MINIREVIEWS

Regional anesthesia for acute pain management in elderly patients

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Abstract

Normal aging is a process that involves loss of functional reserve of most organ systems of the human body, most significantly: cardiovascular, pulmonary, renal and nervous systems. Advancements in both surgery and anesthesia have made it possible to operate more safely on the elderly population and those older patients with multiple severe co-morbidities that were not routinely possible in the recent past. Regional anesthesiologist have proven to be instrumental in this regard as regional anesthetic/analgesic techniques may now permit surgeons to operate on the elderly who were not ideal surgical candidates or unable to tolerate general anesthesia. In addition, regional techniques provide alternatives that may optimize acute pain control and reduce the incidence of devastating side effects during the perioperative period such as: myocardial infarction, pulmonary embolism, pneumonia, and also increases the opportunity to allow for early ambulation and shorter hospital stays. These anesthetic options now provide the elderly patient with better medical care alternatives, but also can show a significant financial impact on health care system resources. Further understanding on aging molecular biology, physiology and pathophysiology, together with technical improvements

of regional anesthetic techniques will continue to make it safer and more efficacious to operate on the elderly population with evidence of reduced morbidity and mortality. Although there is only anecdotal evidence that regional anesthesia (RA) improves survival, there is little doubt that RA plays an important role in perioperative optimization of pain control and decreases pain management complications as well as a reduction in healthcare costs. Beyond traditional operating rooms, elderly patients may increasingly benefit from RA and acute pain management in Emergency Rooms, medical clinics and even within a patient's home. Therefore, the focus of this review is directed toward geriatric patients and beneficial effects of RA on outcomes in the elderly.

Core tip: Perioperative advancements has made operating on the elderly more safe, however, aging involves functional reserve loss and older patients often present with co-morbidities. Regional may prove instrumental and permit operations on those who are not ideal candidates, reduce incidence of adverse effects, optimize pain control, provide medical care alternatives and may reduce financial impact on healthcare systems (early ambulation, shorter hospital stay). Understanding of aging, together with improvements in regional will make it safe to operate on the elderly with reduced morbidity and mortality. Regional plays an important role in pain control, decreases management complications and can reduce healthcare costs.

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INTRODUCTION

The diversity, amount of known consequences and abundant number of theories describing the aging progression demonstrate the multidimensionality and complexity associated with understanding mechanisms of aging. Despite advances in anesthesia, analgesia and drug delivery systems, debate continues as to whether regional anesthesia (RA) is more efficacious and safer in elderly and cognitively impaired patients. However, there is some demonstration and evidence-based outcomes to suggest that RA may be an optimal anesthetic for elderly patients in specific clinical scenarios[1]. One approach to planning perioperative pain management in geriatric patients is to consider possible postoperative complications associated with commonly performed surgical procedures in order to assess benefits of RA.

Common morbidity complications of the elderly include: neurological, pulmonary, and cardiovascular events[2]. The most routinely performed surgical interventions are: orthopedic and general surgery (aside from ophthalmologic procedures). Definition and descriptions of RA are variable as are the various techniques of RA anesthesia and analgesia (Figure 1). Investigations on RA are inclusive of different regimens and regional techniques including: RA alone versus combined RA and general anesthesia (GA), RA only versus combined RA and regional analgesia, thoracic versus lumbar RA, for example. Lack of consistency within RA studies and protocols has inhibited the ability to portray firm indications, suggestions, guidelines, and recommendations about any advantageous or optimal anesthetic/analgesic technique for a particular surgical intervention in the geriatric population. With the ever-increasing diversity of available procedures, it has become increasingly complex to make clear-cut recommendations or suggest guidelines that suit all clinical situations. In addition, geriatric surgical patients have unique age-related changes in physiology and several altered reactions to pharmacology[5] and some examples are identified in Table 1[6].
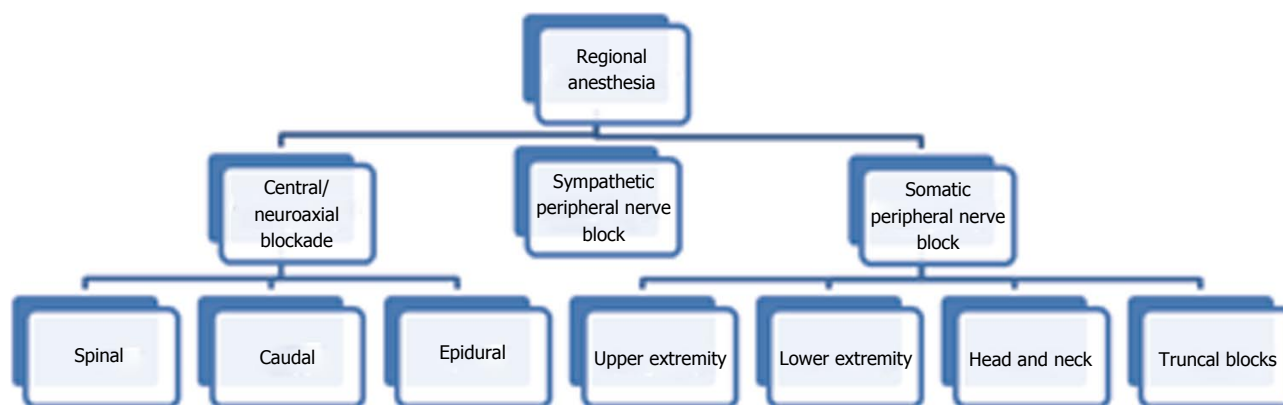
Several age-associated physiological events will also affect pharmacodynamics such as changes in the sensitivity to a specific drug, either up or down, as well as changes in the susceptibility of the elderly to certain drugs. The above-mentioned potential interaction between aging and pharmacodynamics, pharmacokinetics, and polypharmacy, introduces additional concerns when treating the elderly and increases opportunity of exposing older patients to adverse drug reactions. As a result, RA and analgesic options using local anesthetics may provide for a more attractive and safer alternative to avoid systemic administration of various narcotic drugs in addition to other adjunctive analgesic medications.

Many elderly patients have co-morbid disease(s), varying degrees of physical de-conditioning (especially prior to lower extremity orthopedic procedures), poor perioperative health status and compromised organ reserve capacity. Therefore, alternatives to traditional anesthetic/analgesic options, such as local anesthetic drugs, may prove more efficacious to avoid further compromise in older medical and surgical patients. Established and theoretical indications for RA being a competent and safe technique in the elderly and cognitively impaired patients includes profiles from such methods currently being performed in traditional ORs and Emergency Rooms for both diagnostic and therapeutic interventions. Additionally more and more centers are sending patients, even polypharmacy elderly patients, home with continuous peripheral nerve catheters for prolonged benefits of pain management from RA[1,8,9].

Perioperative clinical outcomes associated with RA effectiveness that may result in reduced morbidity (traditional and nontraditional complications)[10] and mortality include: optimal pain management, improved functional and economical outcomes, reduced compromise of functional health status, increased quality of life measurements, along with reduced effects on: cognition, central nervous system (CNS), cardiovascular, pulmonary, gastrointestinal (GI), immune, endocrine, and coagulation systems. Therefore, it is important to consider and recognize patient age, anticipated surgical procedure, patient co-morbidity(s), and potential postoperative pain management requirements when deciding upon an appropriate choice of anesthetic technique and perioperative pain management strategy in the elderly. As an example, although recent studies have shown that exercise and nutrition may slow down protein synthesis impairment and sarcopenia[11] in general the aging body has a skeleton composed of components with significant bone loss and aging skeletal muscles with progressive muscle mass loss along with a decrease in strength and aging joints. Such age-induced pathology (present in up to 80% of the elderly over 65 years) predisposes the elderly to a higher risk of falls and dis-coordination along with an increased incidence of orthopedic injuries[12]. Therefore, a thorough approach to perioperative pain management should consider these influences when selecting an optimal pain therapy protocol.

Anesthesiologists' responsibilities for patient medical care is no longer limited to traditional operating room (OR) environments. Outside OR treatment and therapy is needed and the acute pain control expertise of regional anesthesiologists is becoming more in demand. In the emergency room (ER), in medical wards and intensive care unit settings, physicians are in search of alternatives to provide therapeutic intervention(s) without transporting sick patients to the OR. For example, a lateral femoral cutaneous nerve block can be used as a diagnostic option as well as therapeutic treatment for meralgia paresthetica. Management of elderly orthopedic trauma patients in the ER can involve many regional anesthetic options. In shoulder and upper extremity injuries, an interscalene, supracla-

Figure 1 Regional anesthesia options[3,4].

Table 1 Pharmacokinetics alterations with aging[5,7]

Organ system	Deficits with aging
Liver	Decrease in hepatic blood flow will result in reduction of first pass elimination, phase I metabolism affected earlier than phase II
Kidneys	Reduction in renal blood flow cause decrease in both creatinine clearance, glomerular filtration rate and tubular secretion activities
Plasma drug-binding proteins	Decrease in albumin or other binding proteins will result in higher fraction of plasma free drug
Fluid distribution	Decrease in total body water and muscle, and increase in total body fat may results in smaller effective dose and longer duration of drug effect, especially for lipophilic drugs

vicular, infraclavicular, axillary, and individual nerve blocks could be effective interventions associated with low risk of complications for older patients. Lumbar plexus block, fascia iliaca compartment block and femoral nerve block have been used successfully in elderly hip fracture patients. Hip fractures are one of the most common injuries with the elderly in a traumatic fall and one of the most common orthopedic trauma injuries associated with poor outcomes in the elderly population. Other lower extremity injuries such as ankle fractures can be effectively managed with a distal sciatic nerve block in addition to a femoral/saphenous block. The most common truncal injury, often associated with devastating outcomes in the elderly, are rib fractures (often multiple). Here is another example where such an injury can be managed by a variety of RA techniques such as thoracic epidural, paravertebral, intercostal and intrapleural blocks[1]. In addition, outside of hospitals and surgical center environments, anesthesiologists are treating patients and sending them home with continuous peripheral nerve blockade catheters to continue management of acute pain in surroundings much more familiar to older patients who may be at risk of anxiety and/or depression under prolonged exposure to unfamiliar settings. This beneficial value is in addition to the many known (gastrointestinal dysfunction) and possible (cognitive dysfunction) negative effects from traditional opioid analgesics for dependence of pain management. Some specific indications and contraindications for RA in the elderly, both inside and outside of the operating room arena are included in Table 2[1].

NERVOUS SYSTEM IN THE ELDERLY

Normal aging results in several biochemical and anatomical changes of the brain and spinal cord along with qualitative and quantitative effects on the nervous system (Table 3). Age-related changes in the peripheral nervous system (PNS) and CNS may affect functional outcomes during the perioperative period and should be considered in a patient's preoperative evaluation. Effect of aging on functional reserves of CNS and PNS along with potential surgical and anesthetic ramifications must also be considered.

Aging central nervous system
Anatomical and biochemical changes of the CNS, brain and spinal cord associated with normal aging include: (1) volume of brain mass, number of synapses, and neurotransmitter concentrations; (2) cerebral electrical and metabolic activity; (3) changes in brain nerve fibers; (4) changes within the spinal cord (cervical spinal cord maintains it shape, but decreases in size); and (5) modification of the bony spinal canal (shape and area of spinal cord are independent of spinal canal diameter). Reductions of brain reserve are portrayed as symptoms and signs of neurological dysfunction, decreases in functional activities of daily living, increased risk of postoperative cognitive dysfunction (POCD), and increased sensitivity to anesthetic medications. The major signs, symptoms and changes include altered reflexes, deteriorations of gait and mobility, altered sleep patterns, impairment of memory and intellect, and decrements of the senses (vision, hearing).

Aging somatic peripheral nervous system
Changes that occur in the somatic nervous system of the PNS with aging include: (1) peripheral nerve deterioration; (2) dysfunction of genes responsible for myelin sheath protein components; (3) decreased myelinated nerve

Table 2 List of older patient considerations related to regional anesthesia/analgesia

Indications	Contraindications
Poor cardiac reserve in patients who may not tolerate general anesthesia	Patient refusal
Poor pulmonary reserve: general anesthesia may result in prolonged mechanical ventilation	Sepsis, systemic infection and local infection are relative contraindications, and need to be assessed individually
Known history of adverse cognitive effects due to opioids and/or general anesthesia	Sedation and agitation may place patients at risk during PNB procedures
Severe hepatic insufficiency	Coagulopathy; relative contraindication with superficial PNB where bleeding can be easily controlled by compression
Severe renal insufficiency	Pre-existing neurological disease needs to be documented well and assess risk/benefit ratio
Difficult airway such as in elderly with cervical disk injury/pathology	Hypovolemia and severe aortic stenosis are relative contraindications for neuroaxial blocks, but not for PNBs
Chronic pain patients	Concern that PNB may mask compartment syndrome (controversial), however, collaboration between anesthesiologist and surgeon is necessary
Multiple rib fractures	Allergy to local anesthetics (rare)

PNB: Percutaneous needle biopsy.

Table 3 Nervous system changes in the elderly[11,13-15]

Structural changes: gross and molecular level	Neuronal axon loss and pathology (more than seen with glial cells)
	Neural cytoskeleton changes resulting in neurofibrillary tangles and neuritic plaques (induces glial cell-mediated inflammation)
	Loss of dendrite components and decrease in neural synaptic activity
	Amyloidoses due to amyloid protein accumulation
Biochemical changes	Neurotransmitter imbalance: mostly involves changes in serotonin, dopamine, norepinephrine, acetylcholine
	Circulatory changes: multi-infarct senile dementia; increased BBB permeability
	Metabolic disturbances: atherosclerosis and associated blood flow and O_2 consumption decreases
Functional sequelae	Gait changes
	Sleep and wakefulness alterations and EEG changes
	Cognitive impairment
	Decreased balance stability/physical equilibrium

BBB: Blood-brain barrier; EEG: Electroencephalograph.

fiber conduction velocity; (4) mild motor and sensory discriminatory changes of the feet; and (5) changes of the senses (*e.g.*, pain, touch, proprioception). Aging is associated with deterioration and decreases in the number of myelinated peripheral nerves for all mammals, particularly large myelinated fibers, resulting in atrophy along with degenerative changes of the myelin. The aging process affects levels of expression for key genes encoding major protein components of the myelin sheath such as proteolipid protein and myelin basic protein. Maintenance of myelin sheath integrity involves continued expression of genes specifically associated with myelin sheath protein production. Restoration of myelin sheaths to demyelinated axons (remyelination) is a spontaneous process of the nervous system, but aging has a detrimental effect. Spontaneous remyelination efforts are slowed as is evident by rate (slowing) of reappearance of transcripts of major myelin proteins (proteolipid and myelin basic proteins) and dysfunction of regulatory factors. Oligodendrocyte progenitor recruitment and differentiation are impaired by age-related decline in remyelination. Alterations of inflammatory responses by macrophages also contribute to a decline in remyelination secondary to aging. Aging induces functional changes by decreasing peripheral myelinated nerve conduction velocity as older adults have a 10%-30% decrease of efferent motor fiber conduction velocity. Normal manifestations in patients older than 65 years include some degree of absent ankle reflexes along with mild abnormal sensory and motor symptoms of the feet (absent vibratory sensation of the big toe).

Aging autonomic nervous system
The autonomic division of the PNS also experiences alterations secondary to aging. Autonomic nervous system (comprised of nerves, ganglion and plexus) dictates most of the involuntary physiological functions of the body through parasympathetic and sympathetic divisions. Aging of the autonomic nervous system is characterized by: (1) limited adaptability to stress; (2) net activation of the sympathetic nervous system; (3) decreased basal activity of parasympathetic nervous system; (4) decreased baroreflex sensitivity; and (5) slowing and weakening of homeostatic functions. The aging autonomic nervous system has reduced autonomic abilities that influence a patients' response to physiologic changes, stresses, surgery and anesthesia. Increases in sympathetic nervous system activity are organ-specific with the GI system and skeletal muscle as targets. Neuronal noradrenergic reuptake is reduced in the elderly resulting in an increased sympathetic tone of the heart and an increase in basal adrenal secretions along with attenuation of adrenal adrenergic secretion in response to stress. There is a loss

of beat-to-beat heart rate variability during respiration in the elderly due to reduced respiratory vagal modulation of the resting heart. Findings of decreased baroreflex sensitivity are due to a function of increased arterial stiffness versus aging associated alterations of the autonomic nervous system. The autonomic nervous system and its effectors play an important role in responses to hemodynamic challenges and advancing age could result in an imbalance of homeostatic mechanisms such that findings of orthostatic hypotension, exercise intolerance, increased upper body sweating, and temperature intolerance may be evident.

Aging nervous system and anesthetic considerations

There are a host of factors in older patients predisposing them for cognitive dysfunction. Memory deterioration can occur in > 40% of people older than 60 years of age, and progressive loss of intellectual activity along with mental deterioration (senile dementia) happens in 14% of the population aged ≥ 75[16,17]. Daily living activities can be dramatically affected by age-related memory decline, but is not inevitable. Deficiencies of specific neurotransmitters (related to Parkinson's, Alzheimer's dementia, and other disorders) often occur in geriatric patients. Changes in neurotransmitter activity and amounts have also been implicated as a factor influencing anesthetic agent sensitivity. Cerebral metabolic activity is decreased in older subjects and may be a result of decreased neurotransmitter concentrations and synaptic activity. Degenerative changes of myelin sheaths in the CNS may lead to cognitive dysfunction through changes in nerve conduction velocity leading to disruption of normal timing of neuronal circuits. Further contributions to cognitive decline are due to loss of cerebral white matter nerve fibers resulting in decreased connections between neurons. Although these changes have been identified in the aging brain, the mechanism causing effects on functional activity reserve remain unclear.

Older patients' perioperative evaluation for any surgical procedure should be performed as a multidisciplinary team approach for optimal operative management, therapy and long-term follow-up, when indicated. Elderly patients often present with age-related changes of the nervous system, and whether these changes are normal or pathologic, they are to be considered in the anesthetic plan and during selection of appropriate postoperative pain management. Emphasis on a routine design of an anesthesia assessment plan should be established due to the influence of aging and decreases of functional reserve of both the CNS and PNS. Alterations of functional reserve in the elderly may be reflected as increased susceptibility to POCD, delirium, altered pharmacodynamics, and stroke. Definitions and conditions of the various cognitive changes and dysfunction can be found in Table 4 and partially assessed by Mini-mental-status-exam, but more accurately by a wide array of cognitive assessment tools. While the most common perioperative mental status change is acute delirium, many other deficits have been reported, such as deficits in memory/recall, orientation, attention, language, registration, an ability to follow commands, as well as depression and anxiety.

Cognitive disorders can occur after surgery in which mental function reaches a nadir in the early postoperative period and returns to preoperative levels within one week following surgery. CNS dysfunction is common in elderly postoperative patients, but stroke occurs relatively infrequently[18] . A more common occurrence is the incidence of postoperative delirium (POD; most common psychiatric condition of hospitalized patients) and POCD. Incidence of POD and POCD may exceed 50% in certain surgical settings such as cardiac and orthopedic (femoral neck fracture repairs) surgeries[19,20]. POD and POCD are common complications in elderly surgical patients and the incidence is higher than other postoperative co-morbidities such as respiratory failure and myocardial infarction[21]. Complications of POD and POCD are significant because such adverse outcomes can result in increased length of hospital stay, medical complications including death, and often require discharge to skilled care facilities[22,23]. The economic impact of delirium is considerable, adds costs to hospitalization and is responsible for billions in additional Medicare charges. POD and POCD occur far more frequently in elderly than in younger patients and the elderly surgical population is increasing in number.

Geriatric patients undergoing certain high-risk types of surgery and patients with certain coexisting medical disease(s) (preoperative cognitive dysfunction along with adverse physiological parameters associated with advanced age) are at higher risk for development of postoperative cognitive disorders and long-term cognitive dysfunction. Research has indicated that cognitive disorders in high-risk elderly patients occurs far more frequently than anticipated. This is evident by one such early study that brought formal recognition of this issue in the elderly surgical population; reveiling that patients (n = 1200) older than 60 years had a high incidence (25.8%) of cognition impairment postoperatively, lasting for one week that persisted in some patients (9.9%) to 3 mo following surgery[24]. Functional status of elderly surgical patients may be more relevant than medical morbidity outcomes. Postoperative cognitive status relates directly to the patient's functional ability which is a determining factor in rehabilitation and whether or not a patient is discharged to home or will require a skilled care facility for recovery. In addition, functional status serves as a strong predictor of mortality as a result of hospitalization[25,26]. Decreased neurocognitive function yields a decrease in health related quality of life along with adverse financial and social impact for patients and their care providers. Finally, cognitive dysfunction postoperatively serves as a surrogate for the quality and modalities of continued hospital care[27].

RA ramifications and neurologic morbidity and mortality

There are many theories that RA effects in the elderly will reduce the incidence of POCD[28]. Evidence has shown a decreased incidence in a host of morbidity factors and some mortality specific advantages when using RA in the elderly for certain surgical procedures[29-33].

Table 4 Types of cognitive dysfunction

MCI (4 subtypes associated with causes of dementia)	Concept to describe transitional level of neurocognitive impairment
	MCI is a predictor of future dementia
	Diagnosis by neuropsychological testing and clinical observation
	Divided into 4 subtypes (based on presence of: (1) memory impairment plus; (2) number of other cognitive domains affected)
	Preoperative MCI may result in postoperative delirium
Delirium	Fluctuating consciousness, develops over hour to days
	Altered perception and cognition (not associated with dementia)
	In hospital predictors of delirium include:
	Bladder catheters
	↓ Functional status
	Male gender
	Malnutrition
	Infection
	Depression
	3 or more medications
	H2 antagonists
	Age
	Opioids
	Iatrogenic events
	Benzodiazepines
	Alcohol + drug abuse
POD[74]	Develops on postoperative day 1-3, can be sustained > 1 wk
	Age associated central cholinergic deficiency as a positive predictor
	Two types of postoperative delirium:
	Hypoactive form (more common and more commonly overlooked)
	Hyperactive type
	Perioperative use of benzodiazepines are associated with POD
	Postoperative in-dwelling perineural catheters reduce incidence of POD
Emergence Delirium	Present upon regaining consciousness following general anesthesia
	Predicts postoperative delirium
POCD	Condition in which patients have difficulty in performing cognitive tasks following surgery that they could perform prior to surgery
	Occurs frequently in and following: carotid endarterectomy, hip fracture repair surgery and cardiac surgery patients (most frequent)
	ISPOCD: developed criteria of POCD based on pre- and post-operative neuropsychological testing scores
	Predictors of POCD 1 wk postoperatively include:
	Duration of anesthesisa
	Age (predictor of POCD at 3 mo)
	Postoperative infection
	Low level of patient education
	Pulmonary complications
	Need for a second operation
Dementia Alzheimer's disease (most common form), vascular dementias, frontal lobe, reversible, senile, Lewy body, and Parkinson-associated	Apathy and personality changes occur early
	Behavioral changes appear as the condition progresses
	Psychotic symptoms are late signs (typically difficult to control)
	Multiple cognitive deficits
	Clinical findings are associated with:
	Problems with social activities
	Decline from a previous status
	Problems of occupational activities
	Gradual and progressive loss of mental abilities
	Dementia often results in postoperative delirium

POCD: Postoperative cognitive dysfunction; ISPOCD: International study of postoperative cognitive dysfunction; MCI: Mild cognitive impairment; POD: Postoperative delirium.

There is a reduced incidence of acute postoperative confusion in elderly patients following hip fracture surgery under RA[34]. High delirium risk surgery (such as femoral neck fracture repair) performed under spinal anesthesia (without perioperative premedication or sedation) has reported no incidence of delirium in these elderly patients[35]. Higher degrees of postoperative pain are associated with an increased incidence of cognitive dysfunction[36], so it would seem prudent that control of postoperative pain would decrease the incidence of post-operative cognitive impairment. Therefore, the implication is that different analgesic modalities, which provide different postoperative analgesic levels (and varying side effects), may result in a varying incidence of postoperative cognitive influence or level of cognitive dysfunction. This implication is important for RA techniques because analgesic regimens of local anesthetics were shown to provide superior pain control over systemic opioids[29] and also reduces systemic side effects of opioids that have been associated with the occurrence of POCD[37].

Table 5 Cardiovascular changes associated with the aging process[12]	
Cardiac changes	Coronary artery disease due to atherosclerosis
	Changes in CNS innervations of the cardiovascular system: increase in sympathetic and decrease in parasympathetic activity
	Diminished response to beta-receptor stimulation
	Increase in apoptosis resulting in muscle mass loss, compensatory hyperplagia of remaining cells, abnormal cardiac function that can eventually lead to diastolic and systolic heart failure
	Increase in microtubule component of cytoskeleton of cardiocytes results in contraction dysfunction
Vascular system changes	Decreased blood flow due to increased cell adherence, micro-thrombogenic events, atherosclerosis
	Increased vasoconstriction and vascular wall stiffening
	Impaired endothelium integrity and ability to repair

CNS: Central nervous system.

In addition, epidural analgesia can reduce the incidence of postoperative pulmonary complications that have shown to be connected with an increased occurrence of POCD[24,38,39].

Numerous trials examining intraoperative neuraxial anesthesia compared to GA has not determined preservation of postoperative cognitive function and there is no conclusive evidence that RA and analgesia are associated with a lower incidence of POCD. The problems in evaluating studies addressing issues of cognitive preservation in elderly surgical patients are due to multiple design flaws and methodological variability contained in the literature. Attempts at interpreting past and current evidence provides conflicting results and even in the hierarchy of evidence (meta-analysis of randomly controlled trials and large randomized trials), there is lack of data to demonstrate preservation of cognition beyond the first few hours after surgery when selecting RA[40,41]. However, results from meta-analysis may demonstrate significant improvement in mortality when neuraxial blockade is used without GA[42], but until POCD predictors and consequences are determined, it remains difficult to make recommendations for appropriate treatment and prevention of POCD.

Pharmacokinetic changes that accompany aging can explain some components of the analgesic drug response(s) seen in the elderly. Brain sensitivity to anesthetic and analgesic agents increases with age and is unique to each drug. The mechanism(s) that define altered brain pharmacodynamics to anesthetics and analgesics in the elderly are unclear at the present, although altered brain kinetics may provide direction. Age-related altered brain sensitivity may result from changes in receptors, signal transduction, and homeostatic mechanisms of the CNS. Aging is associated with decreases in cholinergic and dopaminergic neurons and receptors along with decreasing numbers of nervous system synapses. In addition, alterations of brain phospholipid chemistry associated with changes in second messengers, such as diacylglycerol, remain evident[43].

CARDIOVASCULAR SYSTEM IN THE ELDERLY

RA/analgesia and cardiovascular system in the elderly

A variety of morphologic, and functional changes oc-

cur within the cardiovascular system with aging and are identified in Table 5. Aging processes on the heart and vascular systems have important clinical implications in the treatment of elderly surgical patients and considerations of postoperative pain management, especially those receiving RA. Currently, there is little evidence to suggest differences in cardiovascular outcome, morbidity and mortality using RA in the elderly[44,45], although there have been studies showing a significant benefit and influence on short-term survival[30,31,46,47]. There is little suggestion to indicate statistically significant differences in anesthetic technique toward incidence of death or major complications, but analysis does show positive influence on pain management and better cumulative results when considerations are provided for and depending upon the type of surgery being performed. For example, when epidural anesthesia and analgesia are combined with GA for elective abdominal aortic aneurysm repair, there is a shorter duration of postoperative intubation required, reduced time within and resources of the intensive care unit, lower incidence of death and major complications, better postoperative pain relief, and improved overall outcome[47]. In addition, early placement of continuous epidural analgesia in elderly patients for hip fracture surgery versus a regimen of systemic opioids has been associated with a reduced incidence of adverse cardiac events[30].

RA ramifications and cardiovascular morbidity and mortality

Recent meta-analysis of randomly controlled trials ($n = 9559$) showed that patients undergoing various orthopedic procedures and receiving neuraxial blockade had a one-third reduction in overall mortality[39]. Another meta-analysis ($n = 2427$) found that patients who received epidural anesthesia and analgesia (with or without GA) had a reduced incidence of perioperative myocardial infarction and in those instances when a thoracic epidural was maintained for analgesia longer than 24 h, results showed significantly fewer postoperative myocardial infarctions[31,46]. Yet another meta-analysis ($n = 68723$) on Medicare patients found an association of significantly lower odds ratio of death at 7 and 30 d when postoperative epidural analgesia was used[32].

Perioperative stresses of life-style disruption, anesthesia, surgery, postoperative pain, and convalescence will activate (to varying degree) the sympathetic nervous

Table 6 Pulmonary changes and the elderly patient[6]	
Structural aging	Increase of lung parenchymal compliance due to degeneration of elastic fibers
	Loss of respiratory muscle mass resulting in less endurance and less respiratory reserve
	Increased alveolar permeability, which results in bronchial fluid with increased neurophils and increased ratio of CD4/CD8 cells
	Decreased surface area for oxygen exchange
Functional aging	Chest wall rigidity
	Reduced maximum breathing capacity
	A greater in difference between alvelolar and arterial oxygen concentration
	Increase in closing capacity
	Less effective coughing
	Impaired swallowing with high risk of aspiration pneumonia

system of elderly surgical patients with mixed and potentially negative imbalances between myocardial oxygen supply and demand predisposing patients to myocardial ischemia and infarction. Perioperative myocardial infarction and other deleterious cardiovascular events such as congestive heart failure, sudden death, and cardiac arrhythmias typically occur with increased frequency within the first few days following a surgical intervention[48-50]. In addition, patients with a reduced cardiovascular reserve or patients at risk of perioperative myocardial events have a higher incidence of myocardial ischemia and infarction. Another important factor to consider in geriatric surgical candidate that can influence development of perioperative myocardial ischemia and infarction is the negative contribution from hypercoagulation during the surgical perioperative period[48].

Thoracic epidural analgesia may attenuate adverse cardiovascular pathophysiological events (hyper-coagulation) because epidural analgesia has demonstrated an effect of decreasing cardiac sympathetic outflow yielding more favorable balance between myocardial supply and demand. Reduced cardiac sympathetic activity results in decreased inotropy, eases negative hemodynamic effects related to heart rate and blood pressure, mitigates myocardial oxygen consumption, and produces a favorable myocardial balance by improving coronary blood flow to the subendocardial areas of the myocardium at risk for ischemia[51]. There currently remains uncertainty to statistically proven beneficial influence from RA on the incidence of myocardial ischemia, myocardial infarction or myocardial malignant arrhythmias. However, use of thoracic epidural analgesia (not lumbar) has revealed statically significant reduction in ventricular malignant arrhythmias and a decreased incidence of postoperative myocardial infarction[46]. Therefore, physiologic benefits of RA in appropriate surgical settings can decrease adverse cardiovascular pathophysiologic events such as myocardial infarction in the older surgical candidate.

PULMONARY SYSTEM IN THE ELDERLY

RA/analgesia and the respiratory system in the elderly
Significant perioperative risk among elderly patients can often be attributable to respiratory compromise and complications. A substantial portion of risk is explained by both functional and structural changes within the pulmonary system commonly associated with aging (Table 6). In addition, pathology and iatrogenic conditions can further create respiratory risk during the perioperative period. Therefore, clinicians should titrate analgesic medications carefully and assess patients frequently for evidence of analgesic drug adverse side effects and adequate pain control. Epidural analgesic techniques may benefit elderly patients undergoing thoracic and upper abdominal surgery because these techniques allow quick restoration of respiratory function with added benefits of decreasing morbidity, hospital stay and health care costs[49,52].

RA ramifications and pulmonary morbidity and mortality
Although RA is commonly used for older patients, many studies have shown that the anesthetic choice has no significant effect on perioperative morbidity and mortality within any age group. Intuitively it makes reasonable judgment that elderly patients may benefit from RA because they can remain minimally sedated (preservation of pulmonary function), airway manipulation is avoided, postoperative pain control is provided, and recovery from any adverse respiratory influences may be minimized or reducing by eliminating the use of inhalation anesthetics/GA. However, a multitude of factors influence perioperative outcome and these often make it difficult to decide upon the most appropriate anesthetic technique. Therefore, the decision to perform RA must be determined and assessed on a case-by-case basis considering patient's pulmonary function, health status, anesthesiologist expertise, along with type and duration of planned surgery along with both patient- and procedure-specific regional techniques if chosen.

Structure and functional changes of the lungs that occur with aging act to decrease pulmonary reserve[53]. Aging effects on respiratory parameters have minimal influence in unstressed individuals, but functional changes become evident with stress. For instance, age-related decreased respiratory muscle strength becomes relevant under stresses of left ventricular failure or pneumonia. In addition, elderly patients are less able to adequately meet respiratory demands induced by hypoxia and hypercarbia, a greater decrease in arterial oxygen tension is needed to increase minute ventilation in older patients, and the elderly may not increase their minute ventilation under stress of illness or injury with the increased production of carbon dioxide[54].

Functional residual capacity (FRC) reduction is associated with ventilation-perfusion (V/Q) mismatching, an increased alveolar-to-arterial oxygen gradient, and decreased efficiency of gas exchange. Further reductions in FRC are created by assuming the supine position and under influence of GA. GA can reduce FRC by 15%-20% and last 7-10 d following surgery[55]. Older patients undergoing GA are predisposed to atelectasis from a combination of reduced FRC and age associated increases in closing volume. Vital capacity (VC) can be reduced after upper abdominal incisions (25%-50%) and postoperative pain along with use of systemic opioid analgesics, which can contribute to a reduction in tidal volume and impair clearing of secretions (altered cough mechanics).

Hypoxic pulmonary vasoconstriction (HPV) is affected and maybe abolished during inhalation anesthesia. Blunting of HPV in the elderly during GA causes a greater incidence of intraoperative V/Q mismatch and increased alveolar-to-arterial oxygen gradient. Elderly patients have an increased sensitivity to ventilatory depression from opioids, benzodiazepines and inhalation anesthetics because their responses to hypoxia and hypercarbia are impaired. GA has major effects on the pulmonary system since inhalation anesthesia depresses respiratory responses to hypoxia and hypercarbia and these patients commonly require airway manipulation due to a high propensity of obstruction because of respiratory muscle (thoracic) relaxation. These above influences can compromise usual protective responses of the pulmonary system during the perioperative period and are to be considered in elderly surgical candidates. Therefore, negative effects on pulmonary function predispose these older patients to atelectasis, increased risk of hypoxemia and pneumonia, V/Q mismatch, and other postoperative pulmonary challenges[56].

With RA, airway manipulation can be avoided and respiratory parameters of lung tidal volume, respiratory rate, respiratory drive (effort), and end-tidal carbon dioxide concentration can be preserved. Unchanged FRC, from baseline, has been observed during spinal and lumbar epidural anesthesia. However, intercostal blocks, thoracic paravertebrals, cervical or high thoracic epidural blockade can be associated with lung volume reduction secondary to intercostal muscle relaxation. Therefore, choice of anesthesia may affect degree of pulmonary dysfunction in older individuals. Studies have shown that elderly patients undergoing lower extremity orthopedic procedures have fewer hypoxic events with epidural anesthesia (using local anesthetics) compared to systemic opioids; GA in older patients results in lower PaO2 levels (on post-op day 1) compared to epidural anesthesia; and respiratory complications are less frequent with combined epidural plus GA compared to GA with postoperative intravenous morphine analgesia for pain management[33,57].

RA and analgesia with local anesthetics for postoperative pain may provide a greater safety margin for elderly patients compared to systemic or epidural opioids. Using RA and analgesia (without opioids) in the elderly population, especially patients with severe pulmonary dysfunc-

tion, may be more appropriate for postoperative pain relief[44,58]. Oxygen saturation in elderly patients with RA and analgesia without an opioid is typically higher and use of systemic (and epidural) opioids results in a higher incidence of hypoxic events compared to RA and analgesia with local anesthetics alone[59]. A reduced incidence of pulmonary infection, an increase in PaO2, and an overall decrease in pulmonary complications is evident with epidural local anesthetics compared to systemic opioids for postoperative analgesia[38]. However, meta-analysis has found reduced atelectasis from use of epidural opioids compared to systemic opioids (for postoperative analgesia) and that epidural local anesthetics (continuous) or local anesthetic-opioid mixtures result in reduced postoperative pulmonary morbidity following major abdominal and thoracic surgery versus systemic opioids[4,60].

Another meta-analysis has shown that RA (especially epidural analgesia) may decrease pulmonary complications in hip fracture surgery since patients were found to have shortened intensive care unit stays and reduced intubation times versus patients receiving systemic postoperative opioids[34]. A meta-analysis of 141 clinical trials showed a 39% reduction in pneumonia and 60% less pulmonary depression from thoracic epidural anesthesia and analgesia versus GA and postoperative patient controlled analgesia[39]. Therefore, much of the controversy as to why several randomized trials have not demonstrated a consistent statistical advantage to RA in reducing respiratory complications in the elderly may be lack of differentiation and uniformity of epidural analgesic mixtures, whether or not an opioid or how much opioids (systemic and/or epidural) were used, site of surgery, timing and duration of RA and analgesia, and vertebral level of neuraxial blockade insertion.

ENDOCRINE AND IMMUNE SYSTEMS IN THE ELDERLY

RA/analgesia and endocrine/immune derangement in the elderly

Communicating capability of circulating immune cells and cytokines of the immune system serves as one of the body's major defense systems. There is a corresponding reduction and deterioration of the immune system as human beings age. Concurrently, there are reduced cellular and humeral responses seen throughout the entire immune system with aging. The thymus gland and thymulin secretions undergo an involutionary process and decreased production, respectively, as we age. Hormones responsible for mature T-cell modulation and progenitor phenotypic cell maturation processes are reduced and T lymphocyte number contribution into circulation is lessened with aging. Physiologic and immunological processes of aging result in minor clinically significant change of function and overall condition of older individuals within an unstressed state. Immunological changes with aging become evident when older patients become stressed and moved away from homeostatic states. Therefore, mea-

sures taken to ensure homeostasis and reduce stresses placed on surgical patients will help to preserve function of the immune system.

Regional anesthetic ramifications and endocrine/ immune morbidity and mortality in the elderly

GA alone cannot prevent stress response initiation due to surgical trauma in elderly patients. Metabolic effects of surgical stress are hyperglycemia and overall catabolism. RA may provide and maintain the most analogues pre-surgical level of metabolism and physiology during anesthesia for surgery in the elderly and theoretically prevent or reduce surgical stress responses. For example, RA may minimize surgical stress by blocking sympathetic and somatic nervous systems from being activated. Epidural blockade reduces postoperative hyperglycemia and improves glucose tolerance despite plasma insulin concentrations being unchanged[49]. More stable cardiovascular, hemodynamics and attenuation of stress responses to surgery have been demonstrated with RA[61]. Metabolic effects of surgical stress, hyperglycemia and catabolism may predispose patients, especially elderly and critically ill patients, to increased morbidity (polyneuropathy, infection, multi-organ dysfunction/failure) and mortality. Plasma glucose normalization and improved glucose tolerance with RA and analgesia can improve perioperative management of optimal glucose control. RA and analgesia can reduce catabolic response to surgery and improve upon gastrointestinal rehabilitation, economy of proteins, and nutritional status of surgical patients, especially in abdominal surgery.

It has been shown that RA and analgesia can preserve humoral and cellular immune functions in surgical patients (especially for procedures below the umbilicus)[62]. GA and lumbar epidural anesthesia have minor influences on human immune function in absence of surgery, but GA alone may worsen the immunosuppression response that can occur subsequent to surgery. However, RA and analgesia (with local anesthetics) may decrease the postoperative infectious complications from surgery[63].

IMPLICATIONS OF RA ON AGE AND PATIENT OUTCOME

Patient age alone should not be considered a major risk factor or predictive of risks to undergo anesthesia and surgery. More important factors and better predictors for the elderly are overall physical status, medical history and disease state or condition along with consideration for type of surgery. Anesthetic complication rates increase very little with advancing age in absence of coexisting disease. Number and extent of any coexisting diseases and medical condition(s) are more directly related to elderly patient perioperative risk than does chronological age. Adverse medical conditions indicative of need for concern and predictive of higher surgical risk are diabetes mellitus, hypertension and ischemic heart disease[64]. In addition, type and surgical site of planned or emergency operations play an important role as a determinant of risk. Upper abdominal surgical procedures followed by thoracic and open-heart surgical procedures are associated with the highest morbidity and mortality and pose increased risk for elderly surgical patients. Therefore, geriatric patients may be at increased risk of perioperative morbidity and mortality from higher incidence of coexisting disease ($4/5^{th}$ of older patients have at least 1 complicating condition and 1/3 have 3 or more coexisting diseases), but additional issues of concern remain, including type, urgency and potential duration of surgery that serve as important predictors of patient outcome.

Postoperative pain management in the elderly, despite advanced pain management modalities, drug delivery systems and benefits of optimal analgesia, continues to be a problem. Patients and health care providers have become increasingly aware of inadequate postoperative pain relief and that a need exists to better implement current postoperative pain management treatment paradigms and for continued development of new pain management methods. Studies and surveys of surgical patients have reported varying degrees and intensities of pain following surgery and many reports of inadequate postoperative pain management, sometimes necessitating hospital readmission[65,66].

RA and continuous analgesia delivery systems can provide targeted pain relief and may reduce dependence upon, or minimize amounts of, systemic opioids in the perioperative period. Therefore, optimal postoperative RA and analgesic effects (superior physiologic and analgesic benefits) on outcome may be improved when RA is placed in close proximity to the corresponding dermatome distribution of the surgical site[4,37,46,67,68].

Choice of analgesic agents used with RA (local anesthetics with or without opioids and other adjuncts) will also influence patient outcome. Central-neuraxial opioids prove effective in controlling postoperative pain, but only epidural local anesthetics have shown ability to attenuate and influence adverse pathophysiological responses that can contribute to perioperative morbidity. Neuraxial local anesthetics are effective through prevention of spinal reflex inhibition of diaphragmatic and gastrointestinal function, suppression of responses to surgical stress, and through blockade of efferent and afferent nerve signals to and from the spinal cord. Epidural local analgesia used without neuraxial opioids may improve patient outcome as a result of a decreased incidence of respiratory complications and earlier recovery of gastrointestinal motility following abdominal surgery[38,63]. Perioperative RA techniques in the elderly will influence and control perioperative pathophysiologic events by (1) reducing neuroendocrine stress response; (2) improving effective pain control; (3) facilitating return of gastrointestinal function (earlier enteral feeding); and (4) earlier patient mobilization (plays an integral role in management of recuperating patients)[69].

Perioperative RA as part of a multimodal pathway for convalescence of elderly surgical patients has resulted in improved patient outcome, amelioration of many negative pathophysiologic events, and improved analgesia as evidenced by the following studies: (1) Postoperative regional analgesia as part of a perioperative multimodal approach in patients undergoing abdominal-thoracic esophagectomy can result in a shorter time to patient extubation, earlier return of bowel function, superior analgesia, and earlier fulfillment of discharge criteria from an intensive care unit[70]; (2) Patients participating in a perioperative multimodal pathway following major surgery had a decrease in metabolic and hormonal stress along with improvement in convalescence[71]; and (3) Patients undergoing colon resection incorporating epidural analgesia and receiving a multimodal approach to surgical rehabilitation showed a decreased length of hospitalization from 6-10 d to a median of 2 d[72]. Therefore, incorporating perioperative RA techniques and utilizing a multimodal anesthetic approach to surgical rehabilitation may aid in attenuation of pathophysiological surgical responses, reduce the length of hospitalization, and result in accelerated patient recovery for the elderly[73].

CONCLUSION

To properly assess and consciously consider the many effects of aging, medication, therapy and treatment options in the elderly has resulted in a need for the Geriatric Patient Population to be subspecialized. Epidemiology data identifies the aging population as the most rapidly growing sector within the United States and larger numbers of elderly patients are presenting to the hospital, surgical centers and emergency rooms more frequently as older individual are staying healthier and more active (patients over 65 years are 3.5 times more likely to be operated upon than those under 65). Therefore, consideration of re-defining the roles of healthcare providers must be considered. Orthopedic injury and general surgery remain the most common reasons why the elderly present to the OR and ER. Goals of perioperative management and acute pain control for the elderly remains the same as for those under 65 years except it may often be more difficult as the elderly tend to under-report acute pain, many suffer from chronic pain, others often present with comorbidities, many are complicated due to polypharmacy, others can present with cognitive dysfunction, and several other possible physiologic changes can be associated with aging[74,75]. Therefore, the issue becomes whether RA/analgesia in the elderly can provide optimal pain control, help to avoid/reduce negative effects of general anesthesia, prevent adverse reactions and avoid the many potential side effects from systemic opioid pain medications (nausea, vomiting, urinary retention, ileus, mental status changes, drowsiness, delirium, cognitive decline and depression).

There can be multiple detrimental effects of poorly controlled pain in the elderly. There is no consistent evidence that regional "directly" improves patient outcome in the elderly, yet RA remains a well-accepted option to: reduce cognitive dysfunction (delirium), helps to minimize stress (tachycardia and hypertension), reduce intra- and post-operative opioids consumption, result in less pulmonary compromise (atelectasis, pneumonia, prolonged mechanical ventilation) and other positive predictors in a host of medical/surgical situations. RA can also offer enthusiastic patient cooperation with postoperative recovery (*e.g.*, physical therapy), superior pain control during dynamic activity[2], early ambulation and provide for venous thrombosis prevention. In addition, regional can minimize opioid side effects and provide for a more "ideal" pain control environment.

With improved technological interventions and more non-opioid related alternatives to pain management, RA has entered into an era of precision and effective patient care[76]. There is now the option to target anesthetic care and pain control both inside and outside the hospital and operating room environments. Whenever possible, RA should be considered as a major part of geriatric anesthesia due to its unique "local" acting properties. Since aging alone often results in multiple organ system dysfunction(s) and loss of functional reserve, healthy aging remains important for the elderly. Therefore, RA may provide for more than just optimal pain management, but could prove beneficial due to its many indirect effects in the perioperative environment (*e.g.*, help the elderly to reduce the incidence of muscle wasting with earlier and more robust postoperative physical therapy). So an ultimate solution and optimal goal would be to decrease complication rates in perioperative elderly patients, implement multidisciplinary interventions/actions (multimodal therapy), and practice patient- and surgery-specific RA toward achieving such an endeavor.

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