Pathophysiology of Major Surgery and the Role of Enhanced Recovery Pathways and the Anesthesiologist to Improve Outcomes

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KEYWORDS

• Enhanced recovery pathway • Fast-track surgery • Anesthesia • Perioperative care
• Pathophysiology of surgery • Stress response to surgery
• Metabolic response to surgery • Minimally invasive surgery

KEY POINTS

- Enhanced recovery pathways aim to reduce the stress response and improve the metabolic response to surgery restoring the patient to preoperative function more quickly.
- It is increasingly recognized that rapid, uncomplicated, recovery reduces not only the cost and length of stay of the patient episode but medical and possibly surgical related complications. Provided defined discharge criteria are met readmission rates are not increased.
- Minimally invasive surgery is a key component of enhanced recovery to reduce the primary injury of tissue damage and blood loss, which both drive the stress response and metabolic response to surgery.
- All elements of an enhanced recovery pathway are important because they interact positively with each other, a term likened to the sum of small gains.
- The anesthesiologist plays a key role in optimizing surgical outcomes by controlling a patient's physiology throughout the perioperative pathway.

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INTRODUCTION

This article provides an overview of the pathophysiologic process of major surgery and how the perioperative management of patients within an enhanced recovery pathway (ERP) can improve recovery after surgery with the aim of reducing stress and complications and improve postoperative function and outcomes.[1–4] A detailed presentation of the biochemical, neuroendocrine, and immunologic changes is beyond the scope of this article.

ERPs, or fast-track surgery, were originally implemented by Henrik Kehlet in colorectal surgery in Denmark in the late 1990s.[5] He asked the fundamental question: why is the patient still in hospital after surgery? He noted that although the causes were multifactorial the common end points were that patients did not have return of gut function and had poor postoperative mobility and function. He devised a protocolized pathway aimed at addressing these issues by reducing any small element that had a negative impact on recovery and promoting early enteral feeding and mobility. The main elements to reduce the stress response and alter the metabolic response to surgery were formalized in a Consensus Guideline by the Enhanced Recovery After Surgery (ERAS) Society in 2005 by Fearon and colleagues for colorectal surgery. Since then the colorectal guidelines have been revised twice by the ERAS Society with the view of keeping the evidence up to date. For instance, in the 2012 guidelines there was an important change in direction recognizing that in laparoscopic colorectal surgery the benefits of thoracic epidural anesthesia (TEA) seen in open colorectal surgery were not directly transferable to laparoscopic surgery.[6]

There are now multinational guideline groups developing guidelines across all surgical specialties and so far evidence-based guidelines have been published or are being developed in pancreatectomy,[7] gastric resection,[8] cystectomy,[9] pelvic and rectal surgery,[10] gynecology, and esophagectomy. The spread and adoption of ERPs has been rapid and some centers in the United Kingdom now have ERPs in all elective surgical specialties, and emergency orthopedic and abdominal surgery.

The ERAS elements are shown in **Fig. 1**, grouped into preoperative, intraoperative, and postoperative factors. The elements themselves and evidence base behind them are not listed here because they are covered elsewhere in this issue and in the article by Gustafsson and coworkers.[6] The ERAS elements can be further categorized into the following groups with some appearing in more than one group:

1. **Preadmission:** counseling, assessment, and optimization
2. **Standards of care:** antibiotic prophylaxis, thromboprophylaxis, prevention of postoperative nausea and vomiting, maintenance of normothermia
3. **Elements to reduce the pathophysiologic insult:** avoidance of bowel preparation, avoidance of nasogastric tubes, minimally invasive surgery, short-acting anesthetic agents, TEA in open surgery, no drains, early removal of catheters
4. **Elements to avoid postoperative gut dysfunction and ileus:** avoidance of salt and water overload, minimally invasive surgery, stimulation of gut motility, nonopioid oral analgesia and nonsteroidal anti-inflammatory drugs, regional anesthesia
5. **Elements to improve the metabolic response to surgery:** avoidance of prolonged starvation, carbohydrate loading, early enteral feeding
6. **Audit:** compliance and outcome

A key issue to ensure the success of an ERP is compliance with all the elements.[11] Gustafsson's group using a large database showed that with increasing compliance with the number of ERAS elements there was a proportional reduction in length of

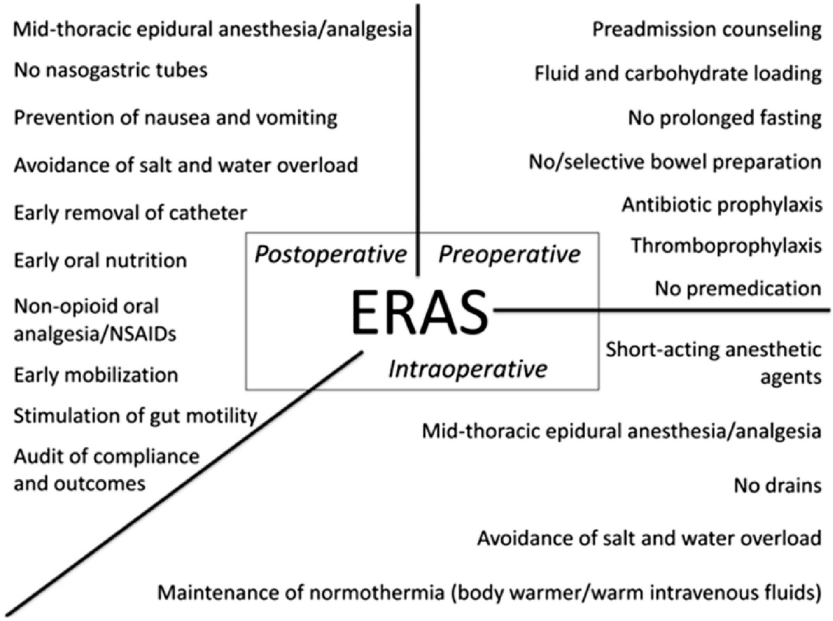

Fig. 1. Enhanced recovery after surgery elements. NSAID, nonsteroidal anti-inflammatory drugs.

stay and complications.[12] It is therefore important to have regular audit and compliance even in centers with established ERPs.

OVERVIEW OF CELLULAR INJURY AND THE STRESS AND METABOLIC RESPONSE TO SURGERY

Primary cellular injury during the perioperative process can be caused by direct surgical injury (from trauma, heating, vaporization, traction, and so forth) or indirect injury from changes in global or local perfusion impairing oxygen and nutrient delivery.

Secondary injury is caused by the effect of locally released inflammatory mediators or the systemic effect of cytokines, inflammatory mediators, or hormones, often termed the stress response to surgery. The consequential injury that results if left untreated is a patient who is catabolic, immobile, feeling weak, and with gut dysfunction. This compounds the injury, delays healing, may lead to complications. The stress response is an evolutionary response to limit further injury, conserve fluid, and mobilize substrates. The benefit the stress response confers to the patient within modern surgery with the availability of modern medical treatments (eg, intravenous fluid, which can maintain or restore altered physiologic parameters to normal) is questionable and in some instances may even impede recovery (**Tables 1** and **2**).

PRIMARY INJURY

Direct Cellular Injury

Surgical access, tissue dissection, mobilization, and extraction

The stress response to surgery is proportional to the type of injury and duration of insult. This results in localized tissue trauma, and cytokine and inflammatory mediator release, which drive a complex bundle of metabolic, hormonal, and immunologic processes in the body, the so-called stress response. Minimizing this process can

Table 1
Primary and secondary injury following surgery

Primary injury	Direct	Surgical access (wound/organ mobilization) Organ removal (dissection/tissue injury)
	Indirect	Blood loss, perfusion, anesthetic technique
Secondary injury	Directly mediated	Cytokine, hormonal, neural
	Consequential	Fasting immobilization

have a profound effect on how the body responds to surgery. However, some surgical procedures have more impact than others, even through similar surgical access sites, because the organ being removed or operated on can trigger a large systemic inflammatory response or impair gut function, which can impair the restoration of normal homeostasis (eg, open two-stage esophagectomy). The development of laparoscopic and robotic-assisted surgery has led to a reduction in the total abdominal wall wound area for patients and reduced intra-abdominal tissue damage by using surgical planes with modern instruments for dissection, which in turn reduces blood loss (**Figs. 2** and **3**). In addition to reducing direct injury, the pain requirements after

Table 2
Key pathophysiologic differences between laparoscopic and open surgery

	Laparoscopic Surgery	Open Surgery
Cardiovascular risk	Equal to open surgery	Equal to laparoscopic surgery
Oxygen delivery	Can be reduced compared with open surgery because of increased aortic afterload and head down or head up position	Can be increased because of epidural block causing vasodilatation
Oxygen consumption driven by cellular injury	Minimized compared with open surgery depending on tissue damage	Depends on primary and secondary cellular injury
Pain after surgery	Severe pain settles after 12–24 h so can be addressed with oral analgesia	Severe pain up to 72 h
Fluid shifts	Minimized after 6 h unless bleeding or gut ileus	Depends on surgery, up to 24 h postoperatively
Postoperative fluid requirements	Intravenous fluid rarely needed beyond 24 h	Intravenous fluids often carried on for duration of epidural
Systemic inflammatory response syndrome	Reduced compared with open surgery	Substantial because of surgical cuts and bowel handling
Gut ileus	Reduced, less surgical bowel handling; lower total intravenous fluid volumes	Can be prolonged
Renal function	Renal perfusion reduced during surgery	Renal perfusion reduced
Mobility after surgery	Good	Often impaired by pain and pumps
Lung function after surgery	Improved compared with open surgery	Can have reduced functional residual capacity, especially if inadequate analgesia or abdominal distention

Fig. 2. Robotic surgery.

minimally invasive surgery are such that at 24 hours most visceral pain has diminished so that analgesic requirements can be met with oral analgesics rather than the more complex forms of analgesia used in open surgery, such as TEA or rectus sheath and wound catheters. The reduction of pain also reduces the total surgical stress response through reduction in the neural pathways (see later). Although minimally invasive surgery is increasing there are still many operations where open surgery remains the standard. Advances in surgical technique and the use of modern instruments in open surgery, such as harmonic scalpel, have also led to less tissue injury and blood loss. The fluid shifts as a result are reduced, which in modern ERPs where early enteral

Fig. 3. Laparoscopic surgery.

feeding is promoted has led to simplification of fluid therapy and the reduction in the use of postoperative intravenous fluids. Importantly, reducing the amount of tissue injury also reduces the increased metabolic requirement for oxygen postoperatively (**Box 1**).

Indirect Cellular Injury

Indirect cellular injury during surgery is caused by changes in blood supply or oxygen and nutrient delivery.

Blood loss

Blood loss reduces global oxygen delivery, which can lead to reduction in localized tissue oxygen delivery. Total oxygen delivery is determined by the combination of cardiac output, hemoglobin concentration, and oxygen saturation. Local oxygen delivery can be further complicated by changes in local perfusion, the causes of which are discussed next. Blood loss also triggers a systemic inflammatory response syndrome (SIRS), particularly if intravascular volume is compromised to cause organ dysfunction.[13,14] It is likely this effect is proportional to the total volume of blood loss. Thus, blood loss of up to 5 mL/kg is well tolerated, but increasing losses after this have a greater physiological impact.

Local perfusion and microvascular changes

Local perfusion to organs can be affected by a multitude of factors. Retraction of tissue, clamping or coagulation of blood vessels, and mobilization of the gut can alter local perfusion and delivery of oxygen and nutrients to the cells causing cellular dysfunction. Local perfusion may also be affected during pneumoperitoneum because of direct pressure effects and changes in oxygen delivery[15] and effects on vital organs.[16] Even after surgery there is evidence that microcirculatory blood flow around surgical sites, such as anastomosis, can be impaired for a significant period postoperatively even in the face of normal global oxygen delivery.[17]

Box 1
Key points to reduce the stress and metabolic effects of surgery

Surgical factors

- Reduce primary surgical injury.
- Reduce blood loss.

Anesthetic factors

- Individualized control of patient's physiology during surgery to optimize outcomes.
- Optimal analgesia using regional and local anesthetics, multimodal analgesia, and avoidance of drains to reduce neural activation of stress response. Aim is to reduce total opioid use to avoid risk of gut ileus.
- Individualized fluid therapy to maintain cellular perfusion, reduce extracellular fluid flux, and avoid salt and water overload, which can lead to gut ileus.

Postoperative goals

- Early gut function and enteral feeding to get benefit of hormonal effects of duodenal feeding, maintain gut perfusion, reduced surgical insult, avoid nasogastric tubes, regular small quantities of nutrition.
- Early mobilization to reduce complications, such as chest infection and deep vein thrombosis; stimulate muscle function to maintain strength and reduce insulin resistance.

Anesthetic technique

Anesthetic agents and techniques can have direct and indirect effects on cellular function. The physiologic effects of intermittent positive pressure ventilation have a multitude of effects. Hepatosplanchnic blood flow and renal blood flow are reduced and there is a change in intrathoracic pressure affecting preload and afterload, all of which can lead to alterations in cardiac output and blood pressure with subsequent changes at a microvascular and cellular level. In the presence of Thoracic Epidural Anesthesia (TEA) the gut is pressure dependent such that even if the cardiac output is good a mean arterial pressure less than 60 mm Hg may lead to hypoperfusion.[18]

Most anesthetic drugs reduce vasomotor tone and interfere with autoregulatory mechanisms to maintain local pressure and flow. Remifentanil, which is popular as a continuous opioid infusion for rapid awakening, can reduce venous tone and pulse pressure. TEA and spinal anesthesia effect arteriolar and venous tone because of a sympathetic block, which leads to vasodilatation and hypotension unless corrected by the anesthetist. Vasopressors can restore these physiologic effects but if used inappropriately they can also cause problems particularly if vasoconstriction is maintained in the face of hypovolemia. Boluses can lead to erratic changes in blood pressure and venous tone because there is variation in arteriolar and venous effect of vasopressors depending on the patient and their intravascular volume status.

Fluid therapy is an important component of Enhanced Recovery under the control of the anesthesiologist. Fluid therapy has a direct effect on intravascular volume and cardiac output with a resultant effect on oxygen and nutrient delivery to the tissues. There are also complex effects downstream on the microcirculation and vascular beds. There are 2 dedicated chapters on fluid therapy and the use of advanced hemodynamic monitoring in this series so the reader is referred to these and this subject is not covered further in this chapter.

The position of the patient during surgery (head up, head down, legs up, legs down) effects intravascular volume and perfusion pressure gradients across tissues. Factors influencing local tissue perfusion by effects on vasomotor tone, vascular volume, or localized blood supply include the following:

Surgical and operative factors
1. Surgical retraction, dissection, mobilization, and extraction
2. Blood loss
3. Pneumoperitoneum

Anesthetic factors
1. Induction of anesthesia
2. Intermittent positive pressure ventilation
3. Ventilatory strategy and positive end-expiratory pressure
4. Patient position: head up, head down, legs up
5. Anesthetic agents
6. Opioids, particularly remifentanil infusions
7. Epidural or spinal anesthesia
8. Vasopressor use: type and dose and whether delivered by infusion or bolus
9. Fluid therapy: can effect central compartment and microvascular flow

SECONDARY INJURY

Secondary injury from surgery is classically described as the stress response. This process releases local cytokine and inflammatory mediators driving a complex process of metabolic, hormonal, and immunologic processes in the whole body. The

peak cytokine response and duration is proportional to primary surgical injury and blood loss. These can be minimized by surgical technique. The hormonal and metabolic effects in response to surgery are one of the key factors that an ERP attempts to modify, principally by achieving early gut function (to reverse the catabolic response to surgery) and restoring the patient to independent mobility. Neural effects can also be minimized by appropriate analgesic techniques to reduce the central effects of pain and improve mobility, function, and sleep postoperatively.

Directly Mediated Effects

Cytokine

Cellular injury causes the release of cytokines and inflammatory mediators, such as interleukin IL-6, IL-1, IL-8, tumor necrosis factor-α, and C-reactive protein. This causes local inflammation and stimulation of afferent neurons, which carry impulses through the spinal cord up to the brain. There is release of corticotrophin from the hypothalamus and activation of the locus-coeruleus-noradrenergic systems. Both systems have a positive feedback on each other. The coeruleus-noradrenergic system stimulates the sympathetic nervous system and catecholamine release from the adrenal medulla. Circulating catecholamines have a varied effect on organs and tissue throughout the body. The effect on β cells of the pancreas is to inhibit the secretion of insulin, which is an anabolic hormone.

Hormonal

Hormonal effects after surgery are complex and variable. The key issue for surgical outcome is that the body develops a state of insulin resistance. Insulin is needed for the passage of glucose and amino acids into cells, so this has a direct effect on cellular function and crucially, healing of damaged tissue. Several studies have shown that the degree of insulin resistance is proportional to the magnitude of surgery. Insulin resistance can usually be overcome with administration of more endogenous insulin.[19] Glycemic control has been shown to be an important predictor of complications.[20] Glycemic control within the range of 8 to 10 mmol/L with the use of exogenous insulin is normal practice on intensive care units with the Leuven study showing improved outcomes[21]; however, overaggressive management of blood sugar levels was shown to increase mortality.[22] Early feeding (hormonal effects) and mobility (muscle effect) help to reverse the state of insulin resistance.

Neural

The neural mechanism of the stress response is mediated by receptors activated by tissue injury and subsequent inflammation. Surgical access causes damage to skin and muscle injury, and injury to intra-abdominal organs and the peritoneum cause visceral fiber activation. The ascending pathways cause release of corticotrophin from the hypothalamus and activation of the locus-coeruleus-noradrenergic systems as outlined previously. The key issue for the anesthesiologist is that the use of local, truncal, and regional anesthetic techniques can alter this part of the stress response.[23,24]

Consequential Effects

The result of the stress response, pain and gut dysfunction after surgery, leads to a state of fasting and immobility that can further exacerbate an altered metabolic state of insulin resistance, which reduces the availability of glucose and amino acids for cellular function and repair. Unfortunately, this process is often exacerbated by medical intervention. For instance, the normal treatment of ileus can be insertion of a nasogastric tube and intravenous fluids (often with high sodium), which can lead to further bowel edema and prolong the period of ileus. The abdominal distention leads to

pressure on the diaphragm and pulmonary basal hypoventilation, which leads to hypoxia and increased risk of pulmonary infection and a SIRS response. Therefore, a multimodal strategy to prevent ileus is extremely important. The key factors to reduce ileus are reducing surgical manipulation and handling of the gut; maintaining gut perfusion during the perioperative period; avoiding fluid excess, particularly above 30 mL/kg total fluid gain; avoiding salt overload; and reducing opioids to a minimum.

Fasting

Inappropriate postoperative fasting leads to metabolic changes in the body at the time when the body has a high energy requirement to heal injury and maintain immune function. European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines for surgical patients are to reduce periods of fasting to a minimum.

Immobility

The cause of postoperative immobility is usually multifactorial. Patients may be in pain and not able to mobilize, or feel weak and not be able to mobilize without help. Interventions, such as surgical drains, continuous pumps delivering intravenous fluids, and analgesic methods (eg, TEA), make it difficult for patients to move independently. The pathophysiologic result is that the lack of muscle use and the catabolic response of surgery lead to further weakness and muscle loss. Immobility is also a risk factor for developing deep vein thrombosis, which can lead to pulmonary embolus. Respiratory function is also compromised, particularly after abdominal surgery where there is often basal atelectasis and loss of functional residual capacity. The problem is compounded if the patient has poor analgesia or has abdominal distention caused by ileus. This can lead to the development of postoperative chest infection, which in turn can lead to a SIRS response and sepsis (**Fig. 4**).

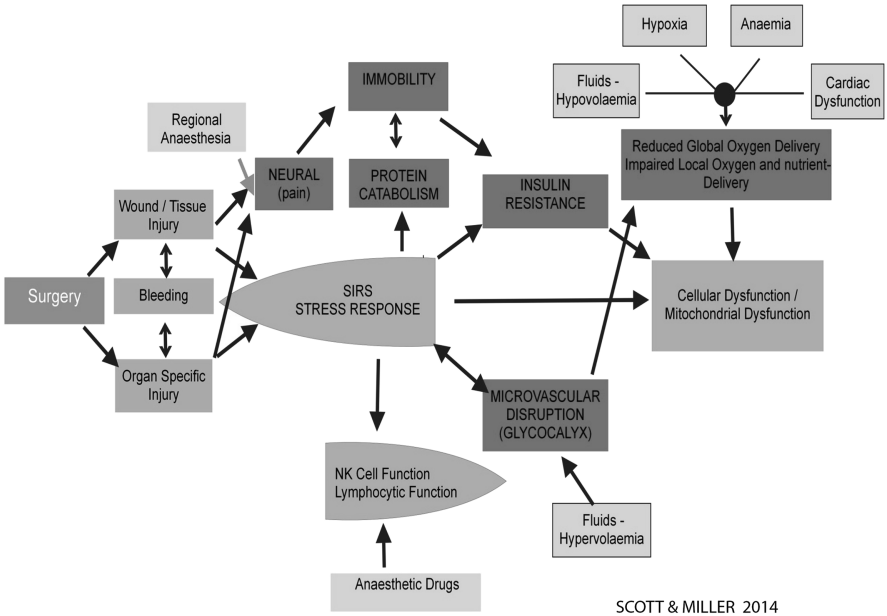

Fig. 4. Diagram showing overview and interrelationship of surgical injury, the stress response, immune response, and cellular dysfunction. Other factors that compound cellular dysfunction are included and key intervention points delivered by the anesthetist. NK, natural killer; SIRS, systemic inflammatory response syndrome.

THE ENHANCED RECOVERY PATHWAY AND ROLE OF THE ANESTHESIOLOGIST

The anesthesiologist is in a position to have significant input into the entire ERP. The ERP starts preoperatively with counseling of the patient. There is increasing recognition of the importance of preoperative assessment, informed decision-making, and risk assessment to ensure the patient is placed on the correct perioperative care pathway. This decision-making process may also be not to operate and for the patient to follow a different clinical treatment modality, such as radiotherapy or chemotherapy. Prehabilitation aims to improve outcomes after surgery by improving the patient's physiologic reserve (discussed elsewhere in this issue).[25]

The anesthesiologist must deliver a suitable anesthetic from which the patient can awaken rapidly with minimal pain, avoiding postoperative nausea and vomiting, and in a fluid-optimized state. Reducing secondary injury is done by modulating the stress response by effective analgesia and early oral intake of food, which stops the catabolic response and promotes anabolism and healing. To achieve this optimal analgesia and fluid therapy are the key components delivered by the anesthetist. By ensuring effective analgesia the stress response is minimized and the patient can mobilize, which in turn leads to reduced pulmonary and thromboembolic complications. Individualized fluid therapy ensures cells have adequate oxygen and nutrient delivery, which in turn avoids cellular dysfunction and complications. The gut perfusion is maintained and enables early feeding, and avoiding fluid overload reduces the risk of ileus. Early feeding and anabolism ensures optimal healing and leads to reduced complications and earlier return to preoperative function. This has led to the description of the trimodal approach delivery of enhanced recovery for anesthesiologists whereby the anesthesiologist delivers individualized fluid therapy and optimal analgesia and most of the other nonsurgical enhanced recovery elements are protocolized in the perioperative care pathway (**Fig. 5**).[26]

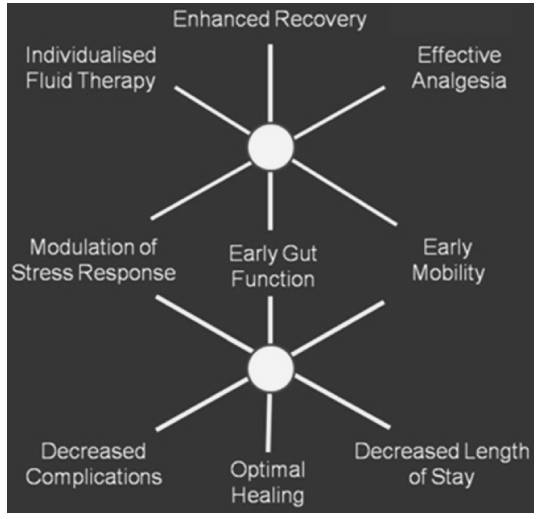

Fig. 5. Trimodal approach to enhanced recovery for the anesthesiologist. (*From* Mythen M, Scott M. Anaesthetic contributions in enhanced recovery. Chapter 4. In: Francis N, Kennedy RH, Ljungqvist O, et al, editors. Manual of fast track recovery for colorectal surgery. London: Springer Science & Business Media; 2012; with permission.)

EVIDENCE BASE FOR ENHANCED RECOVERY PATHWAYS

The adoption of ERPs has now spread across the globe. The evidence base has been growing in open and minimally invasive surgery. The key benefits of ERPs are reducing patient stay (without increase in readmission), improving consistency of length of stay, and improving patient outcomes by reducing complications and restoring patients to preoperative function more quickly.

In the United Kingdom data from the Hospital Episodes Statistics (www.hscic.gov.uk) has shown that since the introduction of ERPs in colorectal, gynecologic, musculoskeletal, and urologic surgery there has been a year on year reduction in length of stay in hospital (LOSH) with no increase in readmission rates. The number of hospitals with unusually high LOSH has been reduced. It is estimated the program has released 118,000 bed-days in the United Kingdom per annum.

A meta-analysis by Varadhan's group in 2010 showed ERPs reduce length of stay in colorectal surgery without increasing admissions.[27] There have been 10 meta-analyses since including newer and similar studies with different conclusions. A critical appraisal of these meta analysis by Chambers and colleagues[28] for ERPs in colorectal surgery concludes that using ERPs there is a reduction in LOSH of 2.5 days. Ultrashort lengths of stay showing the benefit of combining minimally invasive surgery and ERPs have been published with no increase in complications and with good patient satisfaction.[29] There is increasing evidence that good compliance with ERPs can lead to a reduction in complications.[30,31]

Measuring the stress response, immune function, and insulin resistance after surgery and interpreting the results can be difficult. The LAFA study looked at four groups of surgical patients undergoing colorectal surgery: (1) open surgery within an ERP, (2) open surgery without an ERP, (3) laparoscopic surgery within an ERP, and (4) laparoscopic surgery without an ERP.[32] IL-6 and C-reactive protein levels were highest in the open surgery group, as expected. The biggest impact on improving postoperative immune function (measured by effect on HLA-DR) was having laparoscopic surgery and the addition of an ERP improved this further. The open surgical group also demonstrated an improved response within an ERP.

Insulin resistance is difficult to measure in the perioperative setting. In 2012 Ren's group published data from almost 600 patients undergoing surgery either within an ERP or not. They measured insulin resistance using homeostatic model assessment for insulin resistance (HOMA-IR) and showed reduced insulin resistance within the ERP group. Cortisol and cytokines, such as IL-6, IL-1, and tumor necrosis factor-α, were also reduced in the ERP group.[33]

SUMMARY

The pathophysiologic changes during the perioperative surgical pathway are varied and complex. The process is driven by primary surgical injury. ERPs aim to reduce the resulting secondary injury by using a group of evidence-based elements. All the elements in an ERP aim to return the patient to independent mobility with early enteral feeding and restoration of preoperative function as quickly as possible. It is difficult to identify the benefits of each ERP element individually and it is the sum of all the small gains that make the pathway successful. ERPs reduce length of stay, and improve the consistency and quality of the surgical care pathway. There is increasing evidence that there is a reduction in complications and improvement in long-term outcomes. The anesthesiologist plays a key role in delivering care in an ERP by controlling the patient's physiology during surgery and the perioperative period. The anesthesiologist is responsible for two key elements that affect

outcome: fluid therapy and optimal analgesia. The surgeon is responsible for reducing primary injury (see **Box 1**).

Clinicians are entering a new era of surgery and perioperative care where it is now recognized that the whole perioperative pathway has an impact on short- and long-term outcome after major abdominal surgery.

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