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In Humans, Chronic Atrial Fibrillation Decreases the Transient Outward Current and Ultrarapid Component of the Delayed Rectifier Current Differentially on Each Atria and Increases the Slow Component of the Delayed Rectifier Current in Both

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Objectives The purpose of this study was to compare the voltage-dependent K^+ currents of human cells of the right and left atria and determine whether electrical remodeling produced by chronic atrial fibrillation (CAF) is chamber-specific.

Background Several data point to the existence of interatrial differences in the repolarizing currents. Therefore, it could be possible that CAF-induced electrical remodeling differentially affects voltage-dependent K^+ currents in each atrium.

Methods Currents were recorded using the whole-cell patch-clamp in myocytes from left (LAA) and right atrial appendages (RAA) obtained from sinus rhythm (SR) and CAF patients.

Results In SR, LAA and RAA myocytes were divided in 3 types, according to their main voltage-dependent repolarizing K^+ current. CAF differentially modified the proportion of these 3 types of cells on each atrium. CAF reduced the Ca^{2+}-independent 4-aminopyridine-sensitive component of the transient outward current (I_{to1}) more markedly in the LAA than in the RAA. Therefore, an atrial right-to-left I_{to1} gradient was created by CAF. In contrast, the ultrarapid component of the delayed rectifier current (I_{Kur}) was more markedly reduced in the RAA than in the LAA, thus abolishing the atrial right-to-left I_{Kur} gradient observed in SR. Importantly, in both atria, CAF increased the slow component of the delayed rectifier current (I_{Ks}).

Conclusions Our results demonstrated that in SR there are intra-atrial heterogeneities in the repolarizing currents. CAF decreases I_{to1} and I_{Kur} differentially in each atrium and increases I_{Ks} in both atria, an effect that further promotes re-entry. (J Am Coll Cardiol 2010;55:2346–54) © 2010 by the American College of Cardiology Foundation

At least 2 types of atrial action potentials (APs) may be recorded in human right atrial (RA) preparations: those with a prominent spike of fast repolarization followed by a plateau and those without spike and prominent plateau phase (1). More recently, 3 RA cell types were identified on the basis of their outward K^+ repolarizing currents and, consequently, on the morphology of their AP (2). In humans, as in other species, the atrial refractory period (ARP) is shorter in the left atrium (LA) than the RA (3), which points to interatrial differences in the currents underlying the AP. In fact, inward rectifier currents have been shown to be larger in cells from the LA than the RA of animals and humans (4,5). However, studies comparing the voltage-dependent repolarizing currents in the human RA and LA are scarce or absent. A genomic comparison among heart chambers did not find ion channel gene expression differences between RA and LA (6).

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Acute atrial fibrillation (AF) and chronic atrial fibrillation (CAF) are characterized by shortening of ARP and AP duration (APD), increased ARP dispersion, and loss of APD adaptation to changes in frequency (7,8). Such alterations in atrial electrical properties (electrical remodeling) are caused by derangements in ion channel expression (7,9). Surprisingly, in all studies thus far, human RA cells were considered identical, and no data were provided on whether electrical remodeling differentially affected diverse RA cell types.

Studies in animal models and humans have demonstrated LA versus RA differences in AF frequency and dynamics, with the LA usually activating at faster rates (4,5,10,11). This is particularly evident in patients with paroxysmal AF (10,11). Assuming that electrical remodeling is a consequence of the fast frequency of activation (9), it is possible that LA remodeling is more marked than RA. However, it is currently unknown whether the electrical remodeling process is chamber specific. Therefore, we studied the distribution of cell types in the right atrial appendages (RAAs) and left atrial appendages (LAAs) of sinus rhythm (SR) patients according to differences in the main voltage-dependent K^+ current. We also determined how CAF modified this distribution in each atrium. Our results demonstrate that in SR there is heterogeneity in the repolarizing currents within each atrium. CAF decreases the Ca^{2+}-independent 4-aminopyridine (4-AP)-sensitive component of the transient outward current (I_{to1}) and the ultrarapid component of the delayed rectifier (I_{Kur}) differentially on each atrium. Furthermore, CAF increases the slow component of the delayed rectifier (I_{Ks}) in both. This latter effect may contribute to CAF-induced shortening of APD and to promote re-entry.

Methods

The study was approved by the Investigation Committee of the Hospital Universitario Gregorio Marañón (CNIC-13) and conformed to the principles outlined in the Declaration of Helsinki. Each patient gave written informed consent.

Myocytes were enzymatically isolated (12) from RAA and LAA pieces obtained from SR and CAF patients undergoing cardiac surgery (Online Table 1). Currents were recorded using the whole-cell patch-clamp configuration. messenger ribonucleic acid (mRNA) was isolated from human atrial appendages, and semiquantitative reverse transcription polymerase chain reaction analysis (13) was performed using the primers described in Online Table 2.

Results are expressed as mean ± SEM. Unpaired *t* test or 1-way analysis of variance followed by Newman-Keuls test were used to assess statistical significance where appropriate. Comparisons between categorical variables were done using Fisher exact test. A value of $p < 0.05$ was considered significant. An expanded Methods section is available in the Online Appendix.

Results

For electrophysiological experiments, we analyzed 22 and 11 samples obtained from patients in SR and CAF, respectively. Figure 1A shows the number of myocytes from the LAA and RAA studied from each group of patients. The mean size of LAA and RAA myocytes from CAF patients was greater than that of myocytes from SR patients as assessed by cell capacitance measurement. However, in both SR and CAF patients, cell capacitance of LAA myocytes was indistinguishable from RAA myocytes (Fig. 1B).

Considering the main K^+ current elicited at plateau potentials, and following standardized criteria (Online Appendix), 3 types of cells can be differentiated (Fig. 2A). Currents were recorded in randomly selected rod-shaped healthy myocytes. Figure 2A shows families of currents elicited by 250-ms pulses from −80 mV to potentials ranging from −90 to +50 mV in 3 representative cells. Approximately 35% of the LAA myocytes from SR patients exhibited an outward current mainly composed of a fast-activating and inactivating component (Fig. 2B). In these cells, the amplitude of the sustained component recorded at the end of the pulse was ~20% of the peak amplitude. Therefore, the main repolarizing current during the plateau phase in these cells was the I_{to1} (I_{to1}-predominant). I_{to1} was completely absent in 20% of cells, in which a fast-activating noninactivating component was recorded (I_{sus}-predominant) (Fig. 2A). In I_{sus}-predominant cells, the current amplitude at the end of the depolarizing pulses was ~85% of the peak current. Finally, in 45% of LAA cells, an intermediate pattern was detected (i.e., the cells exhibited both an I_{to1} and a sustained component that represented >50% of the peak current [intermediate cells]) (Figs. 2A and 2B). Interestingly, in SR the distribution of these cell types in the LAA and the RAA was almost identical (Fig. 2B). Figure 1C shows the capacitance of each cell type in SR samples. In both atria, I_{to1}-predominant cells were significantly smaller than I_{sus}-predominant cells.

Figure 2C shows the percentage of each myocyte type found in LAA and RAA samples from CAF patients. In the LAA, we detected a significant decrease in the percentage of I_{to1}-predominant cells, which was accompanied by an increase in the percentage of cells that exhibited the intermediate pattern. In the RAA, CAF also significantly decreased

Abbreviations and Acronyms

- **4-AP** = 4-aminopyridine
- **AF** = atrial fibrillation
- **AP** = action potential
- **APD** = action potential duration
- **ARP** = atrial refractory period
- **CAF** = chronic atrial fibrillation
- **I_{Kr}** = rapid component of the delayed rectifier current
- **I_{Ks}** = slow component of the delayed rectifier current
- **I_{Kur}** = ultrarapid component of the delayed rectifier current
- **I_{sus}** = fast-activating noninactivating current
- **I_{to1}** = Ca^{2+}-independent 4-aminopyridine-sensitive component of the transient outward current
- **LA** = left atrium/atrial
- **LAA** = left atrial appendage
- **RA** = right atrium/atrial
- **RAA** = right atrial appendage
- **SR** = sinus rhythm

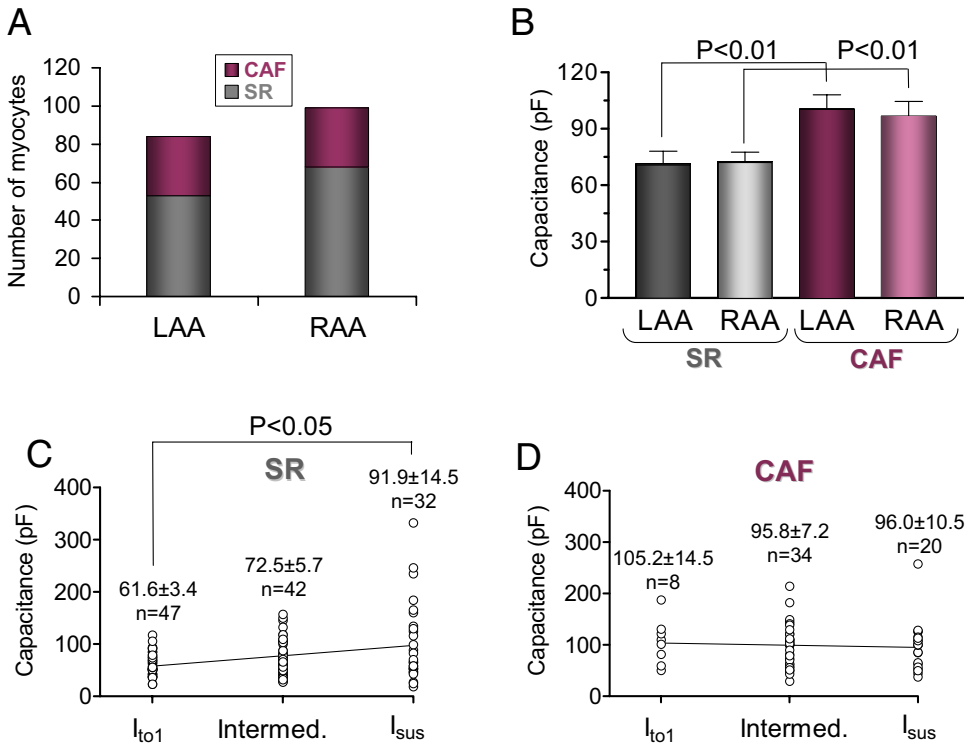

Figure 1 Cell Capacitances

(A, B) Bar graph showing number **(A)** and capacitance **(B)** of left atrial appendage (LAA) and right atrial appendage (RAA) myocytes obtained from sinus rhythm (SR) and chronic atrial fibrillation (CAF) patients. In **B,** each bar represents the mean ± SEM of n > 31. **(C, D)** Capacitance of SR and CAF cells as a function of the main repolarizing plateau current.

the percentage of I_{to1}-predominant cells, which, in this case, was accompanied by a significant increase in the I_{sus}-predominant type. Due to these changes, cell types were not equally distributed in the RAA and LAA in CAF patients. Figure 1D demonstrates that differences in cell capacitance among cell types were annulated by CAF in such a way that I_{to1}-predominant cells were similar in size to the 2 other types.

Figures 3A and 3B show the I_{to1} current-voltage relationships for LAA and RAA myocytes from patients in SR and CAF. In cells with I_{to1}-predominant and -intermediate patterns, I_{to1} was measured as the difference between the peak current and the current at the end of the 250-ms pulse. In the RAA, the I_{to1} amplitude was not statistically different in CAF versus SR patients (Fig. 3B), whereas it was significantly decreased in the LAA at potentials positive to −30 mV (Fig. 3A). Figures 3C and 3D show the I_{to1} density (calculated by normalizing the current amplitude by the cell capacitance) as a function of the membrane potential. In the RAA, the I_{to1} density significantly decreased in CAF patients only at potentials ≥+20 mV. In contrast, in the LAA, the I_{to1} density markedly decreased at potentials ≥−20 mV. CAF did not modify the voltage and time dependence of I_{to1} inactivation (Online Table 3).

Next, we analyzed the I_{to1} amplitude and density at +30 mV, a positive membrane potential that can be easily reached under physiological conditions (Fig. 4). CAF significantly decreased the I_{to1} amplitude in LAA cells but not in RAA cells (Fig. 4A), whereas it significantly decreased the I_{to1} density in both LAA and RAA, the effect being more marked in the former (Fig. 4B). Therefore, CAF established a difference in I_{to1} amplitude and density between the LAA and RAA.

Figures 5A and 5B show the I_{sus} current-voltage relationships. I_{sus} amplitude was measured as the current at the end of the 250-ms pulses. In the LAA, I_{sus} amplitude was indistinguishable in CAF versus SR patients (Fig. 5A), whereas it was significantly decreased in the RAA at potentials positive to −20 mV (Fig. 5B). However, I_{sus} density significantly decreased both in LAA and RAA at potentials positive to −10 and −20 mV, respectively (Figs. 5C and 5D). Figure 4 represents the I_{sus} amplitude (Fig. 4C) and density (Fig. 4D) at +30 mV in LAA and RAA of both patient groups. In SR, both I_{sus} amplitude and density were significantly greater in RAA than in LAA myocytes. In CAF myocytes, I_{sus} amplitude significantly decreased only in the RAA, but remained unchanged in the LAA. Probably due to the cell size increase, CAF significantly decreased the I_{sus} density in both atria. Consequently, in CAF, I_{sus} density became similar in both atria.

Components of I_{sus}. The next goal was to identify the current/currents that underlie I_{sus} in RAA and LAA of both SR and CAF patients using a pharmacological

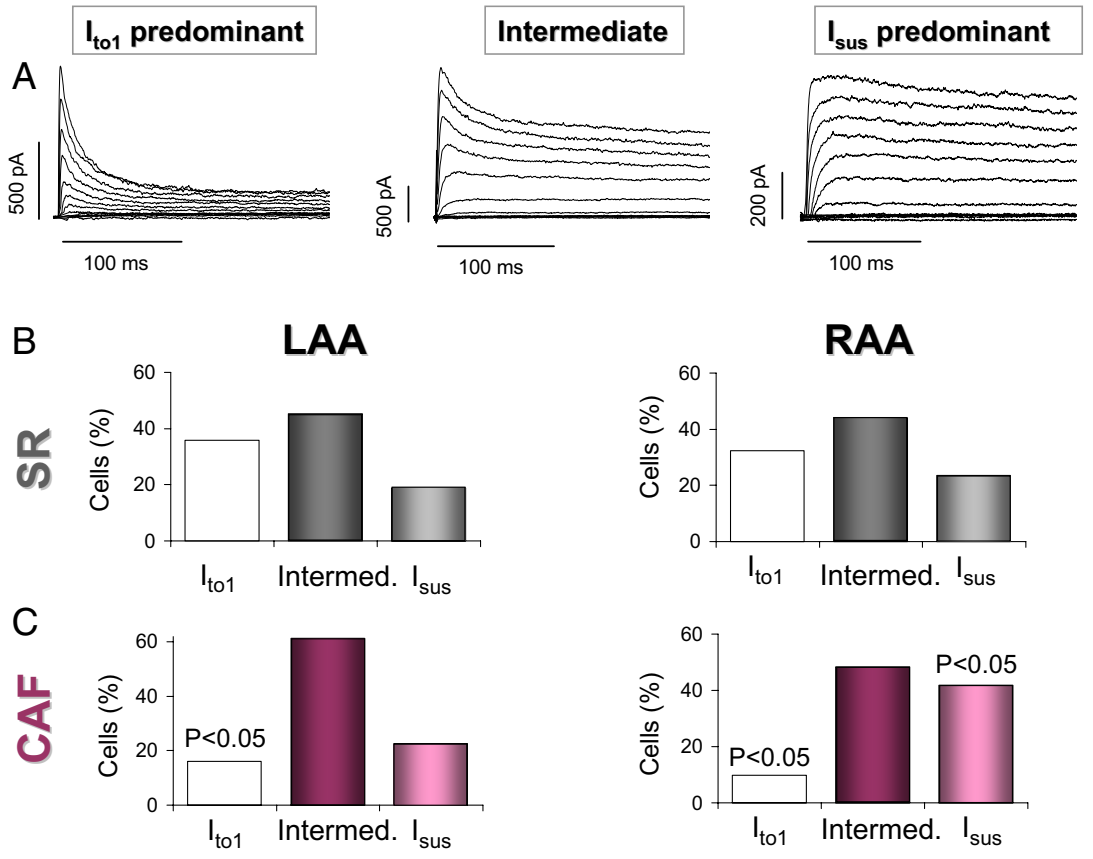

Figure 2 **Cell Types According to the K+ Plateau Current**

(A) Families of current traces elicited in 3 different RAA cells obtained from SR patients. **(B, C)** Percentage of cells that exhibited I_{to1}-predominant, I_{sus}-predominant, and intermediate patterns in SR **(B)** and CAF **(C)**. $p < 0.05$, CAF versus SR. Abbreviations as in Figure 1.

strategy. Figure 6A shows the outward current recorded in an RAA cell obtained from an SR patient with an intermediate pattern in control conditions and after perfusion with 1 μmol/l of dofetilide, a specific blocker of the rapid component of the delayed rectifier current (I_{Kr}) (14). The I_{Kr} amplitude, measured as the dofetilide-sensitive current obtained by digital subtraction, was extremely small. Identical results were obtained in LAA cells. Furthermore, I_{Kr} amplitude was not modified in CAF patients, which confirms previous data (15). Thereafter, the cell was perfused with 4-AP at 50 μmol/l, which selectively blocks the I_{Kur} generated by Kv1.5 channels (14,16). Figure 6A shows that the amplitude of the I_{Kur} at the end of the pulse accounts for ≥70% of the amplitude of the I_{sus} described so far. Finally, the cell was perfused with 4-AP at 2 mmol/l, a concentration that blocks I_{to1} (14). As shown in Figure 6A, the remaining current after 4-AP treatment was small, and the morphology of the 2 mmol/l 4-AP–sensitive current coincided with I_{to1} (i.e., fast activation and inactivation). It is noteworthy that the I_{to1} amplitude at the end of the +50-mV pulse was very small. Figure 6C shows the amplitude of the I_{sus} component measured at the end of 250-ms pulses to +50 mV in LAA and RAA cells from SR patients. Consistent with Figure 5, the I_{sus} amplitude was significantly greater in the RAA than in the LAA. Solid bars represent the amplitude of the 2 mmol/l 4-AP–sensitive component, which at the end of the pulse mainly represents I_{Kur}, because as demonstrated in the previous text the amplitudes of both I_{Kr} and I_{to1} at the end of the pulses were negligible. The results demonstrated that the I_{Kur} was significantly greater in the RAA than in the LAA (Fig. 6C).

Figure 6B shows the current elicited in an intermediate pattern cell from the RAA of a CAF patient in the presence and absence of 2 mmol/l of 4-AP. The 2 mmol/l 4-AP–sensitive current was composed of I_{to1} and I_{Kur}, and its amplitude at the end of the pulse reflected the I_{Kur} amplitude. Figure 6C confirms that CAF reduced I_{sus} and demonstrates that I_{Kur} significantly decreased only in the RAA.

The 4-AP–resistant component. Figures 7A and B show families of traces of 2 mmol/l of 4-AP–resistant current recorded in RAA cells from SR and CAF patients, respectively, by applying the protocol shown at the top. Figure 7C represents the current-voltage relationships obtained by plotting the 2 mmol/l of 4-AP–resistant current amplitude

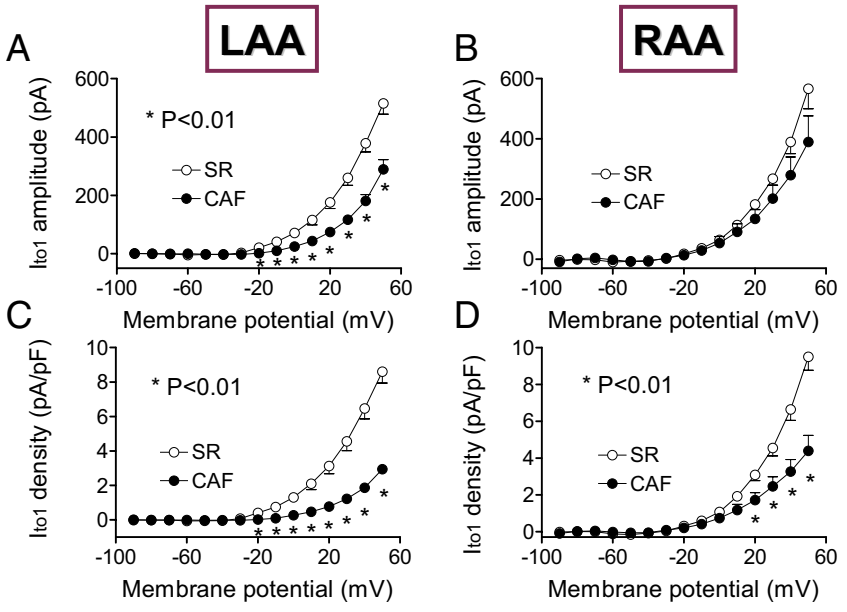

Figure 3 I_{to1} Amplitude and Density

Mean current **(A, B)** and current density **(C, D)** voltage relationships for I_{to1} in LAA **(A, C)** and RAA **(B, D)** myocytes from SR and CAF patients. Each **point** represents the mean ± SEM of n > 24. *p < 0.01, CAF versus SR. Abbreviations as in Figure 1.

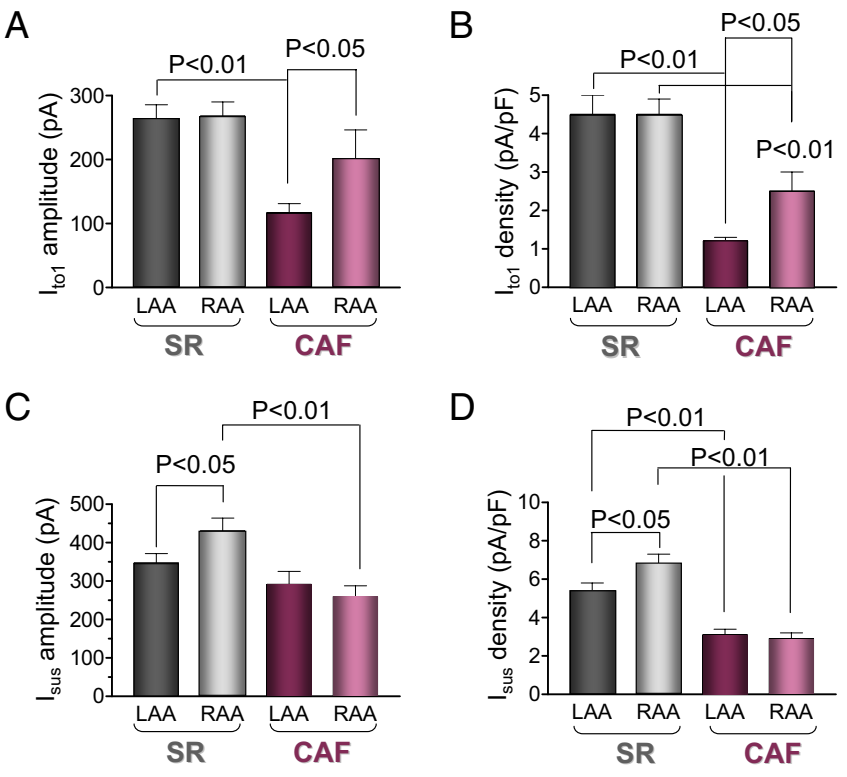

Figure 4 I_{to1} and I_{sus} Amplitude and Density at +30 mV

I_{to1} amplitude **(A)** and density **(B)** at +30 mV in LAA and RAA myocytes from SR and CAF patients. I_{sus} amplitude **(C)** and density **(D)** at +30 mV in LAA and RAA myocytes from SR and CAF patients. Each **bar** represents the mean ± SEM of n > 24. Abbreviations as in Figure 1.

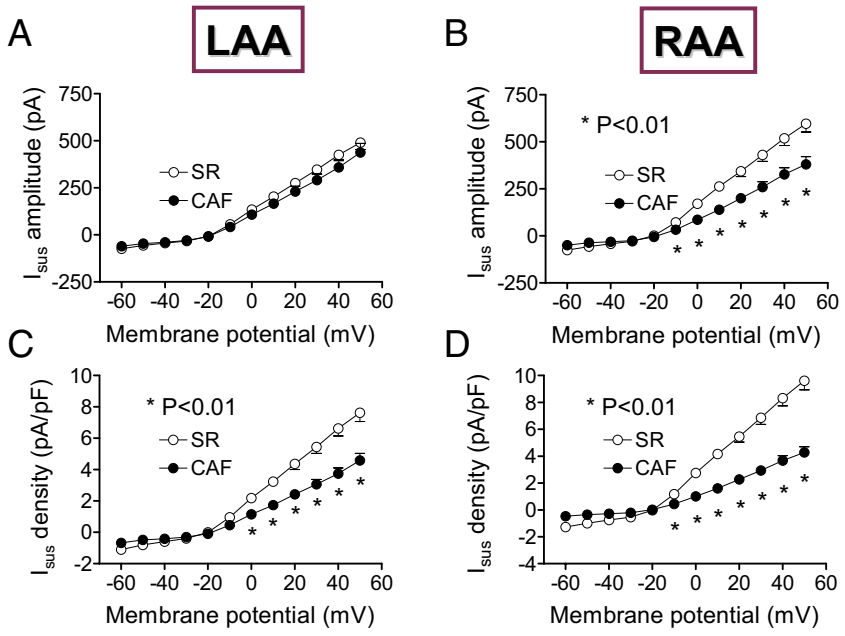

Figure 5 I_{sus} **Amplitude and Density**

Mean current **(A, B)** and current density **(C, D)** voltage relationships for I_{sus} recorded in LAA **(A, C)** and RAA **(B, D)** myocytes obtained from SR and CAF patients. Each **point** represents the mean ± SEM of n > 31. *p < 0.01, CAF versus SR. Abbreviations as in Figure 1.

(measured as the difference between the amplitude at the end and the beginning of the pulse) as a function of the test voltage in the LAA and RAA. At voltages positive to +20 mV, the 4-AP–resistant component was significantly greater in CAF than in SR cells, and this increase was observed in both atria. This current was generated by a voltage-dependent K^+ channel because it was blocked by 10 mmol/l of tetraethylammonium (not shown). Furthermore, it activated with very slow kinetics, even at positive potentials (note that the depolarizing pulses were 4 s in duration). An envelope-of-tail test confirmed that the current was generated by a single population of channels because the I_{Ktail}/I_{Kmax} ratio was constant at 0.27 ± 0.05, regardless of the duration of the pulse (Online Fig. 1). Finally, Figure 7D demonstrates that the current was blocked by HMR-1556 (1 μmol/l), an I_{Ks}-selective blocker (14). Overall these results suggest that CAF significantly increased the amplitude of I_{Ks} in both atria, an effect that overcame the cell size increase, thus producing an increase in the I_{Ks} density (Fig. 7E).

mRNA remodeling. Preliminary analysis of transcriptional changes were determined by comparing gene-of-interest/glyceraldehyde-3-phosphate dehydrogenase and protein kinase C α ratios between SR and CAF samples (Online Appendix). CAF reduced Kv4.3, whereas it did not significantly modify Kv1.5 mRNA levels (Online Fig. 2). Furthermore, CAF slightly decreased Kv7.1 (KvLQT1, the α subunit of Ks channels) mRNA level (Online Fig. 3); the effect was identical in LAA and RAA samples (not shown). In contrast, minK mRNA was detected in all CAF samples, whereas it was only detected in 2 of 4 SR samples. Therefore, CAF significantly increased minK expression (Fig. 7F).

Discussion

Our results demonstrated that CAF reduced the I_{to1} amplitude and density more markedly in the LAA than in the RAA. On the contrary, I_{Kur} was more markedly reduced in the RAA than in the LAA. In both atria, CAF increased the I_{Ks} amplitude and density. Altogether, these changes reveal that CAF promotes interatrial differences in repolarizing currents.

Effects of CAF on the heterogeneity in the K^+ plateau repolarizing currents. Our results demonstrated that myocytes of both atria from patients in SR are electrically heterogeneous. The majority of cells exhibited an intermediate pattern with simultaneous presence of I_{to1} and I_{sus}. Such heterogeneity was also accompanied by cell size differences (i.e., I_{to1}-predominant cells were smaller than I_{sus}-predominant cells). Furthermore, differences in the repolarizing currents must be reflected on the morphology of their corresponding APs, as demonstrated in the RAA (2). Importantly, in SR, the distribution of the 3 types of cells was identical in both atria.

Interestingly, CAF-induced electrical remodeling reduces the RA-to-LA resemblance. In both atria, the percentage of decrease of I_{to1}-predominant cells was similar. However, such reduction was accompanied by an increase in the percentage of intermediate cells in the LAA, but by an increase of I_{sus}-predominant cells in the

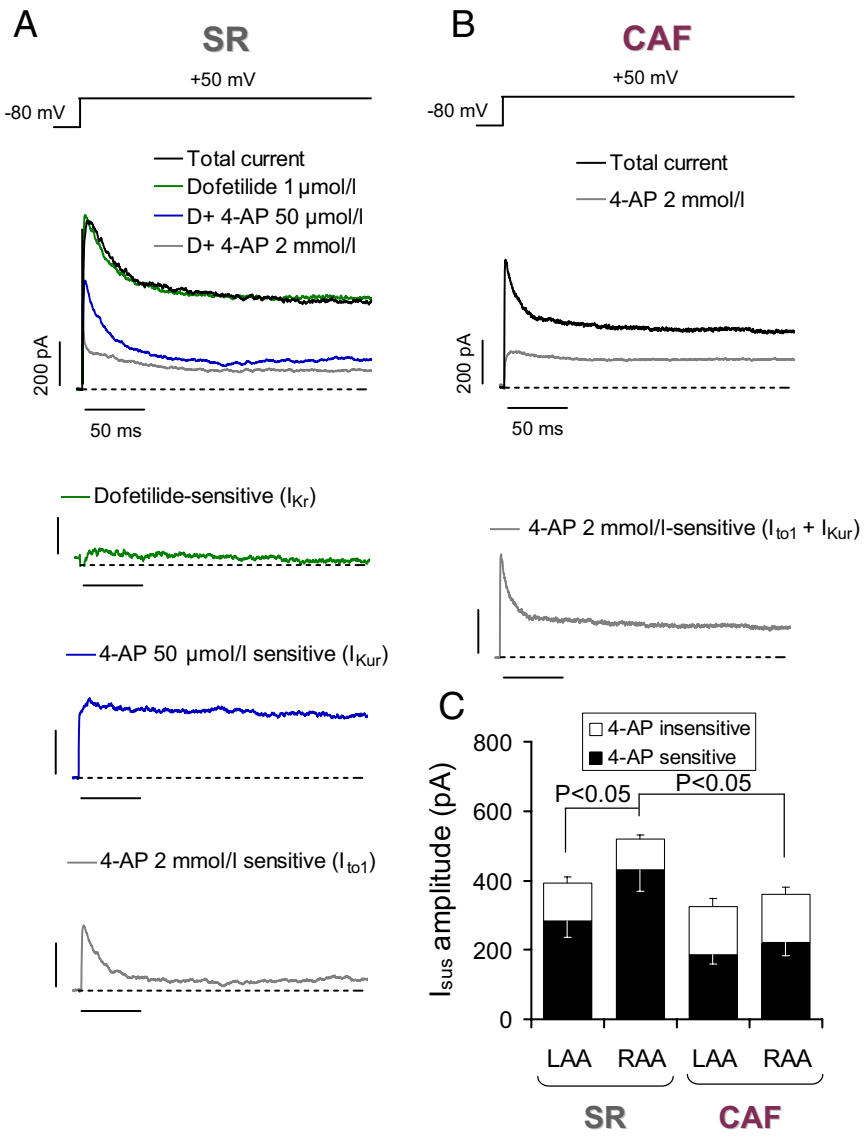

Figure 6 **Components of I_{sus}**

(A) K^+ currents recorded in an RAA myocyte from an SR patient under control conditions and after superfusion of 1 µmol/l of dofetilide alone and plus 50 µmol/l and 2 mmol/l of 4-aminopyridine (4-AP). The panels depicted **below** show dofetilide-, 50 µmol/l-, and 2 mmol/l 4-AP–sensitive currents. **(B)** K^+ currents recorded in an RAA myocyte from a CAF patient under control conditions and after superfusion of 2 mmol/l of 4-AP. The panel depicted below shows the 2 mmol/l 4-AP–sensitive current. **(C)** Amplitude of the 2 mmol/l 4-AP–sensitive and –insensitive currents measured at +50 mV. Each **bar** represents the mean ± SEM of n > 10. Abbreviations as in Figure 1.

RAA. Furthermore, CAF promoted a more marked decrease in I_{to1} amplitude and density in the LAA than in the RAA, which results in a greater density of I_{to1} in the RAA. Therefore, an RAA-to-LAA I_{to1} density gradient was created by CAF. Conversely, because I_{sus} amplitude and density were decreased more markedly in the RAA than in the LAA, the physiological RAA-to-LAA I_{sus} gradient was annulated by CAF. Therefore, it can be concluded that CAF increases the interatrial dissimilarity in repolarizing currents.

Which atrium is the most affected by CAF? Experimental and clinical studies demonstrated that, particularly during paroxysmal AF, the LA experiences faster rates than the RA (4,10). Assuming that electrical remodeling is a consequence of the fast atrial frequency of activation (9), our initial hypothesis was that if remodeling had to be more marked in one atrium than in the other, then the most affected would be the LA. Our results suggest that both atria are profoundly affected, but in different ways. This striking result suggests that other factors besides the increase of the activation frequency produce electrical remodeling. However, it should be stressed that myocytes used in this study came from CAF patients in whom LA frequencies could not be higher than RA frequencies.

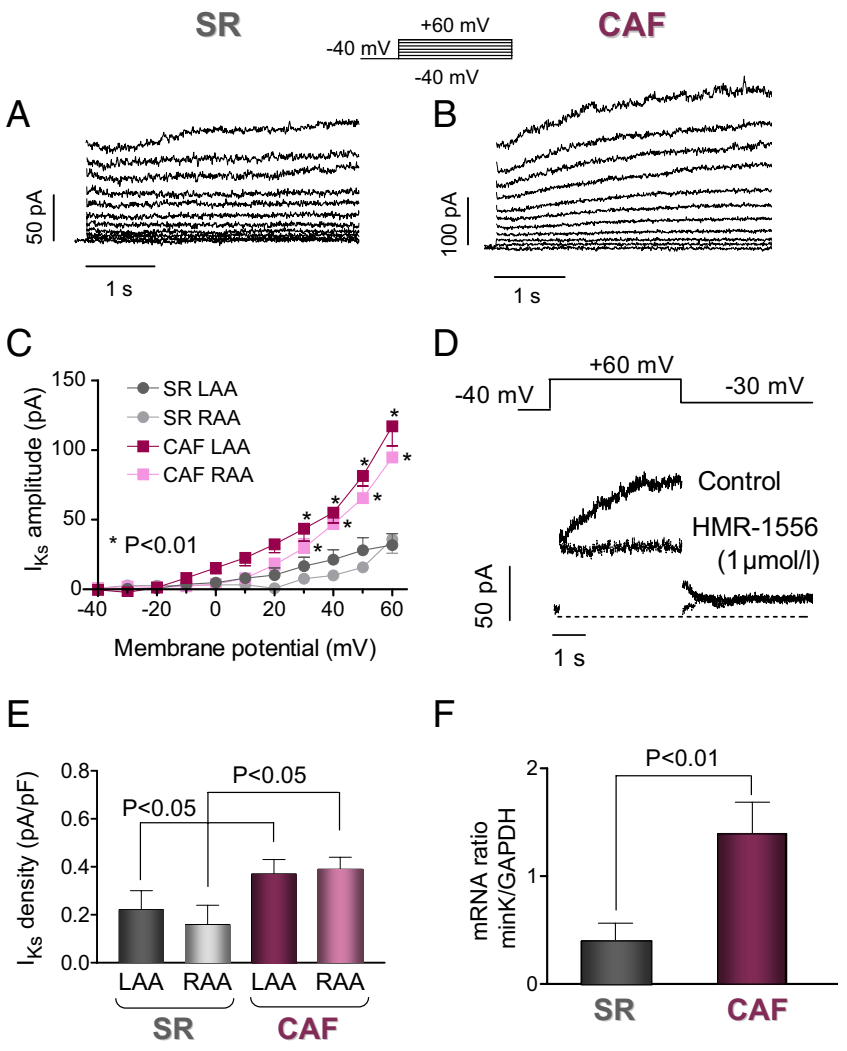

Figure 7 The 4-AP–Resistant Component

(A, B) I_{Ks} traces recorded in RAA myocytes from SR **(A)** and CAF **(B)** patients. **(C)** I_{Ks} current-voltage relationships recorded in LAA and RAA myocytes from SR and CAF patients. *p < 0.01, CAF versus SR. **(D)** I_{Ks} traces recorded in an RAA myocyte from a CAF patient in the absence and presence of HMR-1556. **(E)** I_{Ks} density at +30 mV in LAA and RAA myocytes from SR and CAF patients. Each **point/bar** represents the mean ± SEM of n > 10. **(F)** Histogram of densitometric analysis of minK mRNA in SR and CAF (n = 4). Abbreviations as in Figure 1.

CAF increases I_{Ks}. A novel and relevant result of this study is that, in both atria, CAF increases the amplitude and density of a 4-AP–resistant tetraethylammonium-sensitive component. The envelope-of-tail test demonstrated that this current was composed of a single time-dependent outward current that was sensitive to HMR-1556. These features, together with the positive midpoint of the activation curve (V_h = 7.6 ± 1.2 mV) and the slow activation kinetics (τ_{act} = 2.2 ± 0.1 s at +60 mV), strongly suggest that the increased current was I_{Ks}. This result merits several considerations. This is the first demonstration of a CAF-induced increase of a voltage-dependent K^+ current. Indeed, so far only a CAF-induced increase in voltage-independent inward rectifier currents (the I_{K1} and the agonist-independent component of the I_{KACh}) has been described (9,15,17). The increase in these inward rectifier currents seems to play a critical role in shortening the atrial APD and ARP and in promoting AF maintenance and recurrence (18). Because I_{Ks} accumulates at high frequencies due to its slow deactivation, the I_{Ks} increase would also contribute to CAF-induced shortening of APD and to further promote fibrillatory conduction (19). It is reasonable to speculate that a frequency-dependent inhibition of I_{Ks}, such as that produced by propafenone (20), is useful in the CAF context, thus converting I_{Ks} in a putative antiarrhythmic target (19).

Comparison with previous reports. Our results on I_{to1} and I_{Kur} agree with those of previous reports. A strong reduction of I_{to1}, which was attributed to a decrease in Kv4.3 mRNA level and protein expression, is a consistent finding in patients with CAF (9,15,13,21,22). Further-

more, an I_{sus} decrease, which was attributed to a CAF-induced proteolysis that diminishes the Kv1.5 protein expression without modifying the mRNA level, has also been described (13,15,21). Finally, it is noteworthy to stress that this is the first electrophysiological report on human atrial I_{Ks} remodeling. Reported alterations in Kv7.1 and minK expression have been variable, with both increases and decreases (9,13,23). Our results agree with those demonstrating a simultaneous decrease in Kv7.1 and increase in minK (23).

Study limitations. All samples came from the atrial appendages that could not be representative of the rest of the atria. Furthermore, ionic channel remodeling may be influenced by pharmacological treatment, sex, and/or underlying cardiac diseases of the patients (9). In the SR group, the proportion of patients with valvular and valvular combined with ischemic heart disease was 21 of 26 patients, whereas it was 13 of 15 patients in the CAF group. Thus, the changes described herein could be attributed to the AF itself, because the underlying heart disease was distributed similarly in the SR and CAF groups.

Conclusions

We demonstrate that in SR there is intra-atrial heterogeneity in the repolarizing currents. CAF profoundly, but differentially, affects the voltage-dependent repolarizing currents in both atria, which promotes interatrial differences. Finally, as to our knowledge, this is the first electrophysiological demonstration of CAF-induced I_{Ks} increase, which could be critical in CAF-induced shortening of APD and promotion of fibrillatory activity.

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Key Words: chronic atrial fibrillation ■ voltage-dependent potassium channels ■ electrical remodeling ■ human myocytes ■ slow delayed rectifier.

APPENDIX

For an expanded Methods section, supplementary figures, and supplementary tables, please see the online version of this article.