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Aging Dilates Atrium and Pulmonary Veins*

Implications for the Genesis of Atrial Fibrillation

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Backgrounds: **Aging plays a critical role in the pathophysiology of atrial fibrillation (AF). The left atrium (LA) and pulmonary veins (PVs) are essential components for the genesis and maintenance of AF. The purpose of this study was to investigate the effects of aging on the AF substrate and the initiator (PVs).**
Methods: **A total of 180 patients undergoing multidetector CT were enrolled and classified into six groups according to the decade of their age. LA, LA appendage (LAA), and orifice of the four PVs were measured.**
Results: **The LA anterior-posterior diameter and wall thickness became increased with aging after the age of 50 years ($p < 0.001$). Similarly, the LAA and four PV trunks also became dilated after the patients were > 50 years old ($p < 0.001$). The anterior wall was consistently thicker than the posterior wall in each group. Aging also increased both anterior and posterior wall thickness after the patients became > 50 years old. However, LA diameter, PV diameter, and LA wall thickness in the patients aged 70 to 79 years and > 80 years did not significantly differ. Age correlated well with the four PVs, LA diameter, and wall thickness with linear regression.**
Conclusions: **Age significantly determines LA and PV structures. These findings show the important contributing effects involved in aging-induced AF in the general population.**

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Key words: atrial fibrillation; multidetector CT; pulmonary vein

Abbreviations: AF = atrial fibrillation; BMI = body mass index; CAD = coronary artery disease; LA = left atrium/atrial; LAA = left atrial appendage; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; LV = left ventricle/ventricular; MDCT = multidetector CT; PV = pulmonary vein; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein

Atrial fibrillation (AF) is the most common cardiac arrhythmia observed in clinical practice and induces cardiac dysfunction and strokes.[1,2] The prevalence of AF has been reported to be 1% in humans > 60 years old and up to > 5% in humans > 70 years old.[3] The estimated risk of AF developing during one's life is approximately 2% in humans > 30 years old according to the Framingham study.[4] These findings suggest that aging plays an important role in AF genesis. However, the mechanisms of aging-induced AF have not been fully elucidated. Aging can induce myocyte loss or increase fibrosis and reactive cellular hypertrophy, which will produce ventricular hypertrophy and stiffness.[5] In addition, aging induces mitochondrial damage associated with cell dysfunction in cardiomyocytes.[6,7] An animal study[8] showed that aging may alter cardiac electrophysiology to cause AF. However, information about the effects of aging on human cardiac structures in the general population has been limited. Knowledge about cardiac structures in very old patients (> 80 years old) is also not available.

Pulmonary veins (PVs) are the most important source of ectopic beats with the initiation of paroxysmal AF or foci of ectopic atrial tachycardia and focal AF.[9] Previous studies[10–11] have shown that morphology changes of PVs have significant effects on PV arrhythmogenesis. Enlarged PVs may cause a higher PV arrhythmogenesis to induce AF. However, it is not clear whether aging alters the PV structure resulting in an increase in the PV arrhythmogenesis. Multidetector CT (MDCT) provides better and reliable imaging of smaller cardiac structures.[11–14] A previous study[15] has also shown that MDCT provides accurate and detailed imaging of the left atrium (LA) and PVs. Therefore, by using 64-row scan MDCT, the purpose of this study was to investigate the effects of aging on the atrium (AF substrate) and PVs (AF initiators).

Table 1—*Patient Characteristics

Characteristics	Age Range, yr						
	< 40 (n = 9)	40–49 (n = 53)	50–59 (n = 57)	60–69 (n = 41)	70–79 (n = 13)	≥ 80 (n = 7)	p Value
Age, yr	33 ± 6	46 ± 2	54 ± 3	65 ± 3	73 ± 4	86 ± 2	< 0.001
Male gender	6 (67)	35 (66)	42 (74)	28 (68)	10 (77)	5 (71)	0.947
Body weight, kg	63 ± 10	65 ± 10	65 ± 10	66 ± 11	68±	66 ± 11	0.894
Height, m	1.6 ± 0.14	1.6 ± 0.15	1.6 ± 0.18	1.6 ± 0.12	1.6 ± 0.19	1.6 ± 0.14	0.988
BMI, kg/m^2	24.7 ± 3.2	25.2 ± 3.7	24.9 ± 2.8	25.5 ± 3.6	23.7 ± 2.6	24.6 ± 4.6	0.628
Serum creatinine, mg/dL	1.3 ± 0.3	1.2 ± 0.2	1.2 ± 0.3	1.1 ± 0.3	1.3 ± 0.3	1.3 ± 0.2	0.218
Ejection fraction, %	72 ± 3†	63 ± 8	62 ± 7	63 ± 7	57 ± 5	56 ± 3	< 0.001
Systolic BP, mm Hg	127 ± 7	130 ± 11	129 ± 11	131 ± 9	134 ± 4	138 ± 9	0.156
Diastolic BP, mm Hg	73 ± 4	76 ± 7	77 ± 7	77 ± 8	79 ± 6	80 ± 4	0.185
Hypertension	1 (11)	4 (8)	5 (9)	4 (10)	1 (7)	1 (14)	0.505
Diabetes	0	4 (8)	5 (9)	3 (7)	2 (15)	1 (14)	0.835
Dyslipidemia	0	10 (19)	22 (39)	13 (32)	5 (38)	4 (57)	0.036
Smoking	0	0	5 (9)	12 (29)	5 (38)	0	< 0.001
Metabolic syndrome	0	5 (9)	6 (11)	3 (7)	3 (23)	2 (29)	0.292
CAD family history	2 (22)	6 (11)	8 (14)	5 (12)	5 (38)	1 (14)	0.233
Aspirin use	0	2 (4)	4 (7)	4 (10)	3 (23)	3 (33)	0.110
ACEI or ARB use	0	4 (8)	4 (7)	4 (10)	4 (31)	1 (11)	0.141
CCB use	1 (14)	2 (4)	1(2)	2 (5)	1 (8)	1 (11)	0.150
β-Blocker use	1 (14)	2 (4)	2 (4)	3 (7)	0	1 (11)	0.170

*Data are presented as mean ± SD or No. (%). ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker.
†$p < 0.05$ vs other age groups.

Methods and Materials

Patient Selection

This study received institutional review board approval and enrolled 180 consecutive individuals (126 men and 54 women; mean age, of 56 ± 12 years [± SD]) undergoing 64-row scan MDCT for evaluation of the coronary artery. One hundred thirty-nine patients (77%) from the community, 29 patients (16%) from outpatient clinics, and 12 patients (7%) from hospitals were included. During the study, all subjects were in sinus rhythm and did not have any coronary artery disease (CAD) [> 50% stenosis], with a zero coronary calcium score diagnosed by MDCT. The subjects were classified into six age groups according to their decade of life. The lowest age group was < 40 years, and the highest age group was > 80 years. Each participant underwent a medical history, laboratory assessment, and measurement of weight, height, body mass index (BMI), and BP. Metabolic syndrome was defined according to the 1999 World Health Organization definition as the presence of hyperglycemia (an impaired fasting glucose, impaired glucose tolerance, type 2 diabetes, or insulin resistance) and at least two of the following: dyslipidemia (triglycerides > 150 mg/dL and/or high-density lipoprotein cholesterol < 35 mg/dL in men and < 39 mg/dL in women), elevated BP > 140/90 mm Hg, obesity (BMI > 30 kg/m^2 or waist/hip ratios > 0.9 in men and > 0.85 in women), or microalbumiuria (> 20 g/min).

CT

The patients underwent a 64-row scan (Light Speed VCT; GE Healthcare; Milwaukee, WI) using an ECG-synchronized tube-modulation system. Patients with a heart rate > 70 beats/min were administered a single oral dose of propranolol (10 to 40 mg) at least 40 min before the examination. Images were reconstructed retrospectively in the diastolic phase (at 60% of the start of the RR interval). Nonionic contrast medium was administered in a test dose of 250 mL.

Measurement of the LA, Left Ventricular Dimensions, and PVs

PV diameters were measured using the maximal transverse diameter of the four PV trunk orifices in a virtual endoscopic view. LA diameters were measured with the maximal anterior-posterior distance in the oblique-sagittal view. The orifice of the LA appendage (LAA) was defined as the deflection between the LAA and LA free wall. The largest diameter was measured in the oblique-sagittal view. Anterior and posterior wall thickness were measured by the axial view. Left ventricle (LV) dimensions were measured as the maximal distance from the septum to the lateral free wall at the level of the papillary muscle in the end-diastolic phase in the four-chamber axial view. LV ejection fraction was calculated by integrated computer software in a workstation (AW 4.3; GE Healthcare), which traced automatically in the end-diastolic volume and end-systolic volume phases. Two independent observers were asked to analyze the image measurements in a blinded fashion. The

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Table 2—*Comparison Between Aging and the Anatomies of the LA and PVs and LV Dimension

Variables	Age, yr						
	< 40 (n = 9)	40–49 (n = 53)	50–59 (n = 57)	60–69 (n = 41)	70–79 (n = 13)	≥ 80 (n = 7)	p Value
LA diameter, mm	30 ± 6.2	30.1 ± 7.9	33.9 ± 8.9†	38.3 ± 10†‡§	43.2 ± 5.4†‡§	48.2 ± 5.9†‡§	< 0.001
LA anterior wall thickness, mm	2.0 ± 0.9	2.1 ± 0.5	2.5 ± 0.7†	3.2 ± 0.2†‡§	3.6 ± 0.4†‡§	3.7 ± 0.9†‡§‖	< 0.001
LA posterior wall thickness, mm	0.7 ± 0.2	1.1 ± 0.3	1.5 ± 0.3†‡	1.8 ± 0.2†‡§	1.9 ± 0.2†‡§	2.4 ± 0.4†‡§‖	< 0.001
Anterior and posterior wall thickness difference, mm	1.2 ± 0.4	1.1 ± 0.5	1.0 ± 0.7	1.9 ± 1.1†‡§	1.4 ± 0.5†‡§	1.3 ± 1.2†‡§‖	< 0.001
LAA orifice, mm	15.3 ± 0.6	16.2 ± 0.9	17.4 ± 1.8†‡	22.3 ± 1.4†‡§	24.6 ± 0.8†‡§	24.8 ± 0.9†‡§‖	< 0.001
LSPV, mm	12.0 ± 0.6	12.7 ± 0.9	15.0 ± 1.4†‡	18.6 ± 1.6†‡§	19.6 ± 1.8†‡§	20.5 ± 1.1†‡§‖	< 0.001
LIPV, mm	12.8 ± 0.5	13.9 ± 0.6	15.9 ± 1.4†‡	17.7 ± 0.6†‡§	19.9 ± 0.8†‡§	19.0 ± 0.5†‡§‖	< 0.001
RSPV, mm	12.6 ± 0.7	13.5 ± 1.3	16.3 ± 1.4†‡	18.5 ± 1.2†‡§	19.1 ± 1.2†‡§	20.2 ± 0.9†‡§‖	< 0.001
RIPV, mm	12.5 ± 0.8	13.2 ± 1.2	16.4 ± 1.5†‡	18.5 ± 1.4†‡§	19.6 ± 0.9†‡§	20.7 ± 0.6†‡§‖	< 0.001
LV dimension, mm	40 ± 4.2	41 ± 4.8	44 ± 5.3	45 ± 4.2†‡	51 ± 5.7†‡§‖	52 ± 2.7†‡§‖	< 0.001

*Data are presented as mean ± SD.
†p < 0.05 vs < 40 years.
‡p < 0.05 vs 40 to 49 years.
§p < 0.05 vs 50 to 59 years.
‖p < 0.05 vs 60 to 69 years.

interobserver reproducibility and intraobserver reproducibility were 91% and 97%, respectively.

Statistical Analysis

Continuous variables are expressed as mean ± SD. Comparisons among the six age groups were analyzed by a one-way analysis of variance with a *post hoc* Student-Newman-Keuls method. Nominal variables were compared by a χ^2 analysis with a Yates correction or Fisher exact test. Multivariate regression analysis was used to assess the independence of the variables. A paired Student *t* test was used to compare the LA anterior and posterior wall thickness. Linear regression was used to evaluate the correlation between the age and the structure of the LA and PVs. A p value < 0.05 was considered statistically significant.

Results

Patient Characteristics

Table 1 shows the patient characteristics from the six age groups. The incidence of dyslipidemia increased with

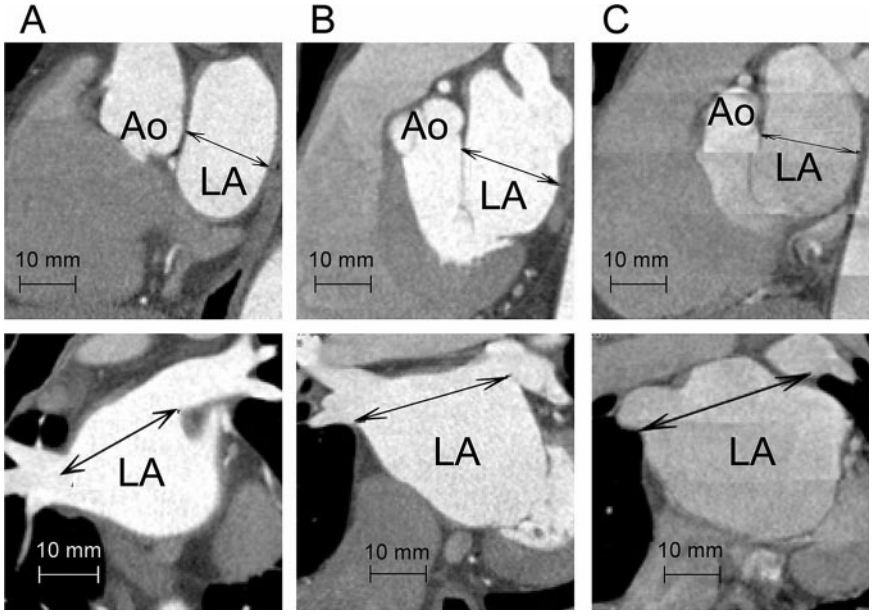

Figure 1. Oblique-sagittal (*upper panels*) and oblique-coronal (*lower panels*) views during MDCT in patients aged < 40 years (*left panels*, *A*), 50 to 59 years (*center panels*, *B*), and 70 to 79 years (*right panels*, *C*). The largest LA anterior-posterior distance was measured in the oblique-sagittal view. The oblique-coronal view exhibited the largest distance from the LSPV to the RSPV. *Left panels*, *A*: LA = 30 mm. *Center panels*, *B*: LA = 35 mm. *Right panels*, *C*: LA = 41 mm. Ao = aorta.

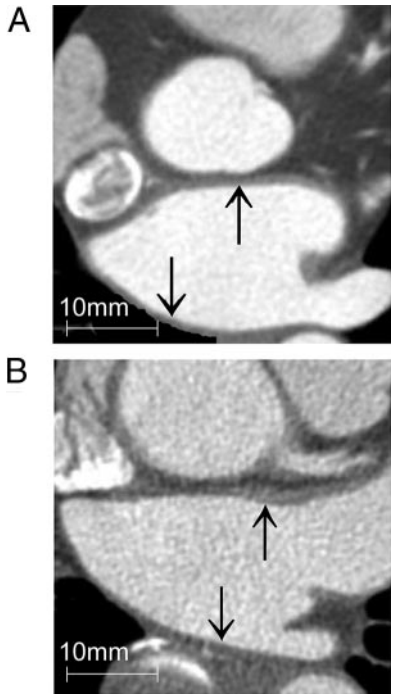

FIGURE 2. Axial views show the LA anterior wall thickness (↑) and posterior wall thickness (↓) in patients aged < 40 years (*top*, *A*) and 70 to 79 years (*bottom*, *B*). Aging increases both anterior and posterior wall thickness. The anterior wall was significantly more thickened than the posterior wall.

aging (Table 1). Body weight, height, and BMI in each age group did not significantly differ. Patients aged 50 to 59 years and 60 to 69 years had higher incidences of smoking as compared to those aged < 40 years or 40 to 49 years. Patients aged < 40 years had a better ejection fraction than the other groups. However, drug therapies, family history of CAD, systolic BP, diastolic BP, presence of hypertension, diabetes, and metabolic syndrome were not statistically different among the six age groups (Table 1), although on multivariate analysis, age group still remains an independent factor for the incidence of dyslipidemia and smoking.

Structural Changes Among Different Age Individuals

Table 2 shows the PV and LA structural parameters in the six age groups. Aging had significant effects on LA diameter. LA diameter increased after the patients became > 50 years old ($p < 0.001$). However, LA diameter in patients aged 70 to 79 years and > 80 years was similar. Compared to those aged < 40 years, patient aged 50 to 59 years, 60 to 69 years, 70 to 79 years, and > 80 years had a larger LA diameter by 13%, 28%, 44%, and 61%, respectively. Figure 1 shows an example of the different LA sizes among the six age groups. In addition, aging also increased both anterior and posterior wall thickness after the patients became > 50 years old. However, anterior and posterior wall thickness in the patients aged 70 to 79 years and > 80 years did not significantly differ. The anterior wall was consistently thicker than the posterior wall in each age group ($p < 0.05$). Figure 2 shows an example demonstrating that aging increased the LA anterior wall and posterior wall thickness. Compared to those aged < 40 years, patients aged 50 to 59 years, 60 to 69 years, 70 to 79 years, and > 80 years had larger LA anterior and posterior wall thickness by 25%, 60%, 80%, and 85% for the anterior wall, and by 114%, 157%, 171%, and 242% for the posterior wall, respectively. Furthermore, compared to those aged < 40 years, anterior and posterior wall thickness differences increased in patents aged 60 to 69 years, 70 to 79 years, and > 80 years (Table 2).

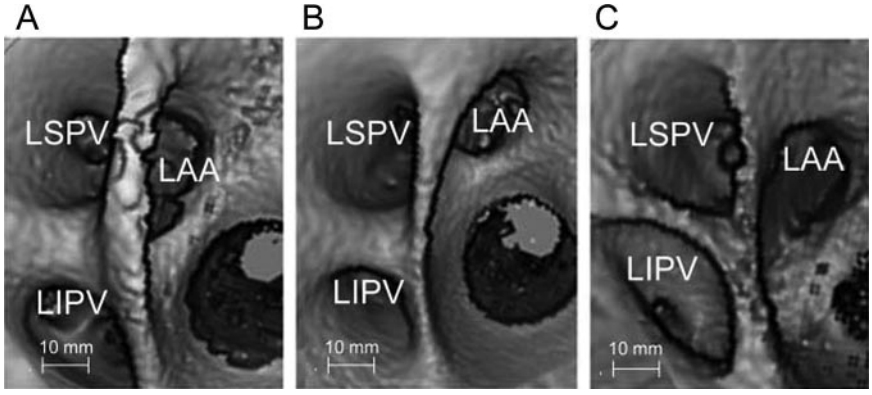

FIGURE 3. Intra-atrial oblique-sagittal views during MDCT from patients aged < 40 years (*left*, *A*), 50 to 59 years (*center*, *B*), and 70 to 79 years (*right*, *C*). The largest diameters of the LSPV and LIPV were measured using the virtual intra-atrial view. LAA orifice diameter was measured using the oblique-sagittal view. *Left*, *A*: LSPV = 12 mm, LIPV = 13 mm, and LAA = 15 mm. *Center*, *B*: LSPV = 15 mm, LIPV = 16 mm, and LAA = 17 mm. *Right*, *C*: LSPV = 19 mm, LIPV = 19 mm, and LAA = 24 mm.

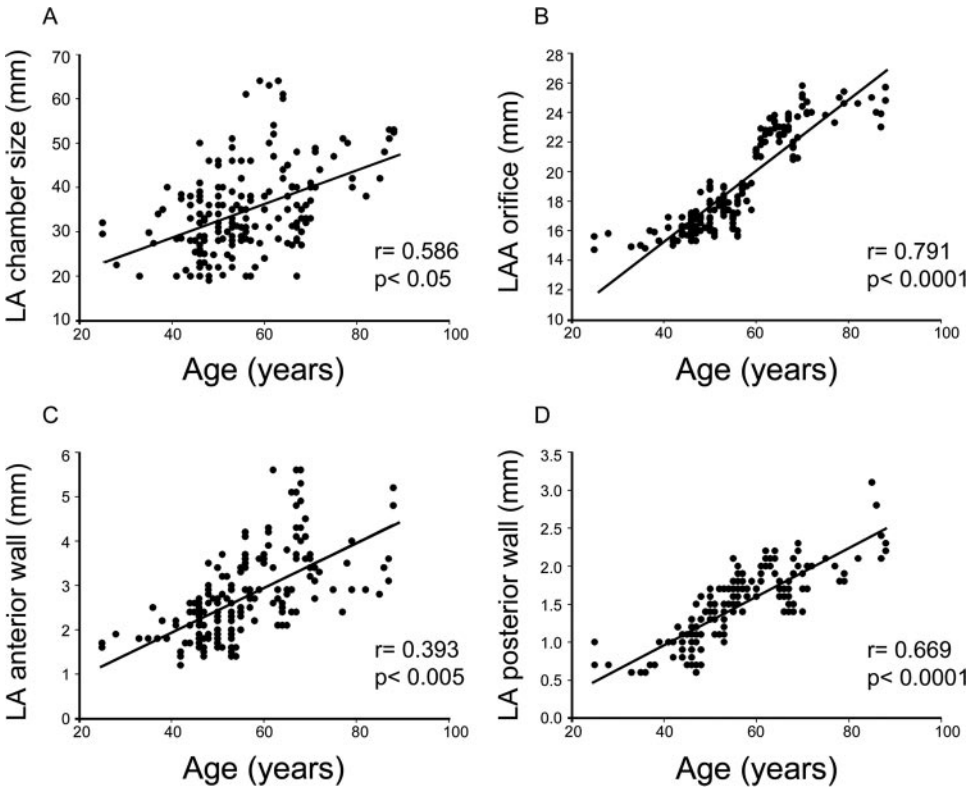

FIGURE 4. Correlation between changes in age and LA chamber size, LAA orifice diameter, and LA anterior and posterior wall thickness.

Figure 3 shows examples of LAA diameter from the different age groups. Aging increased LAA diameter after the patients were > 50 years old. However, LAA diameters in the patients aged 70 to 79 years and > 80 years were similar. Compared to those aged < 40 years, patients aged 50 to 59 years, 60 to 69 years, 70 to 79 years, and > 80 years had larger LAA diameters by 14%, 46%, 61%, and 62%, respectively. Moreover, aging correlated well with LA diameter, LAA diameter, and anterior and posterior wall thickness using linear regression (Fig 4).

Comparisons of the four PV trunk diameters among the six age groups showed that the four PV diameters increased after the patients became > 50 years old (Table 2; Fig 3). Compared to the right superior pulmonary vein (RSPV), left superior pulmonary vein (LSPV), right inferior pulmonary vein (RIPV), and left inferior pulmonary vein (LIPV) in patients aged < 40 years, PVs (RSPV, LSPV, RIPV, and LIPV) in those aged 51 to 60 years were larger by 29%, 25%, 31%, and 24%; in those aged 60 to 69 years were larger by 47%, 55%, 48%, and 38%; in those aged 70 to 79 years were larger by 52%, 63%, 57%, and 55%; and in those aged > 80 years were larger by 60%, 71%, 66%, and 58%, respectively. Aging correlated well with all four PV diameters using linear regression (Fig 5). Moreover, aging also had significant effects on LV dimensions (Table 2). Through multivariate analysis, age group was an independent factor for LV dimensions, LA wall thickness, and the diameters of LA, LAA, and the four PVs.

DISCUSSION

Aging has significant cardiovascular effects and increases the occurrence of AF. However, an extensive understanding of the aging effects on the AF substrate and initiators has not been elucidated. Huonker et al[16] reported age-related cardiac structural changes in the thickening of the myocardium and arrythmias. In this study, we found that aging significantly dilated the atrium and PVs, which may cause aging-related AF. In addition, this study showed that aging increased LA and PV size after the patients become > 50 years old. Patients aged 60 to 69 years had a greater extent of structure changes of the atrial diameter and thickness.[17] All of those results may explain the dramatic increase in the AF in patients aged 60 to 70 years, which then slowly increases after 70 years.[18,19] Moreover, the good liner correlation between aging and the LA or PV structure highly suggests the critical risk effects of aging on AF.

The genesis of AF arises from the changes in the AF substrate (atrium) and initiators (PVs). Atrial enlargement

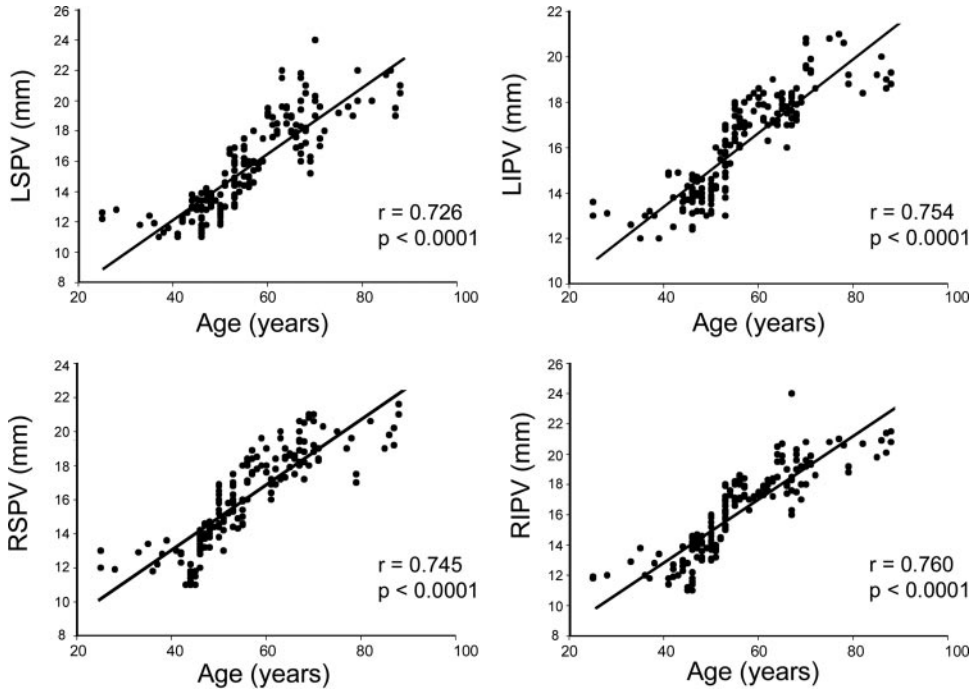

FIGURE 5. Correlation between changes in age and diameters of the LSPV, LIPV, RSPV, and RIPV.

may facilitate the maintenance of AF due to the wavelength theory. Dilated PVs may enhance PV arrhythmogenesis and induce more AF.[20] Therefore, in addition to structure changes, aging may increase AF through mechanoelectrical feedback in the PVs and atrium. Gardin et al[21] reported that aging-related increases in LV mass will add load to the heart and further enlarge LA chamber size and pressure. That effect may lead to fibrosis and electrical remodeling in the atrium and provide a substrate for the development of AF. Moreover, aging could directly impair the ventricular relaxation and increase atrial size.[22,23] Heart failure is an important risk factor for AF.[24–26] It is known that heart failure is very common in elderly population. Risk factors for heart failure are also increased with aging. Similarly, LV ejection fraction was better in patients < 40 years old. Therefore, structure changes occurring during aging may partially arise from subclinical heart failure, although our patients did not have any evidence of heart failure. In addition, the incidence of dyslipidemia also increased during aging in study patients. All of these aging effects can increase the risk for AF.[27] In this study, the incidence of hypertension did not significantly differ among the six age groups, although aging still has a trend to increase BP. It is known that aging increases the hypertension population. Therefore, our patients may not be completely correlated with the general population. The similar hypertension incidence in our patients may reduce the potential hypertension effects and demonstrate more uncontaminated aging effects on the atrium and PVs. Metabolic syndrome is known to induce inflammation and thereby may increase AF risk.[28] However, the similar incidence of metabolic syndrome among the different age groups suggests that metabolic syndrome may not play a significant role in this study.

Aging may accelerate the wall thickness and stiffness by a process of fibrosis and depletion of the elastin and collagen.[29] In this study, for the first time we found that aging increased wall thickness using the MDCT. There was general agreement that MDCT is superior to transthoracic echocardiography or transoesophageal echocardiography for LA or PV measurements. LA wall thickness was difficult to detect by transthoracic echocardiography or transoesophageal echocardiography. Moreover, we demonstrated a consistently thinner wall for the LA posterior wall than for the LA anterior wall using MDCT. These findings may result in a higher arrhythmogenesis in the LA posterior wall than in the anterior wall[30,31] because the thinner wall should have a higher wall stress. Our previous animal study[8] also found that a thinner LA posterior wall may have a higher arrhythmogenesis for inducing AF.

Data from this study should be interpreted with caution due to the limitations of this study. First, we could not completely exclude occult CAD in the study patients because MDCT could not evaluate small vessels (diameters < 1 to 2 mm) accurately or because the patients may have insignificant CAD. Second, the structures measured are three dimensional and not uniformly shaped in all individuals, which may limit the comparative utility of the

linear measurements. Third, we did not evaluate LV diastolic function in this study. Aging has been shown to impair LV diastolic function. This effect may result in the changes in LA and PV structures.

In conclusion, aging has significant effects on LA and PV structure. The anatomic dilation and mechanoelectrical feedback caused by the aging effects may facilitate the occurrence of aging-related AF.

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