads to a decreased risk of postoperative wound complications and faster recovery, probably due to the lesser trauma exerted on the abdominal wall compared with open surgery [7, 27, 28]. However, laparoscopic surgery may not be suitable for repair of giant incisional hernia, even though this has been reported elsewhere [29, 30]. One argument against laparoscopic midline hernia repair is that restoration of the linea alba is technically difficult and thus leaves the patient with an abdominal wall that is still impaired in function [31]. Recently, robotic surgery has gained a place in hernia repair, and reports of abdominal wall reconstruction (AWR) for incisional hernia performed using a robotic approach has surfaced [26, 32]. In addition to open or laparoscopic hernia repair, different approaches exist for release of the lateral abdominal wall muscles (Figure 1). Lateral release procedures are performed to enable closure of the linea alba without creating too much tension on the abdominal wall and thereby raising the intra-abdominal pressure to a pathological level [33]. Anterior component separation (ACS) is performed by incising the aponeurosis of the external oblique muscle and was originally described in 1990 [34]. In order to perform this procedure, large skin flaps are created, which leaves the patient at a high risk of wound complications [35]. A minimally invasive approach to ACS was first described in 2007 [36] and this technique was applied to most patients undergoing giant incisional hernia repair in the studies in this thesis. Most recently, division of the transverse abdominis muscle seems to rapidly gain a place in the management of giant incisional hernia repair, offering low recurrence rates [37, 38]. Transverse abdominis release (TAR) may even be the optimal solution for the treatment of patients with incisional hernias who previously underwent ACS for incisional hernia, those treated with open abdomen, or those who underwent kidney transplantations [38-40].

Figure 1: Axial CT depicting an intact anterior abdominal wall.



Several other techniques exist for the treatment of giant incisional hernia, including variations in incision and mesh placement [41]. Most notably, the 'peritoneal flap', 'sandwich' or 'Malmø' repair is widely used although sparsely described in the literature [42, 43]. This technique utilizes part of the hernia sac to obtain midline closure without increased tension on the abdominal wall, proposedly preserving abdominal wall function as opposed to the different lateral release procedure [44]. Preoperative instillation of air into the peritoneal cavity and injection of Botulinum Toxin A (chemical component separation) into the lateral abdominal wall muscles are preoperative approaches to facilitate midline closure during AWR. These techniques are still relatively sparsely described in the literature [45-47]. As a final alternative to surgical treatment of giant incisional hernias, non-operative handling may be the best solution for some patients. This may include patients who are not bothered by symptoms from their hernia and patients with comorbidities or advanced age that make it unappealing to undergo large surgical procedures [48, 49]. Apart from being a safe alternative in terms of mortality, little is known about patients with incisional hernia treated conservatively [50, 51].

Short-term outcomes after AWR

AWR for giant incisional hernia traditionally was associated with high rates of postoperative complications and long postoperative hospital stays [35, 52-54]. Proposedly, this was because giant incisional hernia repair almost always involved major surgical trauma with adhesiolysis and large wounds, placement of a foreign body (mesh) and altered anatomy, combined with long durations of surgery on mostly overweight and diabetic patients [54, 55]. Naturally, choice of technique impacts on the complication rate postoperatively. Minimally invasive approaches lower the risk of wound complications [35], but aside from this it seems that the different technical approaches lead to similar postoperative complication rates. Either way, wound complications comprise the most common complication after AWR [35] followed by pneumonia and respiratory insufficiency [37, 54].

Increasing amounts of research has been put into optimization of the postoperative course after colorectal and upper gastrointestinal surgery during the last decade [56, 57], however only one preliminary report on postoperative enhancement after AWR existed prior to the study included in this thesis [58]. Consequently the literature on postoperative patient-reported short-term outcomes is limited, which may be surprising considering the extent of trauma caused by AWR and the increasing volume of procedures performed worldwide [7]. An American group has reported promising preliminary results of the use of intraoperatively applied transversus abdominis plane block as primary postoperative analgesia after open repair, and a few studies on instillation of local analgesics after laparoscopic hernia repair has been published [59-62]. Otherwise, little research in the field exists. Hence, optimization of the postoperative course for patients undergoing AWR is an area in need of further research. As with the literature on postoperative enhancement, preoperative optimization in patients undergoing AWR has been sparsely examined in the literature. Most centers performing AWR for giant incisional hernias demand complete smoking cessation from patients preoperatively, as well as weight loss in the obese and tight glycemic control in case of obesity and diabetes [63].

Long-term outcomes after AWR

Traditionally, the most important outcome after hernia repair utilizing AWR has been recurrence of the hernia, followed by postoperative complications and readmissions, and lastly the patient-reported outcomes. As AWR has evolved during the last 20 years, recurrence rates have dropped from more than 50% to below 10% in some publications [8, 52, 64]. Larger hernia defects, obesity, emergency repair and postoperative complications increase the risk of recurrence [65-67], whereas retromuscular placement of a mesh decreases the risk of recurrent hernia, as opposed to onlay or intraperitoneal placement [67]. The surgical technique may also play a role, as recent publications report open repair aided by TAR to lead to superior long-term outcomes in terms of recurrence compared to other techniques [37-40, 52]. Surgeon experience and hospital volume may also impact on the recurrence and complication rates after AWR [68].

Patient-reported outcomes after AWR include QOL, pain and other subjective parameters [54, 69, 70]. Several studies have assessed pain and QOL weeks, months and years after AWR using different metrics. In general, these studies found improvement of both overall health-related and disease-specific QOL after AWR [69, 70]. Direct evaluation of QOL after different surgical approaches to AWR for giant hernia is lacking in the literature. Comparison across different studies is difficult due to the use of different metrics as well as the timing of application of these, and perhaps also because of intercultural differences of patients from different continents.

Few studies have described other postoperative outcomes than the ones mentioned above. A recent review from our group concluded that the literature on abdominal wall function after AWR was limited [20], and since then only one study has emerged, reporting improved truncal flexion six months after AWR utilizing TAR [71]. As a consequence, several hypotheses exist, including claims that division of lateral abdominal wall muscle aponeuroses may harm abdominal wall function [44]. Abdominal wall function is crucial to several important everyday-life activities and extremity movement [72, 73], and plays an important role in the prevention of low back pain [74, 75]. Further, the abdominal wall muscles are important parts of the respiratory mechanics [76, 77], and are thus essential for many of the patient's daily-life activities (Table 1).

No long-term studies of the impact of AWR on respiratory function exist. Moreover, extensive studies on abdominal wall function and whole-body fitness are lacking in the literature. These may be important parameters to assess at a time when recurrence- and postoperative complication rates seem stagnated.

Table 1: Function of the muscles of the anterior abdominal wall.

Muscle	Role in movement	Role in respiration
Rectus abdominis	Flexion of vertebral column, assisting in lateral flexion	Pulls ribcage downwards to assist in (forced) expiration
External oblique	Flexion, rotation and lateral flexion of the vertebral column	Pulls ribcage downwards to assist in (forced) expiration
Internal oblique	Rotation and lateral flexion of the vertebral column	Pulls ribcage downwards to assist in (forced) expiration
Transverse abdominis	Stabilization of the pelvis	Increases intra-abdominal pressure to assist in (forced) expiration

As a consequence of the previously described impact of incisional hernia on the patient and the lack of knowledge about long-term consequences of AWR, the indication for surgical treatment of incisional hernia is consistently up to debate. In a survey of American hernia surgeons, the indication for elective repair of a ventral hernia (which comprise both primary and incisional hernias) aside from strangulation has been reported to be pain, followed by cosmetic complaints, difficulty with defecation or micturition, back pain and respiratory dysfunction [78]. Another group has suggested that "the general indication for surgery should be critically reconsidered in patients with oligosymptomatic incisional hernia"; this statement was based entirely on the incidences of pre- and postoperative pain [79]. These reports reflect how abdominal wall function and respiratory function seem to be of less, if any, importance to many surgeons deciding whether or not an indication for AWR is present. Further, non-operative treatment of patients with a minimum of symptoms from an incisional hernia seems to be trending in recent years, although a noticeable rate of patients who cross over to operative treatment is reported [25, 50, 51].

As a consequence of the lack of knowledge described above, deeper insight into the impact of incisional hernia on the patient and AWR is warranted.

Hypotheses and aims

This thesis relied on the following hypotheses:

- Giant incisional hernia impairs the patient's QOL
- Enhanced recovery after surgery is feasible for patients undergoing AWR
- AWR does not impair long-term pulmonary function
- AWR leads to improved function of the abdominal wall

The overall aim was to examine different aspects of short- and long-term recovery after AWR for giant incisional hernia.

PRESENTATION OF THE STUDIES INCLUDED IN THE THESIS

Study I: Standardized measurement of quality of life after incisional hernia repair: a systematic review [69]

Hypothesis: Several standardized measurements of QOL after incisional hernia exists.

Aim: To evaluate the existing standardized methods to measure QOL after incisional hernia repair.

Methods: This study was descriptive of nature and a systematic review of the existing literature published from January 1980 to November 2013. The literature databases Pubmed and EMBASE were searched using the terms "incisional hernia AND quality of life" combined with the medical subject heading terms "pain", "pain measurement", "questionnaires", and "hernia, ventral", including only full-length articles written in English language. Inclusion criteria were studies reporting QOL after incisional hernia repair using a standardized method.

Results: After initially identifying 365 studies, a total of 26 studies using standardized questionnaires for the assessment of QOL were included in the review. Overall health-related QOL was assessed by the Short-Form (SF) 36 (14 studies), SF 12 (1), Gastrointestinal Quality of Life Index (4), EuroQol-5D (1), Karnofsky Performance Status Scale (1) and 15D (1). Two different disease-specific questionnaires were used: Carolinas Comfort Scale (5) and Hernia-Related Quality of Life Survey (1). Considerable variations in the timing of QOL assessment before and after hernia repair were found making it difficult to compare the results across studies.

Limitations: This study was primarily limited by the methodology. The assessment and selection of studies for inclusion in the review was done by the first author alone, allowing for a risk of selection bias. This could have been accounted for by having a second author assessing the studies identified in the literature search, and subsequently compare the results of the two independent assessment processes. The study describes the different standardized assessment methods available, however does not analyze the included questionnaires or potential validity issues. Thus, no comparison of the included assessment methods is performed and hence the conclusions of the review become rather vague in contrast to if a meta-analysis was performed.

Strengths: The primary strength of this study was the high number of studies included, which allowed us to overview the entire field of available methods for evaluation of QOL in patients with incisional hernia. Aside for describing the different existing questionnaires, the study also offers an overview of the effects of incisional hernia repair on patient-reported outcomes. Although not an aim at the time of writing of the manuscript, this turned out to be an additional use of the paper, which was the only published article describing this subject at the time of publication.

Study II: Enhanced recovery after giant ventral hernia repair [55]
Hypothesis: Implementation of an enhanced recovery pathway after AWR is feasible and results in faster recovery and decreased length of stay.

Aim: To assess if the implementation of an enhanced recovery after surgery (ERAS) pathway benefitted patients undergoing AWR.

Methods: This was a prospective study of the postoperative course of patients who underwent AWR for giant incisional hernia at the Digestive Disease Center, Bispebjerg Hospital, from December 2014 to July 2015. On December 1st 2014 a new ERAS guideline for peri- and postoperative care of patients who underwent AWR was implemented at our institution with the aim to improve the postoperative recovery. In comparison with the old treatment algorithm, the new guidelines featured an increased focus on early mobilization and discharge criteria, as well as the introduction of preoperative high-dose steroid. The rate of complications, length of stay, and rate of readmissions of patients subjected to ERAS was compared with patients treated immediately prior to the introduction of the new guideline.

Results: A total of 16 patients undergoing AWR after the introduction of the ERAS pathway were included and compared with 16 patients undergoing AWR prior to the implementation of the pathway. After implementation of the ERAS pathway, a decrease in postoperative length of stay was found (median 3.0 vs. 5.5 days, P = 0.003), accompanied by low reported scores of nausea, pain and fatigue. In absolute numbers, there were more postoperative readmissions (5 vs. 2, P = 0.394), complications (7 vs. 4, P = 0.458), and reoperations (5 vs. 1, P = 0.172) in patients subjected to the ERAS pathway, however none statistically different from prior to the change of practice. The conclusion from this study was, that implementation of an ERAS pathway including preoperative high-dose steroid was feasible with reduced length of stay and good subjective outcomes as a result.

Limitations: The primary limitation to this study was that the patients subjected to the ERAS pathway were compared to a historic control group of patients. Ideally, a randomized controlled trial should have been performed to directly compare the impact of an ERAS pathway to traditional postoperative care. This, however, is hardly feasible due to the many factors involved in postoperative care. Next, a prospective evaluation of the patient-reported outcomes was lacking for the control group, making it impossible to evaluate any impact of the ERAS pathway on these parameters. The study design further allowed for an effect of time to impact on the results, since the experience of surgeons and care personnel may have changed during the study period, potentially resulting in improvement of the outcome for patients treated later in the study period (ERAS group).

During the study period two investigators followed the patients closely in order to register the patient-reported outcomes twice daily. This inevitably increased the attention given to this patient group from both surgeons and nurses, thus introducing a risk of intervention bias. The concerning tendency towards more complications in patients subjected to the ERAS pathway might have been confirmed if more patients were included in the study. Thus, the risk of type-II error, with potential impact on the results, was considerable.

Strengths: This study reflected the reality of performing AWR for giant incisional hernias, since included patients were consecutively treated. The detail-level of the patient-reported outcomes is a strength due to the novelty of this in the literature on AWR for giant incisional hernia. This study was the first to report the use of preoperative high-dose steroid in patients undergoing AWR.

Study III: Abdominal wall reconstruction for large incisional hernia restores expiratory lung function [80]

Hypothesis: AWR for giant incisional hernia does not impair long-term postoperative pulmonary function.

Aim: To examine the pulmonary function of patients undergoing AWR before and one year after surgery.

Methods: This was a prospective study of patients subjected to AWR for giant incisional hernia and a control group of patients with an intact abdominal wall, who underwent colorectal resection. Patients were included at the time of planning of the surgery and examined pre- and one year postoperatively. We examined pulmonary volumes by standard spirometry, in- and expiratory respiratory muscle function, and respiratory QOL using two different questionnaires. The examined lung function measures were forced vital capacity (FVC), forced expiratory volume in first second (FEV1), peak expiratory flow (PEF), maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP). All objectively measured parameters were presented as values relative to the predicted values for healthy individuals (% predicted).

Results: For patients undergoing AWR, %PEF improved significantly from 84% preoperatively to 91% after one year (P = 0.036). %MEP also improved from 74% preoperatively to 93% at follow-up (P = 0.034), whereas there were no significant changes in any of the other objective or subjective measures. After colorectal resection there were no significant changes after one year, compared to preoperative examinations. None of the two groups exhibited changes in respiratory QOL one year postoperatively.

Limitations: As is the case with other studies included in this thesis, lack of a proper sample size calculation is a severe limitation. At the time of the planning of this study, no pilot data for the primary outcome were available, which made a sample size calculation impossible. Thus, we chose to include as many patients as possible, however it was estimated that at least 15 were needed. The lack of a sample size calculation is a concern, since a tendency towards decreased FEV1 was found in patients undergoing AWR. As with study II, a type-II error may be responsible for the lack of statistical significance on this parameter. Post hoc sample size calculations revealed that 326 patients would have been required in order to detect significant changes in this parameter.

Another limitation to this study was that the respiratory examinations were never validated in patients with incisional hernia. Since abdominal wall mechanics seem to be altered in this patient group, one could hypothesize that examination of respiratory volumes and strengths, which are highly dependent on abdominal wall musculature, is of questionable validity. The respiratory QOL was examined using questionnaires designed for patients with known respiratory diseases, to monitor potential changes in symptoms and treatment effect in the current surgical patient population. This potentially limited the value of the results regarding respiratory QOL in the current study, due to low sensitivity. Measurement of the intra-abdominal pressure could have added to the understanding of the mechanisms involved in changes in lung function. The control group was not optimal, as some patients had low-grade malignant disease at the time of preoperative assessment and underwent postoperative adjuvant chemotherapy. Further, the extent of the surgical trauma on the abdominal wall of patients in the control group varied from laparoscopic surgery, with a small pfannenstiel incision as extraction site, to full midline laparotomy.

Strengths: The strengths of this study included the prospective design and the inclusion of a control group enabling assessment of the effect of surgical trauma, anesthesia and postoperative recovery on respiratory function in general. The study is novel, since no previous papers have described the long-term effect of AWR on respiratory function. Even though questions may arise regarding validity of some tools utilized in this study, the results could impact on the daily practice of hernia surgeons.

Study IV: Abdominal wall reconstruction for incisional hernia optimizes truncal function and quality of life [81]

Hypothesis: AWR for giant incisional hernia leads to improvement of abdominal wall function and QOL.

Aim: This study aimed to evaluate the impact of AWR on abdominal wall function, whole-body fitness and QOL.

Methods: Analogue to study III, this was a prospective examination of patients undergoing AWR for giant incisional hernia, who were compared to a control group of patients undergoing colorectal surgery. Patients were examined within one week preoperatively and again one year after surgery. The primary outcome of the study was the change in abdominal wall flexion strength. We secondarily examined changes in abdominal wall extension strength as well as function of the upper- and lower extremities. Lastly, QOL was assessed as overall QOL (SF-36) and hernia-related QOL (Carolinas Comfort Scale©).

Results: The results of this study showed that AWR led to significantly improved abdominal wall function, reflected by increased truncal flexion (from mean 505.6 N preoperatively to 572.3 N postoperatively, P < 0.001) and extension (from mean 556.7 N to 606.0 N, P = 0.005) strength. No changes in upper (from 39.9 kg to 39.9 kg, P = 0.716) or lower (from 215.9 W to 205.4 W, P = 0.059) extremity function was found and we thus concluded that AWR specifically improved the truncal function. Further, the overall physical component of QOL was improved one year after AWR (43.9 vs. 47.8, P = 0.035), while the overall mental component remained statistically unchanged (46.9 vs. 48.1, P = 0.409). The group of patients who served as controls did not elicit similar changes. On the contrary, a decline in abdominal wall function was found in these patients at one-year follow-up (flexion 475.2 N to 449.8 N, P = 0.042, and extension 539.8 N vs 506.9 N, P = 0.026). Direct comparison revealed a statistically significant greater increase in abdominal wall function (relative change in truncal flexion AWR 1.13 vs colorectal resection 0.93, P < 0.001) and physical QOL in patients undergoing AWR for giant incisional hernia compared with patients who underwent colorectal resection (relative change AWR 1.12 vs. colorectal resection 1.00, P = 0.032).

Limitations: The limitations concerning this study are somewhat similar to the limitations to study III. The absence of a proper sample size calculation seems less severe in this study compared to study III. The risk of type-II error is a concern when sample size calculation is lacking, however this turned out to be irrelevant since the hypothesis was confirmed. Increasing the sample-size thus would not change the conclusions on the primary outcome of this study. It may be that secondary outcomes such as the

mental component of QOL could turn out to improve significantly if the sample size was increased, however, as mentioned this would not affect the conclusions of the current study. The use of Carolinas Comfort Scale was suboptimal, as this tool was originally developed for use in patients who underwent inguinal hernia repair with placement of a mesh.

The methods used for examination of physical function naturally may also be questioned. Although never specifically examined for use in patients with incisional hernia, it is unlikely that the presence of an abdominal wall fascial defect could interfere with the results of these examinations. Separate measurements of the muscle groups of the anterior abdominal wall could have improved the understanding of which functions were affected by the surgical procedure. Electromyographic examinations could also have aided in this evaluation. Lastly, assessment of the dynamic abdominal wall function could have led to further characterization of the impact of AWR on the muscle function.

Strengths: There are several strengths to the current study. As with study III, the study was prospectively designed, and registered at clinicaltrials.org, underlining the long-term aim. Secondly, long-term follow-up was completed for all but one patient undergoing AWR and the risk of bias due to dropouts thus seems low. Another important strength of this study was the inclusion of a control group, which served the purpose of assessing the impact of surgical trauma to the abdominal wall, and postoperative recovery period. Furthermore, any systematic measurement bias was indirectly assessed by inclusion of the control group. The examination of upper- and lower extremity strength also adds strength to the study, since these assessments further evaluates the improvements found in truncal strength. The method for assessment of truncal strength has been shown to be reliable and reproducible in both patients with incisional hernia and healthy controls [21]. The Legrig and hand grip strength dynamometer has been extensively used and validated previously [82, 83].

DISCUSSION

Principal findings

The studies included in the current thesis lead to the following conclusions:

- Consensus regarding QOL assessment in relation to hernia repair is lacking, limiting the comparison across studies.
- Enhanced recovery after AWR for giant incisional hernia is feasible and leads to good patient-reported outcomes and short length of stay.
- AWR for giant incisional hernia improves expiratory lung function, while other respiratory parameters remain unchanged long-term.
- AWR for giant incisional hernia leads to improved muscular function of the truncus and improved physically related QOL long-term.

Quality of life

Because incisional hernia is not associated with increased risk of long-term mortality [84], it is not considered a dangerous condition. Thus, QOL is an essential parameter to assess in patients with incisional hernia, as is the case with other diseases that are not potentially life-threatening, e.g. most orthopedic conditions requiring surgery [85]. In the studies included in this thesis, QOL was assessed by several different metrics, perhaps reflecting the lack of consensus on how to assess QOL after AWR. Health-related QOL is vaguely defined and comprises different aspects of the patients' perception of personal health and its impact on everyday life. As it cannot be measured directly, QOL is often evaluated on scales in the form of questionnaires [86]. When assessing the impact of an incisional hernia on the everyday life, a natural variation of the extent of the impact on the patient may exist [87]. One example may be a sedentary octogenarian who sits in his couch most of the day as opposed to a 40-year old female who is actively working, and unable to perform several physical activities due to limitations inflicted on her by the hernia. These two patients may have the same hernia and report equal symptoms. However, the impact on their everyday QOL may differ substantially. Even so, it may be that both patients are equally mentally bothered by the hernia, underlining the many aspects of QOL.

An important aspect when evaluating QOL is the differentiation between overall health-related QOL and disease-specific QOL. It has been stated that in order to examine patient-reported outcomes properly, both generic and disease-specific measures are required [88]. Overall health-related QOL may not change after AWR, while the abdominal wall-related QOL improves dramatically, as was the case in study IV in this thesis. The opposite mechanism may be present in patients undergoing colorectal cancer resection, as was the case with some patients in the control group in study IV. Presumably, the overall health-related QOL should improve after surviving surgery for a life-threatening, malignant disease, but this is not always the case [89]. Analogue to patients undergoing AWR for giant incisional hernia, there may be a dramatic change in cancer-related QOL in patients who elicited no changes in generic QOL after colorectal cancer resection. Therefore, assessment of QOL essentially relies on asking the right questions, which again depends on what we want to know [90].

Due to the described potential pitfalls in the evaluation of QOL, simplification may be needed in the field of AWR. If patients are physically or mentally bothered by an incisional hernia they often request surgery. It may be that it does not matter if the measured QOL improved by AWR for incisional hernia, since the patient presented with a problem which disappeared after the surgical repair. Thus, a simple evaluation of the impact of AWR could be to ask the patient the simple yes or no question: "Is the bother from the hernia gone now?" It can be hypothesized, that any patient able to answer this question with a 'yes' could rightfully be classified as successfully treated.

No correlations between abdominal wall function and either generic or hernia-related QOL was found in study IV. This is in direct contrast to studies on sedentary office workers and older adults with lumbar osteoarthritis, where abdominal muscle strength was significantly associated with health-related QOL [91, 92]. It is tempting to conclude that low sensitivity of either parameter is the cause for the lack of correlation between these two parameters in study IV. The explanation may be simpler though: Patients who were used to live with a giant hernia improve dramatically in QOL after the hernia repair, regardless of any potential optimization of the abdominal wall function. Theoretically, if it was possible to improve the abdominal wall function without repairing the giant hernia, it might be that the QOL of patients would not change at all.

Postoperative short-term recovery

The importance of enhanced postoperative recovery after surgery in general seems clear: ERAS pathways lead to fewer

postoperative complications and decreased length of stay compared to non-ERAS pathways [57]. Study II in this thesis seems to confirm that an ERAS pathway leads to decreased length of stay, whereas a synchronous reduction in postoperative complications was not found. On the contrary, a tendency towards more complications and re-interventions was found after the introduction of the ERAS pathway. Due to the non-randomized design and the low number of patients included in the study, no conclusions can be drawn from this tendency. Since the completion of study II, an American group has published the results of an ERAS pathway for patients undergoing open hernia repair [93]. The main difference between the ERAS pathway reported in that study and study II in this thesis is the addition of preoperative high-dose steroid, perhaps explaining the longer time to discharge in the American study. Noticeably, the readmission rate was only 4% after the implementation of the ERAS pathway in the American study, which is quite impressive. Whether this low number is biased by readmissions to hospitals different from the one performing the procedures is unknown.

It can be hypothesized that patients undergoing AWR for giant incisional hernia are different from patients undergoing other abdominal procedures, as the development of incisional hernia is often preceded by wound healing deficiency and high rates of postoperative wound morbidity [35]. This may explain why the implementation of ERAS pathways after AWR is happening at a slower pace compared with other abdominal procedures [94-97].

Even if future studies show that ERAS pathways do not impact negatively on short-term postoperative complication rates after AWR, it remains to be examined if the long-term hernia recurrence rate is affected. Referring to the classical postoperative regimens, wounds need time and rest to heal. It may thus be hypothesized that early mobilization and hospital discharge impairs the wound healing and mesh ingrowth into the abdominal wall. Recently, postoperative physical rehabilitation has been proposed as an important element in the treatment of patients undergoing AWR with promising outcomes as a result [98]. In the pathway described in study II, however, rehabilitation was not a part of the program, perhaps reflecting that little is known as to the recommendation on physical activity in the immediate postoperative period after AWR.

High-dose glucocorticoid was administered preoperatively as part of the ERAS pathway described in the current thesis. Randomized trials have shown that this leads to fewer postoperative complications, decreased pain and shorter length of stay after major abdominal surgery [99-101]. Although concerns were traditionally raised regarding wound healing in patients treated with steroids, wound complication rates are not affected negatively by preoperative high-dose glucocorticoid [99]. It therefore seems reasonable to assume that a single-shot high-dose glucocorticoid does not impair wound healing in patients undergoing AWR for giant incisional hernia. Long-term follow-up including hernia recurrence rates are needed to confirm this.

From a clinical perspective it seems as if patients who undergo open AWR for giant incisional hernia have more pain than patients who 'only' undergo midline laparotomy on other indications. The underlying cause for increased pain has been proposed to be muscle spasms due to the lateral release of muscles, soft tissue irritation from the mesh and (if used) transfascial sutures for mesh fixation [93]. Transfascial sutures were not used in any patients in study II, whereas most underwent lateral release procedures, and in all cases a mesh was placed. Even though the median pain scores were low, some patients still reported severe pain, and for these patients the optimal analgesic treatment is still challenging. Opioids are associated with an increased risk of postoperative ileus and should be avoided in a postoperative setting [102]. In recent years, transverse abdominis plane block has emerged as an effective treatment of postoperative pain after laparotomy [103], and this analgesic regimen has also been suggested as a treatment for postoperative pain after AWR using intraoperative administration [58, 59]. In study II, rescue analgesics (opioids) were required in 10 of 16 patients prior to discharge, suggesting that transverse abdominis plane block may be indicated in selected patients who experience severe postoperative pain.

Respiratory function

Study III is the first in the literature to report on the long-term respiratory function after AWR for giant incisional hernia. Previous studies addressing the respiratory function after AWR have focused on the immediate postoperative period, reporting a high incidence of both pneumonia and respiratory insufficiency [53, 104, 105].

The findings of study III have several clinical implications. Preoperative examinations revealed that patients with giant incisional hernia have a reduced %PEF and %MEP compared to patients without an abdominal wall defect. This is potentially of high importance, since population studies have found that reduced PEF is an independent predictor of hospitalization [106], subsequent disability and death [107]. Thus, reduced expiratory function may be an additional indication for AWR in otherwise asymptomatic patients, even though respiratory dysfunction is not reported as a complaint by patients with an incisional hernia [108]. If future studies confirm that the expiratory function is compromised in patients with giant incisional hernia, lung function assessment may gain a place when choosing between surgery and a non-operative treatment strategy. A non-operative approach could thus potentially include respiratory muscle training, as this has been found to improve MEP in other patient groups [109].

Preoperative MEP has been found to be inversely associated with duration of invasive mechanical ventilation in patients undergoing cardiac surgery [110]. As length of invasive mechanical ventilation further predicts the risk of postoperative complications, the expiratory dysfunction may in part explain the high incidence of postoperative pulmonary complications after AWR for giant incisional hernia [111]. Consequently, preoperative respiratory muscle training holds a potential for reducing postoperative complication rates after AWR. Future research in perioperative optimization in patients undergoing AWR should thus include respiratory muscle testing and training.

The reason for a compromised expiratory function in patients with giant incisional hernia is unknown. Referring to the previously described 'piston in a cylinder' model, it is tempting to assume that a diaphragm dysfunction is involved. However, the diaphragm acts mostly in the inspiration [16]. The muscles primarily involved in forced expiration are those of the anterior abdominal wall, of which the rectus muscles are the most important [112] (Table 1). Therefore it can be hypothesized that the compromised expiratory respiratory function in patients with giant incisional hernia is a direct result of reduced abdominal wall function, as found in study IV. We examined this in the data without finding a statistical significant correlation between truncal flexion strength and PEF or MEP (data not shown), perhaps due to the small sample size. Another reason for this lack of correlation may be, that the strength of the muscles matter less with regard to the expiratory function, whereas an intact linea alba, that serves as a fixa-

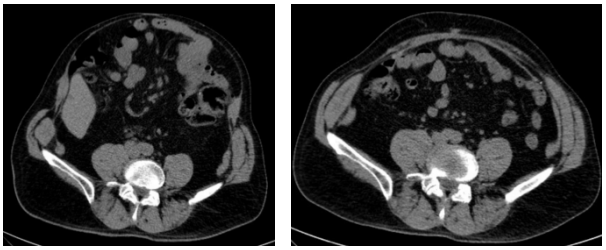
tion point for the abdominal wall muscles, are of higher significance. The lack of an intact linea alba may result in a deficit in the ability to increase the intra-abdominal pressure [113], which is dependent of the rectus and transverse muscles. This hypothesis could have been tested in study III by measuring intra-abdominal pressure pre- and postoperatively. Further, intra-abdominal pressure measurement before and during Valsalva's maneuver could help examine if an abdominal wall defect affects the ability to defecate [114]. It is not surprising that there was no change in the %FEV1 one year after AWR, since FEV1 is more dependent on the airway diameter than the force used to generate flow.

Abdominal wall function

In study IV, improvement in abdominal wall function was found after AWR for giant incisional hernia. Only one other study assessing pre- and postoperative abdominal wall function exists. That study reported improvement in abdominal wall flexion strength six months after AWR, but did not examine whole-body fitness or truncal extension [71]. Other studies on abdominal wall function in relation to AWR have been published, but none of these report on abdominal wall function both pre- and postoperatively [20, 115-119].

The mechanisms resulting in improved abdominal wall function after AWR were not studied in this thesis. Intuitively, repositioning of the rectus muscles is the main reason, due to a straightened force vector between the fixation points of the muscles, which are the pubic symphysis, pubic crest and the ribs (Figure 2). However, reconstruction of the linea alba may also be of importance, allowing for fixation of the lateral abdominal wall muscles. The latter may be important when distinguishing between open and laparoscopic hernia repair, since it has been reported that the laparoscopic approach in fact also leads to medialization of the rectus muscles [31]. Whether this results in improved abdominal wall function remains unknown.

Figure 2: Axial CT scan of a patient with giant incisional hernia preoperatively (left) and one year postoperatively (right).



Whether the abdominal wall function improves after laparoscopic hernia repair is unknown. It may be that only the placing of a mesh to cover the fascial defect is needed to restore abdominal wall function and regain the trunk stability. Further, the mesh placed laparoscopically may act as a reconstructed linea alba and provide the fixation needed for the lateral abdominal wall muscles. Recently, closure of the fascial defect has been proposed to improve the functional outcome of laparoscopic hernia repair [120]. To our knowledge though, this has only been examined in one case-control study, using a questionnaire (Activities Assessment Scale) [121], and thus it remains unclear whether functional improvement indeed occurs after laparoscopic hernia repair.

The aim for surgeons performing AWR today almost always is to reconstruct the abdomen and improve the patient's QOL without long-term recurrence of the hernia. Patients inevitably most often have the same aim; otherwise they would not succumb to AWR surgery. However, if the goal of repairing the hernia and improving the patient's QOL without recurrence can be achieved in different ways (ie. using different surgical techniques), other outcomes become increasingly important. In study IV, we found that reconstruction of the linea alba and restoration of the rectus muscle anatomy led to significant improvement of abdominal wall function. It may thus be that techniques involving reconstruction of the linea alba are desirable for patients bothered by loss of abdominal wall function. It has been reported that 50% of patients with symptomatic hernias are bothered by loss of function [108], indicating that the surgical technique and results of the current study are of importance to a high number of patients.

Patients with incisional hernia report a reduced physical function compared to patients without a hernia [14]. Whereas this may in part be attributed to the bulge itself, this finding may be a consequence of a compromised function of the abdominal wall muscles and pain. Naturally, a deficit in physical function impacts on the QOL, and thus abdominal wall function and QOL should be highly correlated. As previously discussed, however, evaluation of QOL is highly dependent of the questions asked and therefore statistically significant correlation between generic QOL and abdominal wall function may be hard to find. Conversely, hernia-related QOL and abdominal wall function may correlate excellently, as has been reported previously [71].

The data in study IV revealed a lack of correlation between fascial defect size and truncal strength improvement (data not shown). This was surprising as we hypothesized that the diastasis between the rectus muscles was the cause for a decreased truncal function. In patients with diastasis recti, a significant correlation between intraoperatively measured rectus muscle diastasis and preoperative truncal flexion strength has been found, while preoperative clinical assessment and CT measurement did not correlate with preoperative truncal flexion strength [122]. Patients with rectus diastasis have an intact, although widened linea alba, and thus it is possible that these results do not translate to patients with incisional hernia, with a defect linea alba. Further, it has been reported that clinically assessed, not CT measured defect size is correlated to abdominal wall function [123]. There is considerable variability of abdominal wall function in patients with giant incisional hernia. In a previous validation study we found that abdominal wall function seemed to vary within one week, perhaps indicating intra-individual variability in symptoms caused by this disease as compared to patients with chronic medical disease, e.g. rheumatoid arthritis [21, 124].

CONCLUSION

In the current thesis some of the aspects of recovery after AWR were evaluated. The field of AWR is presently evolving at an amazing pace, with new innovative techniques and approaches appearing regularly. Even so, the current thesis holds important findings regarding the short- and long-term consequences of AWR.

It was demonstrated that several different metrics for measuring QOL after AWR exist, but a lack of consensus about method and timing of QOL measurements makes comparison across studies difficult. Enhanced recovery after AWR for giant incisional hernia is feasible with promising patient-reported outcomes and should be implemented to improve patient-reported outcomes and recovery in the immediate postoperative period.

Patients with giant incisional hernia suffer from deficits in expiratory lung function, abdominal wall function and QOL, all of which improve one year after AWR. Consequently the indications for surgical repair of giant incisional hernias should be revisited, as these patients may experience impairments which traditionally are not examined during the process of deciding between surgery and a non-operative approach.

Therefore, unless reasonable arguments against surgery exist, giant incisional hernia is an illness that should be treated.

PERSPECTIVES FOR FUTURE RESEARCH

An evolving field like AWR requires continuous robust research, and the studies included in the current thesis potentially impact on the future research in this field.

The last years have seen international registry collaboratives form, enabling large data generation [125, 126]. Some studies have already been published from these databases, describing changes in hernia-related QOL after AWR [54, 127]. These data provide valuable insight into differences between various surgical approaches, but may still be limited by the selection bias which naturally occurs when surgeons decide on surgical approach for each patient. The future research into QOL before and after AWR thus seems to be based on information from these registries, supplemented by smaller prospective studies examining associations between QOL and specific parameters (ie. study IV). Currently, our group is examining the correlation between abdominal wall function and QOL after laparoscopic repair of medium-sized hernias (clinicaltrials.gov NCT02320071).

The results of study II have already made an impact. Due to the promising patient-reported results after introduction of the ERAS pathway, we chose to examine whether this was due to the administration of high-dose preoperative steroid by designing a randomized controlled trial comparing a preoperative single-shot high-dose steroid to placebo (clinicaltrials.gov NCT025942410029) [128]. Hopefully, this study will further add to our understanding of the components necessary for an optimal postoperative course after AWR.

Another important aspect touched upon by many patients after AWR for giant incisional hernia is how to proceed after discharge from the hospital. Recommendations regarding the amount of physical activity, use of abdominal binder and when to initiate physical rehabilitation are areas which are almost undescribed in the literature. Thus, the current recommendations on binders and physical activity vary to a great extent across different centers, and are not evidence-based.

As briefly discussed, the choice of surgical technique may depend on the patients symptoms, and it may be that restoration of the abdominal wall midline is key in the effort to achieve optimal function of the abdominal wall. Presently, there are no studies of abdominal wall function after laparoscopic or robotic AWR, and it is unknown if the technique elicited on the patients included in this thesis is superior to minimally invasive approached in terms of optimization of abdominal wall function. Comparative studies of different techniques for AWR are thus warranted, but these are difficult to conduct, because the treatment plan for each patient is individual and depends on several factors such as age, concomitant diseases, symptoms, previous abdominal wall surgery, anatomy, hernia site, and lastly the surgeon's preference and skill set.

The long-term consequences of lateral release procedures are another important aspect of abdominal wall function after AWR. Presently it is unknown if incision of the external oblique aponeurosis or transverse abdominis muscle lead to long-term lateral hernia, bulge, pain or loss of function [44]. As it is now established that AWR leads to improved truncal flexion and extension strength, future research in this area should focus on how anterior and posterior component separation affect patients long-term. It has been reported that AWR aided by ACS or TAR leads to hypertrophy of the rectus muscle measured on axial CT, whereas atrophy was found in the external oblique after ACS and in the transverse abdominis after TAR [129, 130]. These results could be a measure of the muscle strength indicating that the function of the released lateral muscles decline after these types of AWR. This, however, is still only a hypothesis, as the configuration of the lateral muscles also changes dramatically, secondary to loss of tension due to the incision of the aponeurosis/muscle. These alterations potentially limit the value of measuring cross-sectional muscle areas.

Compared to abdominal wall function, the literature on pulmonary function after AWR is even sparser, once again calling for further research in this area, preferably by studies comparing different techniques for AWR. As we found no negative consequences of AWR on respiratory function in study III, future research should focus on the patients with a reduced respiratory capacity, as this subgroup of patients may be more prone to respiratory complications after AWR than the patients described in this thesis [131].

Recently it has been proposed that a watchful waiting approach to patients with incisional hernia is a safe alternative to surgical repair [25, 50, 51]. Proponents of a non-operative treatment highlight the high risk of postoperative morbidity and recurrence as arguments against AWR in a- or oligosymptomatic patients, whereas risk of hernia incarceration traditionally has been the main indication for AWR in this patient group. The findings of study III and IV may change these perceptions in the future. As we found that patients with incisional hernia had reduced %MEP and %PEF, pulmonary testing may serve as a future diagnostic tool to evaluate conservative versus operative approach for otherwise asymptomatic patients. Analogue to this, abdominal wall dysfunction may be an indication for repair, although cohort studies on abdominal wall function in healthy subjects are lacking, making it difficult to determine whether a deficit in abdominal wall function in fact is present. Either way, the current results should have immediate impact on the questions surgeons ask patients with incisional hernia in order to choose between operative or non-operative treatment. Complaints regarding core instability, inability to perform physical tasks involving abdominal musculature or pulmonary complaints seem indications for AWR based on the studies included in the current thesis.

SUMMARY

Incisional hernia is a common long-term complication to abdominal surgery, occurring in more than 20% of all patients. Some of these hernias become giant and affect patients in several ways. This patient group often experiences pain, decreased perceived body image, and loss of physical function, which results in a need for surgical repair of the giant hernia, known as abdominal wall reconstruction. In the current thesis, patients with a giant hernia were examined to achieve a better understanding of their physical and psychological function before and after abdominal wall reconstruction.

Study I was a systematic review of the existing standardized methods for assessing quality of life after incisional hernia repair. After a systematic search in the electronic databases Embase and Pubmed, a total of 26 studies using standardized measures for

assessment of quality of life after incisional hernia repair were found. The most commonly used questionnaire was the generic Short-Form 36, which assesses overall health-related quality of life, addressing both physical and mental health. The second-most common questionnaire was the Carolinas Comfort Scale®, which is a disease specific questionnaire addressing pain, movement limitation and mesh sensation in relation to a current or previous hernia. In total, eight different questionnaires were used at varying time points in the 26 studies. In conclusion, standardization of timing and method of quality of life assessment after incisional hernia repair was lacking.

Study II was a case-control study of the effects of an enhanced recovery after surgery pathway for patients undergoing abdominal wall reconstruction for a giant hernia. Sixteen consecutive patients were included prospectively after the implementation of a new enhanced recovery after surgery pathway at the Digestive Disease Center, Bispebjerg Hospital, and compared to a control group of 16 patients included retrospectively in the period immediately prior to the implementation of the pathway. The enhanced recovery after surgery pathway included preoperative high-dose steroid, daily assessment of revised discharge criteria and an aggressive approach to restore bowel function (chewing gum and enema on postoperative day two). Patients who followed the enhanced recovery after surgery pathway reported low scores of pain, nausea and fatigue, and were discharged significantly faster than patients in the control group. A non-significant increase in postoperative readmissions and reoperations was observed after the introduction of the enhanced recovery after surgery pathway.

Study III and IV were prospective studies of patients undergoing abdominal wall reconstruction for giant incisional hernia, who were compared to a control group of patients with an intact abdominal wall undergoing colorectal resection for benign or low-grade malignant disease. Patients were examined within a week preoperatively and again one year postoperatively. In study III, the respiratory function and respiratory quality of life were assessed, and the results showed that patients with a giant incisional hernia had a decreased expiratory lung function (peak expiratory flow and maximal expiratory pressure) compared to the predicted values and also compared to patients in the control group. Both parameters increased significantly after abdominal wall reconstruction, while no other significant changes were found in objective or subjective measures at one-year follow-up in both groups of patients.

Lastly, study IV examined the abdominal wall- and extremity function, as well as overall and disease specific quality of life. We found that patients with a giant hernia had a significantly decreased relative function of the abdominal wall compared to patients with an intact abdominal wall, and that this deficit was offset at one-year follow-up. Patients in the control group showed a postoperative decrease in abdominal wall function, while no changes were found in extremity function in either group. Patients reported improved quality of life after abdominal wall reconstruction.

In summary, the studies in this thesis concluded that; standardization of patient-reported outcomes after incisional hernia repair is lacking; enhanced recovery after surgery is feasible after abdominal wall reconstruction and seems to lower the time to discharge; patients with giant incisional hernia have compromised expiratory lung function and abdominal wall function, both of which are restored one year after abdominal wall reconstruction.

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