Age-associated changes in electrophysiologic remodeling: a potential contributor to initiation of atrial fibrillation

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Abstract

Objective: Although the incidence of atrial fibrillation (AF) increases with age, the cellular electrophysiological changes that render the atria of aged individuals more susceptible to AF remain poorly understood. We hypothesized that dispersion of atrial repolarization increases with aging, creating a substrate for initiation of AF.

Methods: Four groups of dogs were studied: adult and old dogs in normal sinus rhythm (SR) and adult and old dogs with chronic AF (CAF) induced by rapid atrial pacing. In each dog, action potentials (AP) were recorded with microelectrodes from isolated endocardial preparations of four regions of right atrium and three regions of left atrium. Two indices of AP duration (APD) heterogeneity were obtained in each dog by calculating standard deviation (SD) and the coefficient of variation (COV=[SD/mean]×100%).

Results: In SR groups, APD averaged across all regions was significantly longer in old than in adult tissues. Both indices of APD heterogeneity were higher in old dogs in comparison to adult. At both ages, CAF was associated with significant APD shortening and a decrease in APD adaptation to rate. While CAF significantly increased both indices of APD heterogeneity in adult dogs, it significantly decreased them in old dogs.

Conclusions: The increase of spatial variability in repolarization in old atria may contribute to the initiation of AF in the aged. CAF-induced APD shortening and a decrease in APD adaptation appear to be important for the maintenance of sustained AF in both adult and old atria. The CAF-induced increase in dispersion of repolarization may be important for AF stabilization in adults, while previously reported fibrosis and slowed conduction of premature beats may be important in the old for both AF initiation during SR and subsequent stabilization of AF.

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1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in man, and its prevalence increases with age [1–4]. Although the functional mechanisms underlying AF have been investigated in humans and in animal models, the cellular electrophysiological changes that render the atria of aged individuals more susceptible to AF than those of adults remain poorly understood.

AF is a reentrant arrhythmia [5], and the potential importance of dispersion of atrial refractoriness for the induction and maintenance of reentry has long been recognized [6]. Although some dispersion of repolarization is present in normal atria [7–9], AF does not arise spontaneously in healthy hearts. Rather, it appears that increased dispersion of repolarization and refractoriness are important factors in experimental models and clinical populations with AF. For example, increased dispersion of refractoriness plays a central role in vagally induced AF in adult dogs (age not
specified) \cite{10,11} and is the major determinant of AF induction by premature beats \cite{10}. It is associated with paroxysmal AF in adult and old human hearts \cite{12,13} and is seen as a result of atrial tachycardia in adult animal models \cite{14,15}.

In these experiments, we tested the hypothesis that dispersion of atrial repolarization increases with age, creating a substrate that would favor the initiation of AF. We studied atrial heterogeneity by recording AP from preparations isolated from seven atrial regions of four groups of dogs: adult and old dogs in normal sinus rhythm and adult and old dogs with chronic AF (CAF).

2. Methods

2.1. Study animals

The investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996) and the rules of the Columbia University Institutional Animal Care and Use Committee.

Twelve adult (1–3 years) and 12 old (more than 10 years) mongrels of either sex weighing 16–25 kg were used in the study. The ages of the dogs were estimated by a veterinarian based on standard measures for age, including dentition, coat, eyes and musculoskeletal and conformational descriptors. Six-lead ECG measurements were made on conscious dogs resting quietly using Dr Vetter software (Dr Vetter, Baden-Baden, Germany). Dogs of each age were randomly divided into two groups of six animals each. Group I was used to study atrial electrophysiological properties of animals in sinus rhythm; group II to study CAF, defined as persistence of AF for at least 5 days.

2.2. Induction of chronic AF

Animals were anesthetized with thiopental sodium (17 mg/kg IV) and ventilated with isoflurane, 1.5–2%, and O2, 2 l/min. Morphine sulfate 0.15 mg/kg was injected into the epidural space for postoperative analgesia. Using sterile techniques, a right intercostal thoracotomy was performed, the pericardium was opened, and the heart was suspended in a pericardial cradle. Bipolar Medtronic active fixation leads (Model 5058) were attached to the epicardium of the left atrial appendage and right ventricular free wall. The leads were tunneled subcutaneously, and the left atrial lead was connected to a Medtronic Itrel Pulse Generator 7424, while the right ventricular lead was connected to a single chamber pulse generator (Minix 8340). Both pulse generators were implanted in subcutaneous pockets on the right posterior chest wall. Complete heart block was produced by injection of 0.1–0.3 ml of 40% formaldehyde into the AV node \cite{16}. The ventricular pulse generator was programmed into a VVI mode at 60 bpm. After the incisions were closed and the dogs recovered from anesthesia, they were monitored for 2–3 days in the recovery room before moving to routine care. The dogs were treated prophylactically with cefazolin, 25 mg/kg IV once before surgery and twice daily for 2 days after surgery. They were allowed to stabilize for 3–4 weeks and then were paced from the left atrial appendage at 600 bpm to induce CAF. Dogs were used for in vitro study after they had been in CAF for ≥5 days.

2.3. Atrial preparations

On the study day, animals were anesthetized with sodium pentobarbital (30 mg/kg i.v.). Their hearts were removed through a left lateral thoracotomy and immersed in warm (35 °C) Tyrode solution equilibrated with 95% O2/5% CO2 and containing (mmol/l): NaCl 131, NaHCO3 18, KCl 4, CaCl2 2.7, MgCl2 0.5, NaH2PO4 1.8 and dextrose 5.5. Tissue strips (~10×5×0.5 mm) from four regions of the right atrium (crista terminalis, appendage, atrioventricular ring and pectinate muscles) and three regions of the left atrium (appendage, atrioventricular ring and free wall near the pulmonary veins) were then dissected. The preparations were placed in a tissue bath endocardial side up and superfused with control Tyrode solution (T=37 °C, pH 7.35±0.05). Solution was pumped at 12 ml/min, changing chamber content three times/minute. The bath was connected to ground via a 3 M KCl/Ag/AgCl junction. Tissues equilibrated in the Tyrode solution for 2 h before the study commenced.

2.4. Electrophysiologic studies

The experiments were performed simultaneously by two investigators at separate microelectrode stations. The sequence of preparations used was randomized. All preparations were impaled with 3 mol/l KCl-filled glass capillary microelectrodes having tip resistances of 10–20 MΩ. The maximum upstroke velocity of the action potentials (AP) (V_max) was obtained by electronic differentiation with an operational amplifier. The electrodes were coupled by an Ag/AgCl junction to an amplifier with high input impedance and input capacity neutralization. Transmembrane action potentials and V_max signals were digitized with an analog-to-digital converter (D-210, DATAQ Instruments) and stored to PC for subsequent analysis.

For stimulation of preparations, standard techniques were used to deliver square-wave pulses 1.0 ms in duration and 1.5 times threshold through bipolar PTFE-coated silver electrodes. Experiments were started after 2 h of superfusion in control Tyrode solution at which time preparations had fully recovered and displayed stable electrophysiological characteristics. To investigate frequency dependence of AP parameters, preparations were driven at cycle lengths (CL) of 2000, 1000, 500 and 250 ms in sequence. Each frequency was maintained for 3 min before data were collected. Two impalements were maintained throughout the entire protocol in each preparation.
2.5. Data analysis

Microelectrode data were analyzed from impalements maintained throughout the course of each experiment. AP characteristics measured were MDP, amplitude of phase 0 (APA), maximum upstroke velocity ($V_{\text{max}}$), potential at the peak of the plateau (plateau) and AP duration (APD) to 30%, 50% and 90% repolarization (APD$_{30}$, APD$_{50}$ and APD$_{90}$, respectively). An index of APD$_{90}$ heterogeneity in each dog was obtained by calculating standard deviation (SD) and the coefficient of variation (COV APD$_{90}$=[SD/mean]$\times100$%) of the regional APD$_{90}$ values, as we have reported previously [17].

Data are expressed as mean±S.E.M. The statistical techniques used were one-way or two-way analysis of variance for repeated or nonrepeated measures, with Bonferroni test when the $F$ value permitted. Significance was determined at $P<$0.05.

3. Results

3.1. ECG data

ECG data for one adult and one old group studied in sinus rhythm are shown in Table 1. As previously reported [18], the ECGs of the old dogs manifested longer P-wave durations and PR intervals than adults. Other variables did not differ. There was no difference between the two groups in time to onset of CAF; the adult dogs developed CAF after 49±4 days and old dogs after 58±9 days of atrial pacing ($P>$0.05).

3.2. Atrial electrophysiology of adult and old dogs in SR

3.2.1. Action potential characteristics

Representative recordings and summary data for major AP parameters averaged across all atrial regions in age group in sinus rhythm are shown in Fig. 1. Tissues from old atria were depolarized (B), had lower $V_{\text{max}}$ (C) and longer AP duration (D) in comparison to adult. The values for other AP characteristics are summarized in Table 2A; AP amplitude and plateau potential were significantly lower in old tissue. Similar differences in AP contour between adult and old atria have been demonstrated for pectinate muscle [18] and Bachmann bundle [19] preparations.

3.2.2. Heterogeneity of AP duration

Fig. 2A depicts AP recorded from all regions in one adult and one old dog in sinus rhythm. A prominent interregional variability in shape and duration was seen in both dogs. Superposition of all AP in each dog reveals greater variability in AP duration in the atria of the old dog. Fig. 2B shows values of APD$_{90}$ of all action potentials.
recorded in the two groups. The range of APD90 distribution was wider in the old group in comparison to adults as a result of an increase in duration occurring mainly in the right atrium.

Fig. 2B also shows that a pattern of APD90 distribution along the atrial muscle varied among dogs; that is, the shortest and longest APD90 were observed in different regions in different dogs. Therefore, to characterize the heterogeneity of APD90, we used a measure of global dispersion that is derived from recordings at multiple sites without regard to their location. Global dispersion can be characterized by range (maximum difference), standard deviation (SD) and coefficient of variation (COV) [20]. Because the range is dependent only upon the two extremes and is greatly affected by random variation, we used instead the SD (absolute measure) and the COV (relative measure). The values of interregional SD APD90 and the COV APD90 were calculated in each dog and averaged in each group (Fig. 3). Both indices of APD90 variability were significantly higher in old than in adult tissues at all cycle lengths.

### Table 2
Averaged parameters of action potentials recorded in atrial preparations obtained from adult and old dogs in sinus rhythm (SR) and with chronic atrial fibrillation (CAF) at a cycle length of 1000 ms

<table>
<thead>
<tr>
<th>Group</th>
<th>APA (mV)</th>
<th>Plateau (ms)</th>
<th>APD30 (ms)</th>
<th>APD50 (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(A) SR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>95±2</td>
<td>-10±1</td>
<td>31±4</td>
<td>59±4</td>
</tr>
<tr>
<td>Old</td>
<td>84±3*</td>
<td>-15±2*</td>
<td>29±3</td>
<td>68±4</td>
</tr>
<tr>
<td><strong>(B) CAF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>102±3**</td>
<td>-4±2**</td>
<td>25±4</td>
<td>53±4</td>
</tr>
<tr>
<td>Old</td>
<td>99±1**</td>
<td>-6±1**</td>
<td>20±1**</td>
<td>53±2**</td>
</tr>
</tbody>
</table>

APA—action potential amplitude; plateau—plateau potential; APD30 and APD50—action potential duration to 30% and 50% repolarization. Mean ±S.E.M. are shown (n=84 per group).

* P<0.05 versus adult.
** P<0.05 versus the same age group in SR.

3.2.3. Heterogeneity of MDP and \( V_{\text{max}} \)

Prominent interregional variability was observed not only for AP duration but for MDP and \( V_{\text{max}} \). Although

![Fig. 2](https://example.com/fig2.png)

Fig. 2. Heterogeneity of AP duration in adult and old dogs in normal sinus rhythm. (A) Transmembrane potentials recorded from seven regions of one adult (left) and one old (right) dog at a cycle length of 1000 ms. In the right lower image at each age, the upstrokes of all AP are superimposed to facilitate comparison of the extent of dispersion. (B) Values of APD90 obtained from each impalement in all regions are shown at a cycle length of 1000 ms for each adult and old dog. Dotted lines are drawn for maximum and minimum values in each group; solid lines represent APD90 averaged over all regions. Two impalements were made in each preparation. Preparations from four regions of the right atrium, pectinate muscles (RPM), crista terminalis (RCT), atrioventricular ring (RAVR) and appendage (RAA), and three regions of the left atrium, free wall near the pulmonary veins (LPV), atrioventricular ring (LAVR) and appendage (LAA), were dissected in each dog.
variation of these parameters was seen in every adult and old dog, the extent of the variation was wider in old atria in comparison to adult. Fig. 4 shows indices of MDP (A and B) and $V_{\text{max}}$ (C and D) variability in both sinus rhythm groups. Similar to APD$_{90}$ dispersion, both indices of MDP and $V_{\text{max}}$ variability were significantly higher in old than in adult tissues. Regression analysis showed no correlation between APD$_{90}$ and MDP and a strong and significant correlation between $V_{\text{max}}$ and MDP (at a cycle length of 1000 ms, $V_{\text{max}} = -8.15 \times$ MDP $-443$, $r = 0.740$, $P < 0.05$). The data suggest that, whereas AP duration and MDP varied independently, interregional heterogeneity of $V_{\text{max}}$ resulted from heterogeneity of MDP and increased dispersion of $V_{\text{max}}$ in old atria reflected increased dispersion of MDP.

3.3. CAF-associated alterations in atrial electrophysiology of adult and old dogs

3.3.1. Changes in action potential characteristics

CAF and rapid atrial pacing can lead to electrical remodeling of myocardium, but this may not be the same in adult and old animals. Therefore, Fig. 5 compares major AP parameters of adult and old dogs in sinus rhythm and those with CAF. CAF was associated with a significant hyperpolarization of the membrane in both adult and old tissues (B and F). The extent of hyperpolarization was the same in both CAF groups leaving adult tissue more polarized than old. CAF led to a significant increase in $V_{\text{max}}$ in old (G) but not adult (C) tissues such that CAF values for $V_{\text{max}}$ in both groups became similar. APD shortened with CAF in both adult (D) and old (H) groups with more shortening in the latter resulting in no difference between APD$_{90}$–CL curves in CAF groups. In addition, in both tissues, CAF was associated with a significant decrease in APD adaptation to rate change (D and H). The effects of CAF on other AP characteristics in adult and old dogs are summarized in Table 2 (compare parts [A] and [B]). CAF led to a significant increase of AP amplitude and plateau potential at both ages and shortening of APD$_{30}$ and APD$_{50}$ in old atrial tissue. No differences in AP characteristics were seen between adult and old tissues obtained from CAF dogs (Table 2B).

3.3.2. Effects of CAF on APD heterogeneity

Fig. 6A depicts AP recorded from all regions in one adult and one old dog with CAF. Similar to dogs in sinus rhythm (Fig. 2A), a prominent interregional variability in shape and duration was seen in both dogs with CAF. However, unlike dogs in sinus rhythm (Fig. 2A), superposition of all AP reveals a greater variability in APD in the atria of adult dogs (Fig. 6A—left panel). Fig. 6B shows values of APD$_{90}$ of all action potentials recorded in the two CAF groups. In contrast to dogs in sinus rhythm (Fig. 2B), the range of APD$_{90}$ distribution was wider in adults than in the old. At both ages, APD shortened significantly compared to animals in sinus rhythm.

While average APD approached the same values with CAF in both adult and old dogs (Fig. 6B), CAF was associated with significant and opposite changes of both indices of APD variability in adult and old tissues (Fig. 7); CAF led to an increase of APD dispersion in adults (A and B) and a decrease in old dogs (C and D). As a result, in CAF groups, there were no differences in SD APD$_{90}$ between adult and old dogs (A and C), and the values of COV APD$_{90}$ were significantly higher in adult than in old tissues (B and D). In sum, CAF results in an APD that is more uniform in old atria and less uniform in adults.

3.3.3. Effects of CAF on MDP and $V_{\text{max}}$ heterogeneity

CAF was associated with significant changes of indices of MDP and $V_{\text{max}}$ variability in both adult and old dogs (Fig. 8). As for APD$_{90}$ variability, the directions of the changes in adults were opposite to those in the old. As a result, in CAF groups, the values of SD MDP and SD $V_{\text{max}}$ were significantly higher in adult than in old tissues. Qualitatively similar results
were found for COV MDP and COV $V_{max}$ (data not shown).

4. Discussion

4.1. Aging-associated changes in atrial electrophysiology

A central finding in the present study is a larger interregional dispersion of AP duration in old in comparison to adult atria in dogs in sinus rhythm. Dispersion of refractoriness is a frequent precipitating factor in the generation of AF [5,21]. Spatial differences in refractoriness may cause transient conduction block in localized areas, and slow conduction in such a setting may be dependent on encroachment into the relative refractory period [22]. It has been demonstrated that areas with a relatively long refractory period coincide with sites of conduction block and intramyocardial reentry [22]. Thus, aging-associated increases in interregional dispersion of APD might render old atria that are in sinus rhythm more susceptible to initiation of reentrant arrhythmias.

We questioned the extent to which our data for dispersion in isolated tissues reflect data from the intact heart. Fareh et al. [15] measured ERP at a CL=300 ms in five atrial regions of the canine heart in situ. They found that, in a control group, COV ERP=14.9±0.9% and significantly increased to 20.7±0.9% in dogs subjected to rapid atrial pacing for 24 h. Our results for APD heterogeneity in adults are similar to those of Fareh et al. for ERP; at CL=250 ms, COV APD=13.6±1.1% in tissues from animals in sinus rhythm and increased to 18.4±2.0% ($P<0.05$) in the chronic AF group (Fig. 7B).

In addition to interregional dispersion of AP duration, increased spatial heterogeneity in conduction may provide a basis for unidirectional conduction block, creating a substrate for atrial reentrant arrhythmias [23,24]. Conduction velocity is determined by the active membrane properties of each cell (largely a function of $I_{Na}$) and tissue resistivity (electrical coupling among cells) [25]. Although we did not measure conduction velocity in this study, we did record maximum upstroke velocity, which reflects $I_{Na}$. We found that dispersion of $V_{max}$ was significantly greater in old atria in comparison to adult that implies increased heterogeneity.
in conduction in old atria. In an earlier study of just one region of atrium (right pectinate muscle), we found that the age-dependent attenuation of the voltage-time course of repolarization was such that premature impulses propagated more slowly in old than adult atria [18]. Hence, there is not only an implied increase in dispersion of conduction velocity seen in the present data but an earlier direct measure of slowed conduction in the literature [18].

The mechanisms for increased dispersion of AP parameters in old atria are interpretable in light of recent data on the ionic mechanisms of regional heterogeneity in normal adult and old atria. In one study, regional differences in canine right atrial AP morphology and duration during sinus rhythm were reported to result from variations in the densities of $I_{to}$, $I_{Ca}$ and $I_{Kr}$ [9]. However, this study did not control for the ages of the adult animals. In another study, we examined changes in inward and outward currents in old canine right atrial pectinate muscle. Myocytes from old animals were larger than adult as seen in an increased membrane capacitance [26]. When $Ca^{2+}$ was used as the charge carrier and $Ca_{i}$ chelated with BAPTA, $Ca^{2+}$ currents were nearly 50% lower in old versus adult right atrial free wall cells obtained form animals in sinus rhythm [26]. Peak $I_{Ca,L}$ also decayed faster and had an altered recovery from inactivation. Peak $Ba^{2+}$ currents in aged atrial cells were reduced by nearly 40%, and there was some acceleration of decay. Thus, $I_{Ca,L}$ is reduced in aged cells partially due to the greater capacitance of these cells and partially due to $Ca^{2+}$ dependent and independent changes in $Ca^{2+}$ channel kinetics.

With regard to outward currents from hearts in sinus rhythm, sustained outward potassium current ($I_{sus}$) was significantly larger, and the decay of $I_{to}$ and the time constant of recovery of $I_{to}$ were slower in old than adult.
right atrial cells [27]. However, $K$ currents in left atrial cells from the same old atria did not show the same prominent increase in $I_{\text{sus}}$ seen with aging in right atrial cells. This appears to be due to chamber-specific (and likely region-specific) differences in a tetraethylammonium-sensitive current [27]. These data suggest that aging-associated changes in ionic currents may be spatially heterogeneous, thereby contributing to the increased dispersion of AP parameters. Finally, there is also an increased fibrosis in old atrial tissue in sinus rhythm [18]. This adds a structural substrate favoring reentry to the electrophysiologic substrate we have just described.

4.2. Impact of CAF on electrophysiology of adult and old atria

Many experimental studies have demonstrated that AF remodels atrial electrophysiology to facilitate its own recurrence [28–31]. To date, all such studies have been performed in normal adult animals. AF-induced electrophysiological remodeling in the adult results from rapid atrial activation, and rapid atrial pacing produces similar action potential changes [29,30]. Yet, the mechanisms for the action potential changes seen with this remodeling may differ, as we have shown previously. In our study of $I_{\text{to}}$ and $I_{\text{sus}}$ in right atrium from adult dogs in sinus rhythm and in AF, we found that chronic AF cells have reduced $I_{\text{to}}$ versus control [32]. It appeared that $I_{\text{to}}$ in AF was remodeled by the AF per se rather than being consequent to the rapid pacing rate used to induce AF. The major electrophysiologic characteristics of electrical remodeling are reduction in the atrial refractory period [28,29] and loss of APD adaptation to rate [29]. In agreement with these data, we found CAF to be associated with a marked shortening of APD90 and a decrease in its adaptation to rate at both ages. In adult atria, AF-induced decreases in APD have been explained by the reduction in $I_{\text{Ca,L}}$ [31,33]. In our previous studies of adult canine right atrial free wall, enhanced Ca\(^{2+}\)-dependent inactivation processes contributed significantly to the reduced Ca\(^{2+}\) currents in the setting of nonsustained AF, whereas in chronic AF (the model used in the present study), the change was interpretable as resulting from reduced protein levels accompanying the reduction in $I_{\text{Ca,L}}$ [34]. The present study also demonstrated a marked hyperpolarization of atrial tissues in both adult and old CAF groups. Such membrane hyperpolarization in pacing-induced AF has been noted previously in adult tissues [35] and may be a consequence of increased basal $I_{\text{K1}}$ [33].
It previously has been shown in adult animals that pacing-induced atrial remodeling is spatially heterogeneous, increasing the heterogeneity of atrial refractoriness \[14,15\]. The combination of decreased refractoriness and increased heterogeneity of refractoriness may promote multiple-circuit reentry and therefore contribute to AF maintenance\[15,36\]. The adult canine data in our study are consistent with these observations in that CAF is associated with a significant increase in spatial heterogeneity of AP duration. However, in old dogs, the effects of CAF on heterogeneity of AP duration are the opposite in that CAF reduced the spatial heterogeneity of APD. What is common to both ages is the shortening of APD and the decrease in APD adaptation to rate changes. Both these effects are more prominent in old tissue resulting in a complete coincidence of APD–CL curves in both ages. Thus, AF was sustained in two different substrates: one with short AP duration and with expanded heterogeneity of AP parameters (adult) and one with short AP duration but limited heterogeneity (old). This emphasizes the importance of decreased AP duration and adaptation to rate changes as important factors with regard to maintenance of AF across ages. These data also suggest that the increased dispersion in atrial electrophysiology that occurs in adults may be an important additional contributory factor for AF stabilization at this age, while the occurrence of fibrosis and slowed conduction of premature beats that has been demonstrated previously \[18,37\] may be more contributory in the old.

4.3. Study limitations

Although the incidence of AF increases with age in human subjects \(1–4\), we did not find greater inducibility of AF in old canine atria. One explanation is that mechanisms of rapid pacing-induced AF may be significantly different from those of disease- or age-associated AF in human subjects. We know that, even in the dog, the electrophysiologic changes and pharmacological responsiveness of AF induced by pacing differ from those occurring when a congestive failure-induced AF model is used (reviewed in Ref. \[38\]). Hence, there is a very specific scope of the present studies (i.e., electrophysiologic profile with aging in
absence of disease state and with addition of rapid pacing), and the superimposition of experimental or clinical disease states or instances of neurohumoral modulation may well result in profiles of AF manifesting action potential characteristics different from those reported here.

5. Conclusions

Aging is associated with a significant interregional increase in dispersion of atrial AP parameters that may contribute to the initiation of AF. CAF induces APD shortening and a decrease in APD adaptation to rate changes at both ages but affects dispersion of AP parameters differently in adult and old atria, increasing dispersion in the adult and decreasing it in the old. Thus, CAF-induced remodeling may create a different substrate for its maintenance in adult and old atria. The increased dispersion of atrial electrophysiology may be an important contributory factor for AF stabilization in the adult, while the occurrence of fibrosis and slowed conduction of premature beats may be more important in the old. An important implication is that cardioversion in old atria may be complicated by a higher incidence of recurrence of AF as a result of the inhomogeneity of repolarization of old atria in sinus rhythm.

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