INTRODUCTION

In addition to the ethical and humanitarian reasons for minimizing pain and suffering, is the recognition that both physiologic and pathophysiologic responses to poorly controlled pain may have deleterious effects on postsurgical outcomes. Consequences may be particularly serious in elderly and critically ill populations. In these individuals, pathophysiologic responses to large incisions, extensive dissection, or visceral manipulation negatively affect cardiovascular pulmonary function and incite maladaptive behaviors (Table 2.1). 1–4

Commonly observed pathophysiologic changes include, but are not limited to, the following: (1) Neurohumoral alterations termed peripheral sensitization occurring at the site and in regions immediately adjacent to injury; (2) alterations in synaptic function and nociceptive processing occurring within spinal cord and limbic cortex; (3) sympathoadrenal activation resulting in an elevation of heart rate and blood pressure and a diminution in regional blood flow; and (4) neuroendocrine responses mediating hyperglycemia and a negative nitrogen balance.

HYPERALGESIA

Acute surgical or traumatic injury is followed by a series of neurohumoral reactions originally described by Lewis5 and termed the inflammatory triple response. The classical response is characterized by increased blood flow (flare) tissue edema (wheat) and sensitization of peripheral nociceptors hyperalgesia. Hyperalgesia defines an altered state of sensibility in which the intensity of discomfort associated with repetitive noxious stimulation is markedly increased.6–8 Allodynia refers to a condition in which ordinarily nonnoxious stimulation such as pressure and light touch is perceived as being exquisitely painful. Hyperalgesia accompanies most inflammatory processes, abrasions, incisions, and burns injuries. Two forms of hyperalgesia, primary and secondary, have been defined and are described in Chapter 1 (Pain Pathways and Acute Pain Processing).

Primary hyperalgesia reflects enhanced noxious sensitivity, which becomes evident within minutes of the injury and is characterized by increased responsiveness to light touch, heat, and mechanical stimuli.4–8 The development of primary hyperalgesia correlates with a diminution in pain threshold and enhanced sensitivity of C and Aδ mechanohot nociceptors.

At the site of injury, peripheral nociceptor endings are stimulated by release of intracellular H+ and K+ ions and synthesis of prostaglandins. Nociceptors are further sensitized by locally released mediators such as bradykinin, serotonin, and histamine.9–11,12 Humoral factors and proinflammatory cytokines, including interleukin (IL)-1β, IL-6, increase peripheral edema and allodynia.4,8,10,12 Genetic polymorphisms that influence production of these proinflammatory cytokines may be responsible for interindividual differences in postsurgical pain intensity scores and development of persistent pain.13,14 Several antidromically delivered sensitizers, including substance P, and norepinephrine are released from activated sensory and sympathetic nerve endings further enhance pain sensitivity.4,10,12 Mediators responsible for nociceptor activation and inflammation are depicted in Figure 2.1.

Secondary hyperalgesia refers to delayed alterations in noxious sensitivity observed in nontraumatized regions surrounding the injury site.14–15 It is now recognized that secondary hyperalgesia is mediated by neuronal sensitization and adaptive facilitatory changes in the spinal cord, brainstem, and limbic cortex. Central facilitation is initiated by the action of neuropeptides and excitatory amino acids (EAA), such as aspartate and glutamate on N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors.14–15 Activation of NMDA receptors (NMDARs) increases the responsiveness of dorsal horn wide dynamic range (WDR) neurons to noxious input.16–22 The initial phase, termed wind-up, is characterized by an immediate increase in WDR firing rate and associated behavioral responses lasting about 5 minutes.4,14,20 This is followed 15 to 20 minutes later by a second phase, termed long-term potentiation, in which WDR neurons exhibit enhanced sensitivity for prolonged periods.14–17 This second phase of excitability outlasts the initial barrage of sensory input, does not require further noxious stimulation to be maintained, and is not antagonized by inhalational anesthetics or moderate doses of parenteral opioids.19–22 Secondary
Table 2.1: The Acute Injury Response: Potential Benefits after Traumatic Injury versus Disadvantages in Controlled Postsurgical Settings

<table>
<thead>
<tr>
<th>Beneficial Effects after Traumatic Injury</th>
<th>Adverse Effects in Patients Recovering from Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Maintenance of intravascular volume and mean arterial pressure</td>
<td>1. Hypertension, hypervolemia, increased risk of hemorrhage, stroke</td>
</tr>
<tr>
<td>2. Maintenance of cardiac output and cerebral perfusion</td>
<td>2. Tachycardia, arrhythmias, myocardial ischemia, congestive heart failure</td>
</tr>
<tr>
<td>3. Enhanced hemostasis</td>
<td>3. Hypercoagulable state, increased risk of arterial and deep venous thrombosis's Substrate mobilization, enhanced energy production.</td>
</tr>
<tr>
<td>4. Immobilization: minimizing further tissue injury</td>
<td>4. Hyperglycemia, negative nitrogen balance</td>
</tr>
<tr>
<td>5. Learned avoidance</td>
<td>5. Reduction in respiratory volume and flow rates hypoxia, pneumonia</td>
</tr>
<tr>
<td>6. Anxiety, fear, demoralization, prolonged convalescence</td>
<td>6. Anxiety, fear, demoralization, prolonged convalescence</td>
</tr>
</tbody>
</table>

hyperalgesia provides the neurochemical basis for splinting and other adaptive behaviors. These include elaboration of ipsilateral and contralateral flexion reflexes and alterations in regional sympathetic tone.1,4,14,17,18 Pain is perceived at dermatomes above and below the site of injury and is worsened by ambulation or movement. The impact of primary and secondary analgesia on acute pain intensity and the development of persistent pain is depicted in Figure 2.2.

**SYMPATHOADRENAL RESPONSES**

The stress response to surgical or accidental trauma has been described as a general adaptation syndrome focused on tissue repair and improved survival. The sympathoadrenal response to traumatic injury evolves in three stages. The initial alarm stage or “fight-flight reaction” allows rapid withdrawal from the traumatic event and is followed by a “resistance stage,” which maintains blood flow to critical organs, and later by an “exhaustion stage,” which limits mobility and improves tissue repair.1–4,20,21 Following extensive tissue injury, nociceptive impulses stimulate sympathetic cells in the hypothalamus and preganglionic neurons in the anterior lateral horn. Once stimulated, catecholamines released by these cells initiate cardiac inotropic and

---

**Figure 2.1:** Peripheral responses to acute injury. (1) Following tissue injury, potassium (K⁺), hydrogen ions (H⁺), and arachidonic acid (AA) released from damaged cells and bradykinin (BK) released from damaged vessels activate the terminal endings of sensory afferent fibers (nociceptors). Cyclooxygenase 2 (COX-2) is upregulated and is responsible for the conversion of AA into prostaglandin (PGE). Prostaglandin has been implicated in nociceptor sensitization and further increases in vascular permeability and primary hyperalgesia. (2) Orthodromic transmission in sensitized afferents leads the release of substance P (sP) in and around the site of injury. Substance P is responsible for further release of BK. (3) Substance P also stimulates histamine release from mast cells and serotonin (5-HT) from platelets. These substances plus humoral factors TNF-α and (IL-6) form a “noxious soup,” which activates additional nociceptors and further exacerbates the inflammatory response. (4) Reflexes mediated by sympathetic efficients sensitize nociceptors directly via secretion of norepinephrine (NE), indirectly through release of BK and PG, and mediate peripheral vasoconstriction. (Modified from reference 2: Sinatra RS, Bigham M: The anatomy and pathophysiology of acute pain. In: Grass JA, ed. Problems in Anesthesiology Philadelphia, PA: Lippincott-Raven, 1997:10:8–22.)

**Figure 2.2:** Following tissue injury, primary and secondary hyperalgesia increases the intensity of acute pain and may lead to the development of persistent pain.
chronotropic responses, increase peripheral vascular resistance, and redistribute blood flow away from peripheral tissues and viscera to the heart and brain.1,2,20–22 These initial favourable effects can become deleterious in time, particularly in at-risk or debilitated patients where myocardial activity and work of breathing may exceed the oxygen and metabolic supplies.1,2,21–23

Surgical trauma is promptly followed by increases in plasma concentrations of epinephrine and norepinephrine.20,21 The magnitude and duration of catecholamine release is directly related to patient related factors such as the type of surgery, inherent sympathetic response, and patient age. In general, highest elevations in plasma catecholamines are observed following extensive procedures and in younger individuals.20,21 The earliest aspects of the catecholamine response reflect pronounced but transient increases in adrenal medullary secretion, whereas latter aspects reflect continued release of norepinephrine from sympathetic nerve endings.7,12 Pathophysiological changes associated with increased sympathetic tone and altered regional perfusion include the following: (1) an increased incidence of postsurgical hypertension that ranges from 5% following minor, uncomplicated procedures to approximately 50% in patients recovering from more extensive vascular surgery;7,21 (2) Increased peripheral vascular resistance is associated with increases in contractility and myocardial oxygen consumption as the organism attempts to maintain or augment cardiac output.21–23

Increases in oxygen consumption may precipitate myocardial ischemia in patients with coronary artery disease. Enhanced sympathetic tone may be especially deleterious in patients recovering from peripheral vascular surgery because elevations in arterial pressure may risk rupture of vascular anastomoses, whereas intense vasospasm may compromise distal graft patency.1,3,20,21

(3) As perfusion is directed to high-priority organs, microcirculatory blood flow in injured tissues, adjacent musculature, and in the viscera may be significantly diminished.20,21–23 Reductions in circulation have been associated with impaired wound healing, enhanced sensitization of nociceptors, increased muscle spasms, visceral/somatic ischemia, and acidosis.21

(4) Renal hypoperfusion results in activation of the renin-angiotensin-aldosterone axis. Angiotensin is a potent vasoconstrictor that, although capable of increasing renal perfusion, may further accentuate catecholamine-induced changes in regional blood flow and hypoperfusion of lower priority organs (injury site, skin, viscera, etc.).1,2,3,20,21

(5) Catecholamines, angiotensin, and other factors associated with surgical stress may increase platelet activation and accelerate coagulation.22,23 Increased platelet-fibrinogen activation may be especially deleterious in patients with atherosclerotic vascular disease, because increased plasma viscosity, platelet aggregation, and platelet release of vasoconstrictive factors may significantly reduce blood flow in critically stenosed vessels.21–23

NEUROENDOCRINE RESPONSES

Following tissue injury, neurogenic stimuli affecting the hypothalamus, secretory target organs, or both incite alterations in neuroendocrine response.20–22 These well-described changes, termed the stress response to injury, are characterized by an increased secretion of catabolic hormones, including cortisol, glucagon, growth hormone, catecholamines, and inhibition of anabolic mediators, such as insulin and testosterone.20–22 These mediators increase substrate mobilization, resulting in hyperglycemia and a negative nitrogen balance.21,22–24 Associated metabolic changes, including glucoseogenesis, glycogenolysis, proteolysis, and breakdown of lipid stores, provide the injured organism with short-term benefits of enhanced energy production and availability; however, when amplified or prolonged, catabolic aspects of the stress response may adversely affect postsurgical outcome in the following ways: (1) excessive protein loss may lead to muscle wasting, fatigue, and prolonged convalescence and (2) impaired immunocompetence secondary to diminished immunoglobulin synthesis and impaired phagocytosis may decrease resistance to infection.24–26

Hume and Egdalh26 were among the first to propose that nociceptive impulses (traveling up the spinal cord via the midbrain reticular formation) and conscious stimuli from the cerebral cortex were both capable of activating hypothalamic centers and initiating the neuroendocrine stress response. Activated cells in the preoptic region secrete pro-opiomelanocortin, which in turn facilitates release of adrenocorticotropic hormone (ACTH), β-endorphin, and other anterior pituitary hormones.27–29 Sustained secretion of ACTH underlies the adrenocortical response to injury, which then heightens and continuously releases corticosteroids and mineral corticoids. In addition, trauma related release of IL-6 and IL-1β can also increase ACTH and cortisol secretion.22,25,26,27 The relationship between plasma IL-6 and cortisol levels is linear in postsurgical patients.21–23

Significant hyperglycemia and a rise in plasma cortisol are commonly observed in the postsurgical period. Bromage and colleagues22 noted in patients recovering from extensive abdominopelvic surgery and those with preexisting immune disorders to postoperative risk of tumor metastasis. In animal models, initial clinical trials, invasive surgery and poorly controlled pain are associated with profound immunosuppression and increased risk of tumor metastasis.23–25 In surgical settings, immunologic suppression may have minimal consequences in subjects with normal immune function; however, diminished cellular and humoral immunity may predispose debilitated individuals and those with preexisting immune disorders to postoperative infections.24–26

Levels of β-endorphin increase 3-fold following surgical incision and remain elevated well into the postoperative period.24–26,27,28 β-Endorphin mediates a number of systemic effects, including immunosuppression, complement release, decreased peripheral vascular resistance, and initiation of shock.20,24,26,27,28 Finally, plasma levels of the posterior pituitary

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derived octapeptide, arginine vasopressin (AVP), rise dramatically and remain elevated for up to 5 days following extensive surgical trauma. Increased secretion of AVP is responsible for postsurgical fluid retention, plasma hyposmolarity, and oliguria. Figure 2.3 provides an overview of pathophysiologic responses to acute traumatic injuries.

EFFECTS ON KEY TARGET ORGANS

Pathophysiologic consequences related to poorly controlled pain include reduced functional capacity, increased deep disturbance, and delayed wound healing; these consequences result in social burdens, such as decreased quality of life and increased cost of care. Of even greater importance is the fact that in high-risk patients significant cardiovascular and pulmonary dysfunction may significantly increase postoperative morbidity and mortality risks.

Heart

Despite considerable improvements in anesthetic technique and maintenance of intraoperative hemodynamic stability, cardiac dysfunction secondary to myocardial infarction, cardiac failure and arrhythmia continue to account for a significant percentage of postoperative deaths. In high-risk populations, perioperative ischemia is most likely to occur following surgery, most commonly between postoperative days 1–3. Although a variety of factors may contribute to the development of postoperative myocardial ischemia, including hypothermia, anemia, anxiety, and tracheal intubation/suctioning, responses to poorly controlled pain play a prominent role. Catecholamine-induced tachycardia, enhanced myocardial contractility, increased afterload, and hypervolemia, secondary to enhanced release of AVP and aldosterone, are well-characterized factors responsible for increased oxygen demand. Increased oxygen demand, together with hypervolemia, may precipitate ischemia and acute cardiac failure, especially in patients with poorly compensated coronary artery and/or valvular heart disease.

Despite increased myocardial oxygen requirements, oxygen supply may be diminished because of alterations in pulmonary function (refer below). Pulmonary alterations include atelectasis secondary to pain-induced hyperventilation and pulmonary edema resulting from stress-induced hypervolemia. A second cause of reduced oxygen supply includes coronary artery occlusion. Coronary artery blockage may result from (1) high circulatory levels of catecholamines and increased coronary sympathetic tone, (2) stress-induced increases in plasma viscosity and platelet-induced thrombosis, and (3) coronary vasospasm secondary to platelet aggregation and release of serotonin.

Lungs

Thoracic and upper abdominal injuries are associated with a high incidence of morbidity and mortality. In contrast, deceleration injuries and penetrating etiologies, such as surgical incisions, retractors, and other foreign bodies. Thoracic surgery and trauma are associated with a spectrum of injuries, including pneumothorax, hemothorax, myocardial, and pulmonary contusions and rib, scapular, and clavicular fractures. The causes of acute thoracic injury include blunt trauma, for example, deceleration injuries and penetrating etiologies, such as surgical incisions, retractors, and other foreign bodies. Thoracic surgery and trauma are associated with a spectrum of injuries, including pneumothorax, hemothorax, myocardial, and pulmonary contusions and rib, scapular, and clavicular fractures. The causes of acute thoracic injury include blunt trauma, for example, deceleration injuries and penetrating etiologies, such as surgical incisions, retractors, and other foreign bodies. Thoracic surgery and trauma are associated with a spectrum of injuries, including pneumothorax, hemothorax, myocardial, and pulmonary contusions and rib, scapular, and clavicular fractures.
muscle splinting may be noted at many dermatomes above and below the site of injury. Chest wall and upper abdominal hyperpa-
dia are responsible for several pathophysiological alterations, including musculoskeletal and diaphragmatic dysfunction and
impaired gas exchange.21,43–46

Pulmonary function is dramatically altered by surgically
induced pain. Beecher46 was first to describe the classical pul-
monary response to upper abdominal surgery, which included
an increased respiratory rate and decreased tidal volume (TV),
vital capacity (VC), forced expiratory volume (FEV1), and func-
tional residual capacity (FRC). These pathophysiologic alter-
ations reflect acute restrictive pulmonary dysfunction and, as
such, may be associated with clinically significant hypoxia and
hypocarbia.41–44 Atelectasis, pneumonia, and arterial
hypoxemia are common postoperative complications whose
incidence approaches 70% in patients recovering from upper
abdominal surgery.51–56 Such complications have been related to
the above-mentioned reductions in VC and a reduced ability to
tough and clear secretions.43–45

Vital capacity is the first pulmonary parameter to change in
the postoperative period. Significant reductions in VC are evi-
dent within the first 3 hours, and declines to 40%–60% of preop-
erative values have been reported. Following upper abdominal
surgery, reductions in RV, FRC, and FEV1 are greatest at 24 hours;
thereafter, values gradually return to near normal levels by post-
operative day 7.48 In a classic study, Ali and coworkers48 noted
that postsurgical VC was most depressed from day 0 through
day 7 following upper abdominal surgery, less depressed after
lower abdominal surgery, and least affected in patients recover-
ing from superficial procedures, including inguinal herniorrha-
gion, inguinal hernia repair, and inguinal herniorrhaphy. For
patients recovering from multiple abdominal procedures, such as
a splenectomy and lower abdominal procedures, reductions in
VC were most apparent following the first day of recovery.48

Reduction in FRC represents the most detrimental alteration
in postsurgical lung volume.48 As FRC declines, resting lung
volume approaches closing volume. With further reduction, air-
way closure occurs resulting in atelectasis, ventilation/perfusion
mismatch, and hypoxemia. In patients recovering from open
cholecystectomy a delay of 16 hours was noted until maximum
reduction in VC.46 In these individuals, reductions in FRC were
associated with progressive arterial hypoxemia, whereas a grad-
ual improvement toward normal FRC was followed by a decrease
in physiological shunt.

Following thoracotomy, alterations in chest wall motion lead to
an increased work of breathing and require an increased work of breath-
ing if effectual respiration is to be achieved.45–46 Splinting sec-
dondary to poorly controlled pain exaggerates this process by
further decreasing respiratory effort. Perfusion is maintained in
unventilated portions of lung resulting in a shunt and ventila-
tion/perfusion mismatch. Inhibition of diaphragmatic function
represents an additional factor responsible for respiratory dys-
function and morbidity. Noxious impulses from the diaphragm,
chest wall, and upper abdominal viscera result in reflex inhibi-
tion of phrenic nerve motor drive, which further compromises
pulmonary function by increasing atelectasis, airway closure,
alveolar ventilation (V) and pulmonary perfusion (Q) mismatch,
and hypoxemia. If pneumonia or acute respiratory distress
syndrome occurs, the risk of prolonged hospitalization and
mortality increases.45–46 Surgical induced alterations in VC,
peak flow rate and alveolar–arterial (A-a) gradient are depicted in
Figure 2.4.

Vascular System
As blood flow is directed to high-priority organs, perfusion in
injured tissues, adjacent musculature, and in the viscera may be
diminished. Reductions in circulation have been associated with
impaired wound healing, increased muscle spasm, and visceral-
25

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somatic ischemia and acidosis.41,42,46 Inadequately controlled
pain can predispose patients to postsurgical deep venous throm-
boses (DVT) and pulmonary embolism. As previously discussed,
catecholamines and angiotensin released in response to surgical
stress may result in platelet–thrombogen activation and the devel-
oment of a hypercoagulable state.43–46 Severe pain is commonly
associated with an impaired ability to ambulate and decreased
venous flow.43–46 Surgical manipulation in and around the
pelvis may damage venous conduits that return blood from the
lower extremity. These factors make up Virchow’s triad of hyper-
coagulability, venous stasis, and endothelial injury that underlie
the development of DVT.43–45

In addition to concerns of local tissue swelling and venous
stasis, is the worry that thrombembolism may lead to a more
serious complication, pulmonary embolism. As thrombotic
fragments travel to the heart and lungs, occlusions within pul-
monary arteries result in varying degrees of ventilation per-
fusion mismatch and hypoxemia. Because the initial thrombus
incites vigorous local release of vasoactive and inflammatory
cytokines, symptoms associated with pulmonary embolism gen-
erally worsen within a short period of time. If not recognized
and promptly treated, this complication is associated with a
20%–30% mortality.

Finally it is well recognized that high plasma levels of nore-
pinephrine levels lead to vascular constriction and platelet adhe-
sion, which are factors that diminish peripheral limb perfusion and
require reoperation for graft occlusion following vascular
surgery.43–45

Injury Site
As discussed under Heart, humoral and neurochemical alter-
ations in and around the site of injury play important roles in the
development of persistent postsurgical pain and, in some cases,
chronic pain. Continued sensitization of peripheral noce-
tors and second-order spinal cell is responsible for prolonged
hyperalgesia as well as qualitative differences among physiolog-
ic, nociceptive, and neuropathic pain. Elevated levels of IL-1β
and other cytokines exacerbate edematous and irritative com-
ponents of inflammatory pain.49 Cytokines, including IL-1β,
IL-6, and tumor necrosis factor (TNF-α), also play a role in
initiating alldynia and development of persistent pain.51 These
cytokines, initially released from neutrophils, macrophages, and
other mediators, such as nerve growth factor (NGF) and nitric
oxide (NO) that are also released at later stages from activated
Schwan cells, further incite inflammatory neural injury and
worsen neuropathic pain.50,54 Lymphocytes, including T and
NK cells, infiltrate into and further irritate injured nerves; they
also play a role in the development of persistent neuropathic
symptoms. Chronic pain following surgical trauma is often related to
poorly controlled acute pain, neuropathic pain secondary to
neuromas, or myofascial pain syndromes created by procedural
trauma.54–56,67 Heightened reflex activity in sympathetic effer-
ent fibers are responsible for vasoconstriction and noxious
sensitization. Continued alteration in regional blood flow and
Uneventful recovery                                        Progression to pulmonary complications

Lung Volume
Expiratory Flow Rate
A-aDO2
Shunt


Central Nervous System

Nociceptive input affects all levels of the central nervous system and results in neurochemical and neuroanatomical alterations. One of the more disturbing findings associated with analgesic undermedication and severe acute pain is the development of central sensitization. Central sensitization is not only responsible for secondary hyperalgesia, described under Sympathoadrenal Responses, but also sets in motion plasticity changes and prolonged enhancement in noxious sensitivity that may be difficult to reverse.55–58 Many of these changes are mediated by activation of NMDARs and increased Ca2+ influx.59,60 Subsequent neurochemical alterations include upregulation of COX-2 and nitric oxide synthetase and increased synthesis of prostaglandin (PGE) and nitric oxide within sensitized neurons and glial cells.51,56,57

Synthesis of these and other inflammatory mediators induce neuroanatomical changes that, for reasons that remain unclear, appear designed to facilitate noxious transmission and pain processing.54,55–57 These changes include pathophysiologic activation of microglia and neuronal apoptosis. Cells that are most vulnerable to atrophy and death include modulatory enkephalinergic and adrenergic interneurons that normally function to suppress noxious transmission.60 Other neuroanatomical changes include nociceptor axonal sprouting and new connections with dorsal horn cells and redirection of non nocuous afferent fibers to sensitized second-order cells. These forms of plasticity are responsible for many of the allodynic and hyperpathic aspects of persistent somatic and neuropathic pain and also limit the effectiveness of pharmacological management.55,56,57

Figure 2.5: Mediators and temporal changes involved during the transition from acute to chronic pain. (Adapted from Woolf and Salter, *Science*. 2000;288:1765.)
bic system can either modulate the intensity of noxious neuropathic agents (see also Chapter 11, Transitions from Acute to Chronic Pain). Routine procedures should be followed closely and may alter the limbic and cingulate cortices. Patients suffering acute pain are commonly troubled by sleep disturbances that increase lethargy and negatively affect morale, mood, and motivation to participate in rehabilitation. Many patients require anxiolytics and sedatives to experience limited intervals of sleep and generally awake experiencing increased pain. In a study of 102 patients recovering from orthopedic surgery, increasingly severe postoperative pain resulted in greater interference with sleep. Sleep quality and duration was most affected when pain scores were greater than 5 on a scale from 0 to 10. In settings of severe acute pain, sleep deprivation and behavioral alterations may diminish patient morale and their willingness to utilize incentive spirometry or participate in ambulation and physical therapy. In the setting of persistent pain, limbic cortical responses negatively affect quality of life and also mediate anxiety, depression, and other chronic pain behaviors.

Table 2.2: Incidences of Chronic Postoperative Pain and Disability

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Estimated Incidence of Chronic Pain (%)</th>
<th>Estimated Incidence of Chronic Severe (Disabling) Pain (%)</th>
<th>Number of Surgeries in the United States</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputation</td>
<td>30–50</td>
<td>5–10</td>
<td>220 000</td>
</tr>
<tr>
<td>Coronary artery bypass surgery</td>
<td>30–50</td>
<td>5–10</td>
<td>598 000</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>30–40</td>
<td>10</td>
<td>Unknown</td>
</tr>
<tr>
<td>Breast surgery (lumpectomy or mastectomy)</td>
<td>20–30</td>
<td>5–10</td>
<td>479 000</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>10</td>
<td>4</td>
<td>220 000</td>
</tr>
<tr>
<td>Inguinal hernia repair</td>
<td>10</td>
<td>2–4</td>
<td>609 000</td>
</tr>
</tbody>
</table>

* National Center for Health Statistics, United States of America, 1996.
  - > 5 of 10 pain scores.


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provides a temporal outline describing the transition from acute to chronic pain. Other figures describing the neurochemical alterations and spinal plasticity changes responsible for this transition are presented in Chapter 1.

When one considers it, all chronic pain begins as acute pain. Kehlet and coworkers found that a high percentage of patients recovering from commonly performed procedures were troubled by persistent somatic and neuropathic pain a year following surgery (Table 2.2). The highest incidence of persistent pain was noted in procedures where nerve injury is commonly observed, including thoracotomy, mastectomy, and inguinal hernia repair. Pluijms and coworkers noted that patients most likely to develop persistent pain following thoracotomy were those who suffered the highest acute pain intensity during the first postoperative week. Sixty-seven percent of patients who developed chronic pain reported moderate to severe VAS pain scores, whereas 40% reported mild to moderate pain. Patients likely to develop chronic pain also reported a greater total amount of time spent having pain ($P = .02$).

Other risk factors linked to the development of persistent pain include patients with ongoing or preceding pain at the site of surgery, trauma occurring in younger individuals, and patients presenting with either psychosocial abnormalities or specific genetic susceptibilities (Figure 2.6). These factors appear to have strong causality because only a fraction of patients experiencing severe pain following traumatic neural injuries progress to a chronic pain state. Effective pain management and close patient observation during recovery and rehabilitation may be the key to reducing long-term pain disability.

Responses mediated via higher cortical centers and the limbic system can either modulate the intensity of innocuous perception or exacerbate emotional distress, pain complaint, and patient anxiety. Strong anxiety, fear, and loss of control that accompany traumatic injuries may have a profound effect on the hypothalamic-pituitary axis, further altering neuropeptide response. Poorly controlled pain promotes sleep deprivation, reduced morale, and learned helplessness by affecting the limbic and cingulate cortices. Patients suffering acute pain are commonly troubled by sleep disturbances that increase lethargy and negatively affect morale, mood, and motivation to participate in rehabilitation. Many patients require anxiolytics and sedatives to experience limited intervals of sleep and generally awake experiencing increased pain. In a study of 102 patients recovering from orthopedic surgery, increasingly severe postoperative pain resulted in greater interference with sleep. Sleep quality and duration was most affected when pain scores were greater than 5 on a scale from 0 to 10. In settings of severe acute pain, sleep deprivation and behavioral alterations may diminish patient morale and their willingness to utilize incentive spirometry or participate in ambulation and physical therapy. In the setting of persistent pain, limbic cortical responses negatively affect quality of life and also mediate anxiety, depression, and other chronic pain behaviors.

ATTENUATION OF PAIN-INDUCED PATHOPHYSIOLOGY

Innovations in technology, such as neuraxial analgesia and continuous infusion of local anesthetics, have revolutionized postoperative pain management. Evidence-based practice suggests that epidural anesthesia, especially thoracic epidural anesthesia, improves postoperative myocardial infarction, deep venous thrombosis, pulmonary embolism, transfusion requirements, pneumonia, respiratory depression, and morbidity following major operative procedures.

Operative Procedures

<table>
<thead>
<tr>
<th>Surgeries associated with a risk of nerve damage, repeat surgery</th>
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Psychological Vulnerability

<table>
<thead>
<tr>
<th>Anxiety Depression Catastrophes</th>
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Severe Postoperative Pain

<table>
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<tr>
<th>Intensity of acute pain correlates with development of chronic pain</th>
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Gender

<table>
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<tr>
<th>Women report higher levels of postoperative pain</th>
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Genetic Predisposition

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<tr>
<th>Susceptibility to the generation and experience of pain, variable responsiveness to analgesics</th>
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Increased Age

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<tr>
<th>Older patient shown to have reduced risk of chronic posthermorrhoidopathy pain</th>
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Vascular Surgery

Epidural infusions of local anesthetic combined with general anesthesia provide a significant cardioprotective effect for patients undergoing abdominal aortic aneurysm repair. Improvements in outcomes are related to maintenance of hemodynamic stability and reduced arrhythmias following release of the aortic cross clamp. Postoperative hypertension found in up to 50% patients has been related to sympathetic nervous system hyperactivity and not adrenal epinephrine or pituitary secretion of arginine vasopressin is responsible for the development of hypertension following aortic and lower extremity vascular surgery.

The beneficial effect of epidural analgesia on sympathetic hypertension response is mediated by blockage of noxious input as well as the sympatholytic effect of dilute local anesthetics. Epidural morphine has no local anesthetic properties but may suppress sympathetic responses by providing effective pain control. Sympathetic hyperreactivity and efferent outflow are more reliably blocked when local anesthetic is added to an epidural morphine infusion. α2 stimulation also inhibits sympathetic responses and release of catecholamines. Clonidine is an α2 agonist that indirectly inhibits sympathetic responses at major vascular structures.

Catecholamines released in response to surgical stress and poorly controlled pain incite vasospastic, vasoconstrictive, and thrombotic occlusive complications. Vasoconstriction as a result of high plasma concentrations of epinephrine and locally released norepinephrine may compromise distal graft potency in patients recovering from vascular surgery and increase risk of deep venous thromboses in other forms of lower extremity procedures. Compared with general anesthesia, epidural anesthesia followed by continuous epidural analgesia maintains fibrinolysis, reduces the risk of arterial thromboembolism, and is associated with a lower incidence of reoperation for inadequate tissue perfusion.

Although local anesthetics directly inhibit platelet aggregation and have antithrombotic effects, they remain unclear whether local anesthetics absorbed from peripheral or epidural sites of administration have clinically significant effects at the site of vascular surgery.

Cardiac Surgery

Thoracic epidural analgesia allows specific blockade of nociceptive reflex arcs and may reduce or eliminate stress-induced alterations of organ dysfunction. Untoward sympathetic effects on atherosclerotic vessels are suppressed and blood flow to at risk areas of myocardium is improved. Standing the pathophysiology of pain and providing optimal management has become important in cardiac surgery. The use of thoracic epidural anesthesia following coronary artery bypass graft surgery, although controversial from a safety point of view, has been shown to improve hemodynamic stability, reduces the release of troponin and the incidence of supraventricular arrhythmias and allows earlier extubation.

Epidural analgesia with local anesthetics plus opioids, but not opioids alone, blocks noxious impulses to and from the sympathetic ganglia and attenuates activation of the sympathoadrenal axis.

Such suppression helps to explain why a recent analysis of thoracic epidural analgesia continued for more than 24 hours was found to reduce mortality and postoperative myocardial infarction.

Thoracic and Upper Abdominal Surgery

Clinically significant hypotension and hypercarbia are commonly observed in patients recovering from chest wall trauma, thoracotomy, and upper abdominal surgery. Dynamic pain and associated restrictions in VC are difficult to control with either parenteral opioids or intravenous patient-controlled analgesia (IV PCA). Cough-provoked dynamic pain is a more sensitive outcome measure for post upper abdominal and thoracotomy analgesia. Studies employing thoracic epidural infusions of opioids plus local anesthetic have documented improvement in pulmonary volume, flows, and cough-provoked dynamic pain as well as reductions in stress-induced hormonal, metabolic, and physiologic responses. Improvements in pulmonary function observed with thoracic epidural anesthesia are related to several factors, including reduction in opioid exposure, superior relief of dynamic pain, and prevention of secondary hyperalgesia.

Risk of Thromboembolism

Continuous infusions of epidural local anesthetics and continuous lower extremity neural blockade may be advantageous in patients at high risk for venous thromboembolism, particularly when DVT prophylaxis is inappropriate due to patient or surgical concerns.

A recent meta-analysis of all randomized studies, including 141 trials in a total of 9559 patients, concluded that central neuraxial blockade reduces the risk of deep venous thrombosis by 44%, pulmonary embolism by 55%, transfusion requirements by 50%, pneumonia by 39%, respiratory depression by 59%, and myocardial infarction by 30%. Overall mortality was reduced by 30%. These positive findings were obtained predominantly after major orthopedic procedures, whereas no significant effects were found in other procedures (urological, abdominal, and thoracic).

Cytokine Response

Systemic opioids and IV PCA provide useful pain relief; however, they offer minimal to no suppressive effect on sympathetic and humoral responses to traumatic injury. In contrast, continuous epidural or regional anesthesia analgesia suppress sympathoadrenal responses and provide modest suppression of humoral-mediated responses and neuroendocrine reactivity.

Clonidine and other α2-adrenergic receptor agonists offer an alternative pharmacologic approach that provides clinically effective pain relief while suppressing the sympathoadrenal responses to injury and intubation.

Humoral mediators, including cytokines and IL-1β, and peripheral sensitizers, such as PGE, exacerbate inflammatory and inflammatory mediated pain. Interleukin 1β, IL-6, C-reactive protein, and TNF-α are increased in patients undergoing extensive and prolonged surgeries.

In a recent study, patients receiving epidural clonidine reported lower pain scores while coughing, required less intravenous morphine, and benefited from a more rapid return of bowel function throughout the 72-hour postoperative period. Levels of the proinflammatory cytokines interleukin-1 receptor antagonist (IL-1ra), IL-6, and IL-8 were significantly reduced in the clonidine group at 12 and 24 hours after surgery. In a similarly designed study, patients treated with epidural PCA with opioids plus local anesthetics also experienced significant reductions in postsurgical cytokine response.

Proinflammatory cytokines and PGE also have analgesic effects in the central nervous system. In addition to their
Tissue Breakdown and Infection Risk

Parenteral and oral nutrition may compensate for catabolic hormonal stress responses and improve convalescence after major surgery. 

Kehlet and coworkers demonstrated that immediate postoperative administration of β-blockers, amino acids, insulin, and glucose improved nitrogen balance following major abdominal surgery. 

Further improvements in nitrogen balance may be gained by utilizing continuous epidural blockade. 

Impaired host defense mechanisms and immunosuppression caused by surgical trauma and hormonal stress responses may be reduced with epidural analgesia. 

Postoperative epidural analgesia preserved lymphocyte reactivity to a significantly greater extent than IV opioids. 

This improvement in immune status may improve postoperative resistance to infectious disease. 

Sleep Disturbances and Return to Functionality

Epidural and continuous regional analgesia are associated with improved sleep quality and a more rapid return to functionality. Quality-of-life benefits provided by epidural opioid analgesia were evaluated in 100 patients recovering from major surgery. Patients receiving epidural analgesia vs those receiving sham control plus parenteral opioids as required benefited from fewer sleep disturbances, a shorter hospital stay, and more rapid return to work (22 vs 30 days; P < .05). In a second study by Ilfied et al., postoperative pain management and sleep quality were assessed in patients receiving IV and oral opioids supplemented with either regional analgesia or saline control. Patients experiencing effective pain control benefited with significantly improved sleep pattern (P < .05). Pain relief was inferior and sleep disturbances 10-fold higher in the saline control group. 

Epidural analgesia has also been shown to improve functionality following colon surgery. While in the hospital, patients treated with epidural opioids plus local anesthetics experienced significant reductions in effort-related pain intensity scores than others using IV PCA morphine. These improvements continued following hospital discharge, as patients in the epidural group experienced effective pain control benefited with significantly improved sleep pattern (P < .05). Pain relief was inferior and sleep disturbances 10-fold higher in the saline control group. 

As a result, the finding that these initial improvements continued 2 weeks and 3 months following hospital discharge.

Persistent Pain

In an effort to limit development of persistent pain, surgical and anesthetic techniques that reduce the risk of neural and somatic injuries as well as the severity of acute pain and associated stress response have been advocated. 

As illustrated in Figure 2.7, the peripheral and central roles of prostaglandin (PGE) in pain perception, hyperalgesia, and the development of chronic pain can be observed. In addition to their peripheral role in nociceptive transmission and inflammation, prostaglandins incite central sensitization and plasticity changes by a variety of mechanisms, including (1) indirect effects following vascular delivery from the site of trauma to the CNS, (2) indirect effects mediated by cytokine-induced upregulation of COX-2 and PGE synthesis in the vascular endothelium, (3) direct effects of COX-2 upregulation in microglial and sensitized neurons.

Figure 2.7: The peripheral and central roles of prostaglandin (PGE) in pain perception.
discussed above surgical and individual specific factors may increase patient susceptibility to developing chronic pain. Modification of surgical technique may reduce the magnitude and severity of symptoms. In patients at higher risk for developing persistent pain, the use of minimally invasive thoracoscopic, arthroscopic, and laparoscopic procedures should be considered to minimize tissue injury, surgical stress, and risk of nerve damage. When performing mastectomy with auxiliary node dissection, care should be made to avoid damaging the intercostobrachial nerve that can result in upper arm neuropathy. Anesthetic and analgesic management should employ a preemptive and multimodal approach that has been demonstrated to reduce pain intensity and opioid dose requirement (see also Chapters 22 to 24, Perioperative Ketamine for Better Postoperative Pain Outcome, Clinical Application of Glucocorticoids, Antinociceptive and Other Analgesic Adjuncts for Acute Pain Management (Anticonvulsants and α2 Agonists), and Non-pharmacological Approaches for Acute Pain Management), which describe several multimodal approaches for acute pain management. Preemptive and multimodal administration of coxibs, NSAIDs, anticonvulsant analgesics, and ketamine, as well as preemptive initiation of neural blockade, not only reduce acute pain intensity but also may diminish wound hypersensitivity and residual pain intensity many months following surgery.

CONCLUSION
Pathophysiologic responses and adaptive changes to extensive tissue injuries function to maintain hemodynamics, minimize tissue injury, and promote healing. However, the very same neural and hormonal catecholamine responses that promote recovery in healthy young adults worsen pain intensity and promote cardiovascular instability and pulmonary dysfunction and increase infection risk in high-risk patients. Anesthesiologists have traditionally been the physician specialists most familiar with pain physiology and pathophysiology and play the key role in initiating highly effective neuromodulation, regional, and multimodal analgesia. Findings from randomized controlled trials and meta-analyses suggest that continuous epidural analgesia and regional analgesia can significantly reduce pain intensity scores, sympathoadrenal responses, and pulmonary complications. Although these techniques are more expensive, time-consuming, and technically difficult to initiate and require continuous follow-up, their application in high-risk patients has been shown to reduce post-surgical morbidity, mortality, and time to hospital discharge.

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