

# The Morphology of the Aging Heart

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*With advancing age, the cardiovascular system undergoes subtle but progressive changes that result in altered function. The endocardium becomes thicker and opaque, left ventricular (LV) wall thickness increases and there is increased interstitial fibrosis in the myocardium. Although myocyte size increases, the number of myocytes decreases, as does the number of cells in the conduction system. The decrease in the filling rate of LV in early diastole is accompanied by a greater rate of filling in late diastole augmented by atrial contraction. Maximum achievable heart rate and ejection fraction (with exercise) decreases. All these changes make increasing age a significant independent risk factor for heart failure, the most common reason for hospitalisation in patients older than 65 years.*

**Key words:** aging, cardiovascular disease, myocardium, fibrosis, heart failure.

## Introduction

Worldwide, there is an ongoing increase in life expectancy and a major expansion in the population. This increase is even more rapid in the population older than 65 years of age. All the known risk factors for cardiovascular disease, as well as the frequency of their manifestations, increase with age. Cardiovascular diseases such as atherosclerosis, coronary artery disease, hypertension and chronic congestive heart failure reach epidemic proportions in the elderly, making it the leading cause of morbidity and mortality among this age group and a major focus of interest in geriatrics.

The cardiovascular system undergoes subtle but progressive changes with age. These alterations of cardiovascular structure result in progressively altered function with advancing age. A good appreciation of these changes (structural and functional) is therefore essential for a good understanding of clinical symptoms and signs, as well as for better targeted and successful therapeutic interventions.

These age-related changes involve both blood vessels and the heart. In the heart, the changes can be divided into those involving the myocardium (including the interstitium), the cardiac valves, the conduction system, the pericardium and the coronary arteries. In this paper,

we will concentrate on changes within the heart (Table).

## Morphological Changes

### Endocardium

The heart wall has three layers, the endocardium, myocardium and pericardium (outermost layer). The innermost endocardium, a single-cell layer of tissue lining the entire cardiovascular system, is the continuation of the intima of blood vessels. Its integrity—morphological and functional—is essential for a non-thrombotic surface. Ultrastructurally, the endocardium is comprised of a layer of endothelial cells, which has a basement membrane, a thin layer of collagen fibrils, occasional fibroblasts and smooth muscle cells, and a layer of elastic tissue (the internal elastic lamina).

With increasing age, the endocardium that is normally invisible to the naked eye becomes thicker and opaque in areas, a change that is most prominent in the left atrium and least prominent in the right ventricle (RV).<sup>1</sup> Endocardial plaques or friction lesions are found more commonly in the elderly. Left ventricular friction lesions are most commonly found in the posterior wall, “behind” the posterior mitral valve (MV) leaflet, and are associated with changes in MV function, including floppy mitral valves.<sup>2</sup>

## Myocardium

The myocardium is a mass of cardiac muscle fibres, with an interstitium comprised of collagen fibrils and blood vessels. In the ventricles, the muscle fibres are arranged in two to three layers while in the atria they are circumferentially and longitudinally arranged. Common age-related myocardial changes include an increase in thickness of the left ventricular (LV) wall,<sup>3</sup> left atrial muscle fibre hypertrophy, an increase in interstitial fibrous tissue,<sup>4</sup> and a decrease in the number of the myocytes, although the size of the remaining individual myocytes may increase. LV wall thickness has been shown to increase with age, in both males and females.<sup>3</sup>

Table

### Age-related Changes in the Heart

#### Structural Changes

##### Endocardium

Thicker and opaque  
Left ventricular frictional lesions

##### Myocardium

Increased left ventricular wall thickness  
Left atrial hypertrophy  
Decreased number of myocytes  
Increased size of myocytes  
Increased amyloid deposition

##### Pericardium

Increased fibrosis (“milk” patches)

##### Conduction system

Decreased number of cells in sinoatrial and atrioventricular nodes

#### Functional Changes

Decreased early diastolic filling rate

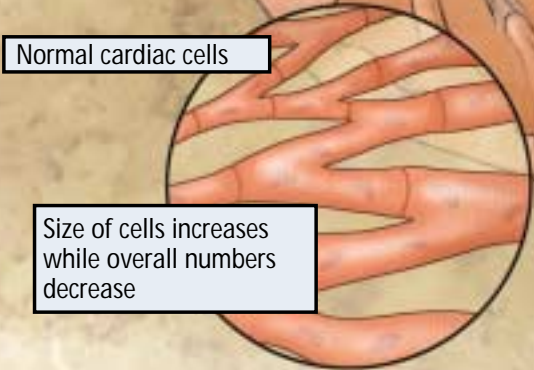
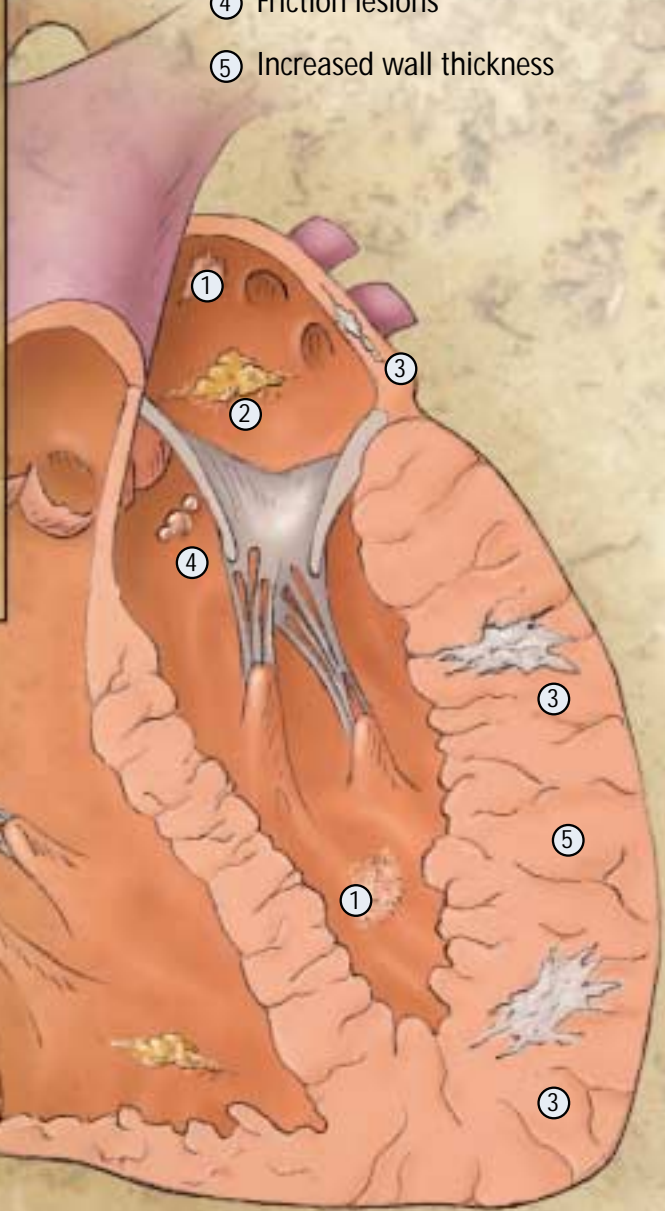
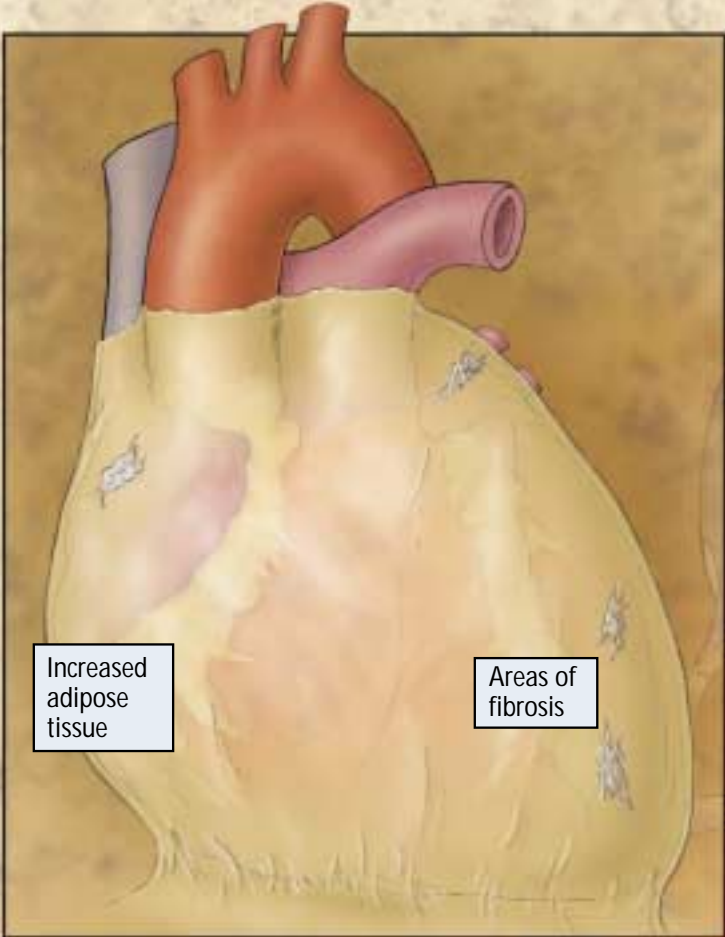
Rapid late diastolic filling

Decreased maximum achievable heart rate

Increased stroke volume

## Morphological Changes in the Aging Heart

- ① Endocardium thickened and opaque in areas
- ② Endocardial plaque
- ③ Fibrosis
- ④ Friction lesions
- ⑤ Increased wall thickness



## Morphology of the Aging Heart

Although it was earlier believed that left atrial dimensions increased with advancing age, a study by Thomas, *et al.* found no change in the maximum (end-systolic) atrial size with normal aging.<sup>5</sup> The reduction of myocytes is attributed mainly to increased necrosis and apoptosis in older hearts, with the decrease being more pronounced in males than in females.<sup>4</sup> In male hearts, the number of mononucleated cells progressively decreases with age while the number of binucleate cells increases in both ventricles. It has been suggested that binucleate cell number increases in pathological conditions.<sup>6</sup> This loss of myocytes results in a greater stress on the remaining muscle fibres, resulting in myocyte hypertrophy and increased interstitial fibrosis. Increased interstitial fibrosis is more pronounced in the atria (especially the left) than in the ventricles.<sup>7</sup> In addition, there is an increase in vascular load due to arterial stiffening that leads to enhanced myocyte size.<sup>8</sup> An apparent increase in interventricular septal thickness may be observed, mainly in the subaortic region, and must be differentiated from septal changes in hypertrophic cardiomyopathy. This age-related subaortic septal prominence is due to a change in the angle that the ascending aorta makes with the left ventricular outflow tract (LVOT), giving the septum a sigmoid shape. However, it is not known to have any clinical significance.

Ultrastructural studies show that myocyte degenerative changes, such as tubular dilation and lipid and lipofuscin deposition, do occur with age in all chambers of the heart.<sup>3,9</sup> Changes in the cellular and molecular mechanisms in the aging heart have been well studied in rodents, providing insight into changes in the aging human heart. There is a decrease in the rate of protein synthesis that delays the replacement of contractile proteins in myocytes and other proteins (or damaged mitochondria), resulting in a decrease in mitochondrial oxidative phosphorylation. Expression of cardiac genes is altered with advancing age, compromising the heart's ability to adapt to hemodynamic changes.<sup>5</sup> Changes in

gene expression that accompany aging affect various steps of the cardiac cycle excitation-contraction-coupling process in rodent hearts, resulting in prolonged action potentials (AP).<sup>10</sup>

Although the LV wall thickness increases slightly with age, the average size of the heart does not change.<sup>9,11</sup> There is an increase in the amount of fat, collagen and elastic tissue with increased foci of fibrosis throughout the heart, even in the absence of coronary artery disease. Increased interstitial and subepicardial fat is most common in the RV-free wall, especially in elderly females.

Amyloid deposition is increasingly seen in the aging heart, with 80% of people older than 80 years having detectable quantities of amyloid in the atria.<sup>1,9</sup> Amyloid dilated cardiomyopathy (DCM) is noted and occurs primarily in the elderly, usually with a restrictive pattern. Senile systemic cardiovascular amyloid is now known to contribute significantly to heart failure in people older than 85 years.<sup>12</sup>

### Pericardium

The most common change in the outermost pericardium is the presence of grey-white areas of fibrosis in the epicardium (the so-called "milk" or "soldier's" patches) of the RV and LV, as well as on the atrial appendages. Histologically, these are areas of fibrosis with mild, non-specific, chronic inflammatory infiltrates. There is an increase in subepicardial adipose tissue with advancing age that is most prominent on the anterior aspect of the RV and the atrioventricular grooves.<sup>13</sup> This fat frequently extends into the RV interstitium, occasionally into the endocardium, and can, at times, be mistaken for the replacement fat seen in arrhythmogenic right ventricular dysplasia.

### Conduction System

The conduction system is comprised of the sinoatrial (SA) node, atrioventricular node, the bundle of His and the left and right bundles. There is an increase in collagen, elastic tissue and fat cells in the conduction system with increasing age. Fat may accumulate in and around

the SA node, leading to its separation from the rest of the atrial myocardium. The number of cells in the SA node decreases with age; the number of cells at 75 years is often only 10% of that in a healthy 20-year-old individual.<sup>14</sup> This striking reduction in the number of pacemaker cells could explain the high prevalence of sick sinus syndrome in elderly people.<sup>15</sup> Although these changes are less pronounced in the atrioventricular node, fatty metamorphosis of this node with or without fibroelastosis can give rise to atrioventricular block.<sup>16</sup> Fibrosis or marked fat in the bundles (left or right) can lead to bundle branch block. The extent of the fibrosis and fat, along with the loss of the cells in the conduction system, may form the anatomic basis for arrhythmias in the elderly.<sup>17</sup>

## Functional Changes

### Diastolic Function

The early diastolic filling rate of the LV decreases with age. With advancing age, there is an increase in the number and activity of cardiac L-type  $Ca^{2+}$  channels, which inactivate slowly.<sup>18</sup> In addition, there is a decrease in outward directed  $K^+$  current which adds to prolonged AP.<sup>19</sup> Reduction in the rate of  $Ca^{2+}$  sequestration by the sarcoplasmic reticulum leads to prolonged  $Ca^{2+}$  transience and myocyte contraction, causing impaired myocardial relaxation during early diastole.<sup>20</sup> This may be partly responsible for the decrease in the early diastolic filling rate in older myocardium.<sup>21</sup> However, these changes are believed by some to be adaptive rather than degenerative—a slow rate of myocardial shortening may be energy efficient, allowing myocardium in the elderly to generate force for a longer time after excitation.<sup>21</sup> Decreased rate of early diastolic filling is accompanied by a greater filling in the late diastole augmented by atrial contraction. Atrial contraction becomes increasingly important with age and repeated vigorous contractions lead to atrial hypertrophy. These strong atrial contractions produce the fourth heart sound.

## Systolic Function

LV systolic function (LV ejection fraction) does not change with aging, though maximum achievable ejection fraction with exercise decreases with age in healthy persons (screened to exclude latent coronary disease).

## Heart Rate

The resting heart rate does not change with aging.<sup>22</sup> However, the maximum heart rate achieved during strenuous physical exercise decreases progressively with age, as does the heart rate in response to most physiological stimuli.

## Clinical Implications

Age has been identified as a significant independent risk factor for heart failure.<sup>23</sup> The risk of developing heart failure almost doubles in persons 75–84 years of age compared to those 65–74 years old. This increased incidence of heart failure not only reflects the increased prevalence of cardiovascular diseases, but also age-related changes, including increased vascular resistance that impedes LV ejection, and reduced sympathetic responsiveness that limits the heart's ability to increase rate and contractility, predisposing the elderly to development of heart failure. Heart failure is the most common reason for hospitalisation in patients older than 65 years,<sup>24</sup> and is seen in approximately 10% of persons older than 80 years of age.<sup>25</sup>

## Summary

In this paper we have summarised the age-related changes in the “wall” of the heart. These changes are insidious and their functional impact is usually seen in old age. While individually many of these age-related changes do not seem to have a demonstrable functional impact, collectively the single most significant effect is the high incidence of heart failure in the elderly. In combination with vascular and valvular changes, this leads to even greater functional effects. ◆

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## References

- Lester WA. Age-related cardiovascular changes. In: Silver MD, Gotlieb AI, Schoen FJ, editors. *Cardiovascular pathology*. New York: Churchill Livingstone, 2001:54-68.
- Salazar AE, Edwards JE. Friction lesions of ventricular endocardium. Relation to chordae tendineae of mitral valve. *Arch Pathol* 1970;90:364-76.
- Gerstenblith G, Frederiksen J, Yin FC, et al. Echocardiographic assessment of a normal adult aging population. *Circulation* 1977;56:273-8.
- Olivetti G, Giordano G, Corradi D, et al. Gender differences and aging: effects on the human heart. *J Am Coll Cardiol* 1995;26: 1068-79.
- Thomas L, Levett K, Boyd A, et al. Compensatory changes in atrial volumes with normal aging: is atrial enlargement inevitable? *J Am Coll Cardiol* 2002;40:1630-5.
- Schneider R, Pfitzer P. [Number of nuclei in isolated human myocardial cells]. *Virchows Arch B Cell Pathol* 1973;12:238-58.
- Klima M, Burns TR, Chopra A. Myocardial fibrosis in the elderly. *Arch Pathol Lab Med* 1990;114:938-42.
- Lakatta EG. Cardiovascular aging research: the next horizons. *J Am Geriatr Soc* 1999; 47:613-25.
- Lie JT, Hammond PI. Pathology of the senescent heart: anatomic observations on 237 autopsy studies of patients 90 to 105 years old. *Mayo Clin Proc* 1988;63:552-64.
- Wei JY, Spurgeon HA, Lakatta EG. Excitation-contraction in rat myocardium: alterations with adult aging. *Am J Physiol* 1984;246:H784-91.
- Olivetti G, Melissari M, Capasso JM, et al. Cardiomyopathy of the aging human heart. Myocyte loss and reactive cellular hypertrophy. *Circ Res* 1991;68:1560-8.
- Kyle RA, Spittell PC, Gertz MA, et al. The premortem recognition of systemic senile amyloidosis with cardiac involvement. *Am J Med* 1996;101:395-400.
- Waller BF, Bloch T, Barker BG, et al. The old-age heart: aging changes of the normal elderly heart and cardiovascular disease in 12 necropsy patients aged 90 to 101 years. *Cardiol Clin* 1984;2:753-79.
- Davies MJ. Pathology of the conduction system. In: Caird FL, Dalle JLC, Kennedy RD, editors. *Cardiology in old age*. New York: Plenum Press, 1976:57-9.
- Wei JY, Gersh BJ. Heart disease in the elderly. *Curr Probl Cardiol* 1987;12:1-65.
- Bharati S, Lev M. The pathologic changes in the conduction system beyond the age of ninety. *Am Heart J* 1992;124:486-96.
- Wei JY. Age and the cardiovascular system. *N Engl J Med* 1992;327:1735-9.
- Josephson IR, Guia A, Stern MD, et al. Alterations in properties of L-type Ca channels in aging rat heart. *J Mol Cell Cardiol* 2002; 34:297-308.
- Walker KE, Lakatta EG, Houser SR. Age associated changes in membrane currents in rat ventricular myocytes. *Cardiovasc Res* 1993;27:1968-77.
- Froehlich JP, Lakatta EG, Beard E, et al. Studies of sarcoplasmic reticulum function and contraction duration in young adult and aged rat myocardium. *J Mol Cell Cardiol* 1978;10:427-38.
- Lakatta EG. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises. Part III: cellular and molecular clues to heart and arterial aging. *Circulation* 2003;107:490-7.
- Fleg JL, O'Connor F, Gerstenblith G, et al. Impact of age on the cardiovascular response to dynamic upright exercise in healthy men and women. *J Appl Physiol* 1995;78:890-900.
- Chen YT, Vaccarino V, Williams CS, et al. Risk factors for heart failure in the elderly: a prospective community-based study. *Am J Med* 1999;106:605-12.
- Tresch DD. Clinical manifestations, diagnostic assessment, and etiology of heart failure in elderly patients. *Clin Geriatr Med* 2000;16:445-56.
- Kannel WB, Belanger AJ. Epidemiology of heart failure. *Am Heart J* 1991;121:951-7.