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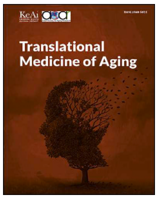

Age in aortic disease: The path towards atrial fibrillation

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ABSTRACT

Background: Aging induces structural remodeling, altering atrial electrogram morphology. Over time, structural and consequently electrical remodeling creates a substrate for atrial fibrillation. In structural heart disease, age-induced remodeling comes on top of a pre-existing degree of structural remodeling due to pressure or volume overload.
Objective: Investigate the severity of age-related electrical remodeling in patients undergoing surgery for structural heart disease by utilizing a high resolution epicardial mapping approach.
Methods: Five seconds of sinus rhythm were recorded intraoperatively at the right atrium (RA), Bachmann's bundle (BB), the left atrium, and the pulmonary vein area. Potential voltage, low-voltage area (LVA) and conduction velocity (CV) were assessed in all regions.
Results: 104 patients were included (62,5 % male, age: 26–84 years) and categorized in three age groups: young-age (age <60 years, $n = 40$), middle-age (age 60–71 years, $n = 33$), or old-age (age ≥ 72 years, $n = 31$) group. Compared to the young-age group, the old-age group had 1) lower median potential voltages at RA (4.65 [3.53–5.62]mV versus 5.94 [4.86–6.79]mV, $p = 0.001$) and 2) lower CV at RA (87.86 [82.53–96.67]cm/s versus 94.81 [90.14–98.59]cm/s, $p = 0.016$) and BB (83.38 [67.72–94.96]cm/s versus 98.84 [86.58–102.90]cm/s, $p = 0.005$).
Conclusions: Age-related electrophysiological changes in patients with structural heart disease include reduction in atrial potential voltages and slowing of CV. These changes were less pronounced in the middle-age group. This indicates that electrical remodeling is a combination of both the underlying heart disease and the aging process. However, the less pronounced changes in the middle-age group may reflect a more gradual progression of age-related remodeling.

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1. Introduction

Age is an important risk factor for development of atrial fibrillation (AF) [1,2]. While the prevalence of AF in the general population is only 0.7 % in individuals younger than 60 years, it increases significantly to 17.8 % at 85 years [1,3]. Aging can lead to significant structural changes in atrial tissue, such as fibrosis, atrial dilation, and impaired cardiomyocyte function [2,4]. This structural remodeling causes age-induced changes in atrial electrogram morphology, even during sinus rhythm (SR). Over time, structural and consequently electrical remodeling creates a substrate for AF development [2,4]. In patients with structural heart disease, age-induced remodeling comes on top of a certain pre-existing degree of structural remodeling due to pressure or volume overload.

However, it remains unknown whether age plays a prominent role in AF development in patients with structural heart disease. The goal of this study is, therefore, to investigate the severity of age-related electrical remodeling in patients undergoing surgery for structural heart disease. Electrical remodeling is assessed by quantifying electrical properties of the atria, using a high-

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resolution epicardial mapping approach of the right atrium (RA), left atrium (LA), Bachman's bundle (BB), and pulmonary vein area (PVA).

2. Methods

2.1. Study population

The study population consisted of patients ($\geq$18 years) without a history of AF undergoing elective aortic valve replacement, isolated aortic surgery or a combination of both in the Erasmus Medical Center Rotterdam. Patient characteristics were obtained from the medical records. This study was approved by the institutional medical ethical committee (MEC 2010-054 & MEC 2014-393) and written informed consent was obtained from all patients. All included patients were grouped into a young-age (age <60 years), middle-age (age 60–71 years), or old-age (age $\geq$72 years) group to create a comparable number of patients into these three groups. The age cut-off of 60 years is based on previous studies [2].

2.2. Mapping procedure

Epicardial high-resolution mapping was performed during open chest cardiac surgery, prior to extracorporeal circulation as previously described in detail [5,6]. Patients will be under general anesthesia and will be monitored continuously throughout the procedure. A temporal bipolar pacemaker wire attached to the RA wall served as a reference electrode and a steel wire fixed to subcutaneous tissue of the thoracic cavity or the chest spreader was used as the indifferent electrode. Furthermore, a surface electrocardiogram is recorded simultaneously with the electrograms.

Epicardial mapping was performed with a 64- (electrode diameter: 0.3 mm) with an interelectrode distance of 1.5 mm or with a 128- (electrode diameter: 0.6 mm), or a 192- (electrode diameter: 0.5 mm) electrode array. Interelectrode distances of both electrode arrays were 2 mm. Mapping was conducted by placing the electrode array along predefined epicardial areas on the RA, BB, PVA, and LA, systematically covering the entire atria, as shown in panel A of Fig. 1. Five seconds of SR were recorded at each mapping site, including a surface electrocardiogram, a calibration signal with an amplitude of 2 mV and a duration of 1000 ms, a bipolar reference electrogram (EGM), and all unipolar EGMs. Data were stored on a hard disk after amplification (gain 1000), filtering (bandwidth 0.5–400 Hz), sampling (1 kHz) and analogue to digital conversion (16bits).

2.3. Data analysis

Unipolar EGMs were semi-automatically analyzed using custom-made software [7]. Premature atrial extrasystolic beats, EGMs with injury potentials, and recording sites in which less than 25 % was annotated were excluded.

For all atrial potentials, the steepest negative slope was marked as the local activation time with a minimum slope threshold of 0.05 mV/ms. The amplitude threshold was set at 0.3 mV. Potential amplitude was defined as the peak-to-peak voltage of the steepest negative deflection. The voltages range P95-P5 was calculated as the difference between the 5th and 95th percentile of the voltage. Low-voltage areas (LVA) were defined as the proportion of potentials with an amplitude <1.0 mV. Local conduction velocity (CV) was computed as an average of velocity estimations between neighboring electrodes (longitudinal, transversal, and diagonal) using discrete velocity vectors as previously described [8] and as demonstrated in panel B of Fig. 1. The P95-P5 range of CV was calculated as the difference between the 5th and 95th percentile of the CV. For each individual mapping site, as illustrated in panel A of Fig. 1, parameters were calculated separately. Subsequently, the four RA locations were grouped together, as were the two LA and two PV locations. Median values, P5 and P95 were then used to represent each of the four main anatomical regions.

2.4. Detection of early post-operative atrial fibrillation

Early post-operative AF (ePoAF) was defined as AF occurring within the first five days after surgery, presenting for at least 30 s. Occurrence of ePoAF was confirmed by documentation in medical records.

2.5. Statistical analysis

Data were checked for normality. Normally distributed data are described as mean ± standard deviation (SD) and tested with an one-way ANOVA test. Skewed data are expressed as median [interquartile range] (IQR) and analyzed with a Kruskal-Wallis test or a Mann-Whitney *U* test. Categorical data are described as absolute number (percentage) and analyzed with a chi-square test.

A p-value <0.05 was considered statistically significant. A Bonferroni correction was applied for the comparison of the three age groups and a p-value <0.017 (=0.05/3) was considered statistically significant.

3. Results

3.1. Study population

Baseline characteristics of the study population (N = 104, 65 male (62,5 %)) are depicted in Table 1. The age distribution ranged from 26 to 84 years and is demonstrated in the upper panel of Fig. 2. Patients were categorized into a young-age (age <60 years, n = 40), middle-age (age 60–71 years, n = 33), or old-age (age $\geq$72 years, n = 31) group. Baseline characteristics of these 3 groups did not differ significantly, except for age (young-age: 53.07 [47.34–56.53] years versus middle-age: 66.29 [63.42–70.14] years versus old-age: 75. 24 [73.80–77.73] years, $p < 0.001$) and body mass index (BMI) (young-age: 29.00 (5.01) kg/m^2 versus middle-age: 26.41 (3.89) kg/m^2 versus old-age: 26.97 (3.49) kg/m^2, p = 0.025).

3.2. Age and ePoAF

Of the 104 patients, 41 (39.4 %) developed de novo ePoAF within the first five days after surgery. As expected, the ePoAF incidence was significantly higher in the old-age group (Old-age: 61.3 % (19 patients), middle-age: 33.3 % (11 patients), young-age: 27.5 % (11 patients), p = 0.011). Most patients developed ePoAF on the second or third day after surgery, as demonstrated in Table S1.

3.3. Age and potential voltage

The middle panel of Fig. 2 demonstrates typical examples of regional differences in median potential voltage in a 55- and a 77-years-old patient. The voltage maps demonstrate that the median potential voltage was lower in the older patient and differences between these two patients were most pronounced at the PVA and superior location of RA. Table S2 summarizes median potential voltage and potential voltages range for every mapping region separately in the three different patient groups.

Median potential at only the RA was lower in old-age patients

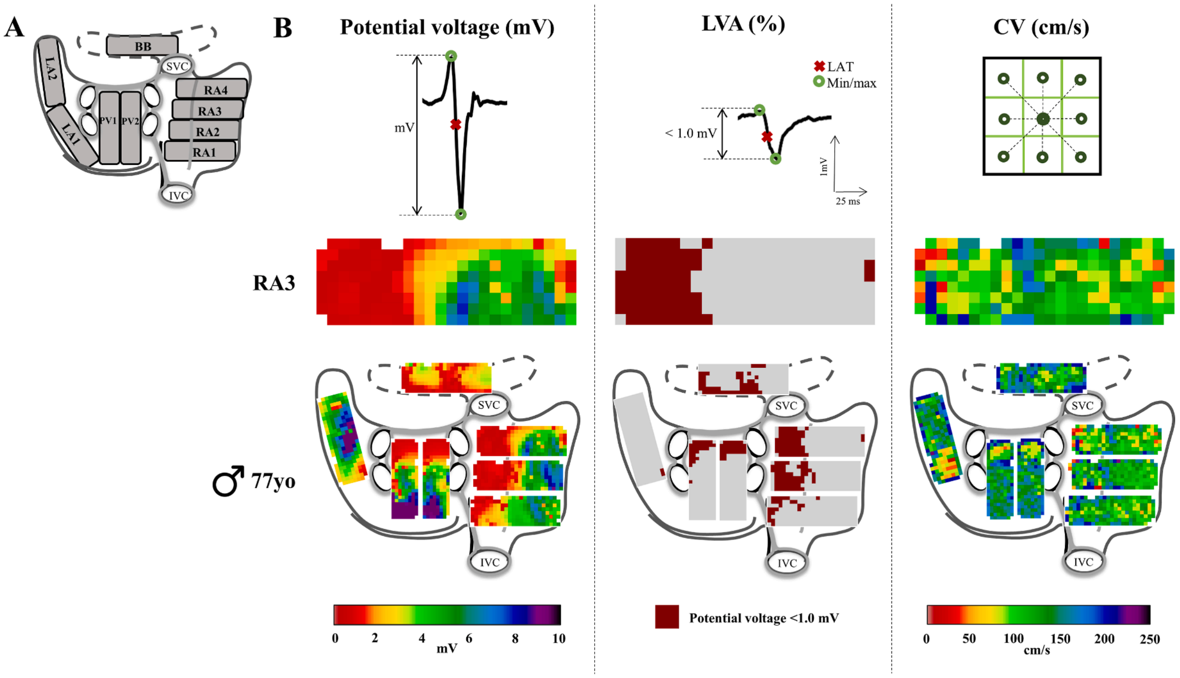

Fig. 1. Epicardial mapping procedure. Panel A: Projection of the 192-unipolar electrode array on a schematic posterior view of the atria. Panel B: the upper part shows that EGM voltage is determined as peak-to-peak amplitude of the steepest deflection, LVA is defined as the percentage of EGMs with a voltage <1.0 mV, and CV was calculated as an average of velocity estimations between neighboring electrodes using discrete velocity vectors. The middle part illustrates a color-coded voltage, LVA and CV map at mapping location RA3. In the lower part typical examples of color-coded signal maps from an old-age patient, showing the potential voltage, LVA, and CV. BB: Bachmann's bundle; CV: conduction velocity; EGM: electrocardiogram; IVC: inferior vena cava; LA: left atrium; LAT: local activation time; LVA: low-voltage area; PV: pulmonary vein; RA: right atrium; SVC: superior caval vein; yo: years old.

Table 1
Baseline characteristics of the study population.

Variables	Young-age group Age <60 years	Middle-age group Age 60–71 years	Old-age group Age ≥72 years	P-value
N	40	33	31	
Age, years, median (IQR)	53.07 [47.34–56.53]	66.29 [63.42–70.14]	75.24 [73.80–77.73]	**<0.001**
Male, N (%)	24 (60.00)	21 (63.64)	20 (64.52)	0.915
BMI, mean (SD)	29.00 (5.01)	26.41 (3.89)	26.97 (3.49)	**0.025**
Type of operation, N(%)				0.133
AVD (+Aorta)	33 (82.50)	32 (96.97)	28 (90.32)	
Aorta	7 (17.50)	1 (3.03)	4 (12.59)	
Aortic valve stenosis, N(%)				0.293
No	7 (17.50)	2 (6.06)	4 (12.90)	
Mild	3 (7.50)	0 (0.00)	1 (3.23)	
Moderate	4 (10.00)	2 (6.06)	1 (3.23)	
Severe	23 (57.50)	26 (78.79)	24 (77.42)	
Max peak gradient, mmHg, median (IQR)	61.00 [21.00–82.50]	75.55 [61.02–91.38]	71.00 [55.00–89.20]	0.125
Max velocity, m/s, median (IQR)	4.00 [2.41–4.38]	4.15 [3.88–4.65]	4.25 [3.37–4.73]	0.346
Asc. Aorta, mm, median (IQR)	45.00 [39.25–49.00]	43.50 [41.38–48.00]	46.50 [41.50–50.50]	0.353
Left atrial dilatation >45 mm/LAVI >35 ml/m^2, N (%)	10 (25.00)	6 (18.18)	6 (19.35)	0.745
Left ventricular function, N (%)				0.587
Normal (EF >55 %)	32 (80.00)	29 (87.88)	25 (80.65)	
Mild impairment (EF 46 %–55 %)	8 (20.00)	3 (9.09)	5 (16.13)	
Moderate impairment (EF 36 %–45 %)	0 (0.00)	1 (3.03)	1 (3.23)	
Hypertension, N (%)	12 (30.00)	11 (33.33)	16 (51.61)	0.147
Dyslipidemia, N (%)	5 (12.50)	7 (21.21)	7 (22.58)	0.526
Diabetes mellitus, N (%)	4 (10.00)	2 (6.06)	2 (6.45)	0.782
Myocardial infarction, N (%)	2 (5.00)	2 (6.06)	0 (0.00)	0.402

Asc.: Ascending; AVD: Aortic valve disease; BMI: body mass index; EF: ejection fraction; IQR: interquartile range; N: number; SD: Standard deviation.

compared to young-age patients (4.65 [3.53–5.62] mV versus 5.94 [4.86–6.79] mV, p = 0.001). At RA and BB, variation in potential voltages was significantly lower in the old-age group compared to the young-age group (P95-P5: RA: 8.30 [7.60–9.98] mV versus 10.36 [9.31–11.41] mV, p = 0.001 and BB: 7.71 [4.99–9.37] mV versus 10.76 [7.97–13.60] mV, p = 0.002). There were no differences between the middle-age group and the other two groups.

3.4. *Age and low-voltage potentials*

The lower panel in Fig. 2 shows an example of regional differences in LVAs between a 55- and 77-years-old patient. LVAs were more frequently observed in the older patient especially at the superior location of RA and the PVA.

There were no significant differences in LVA observed between

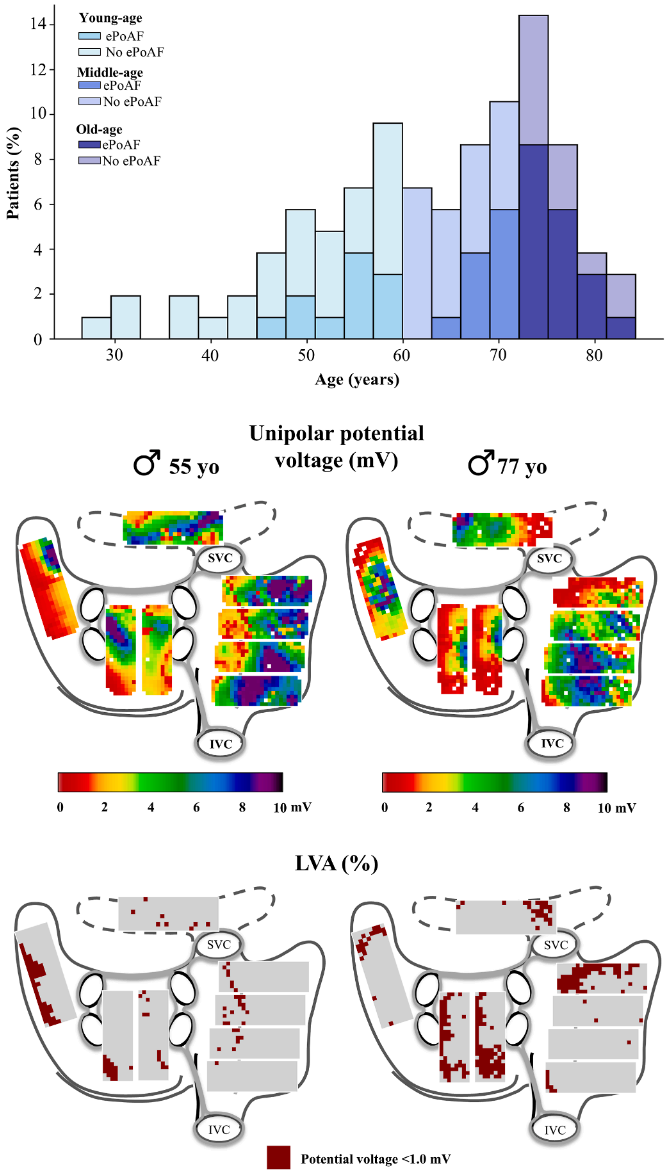

Fig. 2. The upper panel shows a histogram depicting the relative distribution of age and ePoAF in the study population. The lower panel demonstrates the unipolar potential voltage and LVA of a typical young-age (left) and old-age (right) patient. ePoAF: early post-operative atrial fibrillation; IVC: inferior vena cava; LVA: low-voltage area; SVC: superior vena cava; yo: years old.

the three groups at all locations, as demonstrated in Table S2.

3.5. Age and conduction velocity

Fig. 3 depicts median CV and the range of CV measured at the RA, BB, LA and PVA locations in the young-age group and old-age group separately. At RA and BB, CV was significantly lower in the old-age group compared to the young-age group (RA: 87.86 [82.53–96.67] cm/s versus 94.81 [90.14–98.59] cm/s, $p = 0.016$ and BB: 83.38 [67.72–94.96] cm/s versus 98.84 [86.58–102.90] cm/s, $p = 0.005$).

Variation in CV was highest in the old-age group compared to the young-age group at RA (122.33 [114.544–136.55] cm/s versus 112.26 [99.26–122.31] cm/s, $p = 0.002$). CV in the middle-age group did not differ between the young-age and the old-age group.

Median CV and variability in CV for all three groups and mapping locations separately are summarized in Table S2.

4. Discussion

4.1. Key findings

Electrical remodeling in old-age patients (≥72 years) with structural heart disease is characterized by lower median potential voltage at the RA and less variability in potential voltages at both the RA and BB compared to the young-age patients (<62 years). CV was lower in the old-age group at RA and BB, while variation in CV was higher at RA compared to the young-age group.

4.2. Electrophysiological changes related to age

The effects of aging on atrial electrophysiology are on top of a pre-existing arrhythmogenic substrate. In patients with ischemic heart disease, conduction disturbances are primarily caused by localized damage from infarction, inflammation, or atherosclerosis, resulting in local conduction blocks in the ischemic regions [9–11]. As demonstrated in prior mapping studies, conduction abnormalities in these patients are diffusely present throughout the atria, though particularly at the superior RA [12,13]. In addition, it has been demonstrated that there is no difference in the prevalence and severity of conduction abnormalities in the atria between patients with ischemic heart disease and valvular heart disease [13]. Ye et al. [14] demonstrated clear age-related changes in atrial electrophysiology by showing that abnormal electrogram morphologies were significantly more frequent at BB in patients older than 60 years compared to younger individuals with ischemic heart disease.

The majority of our study population consisted of patients with aortic valve stenosis. To the best of our knowledge, there is at present no data on the effects of ageing of atrial electrophysiology in this specific patient group. Age-related declines in CV and potential voltage have also been reported by other investigators. Kodjojo et al. [15] observed a decrease in CV in the RA and LA with increasing age in patients undergoing clinically indicated electrophysiological studies. Compared to our study population, however, their patients were much younger (mean age: 47 years) and had no structural heart disease.

Van der Does et al. [16], found in patients with ischemic heart disease a decrease in median potential voltage at both the RA and BB with advancing age. They also found more LVAs in older patients at RA, BB, and PVA. In our patients with aortic (valve) disease no significant differences were found in the LVAs. Although not significant, we did observe higher LVAs in the old-age group compared to the young age group at RA and BB, see Table S2. We did not find more LVAs in the old-age group at the PVA. A potential explanation may be that ischemic heart disease affects the atria more diffusely as these patients also more often have co-morbidities such as hypertension, diabetes mellitus and obesity which damage atrial tissue. Notably, we found a significant difference in BMI, as the young-age group has a significant higher BMI. Prior studies showed that elevated BMI is associated with an increase in LVAs [17]. Therefore, the higher BMI in the young-age group may have contributed to adverse atrial electrophysiological changes, potentially underestimating the difference in LVA burden between the young-age and old-age group. Also, all patients had the same underlying aortic (valve) disease which can lead to pressure and volume overload and could already exhibit atrial remodeling, particularly in the LA. There were no significant differences in the severity of the aortic stenosis based on max peak gradient or max velocity at baseline, suggesting that the severity of the underlying disease was comparable across the age groups.

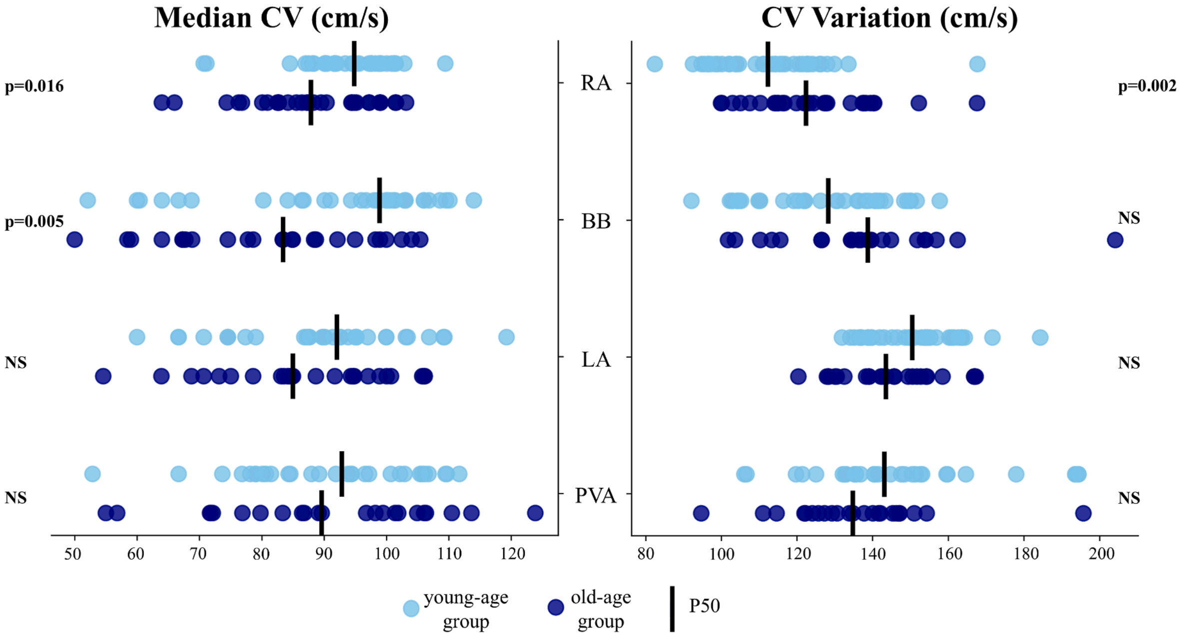

Fig. 3. Comparison of CV and the range of the CV from P5 to P95 between the young-age and old-age patients for all four atrial regions separately. BB: Bachmann's bundle; CV: conduction velocity; LA: left atrium; NS: not significant P: percentile; PVA: pulmonary vein area; RA: right atrium.

Therefore, the degree of atrial remodeling caused by underlying heart disease is expected to be similar. As a result, the additional effect of aging may be less pronounced, leading to minimal differences in LVAs between the three age groups at the LA.

4.3. Electrophysiological changes in the middle-age group

In our study, no significant differences in any of the assessed electrophysiological parameters were observed between the middle-age group and either the young-age or old-age group across all locations. These findings contrast with those from Kristler et al. [18], who reported decreased CV and potential voltage at the RA, along with a significant increase in LVAs in both their oldest (66.4 years) and middle aged (50 years) group compared to their youngest (24.7 years) group. The observed differences in CV, LVA, and potential voltage between the middle- and youngest groups can be explained by their far younger cohort. In addition, aging is a highly heterogeneous process, and biological age does not always align with chronological- and most likely also ‘electrophysiological’ age.

Factors such as comorbidities (e.g., diabetes, dyslipidemia), obesity, lifestyle, and genetic predisposition contribute to individual variation in biological aging, such that individuals with the same chronological age may differ significantly in their biological age [19]. This variability might have contributed to a more gradual change in electrophysiological parameters, limiting differences between the middle-age group and the other groups. Moreover, age-related electrophysiological changes may progress slower over time. This might explain why differences are more evident only in groups with larger age differences, as shown in our young-age and old-age groups.

4.4. Structural changes related to age

Several studies have shown that increasing age is associated with structural atrial remodeling, including loss of cardiomyocytes due to necrosis and apoptosis, which leads to cellular hypertrophy [20,21]. Aging is also accompanied by an increase in atrial fibrosis causing disruption of cell-to-cell interactions [20,21]. Another contributing factor from fibrosis is upregulation of matrix metalloproteinase-2, which degrades extracellular matrix components and promotes atrial dilation [21].

Over time, this structural remodeling can lead to changes in electrophysiological properties. Fibrosis induced cell-to-cell disruption in combination with atrial dilation result in areas of slow and discontinuous conduction [22]. This aligns with our findings, which showed that CV was significantly lower in the old-age group at both RA and BB compared to the young-age group. Additionally, the combined loss of excitable cardiomyocytes and increased fibrotic tissue reduces the amount of excitable tissue and disrupts coordinated electrical activation, giving rise to atrial potentials with lower voltages. These structural changes are consistent with our observation that the old-age group had a significant larger proportion of unipolar potential with low voltages at RA compared to the young-age group [21,22].

4.5. ePoAF and aging

The incidence of ePoAF was twice as high in the old-age group compared to the middle-age and young-age groups. A previous study conducted by van Schie et al. [23] provides evidence that the development of ePoAF is associated with the degree of pre-existing atrial remodeling. They demonstrated that compared to patients who remained in SR, those who developed ePoAF had a lower CV and a higher number of conduction block areas.

Our findings suggest that age-related atrial remodeling may further amplify the ePoAF risk. As individuals age, progressive fibrosis and slowing of CV becomes more pronounced [24]. These age-related changes combined with the pre-existing arrhythmogenic substrate due to the underlying heart disease, create an even more vulnerable substrate for arrhythmogenesis. Overall, we observed an increase in ePoAF incidence around the age of 65. This could reflect a threshold at which the cumulative effects of structural changes reach a critical point, ultimately manifesting as PoAF. This turning point may represent a shift from relatively mild arrhythmogenic substrate to a more severe substrate, making older patients particularly susceptible to PoAF. This concept is supported by studies showing a disproportionate rise in AF incidence with age [25].

4.6. Limitations

Since measurements were not repeated in the same individuals at different ages over time, we cannot investigate the time course of age-induced electrophysiological changes. Aging is a heterogeneous process, and chronological age does not necessarily reflect biological or cardiovascular age. Comorbidities and lifestyle contribute to this variability in cardiovascular aging, which most likely also influence atrial electrophysiology. By dividing our population into three age groups we aimed to divide the truly older patients from the truly younger patients. We only included patients without a history of AF. Hence, the older patients in our population may have a less severe age-induced arrhythmogenic substrate compared to patients of comparable ages who have already developed AF.

5. Conclusion

Age-related electrophysiological changes in patients with structural heart disease include reduction in atrial potential voltages and slowing of atrial conduction. In the middle-age group, age-related electrophysiological changes were less pronounced. These findings indicate that electrical remodeling is a combination of both the underlying heart disease and the aging process. However, the less pronounced changes in the middle-age group may reflect a more gradual progression of age-related remodeling.

CRediT authorship contribution statement

Nicole L.M. de Kruijf: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Anouk I. Freriks:** Writing – review & editing, Writing – original draft. **Mathijs S. van Schie:** Writing – review & editing. **Paul Knops:** Writing – review & editing, Conceptualization. **Vehpi Yildirim:** Writing – review & editing. **Yannick J.H.J. Taverne:** Writing – review & editing. **Maryam Kavousi:** Writing – review & editing. **Natasja M.S. de Groot:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Disclosures

None.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Conflict of interest

The authors have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tma.2025.08.001.

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