*British Journal of Anaesthesia* 1997; **78**: 606–617

# Multimodal approach to control postoperative pathophysiology and rehabilitation

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## Summary

Major surgery is still associated with undesirable sequelae such as pain, cardiopulmonary, infective and thromboembolic complications, cerebral dysfunction, nausea and gastrointestinal paralysis, fatigue and prolonged convalescence. The key pathogenic factor in postoperative morbidity, excluding failures of surgical and anaesthetic technique, is the surgical stress response with subsequent increased demands on organ function. These changes in organ function are thought to be mediated by trauma-induced endocrine metabolic changes and activation of several biological cascade systems (cytokines, complement, arachidonic acid metabolites, nitric oxide, free oxygen radicals, etc). To understand postoperative morbidity it is therefore necessary to understand the pathophysiological role of the various components of the surgical stress response and to determine if modification of such responses may improve surgical outcome. While no single technique or drug regimen has been shown to eliminate postoperative morbidity and mortality, multimodal interventions may lead to a major reduction in the undesirable sequelae of surgical injury with improved recovery and reduction in postoperative morbidity and overall costs. (*Br, J. Anaesth.* 1997; **78**: 606–617).

**Key words**

Surgery, stress response. Pain, postoperative. Complications, morbidity.

Despite continuous advances in anaesthesia, surgery and perioperative care, major surgical procedures are still beset with undesirable sequelae such as pain, cardiopulmonary, infective and thromboembolic complications, cerebral dysfunction, nausea and gastrointestinal paralysis, fatigue and prolonged convalescence. Clearly, such morbidity may be related to the level of anaesthetic and surgical skill, but complications may occur regardless of skill and no single technique or drug regimen has been shown to eliminate postoperative morbidity and mortality.

A common feature shared by all surgical patients is the widespread changes in organ function, the so-called surgical stress response.[1] These functional changes are believed to be mediated by the trauma-induced endocrine metabolic changes and activation of several biological cascade systems (cytokines, complement, arachidonic acid metabolises, nitric oxide, free oxygen radicals etc). Although these responses have evolved presumably to confer an advantage for survival, they may, if amplified and prolonged, also contribute to erosion of body cell mass and physiological reserve capacity.

The key question in our understanding of the pathogenesis of postoperative morbidity is therefore related to the pathophysiological role of the various components of the surgical stress response and whether or not a modification of such responses may improve surgical outcome. More simply, one may ask why a technically successful operation, whether a colonic resection, hip replacement or cardiac operation, should result in an unsuccessful outcome. Additionally, if such surgical sequelae are controlled, one may ask if patients could undergo major surgery on an ambulatory or semi-ambulatory basis.

This article reviews current techniques for controlling postoperative dysfunction by reducing surgical stress and pain. It is hypothesized that multimodal interventions may lead to a major reduction in the undesirable sequelae of surgical injury with accelerated recovery and reduction in postoperative morbidity and overall costs. This discussion will focus on elective surgery, excluding trauma and multiple organ failure, which have been reviewed elsewhere.[2]

## Perioperative risk factors and pathophysiological responses to surgery

Several perioperative risk factors and neurohumoral responses to surgical injury may contribute to postoperative morbidity (table 1).

### PREOPERATIVE FACTORS

#### *Pre-existing disease*

It is well established that concomitant disease and

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*Table 1* Perioperative risk factors or pathophysiological responses to surgery that must be recognized, avoided or treated in order to control perioperative physiology and reduce morbidity

| Factors | Effects on outcome | Treatment |
|---|---|---|
| Pre-operative | | |
| Concomitant diseases | Increase overall morbidity | Preop. assessment and optimization of organ function |
| Malnutrition | Increase infective complications, delays recovery | Preop. nutrition |
| Alcohol abuse | Increase overall morbidity | Preop. abstinence or perioperative alcohol administration |
| Intra-operative | | |
| Surgical stress | Increase organ demands, leads to catabolism, immunosuppression and organ dysfunction | Minimally invasive surgery, neural block, pain relief, pharmacological interventions |
| Blood transfusion | Increase infectious complications and risk of cancer recurrence | Avoid unnecessary use of blood |
| Heat loss | Increase surgical stress responses during rewarming phase | Reduce heat loss or use external heating |
| Post-operative | | |
| pain | Impairs organ function and delays mobilization and overall recovery | Effective, dynamic pain relief with multimodal pain therapy |
| Immunosuppression | Increase infective complications and cancer recurrence | Stress reduction, immunomodulation, avoid blood transfusion |
| Nausea/ileus | Delays recovery and early oral nutrition, enhances catabolism | Pain relief using neural block and NSAID, recluse use of opioid, pharmacological intervention (serotonin antagonists, etc) |
| Hypoxaemia | Increase risk of cardiac, cerebral and wound complications (infection/healing) | Oxygen administration, mobilization, stress reduction, avoid sleep disturbances |
| Sleep disturbances | May increase postoperative hypoxaemia, fatigue and enhance stress | Stress reduction, pain relief, reduce use of opioid, reduce noise and night time interventions |
| Catabolism/muscle loss | Increase all-over morbidity and fatigue, delays recovery | Stress reduction, pain relief, active rehabilitation, early oral nutrition, electrical muscle stimulation, growth factors |
| Immobilization | Increase risk of thromboembolic and pulmonary complications, increase fatigue, hypoxaemia and loss of muscle | Pain relief, active rehabilitation |
| Drains/nasogastric tubes/traditions | Delays recovery, may increase infectious complications | Avoid unnecessary use, revise perioperative care programme |

organ dysfunction are strong determining factors of postoperative complication rates and duration of hospital stay.[3] Accordingly, several clinical guidelines and indices have been developed to assess cardiovascular,[4] pulmonary[5 6] and thromboembolic[7] risks. Such information may serve as a basis for quantifying perioperative risk and outline indications for prophylactic therapy. However, such predictive scoring systems do not *per se* reduce postoperative morbidity, and may be successful only when preoperative optimization of organ function reclassifies a high-risk patient into a more low-risk group.

### *Malnutrition*

Malnutrition is a well established perioperative risk factor, and several nutritional assessment scores have been defined.[8] However, pre- and postoperative nutritional support with parenteral nutrition has been shown to reduce morbidity only in high-risk, malnourished patients.[8]

### *Alcohol abuse*

Recently, preoperative alcohol abuse, even without overt alcohol-related organ dysfunction, has been described as an important operative risk factor.[9] The mechanisms include alcohol-induced immunosuppression, subclinical cardiac dysfunction and an amplified hormonal response to surgery.[9]

## INTRAOPERATIVE FACTORS

### *Surgical stress*

During and after surgical injury, the body responds with profound changes in neural, endocrine and metabolic systems in addition to alterations in organ functions.[1] These changes are characterized by increased secretion of catabolic hormones, decreased secretion or effects of anabolic hormones, hypermetabolism and increased cardiac work caused by autonomic system activation, impaired pulmonary function, pain, gastrointestinal side effects with nausea and ileus, a change in the coagulatory–fibrinolytic systems favouring coagulation and thrombosis, and loss of muscle tissue and immunosuppression.

Although the surgical stress response may represent a universally conserved cellular defence mechanism,[10] the stress-induced changes in postoperative organ function may also be implicated in the development of postoperative complications. Accordingly, the concept of "stress free anaesthesia and surgery" to attenuate the trauma-induced physiological responses with subsequent reduction of morbidity has been proposed.[11] In elective clean surgery the main release mechanism of the stress response is afferent neural stimuli from the surgical area.[12] In addition, several humoral substances such as cytokines, arachidonic acid cascade metabolites, nitric oxide, endotoxins and other biological cascade

systems are involved.[1] The surgical stress response is related to the magnitude of surgical injury, and correspondingly lower morbidity rates are observed after minor surgical procedures, including minimally invasive surgery.

Based on the concept of "stress free anaesthesia and surgery" several strategies to reduce or prevent the surgical stress response have been developed[12 13] (fig. 1). A reduction in the degree of surgical trauma by minimally invasive surgery reduces protein catabolism and markers of inflammation (IL-6 and CRP), pulmonary dysfunction and convalescence, while early responses of catecholamines, cortisol and blood glucose are less modified.[14] The type of general anaesthesia for operation has no important effect on the stress response,[12 15 16] except for high-dose opioid anaesthesia which may inhibit intra-, but not postoperative catabolic hormonal responses.[15] Blocking the afferent neural stimulus by various neural block techniques with local anaesthetics is very effective in reducing the classical catabolic response to operation,[12 16 17] especially in lower body procedures and with the use of continuous extradural analgesia. Thus the usual increase in cortisol, catecholamines and glucose concentrations can be prevented, insulin resistance reduced, and glucose tolerance and nitrogen economy improved.[12 16 17] The unfavourable changes in the coagulatory–fibrinolytic systems are also modified in favour of less thrombosis formation, while most changes in immune function and markers of inflammation (acute phase proteins, IL-6) are unaltered by neural block and concomitant hormonal inhibition.[12 16 17] Pain relief by other techniques such as extradural or systemic opioids, NSAID or clonidine are less effective than neural block with local anaesthetics.[12 16]

Other strategies include administration of non-specific substrates[13] or specific fuels such as glutamine, arginine, omega-3 fatty acids, and growth factors and anabolic hormones, all of which may reduce catabolism.[13] Pharmacological reduction in the inflammatory response may include various cytokine (TNF, IL-1) antagonists, free oxygen radical scavengers and other agents inhibiting neutrophil activation and migration, but these measures have not yet been tested in elective surgery. So far, only glucocorticoids which counteract several proinflammatory substances (cytokines, complement, arachidonic acid cascade metabolites) have been studied in elective surgical procedures. These results suggest that a single large preoperative dose of methylprednisolone reduced pain, hyperthermia, IL-6 and $PGE_2$ responses, and improved conventional impairment in pulmonary function.[18] Obviously, any modulation in inflammatory response has to be weighed against potential side effects, including impaired wound healing and increased risk of infection. So far these questions have not been examined in large-scale studies.

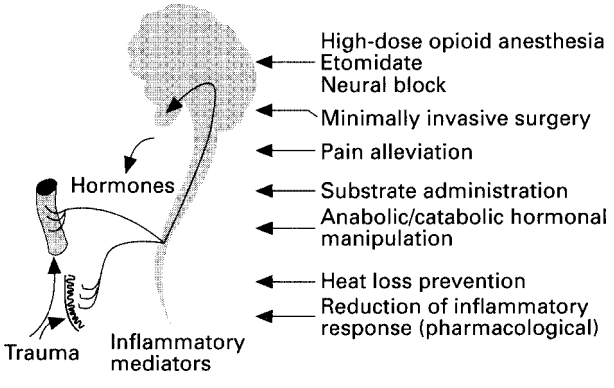


*Figure 1* Interventions which may reduce the stress response to surgery.

In summary, although a reduction in surgical stress may be attractive based on neural block studies, further studies are needed to define those responses which should be suppressed and those which should be enhanced in order to improve outcome. Consequently, the most rational and effective anti-stress or anti-catabolic therapy has not been designed.

### *Heat loss*

Unintended intraoperative heat loss may be a significant risk factor leading to increased stress responses (cortisol, catecholamines, nitrogen loss) and cardiovascular complications.[19–21] Conservation of body heat and prevention of intraoperative hypothermia should therefore be provided whenever pronounced heat loss is expected, in order to reduce the stress responses to rewarming with increased oxygen consumption, catabolic hormone secretion and nitrogen loss.[19 22] This approach is supported by the finding that prevention of intraoperative hypothermia reduced wound infection rate and hospital stay in patients undergoing colonic surgery.[23]

### *Blood transfusion*

Increased blood loss and use of perioperative blood transfusion correlate with increased risk of infective complications and probably recurrence after cancer surgery.[24] The risk is related mainly to the content of white cells and non-cellular transfusion components.[24] Even the use of autologous blood transfusion with prolonged storage time may have detrimental effects, as toxic mediators (histamine, PAI-1, myeloperoxidase, etc) are released from leucocytes and platelets during storage for more than 2 weeks of any blood product containing these components.[24] Leucocyte-depleted blood by bedside filtration may significantly reduce postoperative infective complications.[25]

## POSTOPERATIVE FACTORS

### *Pain*

All surgical procedures are followed by pain, which may amplify endocrine metabolic responses, autonomic reflexes, nausea, ileus and muscle spasm, and thereby delay restoration of function. Optimal treatment of postoperative pain is mandatory in order to enhance recovery and reduce morbidity.

Presently, several techniques are available to treat postoperative pain effectively.[26] Initial therapy in

minor to moderate sized procedures should involve a multimodal approach using incisional local anaesthetics, systemic NSAID and opioids.[26 27] With more severe pain, central neural block techniques using continuous extradural analgesia with local anaesthetics combined with small doses of opioids are necessary to provide dynamic pain relief, that is pain relief that allows normal function.[26 27] Patient-controlled analgesia techniques with opioids provide a high degree of patient satisfaction,[28] but pain relief during mobilization is less than that with the extradural combination techniques.[29]

The effect of improved pain relief *per se* on postoperative outcome is debatable.[12 16 17 26 28] Most controlled studies of extradural analgesia and patient-controlled analgesia have not demonstrated clinically important effects on outcome, except on some specific variables such as thromboembolism, gastrointestinal ileus and intraoperative blood loss (see below).[12 16 17 26 28] Surprisingly, effective pain relief does not automatically lead to increased ambulation and reduction in hospital stay.[30] Nevertheless, effective postoperative pain relief is a prerequisite to attain improved postoperative outcome, and when integrated into an active rehabilitation programme (see below) may reduce the surgical stress response, organ dysfunctions and improve gastrointestinal motility, to allow early oral nutrition and to facilitate early mobilization.

### *Immunosuppression*

Much evidence has emerged to demonstrate pronounced trauma-induced alterations in immunological systems. Major surgery causes immunosuppression with reduced delayed hypersensitivity response to recall antigen stimulation, T-cell-dependent antibody response, IL-2 production and HLA-DR antigen expression, IFN-γ production and T-cell blastogenesis.[31] In contrast, neutrophil and macrophage functions are activated with increased release of oxygen radicals and TNF, and chemotaxis.[31] Smaller operations, including minimally invasive surgery, may result in less change in immune function.[14 31] Perioperative blood transfusion enhances postoperative immunosuppression.[24]

The clinical consequences of pre- and postoperative immunological changes are increased susceptibility to infective complications,[31–33] and probably increased risk of recurrence after cancer surgery.[31] Therefore, much effort has been expended to modify post-traumatic immune function, including the use of thymopentine, immunoglobulins, granulocyte colony-stimulating factor, glutamine, arginine and omega-3 fatty acids, PGG-glucan, histamine-2 receptor antagonists and other biological response modifiers.[31 33] Although most of these studies have shown partial improvement in post-traumatic immunosuppression and a tendency towards improvement in outcome, no final conclusions or clinical recommendations can be made. An exemption is the well documented relationship between the use of blood transfusion, immunosuppression and risk of infective complications.[24 25] Reduction in extent of trauma by minimally invasive surgery is presently the most effective technique to reduce immunosuppression and risk of infection.[14]

### *Nausea and ileus*

Nausea, vomiting and ileus are among the most common postoperative complaints and in addition to being unpleasant they may also be important determining factors in postoperative rehabilitation. Thus early enteral nutrition is critical in reducing post-traumatic infective complications[34] and may also reduce catabolism.[13] The pathogenesis of postoperative nausea, vomiting and ileus is multifactorial, being related to type of surgery, gender, choice of anaesthesia and use of opioids.[35 36] Efforts to reduce nausea and vomiting include the use of antiemetics, with serotonin antagonists being most effective, in addition to effective pain control and opioid sparing with the use of local anaesthetics, and NSAID.[35–37] Continuous extradural analgesia with local anaesthetics, but not opioids, is effective in reducing postoperative ileus[12 16 17 29] because the associated sympathetic intestinal nerve block increases motility. Such techniques should therefore be used whenever possible, in order to facilitate early oral nutrition and postoperative recovery.

### *Postoperative hypoxaemia*

Constant postoperative hypoxaemia lasts for 2–5 days after major abdominal surgery with superimposed episodic hypoxaemia occurring especially at night.[38] The mechanism of constant hypoxaemia is primarily a pulmonary shunt caused by reduction in functional residual capacity,[39] while postoperative episodic hypoxaemia may be caused by ventilatory arrhythmias (hypoventilation and apnoeas) related to rebound rapid eye movement (REM) sleep on the second and third nights after operation.[38 40]

Late postoperative hypoxaemia may be involved in cardiac, cerebral and wound complications. Thus postoperative myocardial ischaemia is a strong predictor of postoperative cardiac complications after non-cardiac operations[41 42] and some studies have shown a temporal relationship between the occurrence of episodic hypoxaemia and myocardial ischaemia and/or arrhythmias in the late postoperative period.[38] As episodic hypoxaemia is most pronounced at night and unexpected postoperative death seems to occur more often at night than during the day or evening,[43] further studies are urgently needed on the pathogenesis of hypoxaemia and its effect on cardiac morbidity. Late postoperative hypoxaemia may also be a factor in wound complications as reduced supply of oxygen to the surgical wound impairs healing[44] and lowers resistance against bacterial wound infection.[45] Finally, postoperative impairment in cognitive function and delirium may be related to postoperative hypoxaemia[46] and postoperative delirium has been treated successfully with supplementary oxygen.[47 48]

As late postoperative hypoxaemia may have important clinical implications for cardiac, cerebral and wound complications, the choice of analgesic technique may be important, as neural block

techniques with local anaesthetics and avoidance or reduced use of opioids may improve oxygenation.[38] Also, early ambulation and avoidance of the supine position may improve postoperative oxygenation.[49] Although oxygen therapy may reduce postoperative tachycardia[50] and be of potential advantage for the wound[44 45] and brain,[46] no definite indications for dosage and duration of postoperative oxygen therapy have been determined. Nevertheless, based on the above mentioned considerations and duration of postoperative hypoxaemia, routine postoperative oxygen administration may be indicated for the first 2–4 days in high-risk surgical patients and in patients with an $Sp_{O_2}$ less than 93%. The use of late postoperative pulse oximetry monitoring is therefore recommended. In the early postoperative period in the post-anaesthetic care unit, pulse oximetry monitoring may indicate changes in care, although a reduction in all-over morbidity has not been documented.[51]

*Postoperative sleep disturbances*

Sleep patterns are severely disturbed in postoperative patients, with a decrease in total sleep time, elimination of (REM) sleep and a marked reduction in slow wave sleep (SWS).[40 52] The pathogenesis of postoperative sleep disturbances is multifactorial, and includes afferent neural stimuli (surgical stress), cytokines, pain, use of opioids, and noise and awakenings during monitoring and nursing procedures.[52] Postoperative sleep disturbances with REM sleep rebound on the second to fourth night may be related to sleep-induced apnoeas, nocturnal hypoxaemia and profound sympathetic activation with haemodynamic instability.[40 52] Therefore, postoperative sleep disturbances may be a pathogenic factor in postoperative cardiac dysfunction and complications, in addition to mental dysfunction.[52] Prevention and treatment of postoperative sleep disturbances have not been evaluated, but may involve reduction in surgical stress, noise, inconvenient nursing procedures and provision of effective pain relief with reduced use of opioids.[52] Laparoscopic surgery may reduce postoperative sleep disturbance compared with open laparotomy.[53]

*Immobilization*

Traditional perioperative care involves bed rest, although it is well known that immobilization may increase the risk of thromboembolic and pulmonary complications.[54] Furthermore, bed rest predisposes to orthostatic intolerance and instability during standing, and to an increased loss of muscle tissue and function.[54] Postoperative hypoxaemia is also more pronounced in the supine position[49] with its potential detrimental effects on cardiac, cerebral and wound function (see above). Finally, early ambulation may improve wound healing.[55 56] Despite this evidence, early ambulation has been controversial in the history of surgery,[57] although the movement towards ambulatory or semi-ambulatory surgery has supported the concept of early ambulation and rehabilitation in order to improve outcome and reduce costs. The prerequisite for early ambulation and active rehabilitation is effective dynamic pain relief using the multimodal approach (see above).

*Catabolism and muscle wasting*

Postoperative catabolism and muscle wasting are important factors for development of postoperative fatigue[58] and in overall recovery. Catabolism is mediated by the surgical stress response, postoperative immobilization and semi-starvation. These physiological changes after routine major surgery may persist for up to several months in patients receiving established routine care.[59] Recovery of muscle strength is delayed further in old compared with young patients,[60] suggesting special efforts to be made in this high-risk group. Therapeutic interventions in order to reduce catabolism and loss of muscle tissue and function may include stress reduction (see above), enforced early mobilization, electrical muscle stimulation[61] and early oral nutrition,[8] supported by pain treatment techniques to accelerate restoration of gastrointestinal motility (see above). Furthermore, a variety of nutritional substrates, growth hormone or other growth factors may reduce catabolism and maintain muscle mass.[13 62]

*Drains/nasogastric tubes/traditions*

Perioperative guidelines are usually developed according to traditional practice, which most often are not validated by scientific studies. These often include the use of drains and nasogastric tubes in addition to traditional "observation" periods in hospital. The traditional routine use of drains seems unnecessary based on available evidence from controlled clinical studies in several operations, including cholecystectomy,[63] joint replacement,[64] colonic surgery[65] and radical hysterectomy.[66] Enhancement of recovery and reduction of hospitalization may also be achieved by home discharge with a drain in place after mastectomy.[67 68] The routine use of nasogastric tubes after elective abdominal surgery is unnecessary and may even contribute to pulmonary complications.[69 70] Furthermore, routine use of nasogastric decompression may delay oral intake and thereby slow recovery because of other sequelae and semi-starvation (see above). Finally, traditional restrictions on early oral intake after abdominal surgery should be abandoned, as they are not supported by scientific data.[71]

These findings therefore suggest that increased efficiency and reduced costs can be achieved if traditional care programmes are adjusted to the available scientific data.

## Postoperative morbidity

Surgical procedures may be followed by undesirable sequelae such as cardiac, pulmonary, thromboembolic and infective complications, etc, which may not be related directly to imperfections in surgical or anaesthetic technique but rather to various perioperative risk factors and pathophysiological

*Table 2* Common postoperative complications, their pathogenesis and prevention

| Complication | Pathogenic factors | Interventions |
|---|---|---|
| Cardiac | Cardiac stimulation (surgical stress), hypoxaemia, fluid disturbances | Stress reduction (minimally invasive surgery, neural block, pain relief), oxygen administration, avoid heat loss and fluid overloading |
| Pulmonary | Impaired pulmonary and diaphragmatic function (surgical stress), pain, immobilization, fluid disturbances | Stress reduction (minimally invasive surgery, neural block, pain relief, physiotherapy, glucocorticoids), avoid supine position and fluid overloading |
| Thromboembolism | Altered coagulatory/fibrinolytic balance (surgical stress), immobilization | Antithrombotic prophylaxis, stress reduction (neural block, pain relief), mobilization |
| Cerebral dysfunction | Surgical stress, hypoxaemia, psychoaffective drugs, withdrawal syndromes | Stress reduction (minimally invasive surgery, neural block), oxygen administration, mobilization, avoid unnecessary opioid, psychoaffective drugs and development of drug withdrawal |
| Infection | Contamination, immunosuppression (surgical stress), hypoxaemia | Avoid contamination, use antibiotic prophylaxis, stress reduction (minimally invasive surgery, neural block), immunosupportive therapy, nutrition, oxygen administration, mobilization, remove catheters and drains as soon as possible, avoid necessary opipoids, use antimetics |
| Nausea and gastrointestinal dysfunction | Afferent stimulation (surgical stress), anaesthetics and opioid analgesics | Stress reduction (minimally invasive surgery, neural block, pain relief), avoid unnecessary opioids, use antiemetics |
| Impaired wound healing | Malnutrition, catabolism, (surgical stress), hypoxaemia, infection | Stress reduction (minimally invasive surgery), oxygen administration, mobilization, avoid infection, provide pre- and postoperative nutrition |
| Fatigue, reduced functional capacity and convalescence | Loss of muscle tissue and function, (surgical stress), immobilization and impaired cardiovascular adaptation to exercise, malnutrition | Stress reduction (minimally invasive surgery, neural block, pain relief), early oral nutrition and ambulation |

responses, including the effects of the surgical stress responses discussed above (table 2).

## CARDIAC COMPLICATIONS

Cardiac complications occur in 1–3% of patients undergoing major surgical procedures, with a higher incidence (2–15%) in those patients with preoperative cardiac risk factors.[42] Although improved intraoperative monitoring and cardiovascular support therapy have reduced cardiac morbidity during operation, most cardiac morbidity occurs from 1–4 days after operation, calling for more attention towards pathophysiological mechanisms of cardiac dysfunction during this period. The pathogenesis of postoperative cardiac morbidity is probably multifactorial, but increased sympathetic stimulation with tachycardia, cardiac hypermetabolism and increased work,[42] together with postoperative reduction in oxygen supply (hypoxaemia) may be most important. Reduction of post-surgical hypermetabolism and sympathetic drive may be achieved by pain treatment, where extradural local anaesthetic techniques are most effective and promising.[12 16 17] However, the evidence for a reduction in postoperative cardiac morbidity by extradural analgesic techniques remains inconclusive, possibly because optimal techniques have not been used and extended sufficiently into the postoperative period, and other risk factors, such as hypoxaemia or fluid overloading, have been neglected. Early postoperative systemic opioid analgesic treatment may reduce cardiac ischaemia,[72] but the overall clinical advantage has not been documented.

Future reduction in cardiac morbidity will probably involve stress reduction by effective pain alleviation techniques, together with therapeutic intervention against episodic and constant hypoxaemia, with a focus on the late postoperative period.

## PULMONARY COMPLICATIONS

Postoperative pulmonary complications (atelectasis, pneumonia) are assumed to be related to the obligatory postoperative impairment in pulmonary function.[39] In addition, intraoperative factors, including general anaesthesia and supine position, lead to impaired pulmonary function and atelectasis,[73 74] which may have further detrimental effects in the postoperative period. The pathogenesis of postoperative impairment of pulmonary function includes a pain-induced decrease in pulmonary mechanics and neurally reflex-mediated inhibition of diaphragmatic function.[5 39] In addition, various humoral cascade systems, arachidonic acid metabolites, cytokines, endothelial adhesion factors, etc, may contribute.[75] Finally, routine postoperative care involving the supine position for several hours daily may impair pulmonary mechanics and oxygenation.

So far, no technique is available to prevent postoperative impairment of pulmonary function and pulmonary complications. During operation a decrease in inspired oxygen concentration[76] and re-expansion of the lungs[77] may reduce or prevent the risk of atelectasis. The effect of chest physiotherapy (conventional or incentive spirometry) is debatable,[78 79] although a slight decrease in complication rate may be obtained.[79] However, these techniques have not been documented to be effective after postoperative pulmonary complications have developed.[79] Deep breathing exercises may be sufficient in low-risk patients and incentive spirometry reserved for high-risk patients.[80] Effective pain relief may improve, but not eliminate, postoperative pulmonary morbidity.[12 16 17] Changing position from the supine to the sitting or standing position is of obvious advantage[49 74] but requires effective pain relief to allow for sufficient ambulation. Also, pharmacological modification of some of the

humoral cascade responses with preoperative glucocorticoid administration may have favourable effects on both pain and pulmonary functional impairment.[18] Finally, reduction in trauma by minimally invasive surgery improves postoperative pulmonary function and reduces pulmonary complications.[14]

Despite currently available therapeutic measures (intraoperative management, postoperative pain relief, pharmacological treatment, minimally invasive surgery, position changes and ambulation) postoperative pulmonary complications continue to be clinically important. However, intervention studies have mostly investigated unimodal therapy, but multimodal intervention may be more promising (see below).

## THROMBOEMBOLIC COMPLICATIONS

Postoperative thromboembolic complications continue to be an important determinant of outcome, despite the existence of several prophylactic regimens.[7] The pathogenesis of postoperative thromboembolism is the unfavourable change in all three components of Virchow's triad with a decrease in lower extremity blood flow, hypercoagulability and increased thrombocyte aggregation, impaired fibrinolysis and loss of vessel wall integrity. Amplifying factors are concomitant diseases and immobilization. Extradural analgesia with local anaesthetics may have favourable effects on all components of Virchow's triad.[12 16 17]

Several controlled studies have documented a pronounced reduction in thromboembolic complications (lower extremity thrombosis, vascular graft thrombosis and pulmonary embolism) after hip procedures, open prostatectomy, knee replacement and vascular surgery with the use of extradural anaesthesia and analgesia.[12 16 17] The effect of minimally invasive surgery on postoperative thromboembolic complications remains to be clarified. Although the reduction in trauma produced by laparoscopic procedures may reduce undesirable pathophysiological changes in coagulation and fibrinolysis, positioning in the reverse Trendelenburg position and pneumoperitoneum may have the opposite effects.[81] However, as early ambulation may be feasible after most minimal invasive procedures, these negative intraoperative factors may not be clinically important.

In summary, much evidence has accumulated that various single modality measures (antithrombotic regimens with heparins, systemic anticoagulation therapy, dextran, mechanical devices, extradural analgesia, ambulation) have resulted in a reduction in postoperative thromboembolism. Further reductions may be possible, and a multimodal approach, combining these techniques in accelerated programmes (see below) should be studied.

## CEREBRAL DYSFUNCTION

Delirium or other acute confusional states are common postoperative complications associated with higher mortality and complication rates, poor functional recovery and longer duration of hospital stay.[82 83] The incidence in major elective, non-cardiac operations in patients $>50$ yr may be approximately 5–10%.[82] Specific risk factors are age $>70$ yr, self-reported alcohol abuse, poor preoperative cognitive and functional status, and markedly abnormal preoperative serum electrolyte concentrations.[82] In addition, the use of psychoactive medications such as opioids (meperidine) and benzodiazepines may contribute to postoperative delirium.[84] Finally, postoperative hypoxaemia[38] and sleep disturbances[52] have been suggested to be risk factors for postoperative delirium. As several of these factors are involved in the surgical stress response, postoperative delirium may be improved by stress reduction using efficient neural block techniques. However, the data available from several controlled studies of such techniques have not demonstrated a reduction in postoperative delirium.[12 16 17 85] Unfortunately, in most of these studies single or short-term treatment was given, without taking advantage of the possibilities of early ambulation and restoration of pulmonary and muscle function. Provision of opioid-sparing analgesia with NSAID or local anaesthetics may be expected to reduce postoperative delirium, but more data are needed for a definitive conclusion.[37 86] Postoperative oxygen therapy has been effective against delirium in only a few small-sized studies.[47 48]

In summary, most studies have involved unimodal intervention strategies, and no major improvement in cerebral postoperative outcome has been documented from such studies. In contrast, multimodal intervention with oxygen therapy, early surgery and maintenance of cardiovascular stability in high-risk patients undergoing acute hip surgery showed a substantial reduction in postoperative acute confusional states and hospital stay.[87] In future, further improvement in cerebral outcome should be sought by multimodal intervention in accelerated stay programmes, including effective pain relief with enforced mobilization and nutrition (see below).

## INFECTIVE COMPLICATIONS

Despite rational and data-based guidelines for antibiotic prophylaxis, infective complications at the surgical site (the wound) or remote places (abscesses, sepsis, multiple organ failure) remain major postoperative morbidity problems. As host defence mechanisms are important to combat infection, efforts should be directed towards counteracting undesirable changes in pre- and postoperative immune function (see above). Such measures include reduction in blood loss and transfusion, enteral nutrition, immunomodulating drugs, use of minimally invasive surgical techniques and measures to avoid late postoperative hypoxaemia.

## GASTROINTESTINAL DYSFUNCTION

Postoperative gastrointestinal dysfunction includes motility disturbances resulting in nausea, vomiting and ileus, and other functional deficiencies which reduce the barrier against translocation of endotoxin and bacteria from the intestinal lumen.

Development of nausea, vomiting and ileus is dependent mainly on the site of injury, anaesthetic

technique and use of opioids (see above). The mechanism of reduced postoperative stomach and colonic motility is predominantly neurogenic with activation of inhibitory sympathetic efferents.[12 16 17] The ileus reducing effect of continuous extradural local anaesthetic techniques is well documented.[12 16 17 29] Nausea and vomiting may also be a result of direct neurogenic stimulation of the vomiting centre, which may be counteracted by serotonin antagonists and reduced use of opioids.[35 36 88]

A systemic or gut insult may promote breakdown of gastrointestinal mucosal barrier function, leading to translocation.[89 90] Although experimental studies suggest that impaired mucosal barrier function and translocation may further increase the systemic stress response caused by absorption of endotoxin and other bacterial products, the prevalence of gut translocation and its relationship to infective and other complications remain to be established in surgical patients.[89 90] The role of fasting and route of feeding may influence the stress response to surgical injury or other injuries, as oral nutrition was found to reduce the response compared with parenteral nutrition in some[91] but not all[92] studies. Nevertheless, even short- term fasting for 1–2 days enhances catabolism.[93]

As controlled clinical studies have shown that early enteral nutrition is effective in reducing nitrogen loss,[13 94] postoperative infective complications and duration of hospital stay,[34 94] in addition to improving immune function,[95 96] every effort should be made for early institution of enteral nutrition. The relative importance of different components in the enteral nutrition regimens (standard diet *vs* enrichment with glutamine, arginine and omega-3 fatty acids) remains to be established.[13 95 96] Provision of early enteral nutrition requires a combined effort with omission of unnecessary nasogastric tubes, use of antiemetics and effective pain regimens to enhance gastrointestinal motility, again representing a multimodal effort in order to reduce postoperative organ dysfunction.

### IMPAIRED WOUND HEALING

In the postoperative patient several factors may contribute to impaired healing and susceptibility to infections. Such mechanisms include hypoxaemia[44 45] and the response to injury and sepsis.[97] Although the relationship between nutrition and wound healing remains to be clarified,[98] early enteral nutrition may enhance wound healing.[99] Furthermore, oxygen administration may reduce infection[45] and be expected to improve wound healing.[44] Therefore, efforts to improve oxygenation such as ambulation[49] or oxygen therapy are important. Early ambulation may also improve wound healing by other unknown mechanisms.[55 56] However, in some operations, for example mastectomy, prolonged immobilization may reduce formation of seromas.[100] Finally, the use of growth factors may have a future role in the postoperative management of wound dysfunction.[13]

In summary, effective therapeutic measures against impaired wound healing and infection may include a multimodal approach towards infective complications (see above), and aggressive pain treatment allowing early ambulation, prevention and treatment of hypoxaemia and early oral nutrition. However, although these views appear rational, there are no controlled data to support this concept.

### FATIGUE AND CONVALESCENCE

Postoperative fatigue is a common feature of the recovery phase and is related to the magnitude of surgical injury, postoperative impairment of nutritional status, loss of muscle mass and function, and postoperative impairment in cardiovascular adaptation to exercise.[58 101] Also, the preoperative level of fatigue may increase the risk of postoperative fatigue, while the level of preoperative anxiety is less important.[58 101] Reduction in trauma and stress by minimally invasive surgery reduces postoperative fatigue and preserves functional capacity.[102] Single modality treatment with effective pain control[58] or nutrition[58 99] have not significantly reduced postoperative fatigue. Most importantly, if nurses and physicians confine patients to bed in the postoperative period, the positive effects of effective pain treatment may not be obtained.[30] Therefore, a multimodal approach to avoid postoperative catabolism and loss of muscle tissue and function seems rational. Although no controlled data are available, such a combined approach seems to be effective in reducing postoperative fatigue and convalescence after colonic surgery.[103 104]

## Multimodal approach to control postoperative pathophysiology and rehabilitation—a unifying concept

The risks and morbidity associated with surgical procedures have been steadily decreasing in recent decades, primarily because of improvements in patient preparation for surgery, and anaesthetic and surgical techniques during operation. One of the most impressive changes has been the introduction of minimally invasive surgery. These developments have also contributed to increased use of ambulatory and semi-ambulatory settings for surgical procedures. Counteracting these beneficial developments is the fact that the proportion of elderly patients presenting for surgery is increasing, and that they represent a high-risk group with increased postoperative morbidity and mortality. Thus despite improvements, major surgical procedures may continue to be beset with well known "medical" complications, including myocardial infarction, delirium, pulmonary dysfunction, thromboembolism, infective complications, fatigue and prolonged convalescence.

Although there has been much effort to improve each of these specific outcome variables (i.e. preoperative assessment, antithrombotic and antimicrobial prophylaxis, etc), therapeutic strategies have usually focused on unimodal interventions. One explanation for the paucity of data with a more global view of the postoperative period probably lies with the traditional orientation of various specialty groups. Thus surgeons have usually focused on surgically oriented postoperative complications, such as wound infection, shock and anastomotic dehiscence,

and have ignored those complications being more "medical" in origin, such as those within the cardiac, pulmonary and cerebral systems. Anaesthetists have focused on those problems arising in the intraoperative or immediate post-anaesthetic period with emphasis on cardiovascular and pulmonary function, but may not see the majority of such morbidity because it arises in the later postoperative period in the surgical ward. Additional progress in postoperative outcome may require more attention to the pathogenesis of common postoperative complications and more focused attention on the later postoperative period (1–4 days) where the peak incidence of complications occurs.

The key pathogenic factor in postoperative morbidity, excluding failures of surgical and anaesthetic techniques, is the surgical stress response with subsequent increased demands on organ function. Much knowledge of the mediators of this response has accumulated in recent years with emphasis on biochemical and endocrine changes,[1] and several techniques have been developed which may attenuate these potentially undesirable responses (fig. 1), thereby providing a sound basis to avoid unnecessary development of postoperative organ dysfunction and associated morbidity. The development of pain-alleviating regimens which allow early ambulation, techniques to reduce nausea, vomiting and ileus, realization that early enteral nutrition is important for recovery and reduction of infective complications, and the use of well established antithrombotic and antimicrobial regimens therefore represent the basis for a global approach to perioperative care. However, an important limiting factor for this approach is inherited from surgical traditions not founded on scientific data. Examples are the inappropriate use of drains, nasogastric tubes, limited oral intake regimens, restrictions on mobilization, observational regimens, etc. A key question to be asked on each postoperative day, for each surgical procedure, is therefore "Why is the patient in hospital today ?" in order to provide continuous analysis and solution to those factors limiting early recovery and contributing to postoperative morbidity.

A rational approach towards control of the postoperative period is therefore multimodal intervention, as shown in figure 2. Before operation, detailed information about the accelerated stay programme must be provided, possibly including a videotape programme. Such detailed preoperative information has been demonstrated in itself to result in less pain and reduction of postoperative stay decades ago.[105] Stress reduction may be provided by currently available techniques (see above and fig. 1), and sufficient pain relief by currently available multimodal regimens. Most importantly, pain relief has to be used for early aggressive ambulation and enforced enteral nutrition to avoid the conventional postoperative functional impairment. Finally, in some high-risk patients, the use of growth factors or other anabolic supportive agents may be indicated.[13]

Unfortunately, controlled clinical studies of such a multimodal intervention to support an accelerated stay programme are not available. However, several

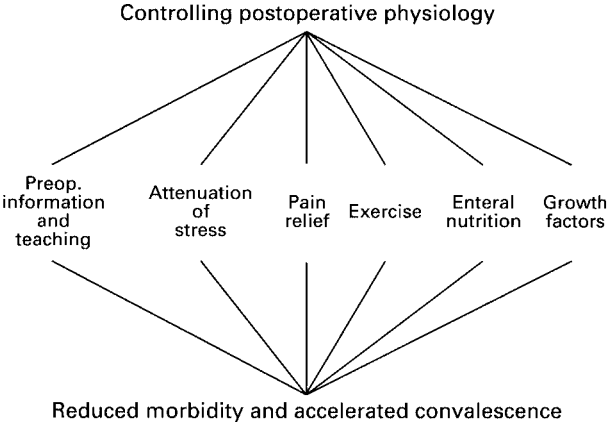


*Figure 2* Multimodal interventions towards control of the postoperative period.

small lines of evidence suggest that such a multidisciplinary effort may result in pronounced improvement in surgical outcome and reductions in morbidity and hospital stay after mastectomy,[67 68] carotid endarterectomy,[106] hip replacement,[107 108] colonic resection[29 103 104 109 110] and coronary bypass.[111 112] In this context it is noteworthy that the combination of laparoscopic-assisted surgery, extradural local anaesthetic, early nutrition and ambulation, and avoidance of opioids reduced hospital stay to 2 days without fatigue or cardiopulmonary, thromboembolic or infective complications in 15 high-risk patients (median age 81 yr) undergoing colonic resection.[103 109] In addition, regionalization of major surgical procedures to one hospital to increase experience and accelerate recovery may reduce costs and improve outcome.[113]

Multidisciplinary collaboration between patient, surgeon, anaesthetist, physiotherapist and surgical nurse represents an expansion of the more traditional "acute pain service" which merely serves to provide analgesia without taking part in the rehabilitation of the patient. We hypothesize that optimal results by postoperative "multimodal recovery intervention" may probably be best achieved by reorganization of the surgical wards into smaller postoperative "rehabilitation units" with a focus on early rehabilitation, nutrition and pain relief, and with a restrictive use of recovery-limiting procedures such as i.v. fluids, urinary bladder catheters, drains, tubes, etc. Such an approach may represent an important step to avoid the usual cascade to dependency in elderly hospitalized surgical patients, who are more sensitive to catabolic stress, immobilization, fluid changes and sensory deprivation.[60 114] Although accelerated stay programmes may reduce costs, these are not developed as enforced discharge programmes to save costs *per se*, but to take advantage of the improved postoperative functional status after such techniques, with early hospital discharge representing only an additional benefit.

## Future developments

Although major progress and improvements in surgical outcome may be expected by accelerated stay programmes, future research should be directed

towards documenting such achievements from large-scale controlled studies or multi-institutional studies. In addition, the mechanisms of postoperative organ dysfunction within the first postoperative week should be explored further. In this context, further knowledge of the release mechanisms for the surgical stress response is required with information on the relative role of the different mediators which influence body organ functions. Presently, we have incomplete knowledge of which responses should be attenuated or stimulated, and which responses should be left unaltered. Nevertheless, the introduction of minimally invasive surgery, leading to reduction of catabolism, immunosuppression and other inflammatory responses with subsequent reduction of morbidity and convalescence, suggest that "stress-free anaesthesia and surgery" [11] may be valid. In this context, further developments in high technology surgery to reduce tissue injury will be promising. Furthermore, extension of research on biological modifiers[33] to improve postoperative immune function, on specific substrates such as glutamine and arginine to support gastrointestinal function and integrity and improve immunofunction,[13] and on various growth factors[13] are promising. Finally, it remains to be established if postoperative patients emerging from "stress free anaesthesia and surgery" with well-preserved organ function and who develop a later surgical complication because of a technical failure, are at reduced risk for subsequent development of multiorgan failure, sepsis, etc. This hypothesis deserves specific attention, as there is preliminary evidence that multiple physiological insults may be a mechanism for development of multi-system organ failure.[115] Thus development of multiple organ failure usually passes the phase of the more benign systemic inflammatory response syn-, drome (SIRS),[116 117] where the initial response to an elective operation may prime the body for development of detrimental consequences to a subsequent stimulus.

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