Aging and the Cardiovascular System

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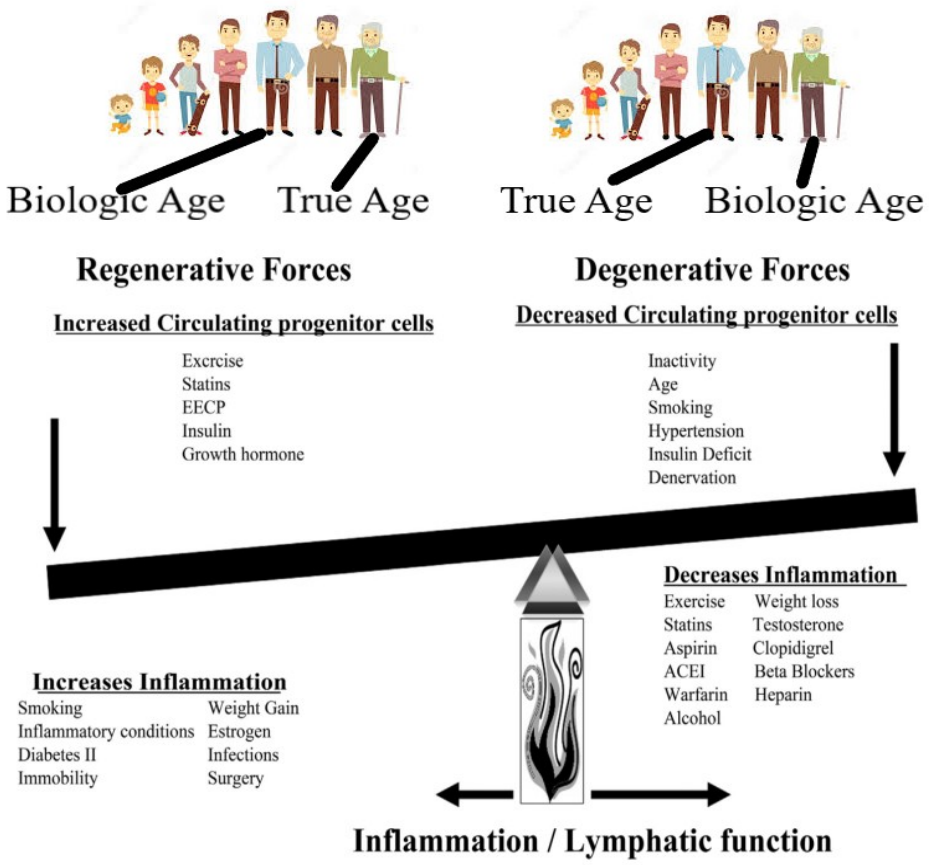

Biology must be consistent with the fundamental laws of physics and chemistry.
Life, as opposed to non-living, exhibits negative entropy, developing order out of chaos. (The energy to support negative entropy is yet to be defined.)
The cell is the fundamental unit of biology
The cell must be in homeostasis with its environment. (This property allows evolution. The environment changes life.)
There must be a distinction between self and the environment. (Immunity and inflammation are defenses against invaders from the environment *and are responsible for repair of damaged and senile cells*.)
Electromagnetic information transfer is necessary for development and regeneration. (Life, with regeneration of tissue, cannot exist in a non-electromagnetic environment, hence denervation)

Abstract

The effect of aging on the cardiovascular performance parameters—preload, afterload, contractility, compliance, geometry and synchronization, neuroendocrine function, blood vessel properties, and lymphatic function—are examined in the context of a model of health and disease framed by 6 fundamental laws of biology. The maladies of the aged include falls, fractures, subdural hematomas, fatigue, exertional shortness of breath, dizziness with standing, orthopnea, edema, myocardial infarctions, strokes, and dementia. These maladies can be related to aging of the cardiovascular system. The aging of the cardiovascular system increases biologic age, shortening survival. Comorbidities further shorten survival. The cardiac performance parameters are examined for problems, consequences, and solutions. Risk factors should be replaced by a more understandable concept, biologic age. How many years is a patient likely to survive? How many years might a patient gain if comorbidities are controlled?

Aging and the Cardiovascular System

Central and Peripheral Cardiovascular Performance Parameters

The cardiovascular system can be described by central and peripheral performance parameters, with the central parameters directly applicable to the heart itself. The central performance parameters include contractility (a systolic measure), compliance (a diastolic measure), preload (the stretch of the myocardial fibers due to filling pressure), and afterload (the resistance to flow represented primarily by the size of the arterioles). The geometry of the heart and the synchrony of the heart's conduction system are also central parameters that can alter performance significantly, by causing mitral regurgitation and loss of ejection efficiency.

The normal heart can accommodate a large range of pumping functions, from low blood pressure and low cardiac output during sleep to high blood pressure and high cardiac output during prolonged and extreme exercise. This range of performance is remarkable, accommodating changes in the body's needs through alterations in heart rate as well as venous and arterial tone. Such adaptations occur almost instantaneously. On an intermediate time scale, the body's homeostatic mechanisms adjust the volume of blood that the heart pumps. These mechanisms include the renal system, lymphatic immune system, blood vessel properties, neuroendocrine system, autonomic nervous system, musculoskeletal system, hematopoietic system, respiratory system, and endocrine system—indeed all major organ systems and regulators of homeostasis. The intermediate compensations provided by these homeostatic mechanisms may take hours, days, or even months to adjust for a failing heart. Compensation on the longest time scale, from months to years, includes other processes that remodel the heart's structure. Those mechanisms include cellular repair, hypertrophy, and fibrosis. The remodeling

can be either positive or negative, allowing patient improvement or steady decline. Thus, compensation in heart failure utilizes multiple peripheral mechanisms and varying time scales to help the structurally failing heart. Yet although the peripheral performance mechanisms can compensate for a failing heart, they can also favor decompensation due to comorbidities. The major comorbidities include renal insufficiency, arrhythmia and conduction deficits, pulmonary hypertension, anemia, obstructive sleep apnea, infection, inflammation, lymphatic dysfunction, edema, ischemic heart disease, ischemic mitral regurgitation, and Type II diabetes.

The peripheral performance parameters include the neuroendocrine system, properties of blood vessels, and the lymphatic immune system. The effect of age on the central and peripheral performance parameters of the cardiovascular system can explain common maladies of aging.

Is Aging a Natural Process or a Disease?

Everyone ages. Biologic age, however, is different from chronological age. Disease processes, inheritable risks, and environmental exposure all contribute to biologic age. To understand biologic age, we need a model of health and disease like that shown in Figure 1, as well as certain fundamental laws of biology.[1,2]

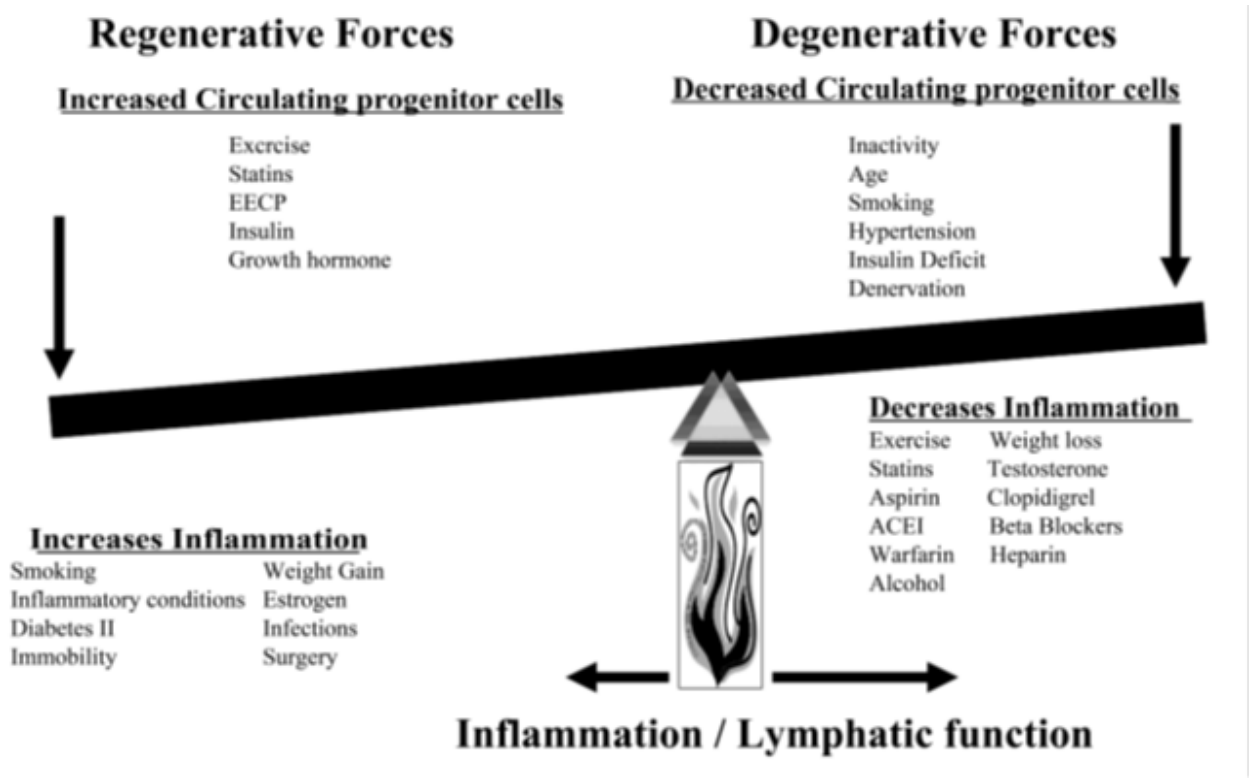

Figure 1. Model of Health and Disease. (Reprinted with permission.[1])

The model in Figure 1 suggests the relationship between health and disease. Within the model, circulating stem cells represent regenerative and degenerative forces. These forces can be modified by the lever representing the immune system, which moves as we age. Before birth, the immune system leans toward tissue repair. A fetal mouse heart's apex can be amputated yet will grow back. A cleft lip can be repaired in utero with no residual scar. After birth, such repair is replaced by fibrosis, so that healing becomes incomplete, with functional status returned quickly.[3] Survival is thus improved at the cost of decline in functional status due to incomplete repair with age.

As we age, the number of circulating stem cells decreases, resulting in less rejuvenation or regeneration and more degeneration. As the number of risk factors for cardiovascular disease increases, the number of circulating stem cells also decreases. Risk factors thus increase biologic age. Exercise, statins, and good health can decrease biologic age by increasing the availability of

stem cells, which reproduce or differentiate into various cell lines. Blood cells, for example, which have a short lifespan, are produced by stem cells, and myelodysplastic syndrome results when stem cells fail to replace blood cells. If blood cells are not replaced, any organ can be affected. Some cells live longer than blood cells; for those cells, a lack of repair is more subtle. Endothelial cells live 25 years. But if the endothelial lining of blood vessels is not replaced, the vessels become thrombogenic, resulting in heart attacks and strokes.[4-12]

The fundamental laws in Table 1 determine biologic age.

Table 1. Fundamental Laws of Biology[2]

1	Biology must be consistent with fundamental laws of physics and chemistry.
2	Life, as opposed to non-living, exhibits negative entropy, developing order out of chaos. (The energy to support negative entropy is yet to be defined.)
3	The cell is the fundamental unit of biology.
4	The cell must be in homeostasis with its environment. (This property allows evolution. The environment changes life.)
5	There must be a distinction between self and the environment. (Immunity and inflammation are defenses against invaders from the environment *and are responsible for repair of damaged and senile cells*.)
6	Electromagnetic information transfer is necessary for development and regeneration. (Life, with regeneration of tissue, cannot exist in a non-electromagnetic environment, hence denervation.)

Life, as opposed to non-living, exhibits negative entropy, developing order out of chaos. (The energy to support negative entropy is yet to be defined.)

Energy is required to maintain order. Innate objects degrade with time, but life is an exception that becomes more orderly, with two cells initially becoming one. These cells take energy from the environment and organize substrates into the growth and development of a human being. Yet this energy eventually depletes, and the organization is replaced by disorganization. Failure to repair repeated injuries (a lack of protein folding) increases entropy and biologic age. Law 2 thus represents entropy, which, simply stated, represents a mathematics

of disorder. Maximum entropy in life occurs when the body dies and has the same temperature as that of the room around it.

Entropy is a major force promoting age. It can be used to model why there are more old women than old men. Men have 46 chromosomes. Women have 45, with 2 Xs instead of an X and Y. Due to this extra chromosome complexity, men have greater entropy and reach room temperature 3.5 years sooner than women.[13]

The concept of negative entropy was introduced by Erwin Schrödinger in the form of a statistical equation; the equation is temperature dependent, but not time dependent:

Negative entropy = Boltzmann's constant times the log of (1/statistical disorder).

The implication of this equation is that lower body temperature correlates with younger biologic age and greater longevity.[14] The equation is also process dependent, accounting for all possibilities of each next step in human development. To ensure that each next step is a biologic success, carrier proteins and other methods ensure that biologic energy favors a success over a mistake. As we age, mistakes occur, causing failures. Medicines that promote low or negative entropy can prolong life. Unhealthy lifestyles, genetics, and injuries promote greater entropy and shorten biologic age.[15]

The microbiome, the largest contributor to entropy, is a strong determinant of biologic age. The sheer number and variety of microbes within the microbiome add complexity to an organism, increasing entropy. Altering one's environment by changes in diet and location (neighborhood) alter the microbiome's makeup. Just as parents contribute biologic age to offspring by means of genetic information, they also contribute to the microbiome in the form of vaginal flora, type of food consumed, and the neighborhood in which they chose to live. The microbiome's role has not been fully evaluated, but it influences 5 of the 6 laws of biology: the

microbiome competes with the fundamental unit of biology, the cell. The microbiome determines inflammatory response. Messenger RNA and other proteins produced by the microbiome can alter the communication and electromagnetic communication between the body's cells.

The cell is the fundamental unit of biology

The cells in the human body, beginning with the union of two cells, contain the information to build, protect, and maintain a human being. Each cell contains 45 or 46 chromosomes, smaller cell-like structures, the mitochondria, and the machinery to produce 2 million different proteins. Cells produce surface receptors, proteins, and connections to the nervous system and circulatory system. Each cell is designed to share information with the 50 trillion cells that make up the human body.

The programming of the cell is critical to meet the demands of the fundamental laws of biology. Processes are in place to promote negative entropy, fight invaders from the environment, and communicate with all the cells. When programming is faulty, biologic life is shortened. It can be shortened by degeneration or unchecked proliferation (cancer). Both processes can be modified and enhanced by the immune system.

The cell must be in homeostasis with its environment. (This property allows evolution. The environment changes life.)

In chaos, there is also creation. Chaos can be introduced by viral manipulation of DNA, changes in toxicity or radiation, or simply entropy, which encourages mutations and mistakes. Sometimes such mistakes provide an advantage for survival in a changing environment, as Darwin's theory of evolution suggests. The environment includes the foods that we eat, the air that we breathe, and the activities that we perform.

Type II diabetes, formerly called adult-onset diabetes, represents a response to environmental changes—to decreased physical activity and increased consumption of carbohydrates. Homeostasis in this changed environment of less activity and increased carbohydrates can result in increased blood sugar, hypertension from sodium, and fluid retention. Insulin excess increases obesity in the abdomen as well as inflammation, and lipids infiltrate blood vessels, raising blood pressure. Although Type I diabetes was diagnosed by the ancient Egyptians thousands of years ago, the modern prevalence of Type II diabetes suggests that it may reflect environmental changes[1] such as those in modern agriculture, with its production of complex plants that interact with the microbiome to cause increased inflammation. Other diseases have come and gone with environmental changes, such as rheumatic fever, and there will be new diseases as the environment continues to change. These environmental changes shorten biologic age.

There must be a distinction between self and the environment. (Immunity and inflammation are defenses against invaders from the environment and are responsible for repair of damaged and senile cells)

Law 5, the fulcrum in the model of health and disease, plays a major role in all disease processes. Our immune system consists of innate, adaptive systems that protect us from the microbiome, which includes bacteria, parasites, fungi, and viruses. Within the microbiome, viruses are the most numerous, so viruses have the greatest ability to increase entropy. For every one of the human being's 50 trillion cells, the bacteriome has 10 bacteria; but viruses inhabit both the bacteria and human cells, so viruses are even more numerous. Their ability to modify disease is even higher than that of bacteria.

Aging increases exposure to viruses, which often lie dormant in cells but play havoc through resurgence, as in the case of shingles. Antigens produced by a virus can confuse the immune system, promoting autoimmunity—another disease that increases with age. Incorporating DNA from other organisms and viral genomes into human DNA could lead to intelligence and evolution toward a more intellectual society. The recent rise of the Zika virus shows that evolution could also direct us backward, as we lose intellectual ability.

Recently, the CANTOS trial has shown that modifications in the immune system can prevent myocardial infarctions.[16] The immune system also provides an advantage in young women as opposed to men in myocardial infarctions.[13] Cyclic changes in estrogen shift the female immune system toward vascular repair from vascular injury.

Electromagnetic information transfer is necessary for development and regeneration. (Life, with regeneration of tissue, cannot exist in a non-electromagnetic environment, hence denervation.)

This law is the least understood. Invisible electromagnetic forces transfer information that changes cells' surface proteins and protein receptors. Electromagnetic mechanisms have not been studied; they represent a gap in traditional biological research. The neural tube directs cell differentiation. The autonomic and central nervous systems serve as an information highway that maintains homeostasis. For tissue repair, nerve viability is necessary. Damage to nerves withers the parts of the body that the nerves supply. Thus if the stem cells may be thought of as bricks, the nerves represent bricklayers. To regenerate organs, artificial electromagnetic signals must indicate the placement of stem cells when nerves are no longer viable.

The central nervous system modifies information flow throughout the body. Thus it modifies hormonal response and the immune system, and it alters homeostasis such that fluid electrolytes and fat are inappropriate for health. The diseases of obesity, diabetes, and

hypertension are of central origin, along with reactions to the changing environment. Allostasis is centrally mediated. It provides the drive to acquire calories in anticipation of future starvation. In today's environment, allostasis is the primary driver of obesity.

In summary, the fundamental laws of biology interact in explaining age-related disease processes. As people age, the model of health and disease implicates degeneration—a lack of circulating stem cells, with inflammation, chaos, imbalance with the environment, and a failure of information transfer.

Effect of Aging on Cardiovascular Performance Parameters

The cardiovascular performance parameters, both central and peripheral, and the model of health and disease can help us understand the cardiovascular effects of aging. The parameters are not independent of each other. Preload, afterload, properties of blood vessels, and the neuroendocrine system are all related. Properties of blood vessels and left ventricular compliance are related. The parameters can provide an understanding of concepts that intertwine with each other and with the laws of biology to produce a disease state. *Preload*, the stretch of the myocardium, can change rapidly under autonomic nervous control to maintain filling of the heart when one stands from a sitting position. In heart failure, preload elevation causes dyspnea and swollen legs. Lowered preload makes patients feel better, but the strategy of lowering preload in heart failure has demonstrated increased mortality with loop diuretics and no mortality benefit of ultrafiltration.[17-19] If preload is very low, cardiac output falls, with ventilation–perfusion (V/Q) mismatches in the lung. This condition is also manifested with shortness of breath. Patients also experience hypotension when preload is insufficient to stretch myocardial cells.

Afterload, the size of the arteries, is under autonomic control and changes rapidly. Some medications can cause significant vasodilation with rapid decline in blood pressure. Afterload

reduction, the mainstay in heart failure treatment, has a mortality benefit. However, preload and afterload are interdependent. When afterload is reduced, the arteries become larger, stealing fluid from preload. If preload is low, lowering the afterload results in hypotension. This is one reason why furosemide increases mortality in heart failure.

Compliance is a diastolic function. Compliance can be visualized by a thick-walled or thin-walled balloon. A thin-walled balloon is very compliant and is easily blown up, whereas it takes more pressure to blow up a thick balloon. Ventricles become stiffer with ischemia, buildup of calcium during diastole, scar, and wall thickening from hypertension or infiltrative disease of the heart. This is the cause of diastolic heart failure. All systolic heart failure patients have diastolic dysfunction. Fifty percent of heart failure admissions present with preserved ejection fraction, representing diastolic heart failure.

Contractility is the squeezing, energy-requiring step that propels the blood from the apex of the heart out through the aortic valve. Individual cell contractility can be affected by the stretch of the cells and by inherited or acquired metabolic derangements. Global contractility can be altered by myocardial infarction, fibrosis, and electromechanical coupling.

Geometry and synchronization constitute a central parameter that determines the efficiency of contraction. If the heart dilates and remodels itself into a sphere, the mitral annulus dilates, and mitral leaflets no longer have proper coaptation, with resultant mitral regurgitation. This condition can further volume load the ventricle with more dilatation and more mitral regurgitation. The conduction system is responsible for coordinated symmetrical contraction. If the left bundle fails, the heart now performs like a V8 engine with two sparkplugs removed. Mitral regurgitation, along with paradoxical septal motion, is the result.

Neuroendocrine function is a peripheral parameter that involves nerves, hormones, electrolytes, and other signaling mechanisms that maintain homeostasis. These factors overlap preload and afterload. Most heart failure medications are directed to altering such pathways. If we indeed evolved from the ocean with its water and salt, our kidneys and neurohormones had to evolve to balance water and salt. When a bleeding event stimulates a vagal response lowering heart rate and blood pressure, decreased flow to the kidney elevates the salt- and water-conserving hormones renin, angiotensin, and aldosterone. In heart failure patients, these hormones are activated because the kidney sees low blood flow.

Properties of the blood vessels can be measured by their stiffness and vasodilator reactivity to ischemia. Environmental food and salt intake influence the properties of the blood vessels. In infants, the vessels are soft, distensible, and free of fat, lipids, inflammatory cells, and calcium. With excess availability of calories and salt, the blood vessels become infiltrated with fat, lipid, inflammatory cells, and calcium. As a result, the vessels become stiffer and less distensible. Salt loading leads to volume excess, putting more volume in the vessels and raising blood pressure. Stiffer blood vessels raise blood pressure, which explain why 9 out of 10 individuals eventually become hypertensive in our modern environment.

The *lymphatic vascular system* is ignored in current treatments of heart failure. But the lymphatic system is responsible for compensating a dysfunctional heart and repairing damaged tissues. Despite its ability to transport 12 liters of fluid per day, transport stem cells to sites of injury, and modify the immune system, the lymphatic system is not considered in congestive heart failure. This system is responsible for the most common symptoms of heart failure, edema and dyspnea. Lymphatic function has a prominent role in most comorbidities that are responsible for cardiac mortality, including cardiorenal syndrome, infection, and inflammation.

The lymphangion is a small pump with valves and cardiac cells that operates in an open vascular system communicating from the lungs, gastrointestinal tract, and skin. It propels lymph from tissues to the thoracic duct, so that interstitial fluid is reintroduced into central closed circulation. *Lymphangiotropy* describes the pumping function of the lymphangion in terms of amplitude and frequency. No systematic classification of drugs assigns positive or negative lymphangiotropy to drugs' effects. Strategies to enhance lymphangiotropy should improve the quality of life by mobilizing interstitial fluid. A paper by Houck[20] from 2013 outlines this strategy. Milrinone, dobutamine, neseritide and digoxin given for decompensated heart failure show positive lymphangiotropy. Other agents, such as calcium channel blockers and Pioglitizon, have shown negative lymphangiotropy and can cause worsening symptoms of heart failure.

Tables 1 and 2 list therapeutic options that alter central and peripheral parameters along with the absolute mortality benefit or harm of those interventions.

Table 1. Central Acting Cardiac Performance Parameters

Cardiac Performance Parameter	Therapeutic Options to Improve Heart Failure	Absolute Mortality Benefit or Harm (-)	Reference no.
Preload	Diuretics	-8%	17
	Nitrates	Unknown	
	Ultra-filtration	-8%	18,19
	Adaptive servo-ventilation CPAP	-3.3%	21
	Tolvaptan	0%	22
	Nesiritide	0%	23
Afterload	Hydralazine/Nitrate	4.2%	24,25
	ACEI/ARB	1.3%	26
	Nesiritide	0%	23
	Valsartan/Sacubitril	3.2% Over ABS	27
	Adaptive servo-ventilation CPAP	-3.3%	21
Compliance	Nesiritide	0%	23
	Valsartan/Sacubitril	3.2% Over ABS	27
	Ranexa	3.2% Unknown	28
	Spironolactone	5.5%	26,29
Contractility	Nesiritide	0%	23
	Valsartan/Sacubitril	3.2% Over ABS	27
	Ranexa	Unknown	28
	Spironolactone	5.5%	26,29
Geometry and synchrony	Bi-V pacing	4.1%	30
	Surgery CABG	5.0%	31
	Surgery MVR	10%	32

Source [53]

Table 2. Peripheral Acting Performance Parameters

Cardiac Performance Parameter	Therapeutic Options to Improve Heart Failure	Absolute Mortality Benefit or Harm (-)	Reference no.
Neuroendocrine	ACEI/ARB	1.3%	26
	Spironolactone	5.5% Over A, B	26,29
	Beta Blockers	3.6% Over A	26
	Nesiritide	0% Short-term	23
	Valsartan/Sacubitril	3.2% Over B, S	27
Properties of blood vessels	Spironolactone	5.5% Over A, B	26,29
	Nesiritide	0% Short-term	23
	Valsartan/Sacubitril	3.2% Over B, S	27
	Calorie restriction	Data limited	33
Lymphatic function, inflammation	Sympathomimetics	-1.5%	34
	Phosphodiesterase I	-1.5%	34
	Digoxin	0%	35
	Nesiritide	0%	23
	Valsartan/Sacubitril	3.2% Over B, S	27
	Lymphedema boots	Unknown	

Note: A = ACEI/ARB; B = beta blockers; S = Spironolactone; I = inhibitors. Source [53]

Preload

Problem: Dysregulation of preload disrupts the heart's ability to maintain volume status. Standing up causes a rush of blood to the veins along with a failure to increase the heart rate, resulting in a dramatic decrease in cardiac output. Bradycardia, a reflex that allows better filling of the heart, responds to small cardiac volumes. Dysregulated preload reduces blood flow to the brain and shuts down central nervous system .function, resulting in unconsciousness. Drugs can depress autonomic function, inducing orthostasis. Additional aggravating factors include causes of dehydration. Dysregulation is a failure of the autonomic system governed by Law 6, electromagnetic information transfer.

Examples of preload dysregulation:

1. Orthostasis of the aged: The autonomic system runs slow, so adjustment of preload takes 30 seconds. The patient experiences transient light headedness. If persistent, symptoms can progress to syncope.

2. Dehydration: The aged may lack proper thirst, or have diuretics prescribed for hypertension or heart failure.

3. Prolonged bed rest: During hospitalizations or at home from illness or depression, bed rest blunts the nervous response.

4. Parkinson's disease and other illnesses that disrupt autonomic function.

5. Medications: Beta blockers blunt reflex rise in heart rate. Anticholinergics, anti-depressants, dementia medications, nitroglycerin contribute to othostactic hypotension. A review of medications in patients presenting with syncope or a fall is beneficial for determining a cause. Polypharmacy is common in the aged.

6. Treating chronic venous insufficiency with diuretics always results in a reduction of preload before edema decreases.

Consequences: Lightheadedness, frank syncope and collapse, hip fractures, subdural hematomas, and frequent falls should all be investigated for orthostatic hypotension.

Solutions:

1. Discontinue the offending medication.

2. Exercise to increase circulating stem cells, improve muscular condition and autonomic dysfunction.

3. Before standing, march in place to raise heart rate, clench fists to increase systemic vascular resistance to maintain blood pressure.

4. Raise the head of the bed 4 inches to keep the veins full while sleeping. If the veins are full due to gravity; there will be no rush of blood when one stands up at night to go to the bathroom.

5. Compression stockings that are impossible for the aged to put on without assistance can decrease the rush of blood into the veins.

6. Midodrine and florinef, if a simpler solution cannot be found, and if there is no co-existing heart failure.

7. Increase the rate and responsiveness for pacemaker-dependent patients.

8. Spironolactone is more effective for chronic venous insufficiency than loop diuretics.

Afterload

Problem: Afterload, or vascular resistance, results primarily from the size of the arterioles and is regulated by sympathetic and parasympathetic innervation and by hormone receptors. These control mechanisms can be targeted with hypertension therapy. Compliance, one measure of blood vessel properties, is reduced in the aged due to fibrosis, infiltration by lipids, and inflammatory cells (see properties of blood vessels).

As vessels stiffen, the ability to rapidly change afterload fails. In advanced conditions, afterload is fixed (the vessels are stiff and calcified) and cannot change. Cardiac output is inversely related to afterload; therefore, cardiac output and stroke volume are fixed. The patient depends on heart rate to increase cardiac output. With higher systolic pressure and lower diastolic pressure, pulse pressure is increased. Low cardiac output and inability to rapidly raise cardiac output become a problem. In addition, coronary perfusion pressure falls. Patients experience low cardiac output syndrome with fatigability and presyncope with exercise. Since preload and afterload are interdependent, preload dysregulation is aggravated.

Examples of Afterload unresponsiveness:

1. Exertion intolerance.
2. Fatigue.
3. Intolerance of rate, slowing medications.
4. Systolic hypertension.
5. Inability to compensate during infections, anemia, and other high-output conditions.
6. Aggravation of orthostatic hypotension.

Consequences: intolerance of beta blockers, intolerance of exercise, hypertension difficult to treat, reduced coronary flow due to decreased diastolic blood pressure, greater preload dysregulation.

Solutions:

1. Avoid betablockers.
2. Consider pacing at higher heart rate.
3. Alter the properties of noncompliant vessels with spironolactone and other antifibrotic medications.
4. Exercise.

Compliance

Problem: The largest contributor to a stiff left ventricle is a stiff arterial system (see properties of blood vessels). Stroke volume distends compliant vessels during systolic ejection, and the elastic recoil of the arteries further increases flow during diastole. This recoil raises diastolic pressure by decreasing the volume of the arteries and further enhancing cardiac output. As we age, the vessels become less distensible, and arterial stiffness feeds back to the ventricle, increasing ventricular diastolic stiffness or ventricular arterial coupling. The ventricle is ejecting

into a thick balloon, which is essentially a fixed stiff conduit without any benefit of diastolic recoil. The energy for flow is distributed only in systole and is not spread through diastole. The left atrial pressure rises, stroke volume decreases, and diastolic heart failure ensues.

In restrictive cardiac disease, with the stiffest ventricles, the ventricle is already full at the beginning of diastole so that slowing the heart will not allow more filling. Fifty percent of those admitted with heart failure present with preserved ejection fraction heart failure, and all reduced systolic function heart failure has diastolic dysfunction. Other reasons for poor ventricular compliance include hypertrophy from hypertension or genetic predisposition, interstitial fibrosis, previous myocardial infarction, infiltrative disease such as amyloidosis, and hemochromatosis. Hypertrophy, infiltration of proteins, and progressive fibrosis increase as we age.

Examples of stiff left ventricle illness:

1. Diastolic heart failure.
2. Atrial fibrillation.
3. Pulmonary hypertension due to diastolic dysfunction.
4. Ischemic heart disease.
5. Ischemic cardiomyopathy.
6. Amyloidosis, hemochromatosis, endocardial fibrosis, interstitial fibrosis.
7. Low output syndromes.

Consequences: Shortness of breath, left heart failure, right heart failure due to left heart failure, renal failure with institution of diuretics. With too much preload, the patient is in heart failure. Diuretics cause too little preload, with reduction of cardiac output and resultant renal failure.

Solutions:

1. Spironolactone.

2. Ranolazine.

3. Brain naturetic peptide (BNP) neserritide, angiotensin receptor blocker/neprolysin inhibitor (ARB/NI).

4. Increase the heart rate to empty the already full ventricle.

5. Regress left ventricular hypertrophy with better blood pressure control, treatment of sleep apnea, chelation of iron.

Contractility

Problem: At rest, contractility is no different between an aged heart and a young heart. With exercise, the aged heart does not have the same increase in contractility that young heart cells do.[36] This difference is best explained by Law 6, electromagnetic signaling. Calcium is responsible for binding actin and myosin during systole, and removal of calcium during diastole is critical to allow the fibers to return to their zero position before the next systole. This pathway is impaired in the aged.

Examples of impaired increase in contractility with exercise:

1. Exercise intolerance.

2. Excessive sitting.

Consequences: Reduction in circulating stem cells with further failure of rejuvenation (degeneration), failure to replace endothelium with greater risk of heart attack and stroke.

Solutions:

1. Lifelong exercise.

2. Enhanced extra-corporeal counter pulsation.

Geometry and Synchronization

Problem: Myocardial infarction causes dilation of the heart. In inferior myocardial infarction, the posterior leaflet is tethered apically, causing an increase in mitral annular dilation and worsening regurgitation. Interventricular conduction defects slow conduction time with chamber dilation, again causing mitral regurgitation. Left bundle branch block causes dyssynchrony, with mitral regurgitation and loss of ejection efficiency increasing chamber dimensions. Valvular insufficiency from primary mitral and aortic disease due to degenerative valve disease with age increases chamber dimension. All these processes increase the size of the heart more frequently with age. The heart can also remodel into a smaller ventricle in the disease processes of amyloidosis and other infiltrative disease. Small hearts due to the thickening of the walls cause low output due to fixed cardiac output. Hypertension and aortic stenosis increase hypertrophy of the walls and are progressive as we age.

Examples of impaired geometry and synchronization:

1. LBBB, right ventricular pacing.
2. Dilated cardiomyopathy, ischemic cardiomyopathy, valvular insufficiency.
3. Hypertension, aortic stenosis, infiltrative diseases.
4. Cor pulmonale alters the geometry of the interventricular septum.

Consequences: Heart failure, mitral regurgitation, low output, syncope.

Solutions due to chamber dilation:

1. Bi-ventricular pacing.
2. Diuresis to shrink the heart.
3. Valvular repair or replacement.

Solutions due to chamber shrinkage:

1. Increase heart rate.

2. Avoid diuretics.

3. Treat underlying infiltrative disease.

Neuroendocrine Function

Problem: With age, the activity of the sympathetic and parasympathetic systems declines.[37] Kidney dysfunction and age-dependent decreased responsiveness of the renin angiotensin systems result in fluid and electrolyte abnormalities and further decline in kidney function.[38]

Examples of impaired neuroendocrine function:

1. Sinus node dysfunction, heart block, manifested as syncope and fatigue.

2. Salt and water retention, heart failure, edema, bowel edema, and abdominal pain.

3. Kidney dysfunction, anemia, increased inflammation.

Consequences: Kidney failure, proteinuria, coagulopathy, fluid retention, hypertension, anemia, systolic and diastolic heart failure.

Solutions:

1. Pacemaker dual chamber.

2. ACEI, ARB, beta blocker, aldosterone.

3. Erythropoietin.

4. Salt avoidance.

5. Exercise rebalancing the sympathetic parasympathetic system.

Properties of Blood Vessels

Problem: Environmental sources of lipid rich food and inflammation from the microbiome infiltrate blood vessels, making them stiffer. Decreased compliance makes the left ventricle less compliant, resulting in diastolic heart failure. This process allows atherosclerotic thrombotic plaque growth, which is the substrate of myocardial infarction and stroke. Men have more

myocardial infarctions than strokes, whereas women have more strokes than myocardial infarctions. This difference is not entirely understood, but it is likely secondary to higher female diastolic heart failure. On the venous side, the valves become incompetent over time with increased venous stasis hypertension,, causing venous insufficiency, blood clots, and pulmonary embolisms.

Examples of diseases associated with property of blood vessels:

1. Diastolic heart failure.
2. Myocardial infarction.
3. Stroke.
4. Claudication, peripheral vascular disease.
5. Hypertension.
6. Aneurysms, dissections, thrombosis of vessels.
7. Chronic venous insufficiency, deep vein thrombosis, pulmonary hypertension.

Consequences: Myocardial infarction, strokes, diastolic heart failure, dissections, and aneurysm.

Solutions:

1. Lifelong diet of fruits, vegetables, nuts, Mediterranean diet, reduction of calorie intake, low inflammatory diet.
2. Avoid salt in salt-sensitive individuals.
3. Exercise.
4. Statins, neuroendocrine blockade.
5. Compression stockings, anticoagulants.

Lymphatic Vascular System

Problem: As we age, the lymphangion has less amplitude and decreased frequency of contraction. Interstitial edema in the legs, bowels, and lungs is cleared more slowly, so that compensation for increased preload of heart failure is compromised. Older individuals thus have more heart failure. The immune system is further compromised, so older patients are more inflamed. Inflammation is an inhibitor of lymphangion, further promoting decompensation in volume-loaded conditions. The lymphatic system has undiscovered roles in disease processes, including cardiorenal syndrome, Takotsubo cardiomyopathy, troponin elevations in sepsis, shock, infections.

Examples of disease associated with lymphatic dysfunction:

1. Preserved ejection fraction heart failure.
2. Reduced ejection fraction heart failure.
3. Adult respiratory distress syndrome.
4. Peripheral edema.
5. Cardiorenal syndrome.
6. Inflammation-exacerbated heart failure.
7. The above disorders are more likely in the aged.

Consequences: More heart failure in the aged; comorbidities have greater symptoms with lymphatic dysfunction, shortness of breath, edema, renal failure.

Solutions:

1. Beta agonists, phosphodiesterase inhibitors, digoxin.
2. Avoid agents with negative lymphangiotrope, calcium channel blockers.
3. Mechanical stimulation with lymphedema boots.
4. Exercise.

Effect of Aging on Comorbidities

Comorbidities that increase with age include renal insufficiency, arrhythmia and conduction deficits, pulmonary hypertension, anemia, obstructive sleep apnea, infection, inflammation, lymphatic dysfunction, edema, ischemic heart disease, ischemic mitral regurgitation, and Type II diabetes. Table 3 lists comorbidities and absolute mortality. The higher the absolute mortality of the comorbidity, the lower the survival. Thus, these comorbidities can raise biologic age above true age. Renal insufficiency is the most common, with the highest mortality, followed by inflammatory conditions, coronary artery disease, and obstructive sleep apnea. Ventricular tachycardia and anemia have similar mortality, with anemia ignored for most patients.

Table 3. Comorbidities/Mortality: Heart Failure Cause/Solution

Comorbidity	Absolute Mortality, Harm (-)	Reference no.	Cause	Solution
Renal insufficiency (% decrease per mL/m of creatinine clearance)	-1%	39	Over diuresis	Stop diuresis
			Bladder obstruction	Bladder scan Urology consult
			Neurogenic	Straight catheterization
			Males, prostrate	Green light vaporization
			Females, pelvic floor	Straight catheterization
			Medications	Stop offending agent
			Decreased cardiac output	Increase cardiac output
			RV failure or restrictive LV	Increase heart rate
Arrhythmia conduction	-11%	40	Atrial fibrillation	Rate or rhythm control
	-19.4%	41	Ventricular Tachycardia	Treat CHF, anti-arrhythmic
			Bradycardia, heart block	Decrease blockers pacemaker
	-3.1%	42	LBBB/IVCD	Bi-V pacemaker/ defibrillator
Pulmonary hypertension	-25.6%	21,43,44	Obstructive sleep apnea	CPAP
			Lung Disease	Optimize medications,

				O_2
			Diastolic dysfunction	Medications, increase HR
			Valvular dysfunction	Valvular intervention
			Pericardial disease	Medications or intervention
Anemia	-17.3%	45	Iron deficiency	IV Iron therapy
			Inflammation	Colchicine
			Renal insufficiency	Erythropoietin therapy
			Myelodysplasia	Erythropoietin therapy
			Testosterone deficiency	Testosterone replacement
			Vitamin deficiencies	Vitamin supplement
Infection	-.8%	46	Flu, viral illness	Immunizations
			Bacterial illness	Immunizations
			Myocarditis Endocarditis	IVIG
Inflammation Hs-CRP	-32%	47	Abnormal immune response	Colchicine
Lymphatic dysfunction			Thoracic duct injury	Lymphedema boots
			Inhibiting medications	Discontinue offending agent
			Infection tissue injury	Treat and support
Edema	-6%	48	Dietary salt intake	Dietary management
			Inflammation	?
			Iatrogenic medications	Remove agents
			Lymphatic dysfunction	Lymphedema boots
Coronary disease	-28%	49	Recurrent myocardial infarction	Surgery Colchicine
Ischemic mitral regurgitation	-20%	50	Annular dilation, LV geometry	Surgery
Type II diabetes	-10.2%	51	Insulin excess Lack of exercise Excessive calories	Emplaglitizone Exercise Good nutrition

Source [53]

Table 4. Medication Use in a Variety of Elderly Conditions

Use of Beta Blocker in the Elderly

Myocardial infarction	**Orthostatic hypotension**	**Shortness of breath, atrial fib**	**Shortness of breath, NSR, normal EF**	**Shortness of breath, NSR, abnormal EF**	**Fatigue, stiff blood vessels**
Acutely to prevent ventricular fibrillation	Avoid	Attempt for rate control	Avoid	Attempt to titrate for systolic dysfunction	Avoid
Consider pindolol if bradycardia		If cor pulmonale, avoid beta blockers, calcium channel blockers; use digoxin	Consider ranolazine	Consider ranolazine	
If bradycardic,					

reasonable ejection fraction, consider discontinuing					

Use of Spironolactone in the Elderly

Myocardial infarction	**Orthostatic hypotension**	**Shortness of breath, atrial Fib**	**Shortness of Breath NSR normal EF**	**Shortness of Breath NSR Abnormal EF**	**Fatigue, stiff blood vessels**
Definite	May use if edema or hypertension	Definite	Definite	May if hypertensive or edema	Definite

Use of ACEI/ARB in the Elderly

Myocardial infarction	**Orthostatic hypotension**	**Shortness of breath, atrial fib**	**Shortness of breath, NSR, normal EF**	**Shortness of breath, NSR, abnormal EF**	**Fatigue, stiff blood vessels**
ARB	ARB if hypertensive	ARB if hypertensive	ARB if hypertensive	ARB ARB/ARNI	ARB

Use of Diuretics in the Elderly

Myocardial infarction	**Orthostatic hypotension**	**Shortness of breath, atrial fib**	**Shortness of breath, NSR, normal EF**	**Shortness of breath, NSR, abnormal EF**	**Fatigue, stiff blood vessels**
Only until volume overload is corrected and salt restriction is successful	Avoid	Only until volume overload is corrected and salt restriction is successful	Only as needed Difficult population, on the fence between renal insufficiency and volume overload	Only until volume overload is corrected and salt restriction is successful	Avoid

Classes of drugs that aggravate orthostatic hypotension include the following:

Antidepressants

- Tricyclics, monoamine oxidase inhibitors, marijuana.

Anticholinergics

- Drugs for the treatment of urinary incontinence, overactive bladder, COPD, Parkinson's disease, and gastrointestinal maladies, including the following commonly prescribed medications: atropine, belladonna alkaloids, benztropine mesylate, benadryl, clidinium, cyclopentolate, darifenacin, dicylomine, desoterodine, flavoxate, glycopyrrolate, homatropine hydrobromide, hyoscyamine, ipratropium, orphenadrine, oxybutynin, propantheline, scopolamine, methscopolamine, solifenacin, tiotropium, tolterodine, trihexyphenidyl, trospium.

Antipsychotic medications

- Chlorpromazine, clozapine, risperidone, thioridazine, quetiapine.

Unfortunately, these drugs are commonly prescribed in the elderly for common afflictions such as insomnia, dementia, Parkinson's disease, bladder dysfunction, and depression. Care must be used to assess the risk and benefit of these medications, and patients need to be monitored for side effects, especially when a new agent such as a diuretic is introduced.

Summary of Aging and the Cardiovascular System

The model of health and disease, with the 6 fundamental laws of biology, can be used to investigate aging and the cardiovascular system. By itself, the term *age* refers to chronological age, whereas *biologic age* implies survival potential. A rise in the number of traditional risk factors decreases the number of circulating stem cells, thus increasing biologic age. Injuries, genetic programming, failing to maintain low entropy, and comorbidities all decrease biologic age, contributing to decreased survival.

The effect on aging shown by the cardiac performance parameters demonstrates adverse cardiovascular effects. Falls are the most common effects, leading to high mortality from fractures and subdural hematomas. Falls commonly result from abnormal preload regulation but can also be due to medications and a non-compliant vascular system. Stiff blood vessels lead to the primary reason for admission to the hospital, heart failure both systolic and diastolic. Failure of circulating stem cells leaves blood vessels with denuded endothelium, the substrate for myocardial infarction and strokes. Age is the greatest risk factor for these maladies, but there is a sex differentiation in vascular disease complications. Women have more strokes than heart attacks, and men have more heart attacks than strokes. This is attributable to higher blood pressures in women.[52]

The lymphatic system is an underappreciated vascular system. It is responsible for all symptoms of heart failure, and, through inflammatory pathways, it may be an instigator in heart failure. Dysfunction of this system with age explains increased hospitalization of older individuals. It also explains the increased incidence of heart failure admissions associated with infections such as the flu.

Combating age-related changes in the cardiovascular system requires picking the right parents, lifelong exercise, nutritious diet, medications that reduce inflammation and increase circulating stem cells, and avoidance of injuries. Areas of future investigation should include both electromagnetic signaling and immune response in repair of damaged cells.

Future Considerations

Risk factors have been useful in identifying individuals with chance of future cardiovascular events. These factors are surrogates, however; generally, they do not have a direct link to thrombosis within blood vessels. The biologic markers of the number of circulating stem

cells and measures of arterial stiffness, body temperature, and possibly endothelial dysfunction would be better predictive of future events and biologic age. A study that records the age, sex, and the parameters presented here with follow-up of mortality could provide an estimate of biologic age. If this approach is successful, developing therapies to increase circulating stem cells, reduce arterial stiffness, and improve endothelial function can lower biologic age and improve survival.

It is time to replace risk factors with the more understandable concept of biologic age. For how many years will a patient likely survive? How many years may a patient gain if comorbidities are controlled? Table 3 provides coefficients for a biologic age predictor. A patient using a biologic age predictor can have a direct understanding of how using a CPAP device, controlling diabetes, or avoiding nephrotoxic agents can add years of survival. Calorie restriction lowers body temperature, decreasing biologic age.

Table 3 is of course related to heart failure patients, but it represents most hospital admissions. Studies that determine the absolute mortality of comorbidities can be applied to everyone. In the future, there will be an equation like the following:

> *Biologic age = function of* {*current age, number of circulating stem cells, body temperature, inflammatory state TH1/Th2 ratio, arterial stiffness, comorbidities of* (*kidney function, obstructive sleep apnea, pulmonary hypertension, anemia, coronary artery disease, Type II diabetes, arrhythmia*)*, genetic codes yet to be determined*}

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