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Mechanisms of Arrhythmias and Conduction Disorders in Older Adults

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Synopsis

Aging is associated with an increased prevalence of cardiac arrhythmias, which contribute to higher morbidity and mortality in the elderly. The frequency of cardiac arrhythmias, particularly atrial fibrillation and ventricular tachyarrhythmia, is projected to increase as the population ages, greatly impacting health care resource utilization. Several clinical factors associated with the risk of arrhythmias have been identified in the population, yet the molecular bases for the increased predisposition to arrhythmogenesis in the elderly are not fully understood. Therefore, only limited therapeutic strategies directed at pathophysiological processes that enhance cardiac vulnerability to arrhythmias are available. This is further compounded by the paucity of outcome studies providing evidence on which optimal management guidelines can be formulated for the very elderly. This review highlights the epidemiology of cardiac dysrhythmias, changes incardiac structure and function associated with aging, and the basis for arrhythmogenesis in the elderly, the understanding of which is critical to formulate preventive strategies.

Keywords

aging; arrhythmias; mechanisms; elderly; atrial fibrillation; ventricular fibrillation; sudden cardiac death

Introduction

Aging is associated with an increased prevalence of cardiac arrhythmias, which contribute to higher morbidity and mortality in the elderly.[1–4] With the aging of the population, the frequency of cardiac arrhythmias, particularly atrial fibrillation (AF) and ventricular tachyarrhythmia, is projected to increase and thereby greatly impact health care resource utilization.[4–7] Several clinical factors associated with the risk of arrhythmias have been identified in the population,[8,9] yet the molecular bases for the increased predisposition to arrhythmogenesis in the elderly are not fully understood. Therefore, only limited therapeutic

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strategies directed at pathophysiological processes that enhance cardiac vulnerability to arrhythmias are available. This is further compounded by the paucity of outcome studies[10,11] that provide evidence on which optimal management guidelines can be formulated for the very elderly.[2,10,12–14] In this review, we highlight the epidemiology of cardiac dysrhythmias, changes in cardiac structure and function associated with aging and the basis for arrhythmogenesis in the elderly, the understanding of which is critical to formulate preventive strategies.

Epidemiology

The incidence of cardiac dysrhythmias, both brady- and tachyarrhythmias, increases with advancing age.[12,15,16] The median age of pacemaker recipients for bradyarrhythmias in the United States is 75 years with more than 80% of pacemakers implanted in those 65 years or older.[16] The major indication for pacemaker implantation in the elderly is to relieve symptoms due to bradycardia and/or chronotropic incompetency from sinus node dysfunction or His-Purkinje disease as a result of aging-related degenerative changes in the atrial pacemaker complex and conduction system that usually manifest in the seventh or eighth decade of life.[16–19]

Among tachyarrhythmias, AF is the most common arrhythmia encountered in clinical practice with a 100-fold higher prevalence in octogenarians (8–10%) compared to those younger than 55 years of age (<0.1%; Fig 1).[2,12,20–22] With a 1-in-4 lifetime risk of development,[23] AF contributes to increased morbidity in the elderly, not only by adversely affecting quality of life but also by deterioration in myocardial function, which increases susceptibility to heart failure, stroke, hospitalization and mortality. AF carries an annual healthcare cost exceeding $15 billion.[5,8,9,20,23–27] The median age of patients with AF is around 75 years with 84% of the patients older than 65. With the rapid increase in the number of elderly[7] and concomitant cardiovascular comorbidities,[24,28] a sixfold increase in the prevalence of AF (to 15.9 million) is projected,[20] highlighting the magnitude of the epidemic of AF and its far reaching implications on the health and economics of the country.[20,24,29]

Aging is also associated with a progressive increase in the incidence of ventricular dysrhythmias, both benign and malignant, with or without structural heart disease. Unexpected death from cardiovascular causes occurs in 250,000 to 300,000 individuals annually with up to 75–80% resulting from ventricular fibrillation or tachycardia, more so in elderly patients with coronary artery disease, and may be the presenting event in 50% of patients.[2,3,30,31] In 15–20% of sudden cardiac death (SCD) victims, advanced atrioventricular block or asystole is documented.[32,33] However, an increase in pulseless electrical activity with a proportionate decrease in ventricular fibrillation as the presenting arrhythmia has been reported in more recent studies.[34,35] The true incidence of bradyarrhythmias causing sudden death in the elderly is not known because by the time the first rhythm is recorded, an arrhythmia beginning as ventricular tachyarrhythmia may degenerate into or appear as asystole. SCD accounts for 13% of all natural deaths and 50% of all deaths from cardiovascular causes.[15,36] Despite advancement in the management of cardiovascular disease, the incidence of SCD in the general population (0.1% to 0.2% per year) has decreased only marginally and is expected to grow with the aging of the population.[11,15,30,31,34] The persistent dismal survival rate of 4–5% after an out-of-hospital cardiac arrest[37] calls for improvement in risk stratification and means to prevent SCD[15] by better defining mechanisms underlying aging-associated increase in the susceptibility to arrhythmogenesis and gathering evidence from clinical trials to develop cost-effective strategies to reduce the burden of arrhythmias in the elderly.[13]

Structural and functional changes in the aging heart

Structural and functional alterations in cardiac mechanical and electrical system, as well as energetics and metabolism associated with the aging process increase predisposition to cardiac arrhythmias.[1,38–40] Bradyarrhythmias, due to reduced normal automaticity and delayed conduction are common in the very elderly, even in the absence of apparent heart disease, and are further exacerbated by comorbidities or use of medications resulting in symptoms that require pacemaker implantation.[16,17,19,41,42] The intrinsic heart rate and heart rate reserve, as determined following cardiac parasympathetic and sympathetic blockade, decreases with aging.[43] This results from aging-associated replacement of pacemaker cells within the sinoatrial node and atrioventricular conduction fibers with an extracellular matrix composed of collagen and elastin fibers[44] and impairment of receptor and post-receptor signaling via beta-adrenergic receptors contributing to the diminished heart rate response and heart rate variability, with resultant reduction in aerobic work capacity in the elderly.[16,44–46] In addition, amyloid, lipid and lipofuscin deposition within the myocardium, particularly around the atrial pacemaker tissue, further contributes to bradyarrhythmias in the aging heart.[1,12,47,48] By age 75, the number of functional pacemaker cells decreases to less than 10% of those in young adults, which, along with the reduction in the expression of ion channels, promotes reduced automaticity.[49] Senescence-induced degenerative changes in the cardiac skeleton, particularly in areas close to the AV node, His-Purkinje tissue and bundle branches, delay conduction and predispose elderly patients to dysrhythmias.[47,50] Electrical and structural remodeling with action potential duration prolongation and connexin remodeling increases the refractoriness of cardiac tissue and slows conduction.[51–53] These changes, along with a blunted response to neurohumoral activation, promote age-related increase in the propensity for chronotropic and dromotropic impairment and for the development of brady- and tachyarrhythmias.[1]

Susceptibility to both supraventricular and ventricular arrhythmogenesis is enhanced in the senescent heart even in the absence of apparent structural abnormalities and is further exaggerated with comorbidities accompanying the aging process.[12,15] This results from both structural and functional alterations – including cell loss, myocyte hypertrophy and interstitial fibrosis – resulting in altered cellular coupling and exaggerated directional differences in conduction (anisotropy), increasing heterogeneity in impulse propagation properties and refractoriness of the myocardium. This creates zones of functional slowing or conduction block that stabilize reentry, enhancing susceptibility to arrhythmogenesis.[46,54–56] Changes in expression, distribution and regulation of ion channels alter action potential waveforms and propagation, further enhancing vulnerability to dysrhythmias.[49,57] In the senescent heart, the action potential duration and repolarization are prolonged,[58–60] in part due to downregulation of potassium currents, including the Ca^{2+}-activated potassium, transient outward (I_{to}), and ATP-sensitive potassium channels and partly due to delay in the inactivation of the calcium current (I_{CaL}).[58,61,62] Along with an increase in sodium-calcium exchanger, this delay increases predilection to Ca^{2+}-overload-mediated triggered activity and reentrant arrhythmias.[59,62–67] A reduction in the expression of the sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA-2)[68,69] and post-translational modifications in the function of SERCA-2, phospholamban and the sarcoplasmic reticulum Ca^{2+}-release channel (RYR2) further alters calcium homeostasis and susceptibility of the aging heart towards arrhythmogenesis.[60,70–74]

The heart, an aerobic organ with high energy demand, is dependent on adequate energy supply from mitochondrial oxidative phosphorylation, which provides more than 70% of ATP.[75] A decline in mitochondrial function including oxidative phosphorylation,[37,76–79] with reduction in the activity of respiratory chain components, adenine nucleotide translocase activity, changes in mitochondrial matrix and membrane lipid pattern, occurs

with the aging process and contributes to an enhanced susceptibility to myocardial dysfunction under conditions of increased energy demand, such as during tachyarrhythmias.[39,59,72,76,80–89] The contribution of age-related changes in cardiac microstructure, including sarcolemma, cytoskeleton, intercellular gap junctions, cellular geometry and interstitium as well as mitochondria[7,90] and other intracellular organelles, on the regulation of cardiac excitability or arrhythmogenesis are not well defined and warrant further studies.

Electrophysiological substrates for AF in the elderly

AF is a heterogeneous disorder with variable etiology, clinical profile and natural history.[77] In the majority of elderly patients, AF occurs in the setting of structural heart disease, with only a small percentage exhibiting AF as a primarily electrical disorder.[14,91–95] Aging is associated with changes in expression, distribution and/or function of ion channels that alter action potential waveforms, propagation and calcium handling, increasing vulnerability to AF.[46,78,79,96,97] In addition, aging-associated loss of atrial cardiomyocytes and increased interstitial fibrosis occurs even in the absence of structural heart disease and promote the substrate for arrhythmogenesis. In humans, this can be demonstrated as fractionated electrocardiograms and low-voltage zones that increase with advancing age (Fig 2).[38] Changes in hemodynamic, mechanical, neurohumoral, metabolic and inflammatory factors that accompany aging or aging-associated diseases, such as heart failure, valvular heart disease, hypertension, myocardial infarction and diabetes contribute to the development of AF, yet the common mechanistic link between these factors and the development of the substrate for AF or its progression in the elderly is not fully understood.

The electrophysiologic basis for the initiation and/or maintenance of AF varies depending on the patient's age, underlying heart disease or other electrophysiological modulating factors.[8,9,98] Both enhanced impulse generation due to increased automaticity or triggered activity within the atria or pulmonary veins and conduction slowing is responsible for the initiation and maintenance of AF in the elderly. A range of adaptive and maladaptive processes in response to day-to-day stressors, such as volume or pressure overload, stretch, ischemia or rapid rates, contribute to triggers that further alter cellular excitability, cell-to-cell coupling and anisotropy. This results in directional slowing of impulse propagation[54] and a source/sink mismatch,[53] creating a milieu that increases predisposition to AF in the senescent atria.[38,52–55,63,73,74,78,99–101]

AF may exist in paroxysmal (spontaneously terminates within 7 days), persistent (requires intervention for termination) or permanent forms, with one-fourth of patients with paroxysmal AF progressing to the permanent form,[9,14] which becomes resistant to pharmacological and nonpharmacological therapies.[102] Extended follow-up of a unique population of young patients (mean age 44 ± 11 years) from Olmsted County, Minnesota, with lone AF (in the absence of structural heart disease or hypertension)[103] allowed assessment of the natural history of AF and determination of the effect of aging and aging-associated comorbidities on the progression of AF and subsequent risk of stroke, heart failure and mortality.[14] The 30-year cumulative probability of development of permanent AF was 29% (95% confidence interval 16–42%), with minimum risk of heart failure, stroke or mortality. Older age at diagnosis, or presence of QRS abnormalities on electrocardiography were predictors of progression to permanent AF, whereas the presence of premature supraventricular complexes/tachycardia was protective and associated with decreased risk of permanent AF. These findings suggest that young patients with premature complexes and supraventricular arrhythmias in the absence of structural heart disease had a different electrophysiological substrate, with a primary electrical disorder compared to older patients or those with electrocardiographic or overt structural abnormalities[104] or with the

development of hypertension, heart failure, diastolic dysfunction or ischemic heart disease with advancing age.[9,14,105] resulting in different progression rates to permanent AF.[12, 14]

Aging and its associated comorbidities have been known to increase the risk of progression of AF and its complications, however, the common link connecting these risk factors to the development or progression of AF is not fully understood. Myocardial fibrosis is a common factor associated with aging and co-morbidities such as heart failure, ischemic or valvular heart disease or other forms of cardiomyopathy and could contribute to aging associated progression of atrial fibrillation. Further research in defining the role of myocardial cell loss and replacement fibrosis is warranted. In animal models, the facilitative role of rapid atrial rate in the initiation and maintenance of sustained AF has been demonstrated.[78,79,106] A progressive decrease in atrial refractoriness, increased heterogeneity and loss of the normal rate-dependent adaptation of refractoriness occurs in this animal model.[78] Slowing of the conduction velocity occurs within the atrium, although late. These changes in electrophysiological properties, termed “electrical remodeling,” of the atrium likely result from reduction in the L-type Ca^{2+} current and transient outward potassium current, a progressive late reduction in the density of voltage-gated Na^{+} channels, and gap junction redistribution that contributes to the slowing of conduction, thus increasing vulnerability of the atria to reentry and creating a condition in which AF perpetuates AF.[79,102,106,107] These electrophysiological changes are different from structural changes that are observed in patients with heart failure or in the senescent atria with gradual loss of myofibrils, myocyte hypertrophy, fragmentation of sarcoplasmic reticulum and fibrosis with changes in the structure and shape of mitochondria.[1,46,62,108–117] Changes in protein expression, similar to a de-differentiation process toward a partially fetal phenotype or that seen in hibernating myocardium, also take place with chronic AF.[108,110] The structural substrate with interstitial fibrosis and atrial enlargement appears to be more important in the pathogenesis of AF and its progression in humans than the electrical remodeling, as suggested by animal models in which AF was induced by heart failure or mitral regurgitation,[78,111–113] and by its high prevalence in the elderly.[9,114] This is further supported by observations that despite reversibility of atrial refractoriness with restoration of sinus rhythm, AF inducibility or recurrences continued to be high,[115,116] indicating that strategy of prompt termination of AF to avoid adverse electrical remodeling is of little clinical benefit in the elderly.

The precise mechanisms underlying atrial structural remodeling in humans are not fully understood, but impaired intracellular calcium handling, oxidative stress and altered energetics appear to play an important role,[107] and mechanisms coupling calcium loading to structural remodeling need to be further defined. Additional unknown factors are operative[102,112,117,118] and need to be elucidated for better understanding of the pathogenesis of AF in the elderly so effective strategies can be instituted for primary and secondary prevention of AF and thereby limit its burden on health care resources.

Electrophysiological substrates for ventricular arrhythmias/SCD in the elderly

The substrate for ventricular arrhythmias in the elderly varies depending on the presence of structural heart disease. The effect of aging on cardiac hemodynamics, structure and function is complex and challenging to study in humans because of difficulty in isolating the effect of aging from diseases associated with the aging process. Ventricular dysfunction and fibrosis after myocardial infarction or with nonischemic cardiomyopathy predispose to ventricular arrhythmogenesis, which contributes to the majority of SCD in the elderly.[119–123] The risk factors for arrhythmias leading to SCD have been well described; however, precise mechanisms underlying the initiation and maintenance or prediction of timing for the development of dysrhythmias causing SCD in the elderly are not completely

understood. This is due to interactions between dynamic transient factors (ischemia, hypoxia, catecholamines, pH and electrolyte changes, stretch or inflammation) on the underlying myocardial substrate that precipitate arrhythmias.[8,78,100] Ventricular tachyarrhythmias may be initiated by one mechanism, perpetuated by another and then degenerate into a different mechanism. This is mainly due to the complex interactions between myocardial cellular and extracellular substrates and triggers that define the overall risk of arrhythmia susceptibility.[78,99,100,101]

Acute ischemia triggering lethal ventricular tachyarrhythmias contributes to the majority of SCD in the elderly.[124] In 50% of patients with coronary artery disease, sudden death is the initial manifestation.[37,125–127] Acute changes in coronary plaque morphology such as disruption or thrombus were found in more than 50% of the victims of sudden death.[128–130] Cardiac events due to inherited arrhythmia syndromes such as congenital long QT syndrome, short QT syndrome, Brugada syndrome or catecholaminergic polymorphic ventricular tachycardia account for only a small percentage of sudden deaths in the elderly.[131,132] Familial clustering of cardiac events, however, does suggest a role of genetic factors in predisposition to sudden death,[133–135] which, in the elderly, appears to be due to influences that increase the risk of a coronary event.[37,125,136–138] Patients with long QT syndrome maintain a high risk for life-threatening cardiac events even in later years, although the risk of aborted cardiac arrest or death conferred by long QT syndrome is attenuated, most likely due to the higher prevalence of comorbidities associated with senescence.[139–143]

Ventricular arrhythmias are common in the elderly, affecting more than 70% of individuals age 60 years and older. With advancing age and presence of structural heart disease, not only do the prevalence and complexity of ventricular arrhythmias worsen but so does their prognostic significance.[15,144–147] Even in asymptomatic elderly the prevalence of ventricular arrhythmias on ambulatory monitoring is as high as 60–90%. Complex premature beats, such as pairs and triplets, occur in up to 10% of such individuals and may be present in up to 60% of the older elderly during exercise. In the absence of heart disease, asymptomatic premature ventricular complexes (PVC) presenting at rest are benign, but when elicited during exercise[148] or post-exercise recovery period,[149] carry adverse prognosis and increased risk of cardiovascular death. In patients with reduced ventricular function, frequent PVCs have poor prognostic significance.[147,150–156] The mechanisms underlying ventricular arrhythmogenesis are variable and depend on the underlying myocardial substrate. During ischemia or the acute phase of myocardial infarction, functional reentry can precipitate ventricular fibrillation, whereas reentry circuits around the scar tissue late after acute myocardial infarction result in ventricular tachycardia that degenerates into fibrillation. The vulnerability of the aging heart to arrhythmogenesis is increased during the peri-infarct period, with a higher likelihood of inhospital cardiac arrest in those ≥75 years and older compared with younger patients.[157] Ventricular tachyarrhythmias occurring within 48 hours of acute ischemic event are associated with an increase in hospital death, however, long-term mortality is not affected unless significant ventricular dysfunction persists.[158] The incidence of scar-related reentrant ventricular arrhythmias increases exponentially, with reduction in left ventricular ejection fraction to below 30%.[125,159]

Evaluation and management of elderly patients with cardiac arrhythmias

Several noninvasive and invasive risk stratification protocols for patients at risk for cardiac arrhythmias who may benefit from interventions to reduce complications and risk of life-threatening events have been developed.[15,16,77] A simple 12-lead electrocardiogram allows identification of the underlying structural or functional substrate, such as conduction system

abnormalities, prior infarction, ventricular hypertrophy, arrhythmogenic right ventricular cardiomyopathy or primary electrical disorders, such as long or short QT syndrome and Brugada syndrome. A prolonged QTc interval in the elderly and a QRS duration longer than 150 ms in patients with severely depressed ventricular function predicts a higher risk of SCD.[3,16,160] A prolonged PR interval or delayed conduction in the atria increases the risk of atrial fibrillation.[77] On signal-averaged electrocardiogram (SAECG), absence of late potentials has a high negative predictive value in excluding wide complex tachycardia as a cause of unexplained syncope in the elderly patient with coronary artery disease.[161,162] Appearance of exercise-induced complex ventricular ectopy or ventricular tachycardia in the elderly during exercise testing may predict an increased risk of mortality compared to patients with simple ectopy observed at rest only.[148,149,163] Microvolt fluctuation in the amplitude or morphology of T waves during rest,[164] exercise testing or atrial pacing may identify high-risk postinfarction or cardiomyopathy patients.[165,166] Assessment of atrial and ventricular dimensions and contractile function with imaging techniques such as echocardiogram are an essential part of cardiac evaluation of patients at risk for arrhythmias.[16,77,167] In patients suspected of ventricular arrhythmias triggered by ischemia,[168] exercise or pharmacological testing to detect ischemia can be performed with imaging using echocardiogram, magnetic resonance imaging or nuclear perfusion scans.[169,170] In patients with ventricular arrhythmias or aborted sudden death, coronary angiography is useful to assess for coronary artery disease. Invasive electrophysiology testing is useful for risk stratification for SCD in elderly patients with ischemic heart disease and moderate left ventricular dysfunction or syncope, but is of limited utility for patients with dilated cardiomyopathy or inherited arrhythmia syndromes.[171–179] Use of multiple risk markers in combination may better predict arrhythmogenic events than a single parameter given the complexity and variability of the underlying substrates predisposing to arrhythmogenesis and SCD.[31]

Discussion of the management of cardiac dysrhythmias are beyond the scope of this article but can be obtained from recent guidelines.[15,16,31,77,180–186] However, little information is available from clinical trials focusing on the efficacy of various therapeutic modalities in the older-elderly such as antiarrhythmic agents, ablation procedures for atrial and ventricular tachyarrhythmias or implantable cardioverter-defibrillators.[13,98] Information about the efficacy of therapies for cardiac arrhythmias in the very elderly with limited life expectancy is difficult to assess, especially in view of the fact that only a select few individuals more than 80 years old were included in randomized clinical trials and nonrandomized data suffers from selection bias.[129] A diminished benefit of therapies such as implantable cardioverter-defibrillator has been demonstrated with pooled analysis of SCD prevention trials due to an increased number of nonarrhythmic cardiac and noncardiac deaths in the very elderly with multiple comorbidities.[130]

Summary

Cardiac dysrhythmias are common in the elderly and their overall prevalence and impact on health care costs is expected to increase with the changing population demographics. Despite rise in the number of elderly with atrial and ventricular arrhythmias, only limited insight into mechanisms underlying aging-associated increase in the susceptibility of the heart to arrhythmogenesis is available. In addition, evidence from well-designed clinical trials in the very elderly supporting safer and effective management decisions is lacking, which limits specific practice guidelines. Ongoing research to fulfill this unmet need may provide novel insights into the pathogenesis of cardiac arrhythmias and improvement in preventive and therapeutic strategies.[13]

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Key Points

1. Aging is associated with an increased prevalence of cardiac arrhythmias, which contribute to higher morbidity and mortality in the elderly. The frequency of cardiac arrhythmias, particularly atrial fibrillation and ventricular tachyarrhythmia, is projected to increase as the population ages, greatly impacting health care resource utilization.
2. Several clinical factors associated with the risk of arrhythmias have been identified in the population, yet the molecular bases for the increased predisposition to arrhythmogenesis in the elderly are not fully understood. Therefore, only limited therapeutic strategies directed at pathophysiological processes that enhance cardiac vulnerability to arrhythmias are available.
3. This is further compounded by the paucity of outcome studies providing evidence on which optimal management guidelines can be formulated for the very elderly.

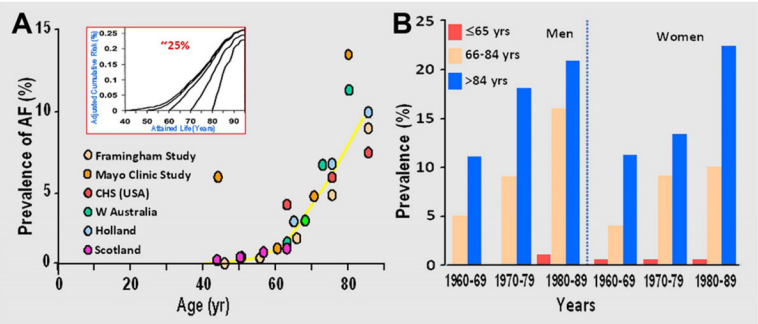

Fig. 1.

A: Prevalence of atrial fibrillation (AF) in older adults doubles with each decade. Prevalence increases 80–100-fold in the very elderly (0.1% at 40 years to ~8–10% in ≥ 80 years). (Adapted from Feinberg et al. Prevalence, age distribution, and gender of patients with atrial fibrillation analysis and implications. Arch Int Med 1995;155:469–73, with permission from American Medical Association.)

Inset: Cumulative lifetime risk for the development of AF (~25%) in the adult population. (Adapted from Lloyd-Jones et al. Lifetime risk for development of atrial fibrillation: The Framingham Heart Study. Circulation 2004;110:1042–*6, with permission from Wolters Kluwer Health.)*

B: Secular trends in prevalence of AF in Olmsted County, MN: 1960–1989. (Adapted from Tseng et al. The prevalence of atrial fibrillation in incident stroke cases and matched population controls in Rochester, Minnesota: changes over three decades. J Am Coll Cardiol 2003;42:93–100, with permission from Elsevier.)

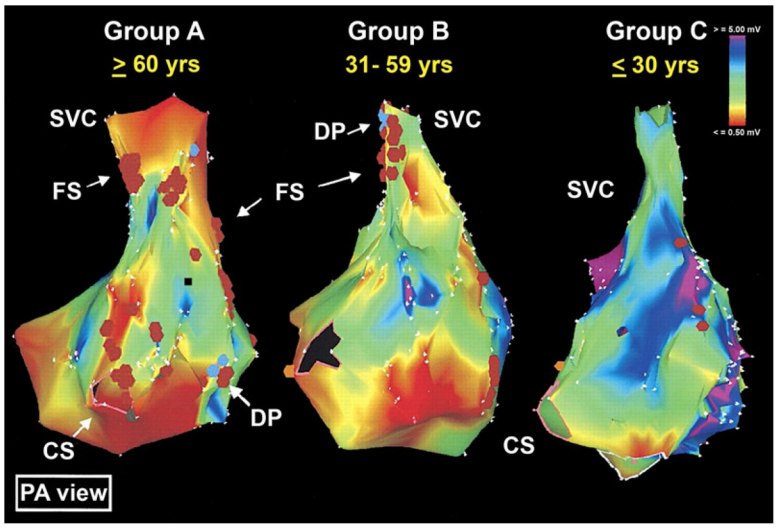

Fig. 2.

Age-related changes in human left atrial voltage loss determined by three-dimensional electroanatomic bipolar voltage mapping. Group A includes those ≥60 years of age; Group B 31–59 years; and Group C ≤30 years. Color annotation: Bipolar voltages from 0.5 mV (in red) to voltages 5 mV (in purple). CS = coronary sinus; DP = double potentials; FS = fractionated signals; PA = posteroanterior; SVC = superior vena cava.
(Reproduced from Kistler et al. Electrophysiologic and electroanatomic changes in the human atrium associated with age. J Am Coll Cardiol 2004;44:109–16, with permission from Elsevier.)