Geriatric Physiology for Surgical Intensivists: Part I

Tae Sun Ha *
Department of Surgery, Soonchunhyang University College of Medicine, Bucheon Hospital, Bucheon, Korea

Introduction

According to a Korean National Statistics Office report, South Korea has become an aged society with 14% of the population aged 65 years and over, and it is expected to become a super-aged society by 2026 which would be at the fastest pace in the world [1]. Population aging and extended life expectancy have raised concerns about distinguishing disease states from normal aging when encountering this population in a clinical situation. Aging is usually defined as an age-dependent or age-progressive decline in intrinsic physiological function necessary for survival and fertility. Aging leads to inevitable deterioration in cellular and physiological function, which results in impaired homeostasis, decreased ability to adapt to stress, increased vulnerability to disease, and increased age-related mortality [2]. The characteristics of aging as distinguished from diseases of aging, do not generally cause symptoms and occur at different rates among individuals, and within individuals. A large variation in physiological parameters among the elderly hinders the differentiation of disease from the normal state. Hence, due to the large and rapid increase in the populations average age, the clinical management of elderly patients is one of the greatest challenges for a surgeon and/or surgical intensivist. Geriatric medicine is a branch of medicine that is concerned with the holistic approach to aspects of illness (clinical, preventative, remedial, and social) in old age. To provide optimal health care management a deep understanding of the normal physiological changes associated with aging, and is necessary to provide insight into the mechanisms of multiple organ impairment and disease in the elderly.

Keywords: aging, nephrosclerosis, vascular stiffness, pulmonary function tests, gastrointestinal tract

ABSTRACT

The elderly population experiences a normal, age-related decline of physiological function in all major organ systems. The age-related changes in lung structure include decreases in chest wall compliance, respiratory muscle strength and elastic recoil, contributing to decreased lung function which increases susceptibility to infection. The age-related changes in cardiovascular structure and function increases the risk of cardiovascular disease. The aging process in the kidney leads to several clinical conditions in the elderly such as impaired drug metabolism and kinetics, loss of homeostasis, and electrolyte abnormalities. With aging, the decrease in gastrointestinal (GI) function in the mouth, esophagus, stomach, small and large intestine, and liver may affect appetite, motility, enzyme and hormone secretion, nutrient digestion and absorption, and gastrointestinal immunity. These changes in GI function may play a significant role in malnutrition and an increased risk of cachexia. Aging leads to inevitable deterioration in cellular and physiological function, which result in impaired homeostasis, decreased ability to adapt to stress, increased vulnerability to disease, and increased age-related mortality. Optimal health care management requires a deep understanding of the normal physiological changes associated with aging, and is necessary to provide insight into the mechanisms of multiple organ impairment and disease in the elderly.

Respiratory System

Aging, accompanied with cumulative exposure to environ-
mental stress, airborne toxins, cigarette smoke, and infectious agents, is associated with multiple changes in anatomical, physiological, and immunological characteristics leading to a progressive decline in lung performance [3]. In addition, the age-related changes in lung structure, including decreased chest wall compliance, decreased respiratory muscle strength, and decreased elastic recoil, contribute to decreased lung function, which increases susceptibility to infection.

1. Structural changes

Age-related osteoporosis causes vertebral fractures, leading to increased curvature of the spine. This increased thoracic kyphotic angle narrows the intercostal space, decreases the length of intercostal muscle fibers, and alters the angle of insertion of the intercostal muscle fibers. In addition, the stiffening of the thoracic cage due to calcification within the rib cage and intercostal cartilage, and arthritis of the costovertebral joints, contributes to decreased efficiency and mobility of an already smaller chest cavity. The structural alterations of the chest wall not only modify its compliance, but also diminish the capacity of the diaphragm (following changes in its curvature) to produce force-generating contractions.

Sarcopenia in the elderly is characterized by a significant reduction in intrinsic skeletal muscle mass and strength, which diminishes the function of the respiratory skeletal muscle with advancing age at an annual rate of 2% [4]. At the cellular level, a decrease in the number of Type II “fast twitch” fibers produce alterations in the neuromuscular junctions, and a decrease in mitochondrial adenosine triphosphate (ATP) reserve which induces diaphragmatic fatigue and a decline in diaphragmatic strength [5]. Therefore, diaphragmatic inspiratory effort gradually weakens, which leads to inadequate ventilation, and decreased ability to clear airway secretions. A decrease in mitochondrial ATP reserve impairs the respiratory capacity to meet a sudden increase in metabolic demand [6]. As a result, the risk of respiratory failure may significantly increase in the elderly with acute respiratory infection or physiological stress as opposed to young individuals, and dependence on a ventilator may occur.

In addition to decreased chest wall compliance, an increase in lung compliance occurs with aging due to a reduction in pulmonary elastic recoil caused by changes in the spatial arrangement and crosslinking of the elastic fiber network or the presence of a pseudoelastin [7]. These changes, which are pronounced after the 5th decade of life, and lead to a decreasing lung volume at an average rate of 0.1 cm to 0.2 cm H2O per annum, followed by a reduced alveolar surface area (due to the flattening of the internal surface of the alveoli), and increasing diameter of alveolar ducts [7]. Homogenous enlargement, in contrast to emphysema with irregular distribution of airspace enlargement, is not associated with the destruction of alveolar walls but results from similar alterations as observed in senile emphysema [8]. Consequently, a premature closure of the small airways due to the reduction in supporting tissues during tidal breathing leads to air trapping and hyperinflation.

Coughing, which requires generation of high force expiratory flow, plays an important role in clearing mucus from the airways. With advancing age, the decline in strength of the respiratory muscles adversely affects the capacity to generate the force for an effective cough. Mucociliary clearance is a protective mechanism where there is unidirectional movement along the upper and lower airway produced by cilia moving in synchrony to remove mucus that may have trapped foreign particulates, and pathogens in the airway. With a decreased frequency of beat of the cilia, mucociliary clearance is gradually delayed, especially after 40 year of age [9]. In conclusion, in the elderly a reduced capacity to cough and to clear particulates in the airway contribute to a decreased capacity to clear mucus.

2. Functional changes

The increased chest wall rigidity and the increased lung compliance result in unchanged total lung capacity. The rapid alterations affecting the lung parenchyma lead to air trapping and hyperinflation, which increase the functional residual capacity by 1-3% per decade and the residual volume by 5-10% per decade. The vital capacity is decreased due to unchanged total lung capacity, which alters the physiologic reserve and increases vulnerability to infection and age-related impairment [10]. A gradual decline in both forced vital capacity by 14-30 mL per year and forced expiratory volume in one second by 23-32 mL per year occurs with aging in both men and women [11]. Chronic smoking accelerates these aging-related alterations. Because of the limited expiratory airflow, the aged have fewer ventilator reserves to adapt to the increased ventilator demand for heavy exercise compared to the young. Increasing the respiratory rate is the only strategy to satisfy the increased ventilation needs in elderly individuals.

With aging, the closing volume and premature closure of the small airways increases in the dependent portions of the lung, and the distribution of pulmonary blood flow changes. These alterations lead to an increase in heterogeneous distribution of ventilation/perfusion ratios. This ventilation/perfusion ratio mismatching increases, dead space ventilation, and alveolar-arterial oxygen pressure differences consequently result in a reduction of PaO2 of approximately 0.3 or 0.4 mmHg/year. This phenomenon is exacerbated during exercise due to lower cardiac output associated with increased tissue oxygen uptake and decreased mixed venous oxygenation. However, despite the increase of dead space ventilation, the PaCO2 level is maintained in the normal range via reduced CO2 production following a decrease in the basal metabolic rate, and an
increase in the total minute ventilation to preserve alveolar ventilation [12]. Therefore, elderly patients have less ventilator reserve because of consistently high ventilation needs.

The gas exchange via alveolar capillary membrane, is estimated using the diffusion capacity for carbon monoxide. Alveolar destruction, increased alveolar wall thickness, and small airway collapse gradually reduces the alveolar surface area from about 75 m$^2$ at 20 years, to about 60 m$^2$ at 70 years. The decrease in alveolar surface area and decreased density of pulmonary capillaries, reduce the diffusing lung capacity for carbon monoxide by 5% per decade in healthy older individuals, which leads to a decrease in the efficiency of alveolar gas exchange [13]. The diffusing lung capacity for carbon monoxide reduces by approximately 50% in the elderly compared with young individuals.

As mentioned above, the elderly individuals exhibit a lower tidal volume and a higher breathing frequency compared with younger individuals. In addition, reduced responsiveness of central chemoreceptors and peripheral mechanoreceptors on the chest wall and lung parenchyma, and integration of the central nervous system, the ventilator response to hypercapnia and hypoxia in older individuals is diminished by 41% and 51%, respectively [14].

### Cardiovascular System

In Korea, cardiovascular disease (CVD) is one of the common causes of morbidity and mortality in elderly individuals, and the incidence of CVD increases gradually with age [15]. The number of vascular-related health conditions is expected to increase in Korea, which was classified as an aging society in 2017. With aging, the increased exposure to risk factors such as hypertension, Type 2 diabetes mellitus, smoking, obesity, and dyslipidemia lead to the development of CVD [16]. However, the normal aging process induces changes in cardiovascular structure and function, which increases the risk of CVD.

### Vascular changes

#### 1. Structural changes

The aging process gradually changes the structure of the arterial wall, which is apparent even in early adulthood. With age, macroscopic changes such as dilatation and convolution, increased vascular lumen, and thickening of the arterial wall are detected prominently in large elastic arteries. The thickening of the arterial wall is attributed to changes in the intima and media. Microscopically, the endothelial cells become irregular in shape and display hypertrophy. Vascular smooth muscle cells migrate and may infiltrate the subendothelial space and proliferation in the intima. The number of smooth muscle cells in the media decreases with age, whereas the remaining cells increase in size. In addition, increased collagen deposition and cross-linking, a decreased production and fragmentation of elastin, as well as calcification occurs in aging arteries [17]. Repetitive mechanical stress due to pulsatile blood pressure affects the aorta and large arteries, which results in collagen deposition and an elastin deficit in the arterial wall. These changes occur not only in the large arteries but also in peripheral arteries, which decreases the arterial compliance, resulting in arterial stiffness with aging [18]. Increased intima-media thickness is an independent risk factor for atherosclerosis and cardiovascular events [19].

#### 2. Endothelial dysfunction

The vascular tone regulates blood flow and the vascular endothelium facilitates anticoagulant and fibrinolytic activities. The vascular endothelium synthesizes and releases various regulatory substances including nitric oxide (NO), prostacyclin, and cyclooxygenase-derived eicosanoids in response to mechanical and chemical stimuli such as acetylcholine, thrombin, and serotonin [20]. NO provides endothelial-dependent vasodilation and regulates the compliance of large arteries. The aging process progressively impairs the diverse functions of vascular endothelium, which may be measured by the reduction in endothelium-dependent vasodilation. The increased vascular stiffness is associated with reduced endothelial function, which decreases the production and bioavailability of NO. The factors underlying the decrease in NO levels remain unclear, but it is attributed to the decreased expression or activity of endothelial nitric oxide synthase and increased breakdown of NO by oxygen free radicals generated in aging [21]. The impaired release of NO relates to a decrease in vasodilatory response to acetylcholine in all circulatory vessels [22]. Consequently, the endothelial dysfunction causing vasospasm and vascular thrombosis increases systemic vascular resistance at the level of the small arteries and arterioles.

#### 3. Arterial stiffness

Arteriosclerosis resulting from the foregoing structural changes leads to stiffness of aorta and large arteries and alters the pulse wave velocity (PWV). PWV is the gold standard index and the most reliable and widely used measure of arterial stiffness [23]. The pulse wave, which is generated by the heartbeat, is reflected back to the heart at the bifurcation of the artery, and is determined by peripheral vascular resistance. The reflected wave velocity depends mainly on the elasticity of large arteries, central blood pressure, and peripheral vascular resistance. In young individuals, the reflected wave, which is slowed by elastic arteries, reaches the heart in the diastolic phase, resulting in increased diastolic pressure and enhanced coronary perfusion. Furthermore, the reflected wave, which
is the returned component of the pulsatile wave to the aorta, limits the transmission of the pulsatile energy to peripheral arteries, and thereby prevents damage to microcirculation. With aging, however, because PWV increases in old individuals, the reflection of the peripheral pulse wave returns to the heart early in the systolic phase. This early systolic enhancement increases cardiac workload and decreases coronary perfusion [24]. Systolic blood pressure increases gradually without changing or decreasing diastolic blood pressure, especially after the 6th decade, resulting in isolated systolic hypertension as the most common type of hypertension. The increased arterial stiffness is an independent predictor of cardiovascular morbidity and mortality, and contributes to cardiac changes [19].

**Cardiac Changes**

1. **Structural changes**

The number of cardiac myocytes decrease with age via apoptosis and necrotic cell death. The decline in myocyte number results in left ventricular (LV) hypertrophy via enlargement of the remaining cardiac myocytes to compensate for the loss of myocytes and increase in LV afterload [25]. With age, the number of fibroblasts increases owing to the gradual decrease in myocytes, as well as an increase in the amount of collagen via collagen cross-linking. The increase of ventricular wall thickness resulting from these structural changes leads to decreased ventricular compliance in early diastole, and impaired left ventricular filling. Together with LV hypertrophy, the decreased diastolic pressure reduces subendothelial perfusion, resulting in subendothelial ischemia and interstitial fibrosis [26].

With aging, calcium may accumulate in the heart, especially the cardiac skeleton, known as the fibrous skeleton of the heart consisting of the annular ring and fibrous trigones. Fibrosis and calcification in the cardiac skeleton occur concomitantly with calcification of the base of the aortic cups, leading to delayed depolarization and increased prevalence of aortic regurgitation.

The number of sinoatrial node pacemaker cells is reduced by 50-75% due to apoptosis of atrial pacemaker cells by age 50, and the increased deposition of adipose tissue, amyloid, and collagen results in sinoatrial node disease [27]. While the atrioventricular nodal cells are relatively well preserved, fibrosis and cellular loss occur in the bundle of His and the bundle branches. These structural changes involving generation and conduction of the electrical stimulus affect the heart rate, which results in an increased incidence of cardiac arrhythmia in elderly individuals. The changes in the Ca++ cycle, which is characterized by prolonged Ca++ inflow at each heartbeat, lead to a decline in LV compliance and increase in LV relaxation time. As a result, an increase in the force of left atrial contraction and atrial contraction contributes to LV end-diastolic volume.

2. **Functional changes**

The continued stress on the heart due to changes in cardiovascular structure alters the cardiac function. The LV ejection fraction is not altered, and the stroke volume is slightly increased or comparable in aging. Thus LV systolic function and cardiac output are well preserved at rest in older adults without pre-existing cardiac disease. In contrast to LV systolic function, however, LV diastolic function is significantly changed at rest in aging hearts. The abovementioned changes characterized by delayed myocardial relaxation due to changes in the Ca++ cycle, and reduced compliance following LV hypertrophy, result in increased end-diastolic pressure and a decline in left ventricular filling rate during early diastole. The increase in end-diastolic pressure leads to left atrial dilatation and atrial hypertrophy and affects pulmonary vessels, resulting in pulmonary congestion. A forceful atrial contraction is needed for the late diastolic filling to compensate for the decline in filling during the early diastole. Because of the diastolic dysfunction in the aging heart, the importance of atrial function increases in the LV diastolic filling phase. Therefore, the tolerance for atrial fibrillation, which is frequently observed in elderly patients, is reduced in patients with diastolic dysfunction. The loss of atrial contraction may result in a significant decrease in diastolic volume and eventually result in diastolic heart failure in the elderly. Recent studies reported that resting cardiac output, ejection fraction, and ejection velocity were preserved in elderly patients without cardiac disease [19,28]. Thus, hypertrophy of the LV wall and diastolic dysfunction may reflect age-related adaptive changes to preserve systolic function under increased vascular stiffness.

Meanwhile, in the right ventricle, not only the diastolic function but also the systolic function decreases during the normal aging process. The increase in pulmonary vascular stiffness leads to a decline in systolic function, and the increased afterload in the right ventricle/atrium of the heart decreases the diastolic function.

The cardiac rhythm regulated by the autonomic nervous system is impaired with aging, which decreases the variability of cardiac rhythm. With aging, tonic parasympathetic outflow decreases, whereas sympathetic neural activity increases [29]. However, the responsiveness to beta-adrenergic stimulation in elderly adults is reduced during normal aging, which results in a decrease in maximal heart rate compared to young adults during exercise. As a result, in stressful situations such as exercise, the reduction of heart rate responsiveness significantly decreases the maximal cardiac output, and decreases aerobic work capacity [30].
3. Response to exercise or stress

The reduced chronotropic and inotropic responsiveness of the aging heart restricts the increase in maximal heart rate and myocardial contractility, resulting in decrease in maximal cardiac output during exercise in older adults. To compensate for age-related changes, the aging heart increases LV end-diastolic volume and the strength of the contraction via increased cardiac stretch, known as the Frank-Starling mechanism. Thus, the elderly individuals increase cardiac output without increasing heart rate during exercise.

Generally, surgical procedures may have a number of adverse effects such as blood loss, an inflammatory response, postoperative shivering, after effects of anesthesia, and potential sepsis, leading to increased physical and metabolic stress. Similar to the response to exercise, the response to surgical stress also increases cardiac output to satisfy the increased metabolic demands of the body. In young patients, blood loss may be compensated by an increased heart rate, whereas elderly patients depend on both vasoconstriction to maintain arterial pressure and the Frank-Starling modulation of cardiac output, without increasing heart rate [31]. Consequently, elderly patients are more sensitive to preload decline compared to young patients.

Renal System

The aging process leads to both histological and physiological changes in the kidney, which leads to several clinical conditions in the elderly, such as abnormalities in drug metabolism, homeostasis and electrolyte imbalances.

1. Structural changes

Renal mass decreases between the ages of 30 and 80 years by 20% to 25%, and mainly involves the cortex. A marked decline in renal mass occurs after 50 years of age. Glomerular replacement by fibrotic tissue and fat in the remaining functional parenchymal tissue, known as glomerulosclerosis, occurs after about 30 years of age and involves a loss of 30% to 50% of cortical glomeruli by the age of 70 years [32]. This process is influenced by varied factors including hypertension, obesity, tissue ischemia, and injury. Compensatory hypertrophy, in which the size and capacity of the remnant functional nephrons increases, compensates for the loss of functional glomeruli due to age-related glomerulosclerosis in the aging kidney [33]. Compared with the thinning renal cortex, the medulla is relatively unchanged during the aging process. Other parenchymal changes, such as atherosclerosis of kidney artery, parenchymal calcifications, and cortical focal scars, occur frequently during normal aging.

Nephrosclerosis is a remarkable change in the micro-angiopathetic examination of the aging kidney. It is characterized by focal and global glomerulosclerosis, tubular atrophy, tubulointerstitial fibrosis, and arteriosclerosis [34]. Renal arterioles show deposition of subendothelial hyaline and collagen fibers resulting in intimal thickening of both the afferent and efferent renal arterioles. The intima of small arteries is gradually thickened due to the proliferation of elastin tissue, which leads to atrophy of the smooth muscle media [32]. As a result, the changes in the aging kidney induce dysfunction of the autonomic renal vascular reflex, which maintains homeostasis to preserve renal function under both hypertensive and hypotensive conditions. Arteriosclerosis of small arteries may induce ischemic damage to the nephrons, which progresses to global glomerulosclerosis, tubular atrophy, and interstitial fibrosis. The ischemic-associated glomerular changes include pericapsular fibrosis, wrinkling of capillary tufts, and thickening of their basement membranes. The renal tubules are affected by decreased tubular number and length, fatty degeneration, and irregular basal membrane thickening with increasing tubular atrophy characterized by fibrosis, resulting in renal medullary hypotonicity. The expansion of hyaline mesangial matrix induces obliteration and destruction of the juxtamedullary nephrons, resulting in the formation of a direct channel between afferent and efferent arterioles [35].

2. Functional changes

The structural changes in the aging kidney result in physiological alteration after approximately the 3rd decade of life. From the age of 30 years, the renal plasma blood flow decreases gradually at a rate of 10% per decade, mainly in the renal cortex compared with a relative increase in medullary blood flow, which leads to glomerulosclerosis by increasing intra-glomerular pressure [32]. Creatinine clearance declines by 7.5 to 10 mL/min/decade [36]. Creatinine in healthy elderly individuals is excreted via glomerular filtration and proximal tubular secretion. The tubular secretion of creatinine does not change or increase during the aging process. The glomerular filtration rate (GFR), however, progressively declines by an average of 1 mL/min/year after 30 years of age. The skeletal muscle mass gradually decreases with age by approximately 0.5% to 1.0% per year after the age of 25 years. Senile sarcopenia is accompanied by a reduction in the production of creatinine in older individuals. Thus, the serum creatinine level does not increase despite the GFR decreasing in aging kidneys [37]. Consequently, serum creatinine has limited use as an indicator of GFR in elderly patients.

The relative capacity to maintain electrolyte and fluid homeostasis is not affected by the normal aging process, but the adaptive system for regulating fluid balance is progressively impaired in older individuals. The capacity to conserve sodium in the aging kidneys is particularly affected
by aging. The elderly individuals show a decreased capacity for sodium handling, such as a slow excretion of sodium loading and a reduced ability to compensate for sodium repletion [38]. The lower distal fractional sodium reabsorption in the thick ascending loop of Henle significantly declines in most of the elderly compared with young individuals, whereas the proximal sodium reabsorption is not generally affected by aging. As the sodium reabsorption in the thick ascending loop of Henle and the basal plasma level of renin and aldosterone decline, along with a decreased response to their stimuli, the 24-hour urinary sodium output and fractional sodium excretion in the aging kidney are significantly higher than in kidneys in younger individuals [39]. Elderly patients exhibit water disequilibrium due to a blunted response of arginine vasopressin and a decrease in thirst regulation. The free water clearance in the thick ascending loop of Henle is also reduced. Therefore, these changes comprising water disequilibrium and senile sodium leakage contribute to chronic hyponatremia in the elderly. Due to medullary hypotonicity in the aging kidneys, older individuals exhibit a decreased capacity to maximally concentrate urine, resulting in a predisposition to dehydration [35]. In addition, the ability to dilute urine is also decreased in the elderly.

The ability to control potassium in the aging kidneys is negatively affected during normal aging, so old individuals are vulnerable to develop hyperkalemia under stressful conditions. In general, renal potassium is secreted by active transtubular transport in the distal nephron and cortical collecting duct and is related to sodium kinetics via aldosterone-regulated Na-K ATPase transporters. Aging patients show impaired potassium excretion due to tubular atrophy and tubular interstitial fibrosis. In addition, hypoaldosteronism, relative resistance to aldosterone at the tubular level, and decreased sodium and chloride delivery to the distal convoluted tubule impair the ability to excrete potassium in aging kidneys [40]. Furthermore, the age-related decline in the number of functional urea channels in the senile distal tubule reduces the capacity for urea reabsorption, leading to nocturia due to osmotic diuresis in elderly patients.

Elderly individuals are more susceptible to conditions of stress or acute illness as well as adrenergic activation. In general, the efferent arteriolar tone in normal kidneys is balanced by the vasoconstrictive effects controlled by the renin-angiotensin-aldosterone system and the vasodilatory effects mediated via prostaglandin. The senile kidney reduces the synthesis of prostaglandin and increases the response to vasoconstrictive stimuli [41]. Furthermore, stress or acute illness related to a decrease in the effective circulating volume, such as bleeding, dehydration, and heart failure, contributes to increased excretion of vasoconstrictive substances, which reduce the already diminished renal blood supply. The function of aging kidneys is conserved via vasodilation by prostaglandin by modulating excessive vasoconstriction [42]. Elderly individuals show increased susceptibility to renal injury induced by non-steroidal anti-inflammatory drugs because of prostaglandin-dependent homeostasis in kidneys in elderly individuals. In addition, the altered pharmacodynamics and pharmacokinetics of drugs due to decreased liver metabolism and renal excretion may increase the risk of drug-induced nephrotoxicity in the elderly [43]. Thus, water-soluble drugs metabolized through kidneys are needed to adjust drug dosage.

The elderly are increasingly dependent on NO to maintain renal blood flow because the enhanced renal sympathetic tone associated with aging increases vasoconstriction. However, the renal vasodilatory effect of vasodilators, including atrial natriuretic peptide, NO, and amino acids, are decreased eventually, resulting in deterioration of renal function [44]. The reduced production of erythropoietin in kidneys in elderly individuals leads to increased anemia [45]. The impaired conversion of 25-hydroxy vitamin D to 1,25-dihydroxy vitamin D in kidneys in elderly individuals results in a lower calcium absorption rate and lower serum 1,25-dihydroxy vitamin D levels, despite normal 25-hydroxyvitamin D levels, and consequently osteoporosis, especially in older women [46]. In general, the kidneys clear about 50% of insulin in the peripheral circulation, but insulin clearance in the aging kidneys decreases due to renal function impairment [47].

**Gastrointestinal System**

With aging, the decrease of gastrointestinal (GI) function in the mouth, esophagus, stomach, small and large intestine, and liver may significantly affect appetite, motility, enzyme and hormone secretion, nutrient digestion and absorption, and GI immunity. Also, environmental factors, lifestyle, and chronic diseases, including respiratory disease, CVD, GI diseases, and cancer, can contribute to impaired GI function in the elderly. These changes in GI function may play a significant role in malnutrition and increase the risk of cachexia.

**1. Physiological anorexia**

Physiological anorexia of aging is prominent in men and is related to various small changes in taste. Taste comprising sweet, salty, bitter, sour, and umami components is a sensation produced by food or drinks that stimulate retro nasal olfactory receptors in the mouth. Olfactory function markedly begins to decline in the 5th decade of life, with elderly individuals showing a decrease in the perception of the 5 types of primary taste [48]. In addition, the sensitivity of the tip of the tongue is decreased in the elderly compared with younger individuals.
The satiety mainly relates to stretching of the antral portion of the stomach by food, and NO generated by the reaction with food relaxes the fundus of the stomach [48]. As NO is reduced in response to food, the adaptive compliance of the fundus decreases, and food in the fundus is rapidly shifted to the antrum, resulting in early satiety due to antral stretching [49]. Cholecystokinin, which is a forceful inhibitor of feeding, is released in response to fat and acts as a satiety hormone. Aging increases the release of cholecystokinin basally and in response to fat. In addition, leptin, which causes satiety, increases with aging [50].

2. Esophagus

Although the overall function of the esophagus is relatively well conserved, healthy older individuals show an increased prevalence of dysphagia. Elderly patients with dysphagia show increased basal pressure of the lower esophageal sphincter and insufficient swallow-induced relaxation [51]. In addition, they manifest significant changes in peristalsis and delayed emptying in esophagus compared with young individuals [52]. These age-related motility changes deteriorate gradually after 40 years of age, and contribute to the development of gastroesophageal reflux disease, resulting in dysmotility-induced aspiration pneumonia.

3. Stomach

Gastric emptying is a regulatory process of gastric content migration from the stomach to the duodenum by the coordinated movement of the proximal stomach, distal stomach, and duodenum, which is regulated by the feedback of neural and hormonal signals in response to ingested nutrients in the small intestine. The effect of aging on gastric motility is still debated because of conflicting results in numerous studies. Madsen and Graff [53] reported no reduction in the gastric emptying rate of healthy elderly individuals using a gamma camera. However, Shimamoto et al [54] reported that postprandial peristalsis and gastric contractile force is significantly decreased with advanced age, and these reductions are more remarkable in inactive elderly persons. The decreased blood pressure following food intake, known as postprandial hypotension, can develop in elderly individuals and frequently occurs in the morning, but it is asymptomatic in many cases.

Gastric acid secretion is the first line of defense against pathogens in ingested food, liquid, and air. Earlier studies indicated that gastric acid production was significantly decreased with aging. However, recent studies showed that gastric acid production remains within the normal range in many older patients without gastric atrophy [55,56]. Atrophic gastritis develops generally with aging and the prevalence of atrophic gastritis is up to 50% in patients above 60 years of age [57]. Atrophic changes of gastric mucosa are related to Helicobacter pylori infection, and not age per se [58]. Gastric mucosa proliferation by H. pylori increases with aging, but the proliferated mucosa is increasingly susceptible to injury. As a result of atrophic changes, the decline in gastric acid secretion induces small intestinal bacterial overgrowth (SIBO) and malabsorption in the elderly. These changes interfere with the absorption of calcium, ferric iron, and vitamin B12.

4. Small intestine

Many studies reported no age-related structural changes in the small intestine, such as surface area, crypt depth, villous height, enterocytes, and brush border. The Brunner’s gland in the duodenum, which produces an alkaline secretion providing the pH conditions for the activity of pancreatic enzyme, is decreased with aging, which affects the drug solubility by altering the luminal pH [59]. The regeneration of small intestinal epithelium characterized by rapid turnover is compromised with aging, but the mucosal barrier function and permeability are not changed in the elderly compared with young individuals. The numbers and density of enteric neurons, which control GI motility and secretion of digestive enzymes, are markedly decreased in the aging small intestine. However, aging per se has no significant effect on the function of the GI tract [60]. Dysmotility of the GI tract seen in the elderly is affected by various drugs, including anticholinergics, calcium antagonists, opioids, and antidepressants, along with co-existing diseases.

There are no meaningful differences in hormone secretion and absorption function of the small intestine in the elderly compared with young people. The effect of aging on lipid absorption is still undefined. Although one study showed no association between age and 72-hour fecal fat excretion, other studies reported increased time of fat absorption and reduced levels of post-prandial bile acids in the elderly [61]. Especially, increased time of fat absorption causes post-prandial satiety in the elderly, leading to a decline in overall ingestion. SIBO commonly seen in the elderly is mainly induced by achlorhydria and small bowel dysmotility [62]. SIBO, which is characterized by symptoms of nausea, vomiting, and chronic diarrhea, leads to weight loss, malabsorption, and secondary nutritional deficiencies involving vitamin D, vitamin B12, and minerals. However, the levels of folic acid, niacin, thiamine, and vitamin K usually remain in the normal range in old individuals with SIBO.

5. Large intestine

The morphological changes in the large intestine involving the enteric nervous system (ENS) and smooth muscle are a natural result of the aging process [63]. It is unclear whether age itself negatively affects GI motility and colonic transit time.
in old individuals. While Metcalf et al [64] showed that age per se did not affect colonic transit time, Madsen and Graff [53] recently reported a prolonged transit time due to decreased propulsive capacity in the colon in elderly subjects above 80 years of age. If some degree of dysmotility in the colon is present, it may be associated with a remarkable decrease in neurons and receptors of the ENS, especially cholinergic type receptors, a decrease in smooth muscle contraction, and a decline in the level of neurotransmitters following reduced NO synthase levels in immunoreactive cells and neurons in the colon [65,66]. These age-related changes in the colon may contribute to inefficient peristalsis, resulting in an increased colonic transit time and constipation.

The prevalence of constipation is increased by 30% to 50% in elderly individuals and more than 50% to 70% of elderly nursing home residents compared to 2% to 28% in the general population [67]. Constipation is more common in older women and those belonging to lower socioeconomic status. Moreover, constipation is substantially influenced by various factors, including a decrease in mobility, cognitive impairment, comorbid medical diseases, intake of several medications such as opioids and anticholinergics, and dietary changes, rather than age-related dysmotility. The age-related anorectal physiological changes, including increased rectal compliance, impaired rectal sense, and impaired defecation, are associated with inefficient interaction between pelvic floor muscles and evacuation mechanism, leading to anorectal constipation. Chronic constipation may cause a significant increase in fecal incontinence ranging between 3.7% and 27% with aging.

The human gut microbiota play a key role in maintaining the integrity of mucosal barrier, protection against pathogens, and supply of nutrients such as vitamins to facilitate nutrient absorption, and regulate the immune system. The predominant bacterial phyla in the human gut are Firmicutes and Bacteroidetes, and the balance between these 2 phyla contributes to maintenance of gut immune homeostasis. Although the human gut microbiota is relatively stable during adult life, the composition of microbiota is modified with aging. The relative ratio of Firmicutes to Bacterioidetes in the elderly is significantly increased, and accompanied by enhanced levels of facultative anaerobes [68]. In addition, the number and species diversity of Bifidobacteria in elderly individuals are decreased, with a reduction of lactobacilli [69]. These changes in the human gut microbiota induce the release of pro-inflammatory cytokines such as interleukins 6 and 17, which result in systemic inflammation. The initiation of a systemic host inflammatory response is a significant feature of early pathogenesis and results in low-grade inflammation, known as inflammaging.

### Hepatobiliary System

The liver, which detoxifies various metabolites, synthesizes proteins and biochemical products for digestion, carries a dual blood supply and abundant reserves, and exhibits resilience, such that the overall function is relatively well conserved in healthy elderly individuals. Hepatic blood flow is generally decreased by 35% to 50% in older individuals, which is related to a reduction of hepatic volume by 20% to 40% [70]. Liver weight is decreased by 6.5% in men and 14.3% in women. The hepatocyte size and the binuclear hepatocyte index are increased, and the area of the smooth endoplasmic reticulum and activity of microsomal enzymes decrease. With aging, the number of mitochondria per hepatocyte decreases but the volume of mitochondria in hepatocyte increases. The accumulation of dense bodies, known as lipofuscin, within hepatocytes leads to characteristic changes known as brown atrophy in the aging liver, which are related to oxidative stress and failure to degrade damaged proteins [71]. Kupffer cells, which play an important role in the handling of antigen-antibody complexes, endotoxins, and tumor cells, show a reduced phagocytic function with aging despite an increase in the number and activation level [72]. These age-related alterations may significantly influence the liver morphology, physiology, and ability to protect against oxidative stress.

Laboratory tests of liver function, including albumin, aminotransferase, international normalized ratio, and high-density lipoproteins, remain within normal range in the healthy elderly. However, the synthesis of low-density lipoproteins is diminished and bilirubin levels may be gradually reduced due to decline of muscle mass and hemoglobin concentrations. The drug metabolism in the liver is composed of Phase I via microsomal oxidation and Phase II via conjugation. First-pass hepatic uptake (Phase I) of drugs is mediated by enzymes of the cytochrome P450 in the smooth endoplasmic reticulum. The concentrations of P450 enzymes in the hepatocyte are gradually reduced with aging, leading to low Phase I metabolism in old individuals [73]. Besides, the decreased hepatic blood flow and liver volume with age adversely affects drug metabolism by decreasing Phase I hepatic metabolism. Consequently, these changes in the elderly may result in decreased clearance of certain types of drugs and increased susceptibility to drug-induced injury. With aging, the capacity of liver regeneration is diminished due to the reduced concentrations of circulating epidermal growth factor (EGF) accompanied by decreased responsiveness of hepatocytes to EGF via age-related decline in EGF receptors [74]. Because the bile duct gradually dilates with aging due to the increase in connective tissue, a study suggested that the normal upper limit of the bile duct in the elderly should be set to 8.5 mm [75]. In addition, lithogenicity of bile salts in the elderly increases
steadily, which increases the risk of gallstone prevalence. As a result, the incidence of gallstones and gallstone-related complications increase significantly with aging.

**Conclusion**

The elderly population experiences a normal age-related decline of physiological function in all major organ systems. These changes may result in decreased physiological reserve, but may not be remarkable in the resting state because of the use of less physiological reserves to maintain homeostasis. However, when older adults face physiological stress such as major surgery or acute illness, the reduced physiological reserves are inadequate to maintain normal homeostasis. As a result, the overall physiological function in the elderly may gradually deteriorate, leading to organ failure or death. In many studies, elderly patients exhibit significantly higher mortality rates compared with younger patients, and advanced age is a significant and independent risk factor in perioperative and ICU mortality. Thus, surgeons should understand normal age-related changes in physiology, and perform preoperative assessment of organ function with careful postoperative monitoring.

**Conflicts of Interest**

The author has no conflicts of interest to declare.

**References**
