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Influence of Dexamethasone on Atrial Ion Currents and Their Early Ionic Tachycardia-induced Electrical Remodeling in Rabbits

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Key Words
Atrial fibrillation • Inflammation • Remodeling • Dexamethasone • Steroids

Abstract
Background: Certain evidence points to a role of inflammation in AF pathophysiology. Thus, anti-inflammatory treatment of AF is discussed. Effects of a dexamethasone treatment (7 days) on atrial ion currents ($I_{Ca,L}$, $I_{to,}$ I_{sus}) and their tachycardia-induced remodeling were studied in a rabbit model. Methods: 6 groups of 4 animals each were built. Rapid atrial pacing (600 min) was performed for 24 and 120 hours with/ without dexamethasone treatment. Ion currents were measured using whole cell patch clamp method. Results: Rapid atrial pacing reduced $I_{Ca,L}$. I_{to} was decreased after 24 hours but almost returned to control values after 120 hours. When dexamethasone-treated animals also underwent atrial tachypacing, pacing-induced reduction of $I_{Ca,L}$ was still observed after 24 hours and was even augmented after 120 hours compared to untreated but tachypaced animals. I_{to} was not influenced by dexamethasone alone. In dexamethasone-treated animals, reduction of I_{to} was not observed after 24 hours but occurred after 120 hours of atrial tachypacing. I_{sus} was neither influenced by rapid atrial pacing nor by dexamethasone. Biophysical properties of all currents were affected neither by rapid atrial pacing nor by dexamethasone. Conclusion: Dexamethasone influenced tachycardia-induced alterations of atrial I_{to}. Our experiments give evidence that - amongst other anti-inflammatory action - impact of dexamethasone on ion currents and their tachycardia-induced alterations might also play a role in treatment/prevention of AF with steroids.

Introduction

Atrial fibrillation (AF) leads to atrial remodeling, a time-dependent adaptive regulation mechanism of atrial myocytes in order to maintain cell homeostasis after onset of the arrhythmia including electrophysiological, mechanical and structural alterations [1]. In long lasting AF, *in-vivo* electrophysiological changes are well studied in several animal models and in humans: progressive short-

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ening, decreased rate-adaptation and increased heterogeneity of atrial effective refractory period (AERP) were observed [1]. On cellular level, many of these observations can be explained by the influence of AF on atrial ion channels and on their regulation [1]. In a rabbit model of tachycardia-induced atrial electrical remodeling, our group has shown that atrial remodeling begins within a few hours of rapid atrial pacing (600/min) [2].

In the past few years, much attention addressed the role of inflammation in AF: as the incidence of postoperative AF in cardiac surgery - a state of intense inflammatory processes - is high, contribution of the inflammatory cascade to the onset of AF was suggested [3]. Inflammatory cells infiltrate atrial tissue of patients with AF [4]. C-reactive protein (CRP), tumor necrosis factor, interleukins and cytokines as inflammatory markers are elevated in AF [4]. Vice versa, treatment and/ or prevention of AF by using drugs with known anti-inflammatory action like for example steroids are also discussed [5], especially in AF following cardiac surgery [6]. Therefore, aim of our study was to examine the effects of dexamethasone on atrial ion currents and accordingly their tachycardia-induced alterations using our rabbit model of early tachycardia-induced atrial electrical remodeling.

Materials and Methods

All animal care procedures were in accordance with the institutional guidelines of the University of Tuebingen and the investigation conforms to the EC Directive 86/609/EEC for animal experiments. New Zealand white rabbits were instrumented with atrial pacemakers as previously described in detail [2]. Study groups consisted of 4 animals each. Animals in control-group (CO) also received atrial pacemaker leads but no atrial stimulation was performed. Rapid atrial pacing (600/ min) for 24 or 120 hours was applied in "paced 24 hours only"-group (P24) and "paced 120 hours only"-group (P120) before heart removal. A detailed time-course of pacing-induced remodeling of $I_{Ca,L}$ and I_{to} with various intervals of rapid atrial pacing between 6 and 120 hours was already obtained in previous experiments of our group [2, 7]. Based on these results, we chose the above-mentioned pacing intervals for our current experiments with dexamethasone. We did not re-obtain data from the CO, P24 and P120 group and we re-used (also because of reasons of animal welfare) data from our previous experiments [2]. To better compare dexamethasone induced alterations in our current experiments, results of our previous experiments are recapitulated. "Dexamethasone only"-group (DO) was treated like CO but with additional dexamethasone treatment in a physiologically relevant dose (0.5 mg/kg bodyweight dexamethasone intramuscular every 24 hours [8] for 7 days before removal of the heart). Dexamethasone dosage was in the same range as in clinical trials examining a potential prevention of atrial fibrillation after cardiac surgery [9, 10]. Finally, "dexamethasone and paced 24 hours"-group (DP24) and "dexamethasone and paced 120 hours" (DP120) were treated like the corresponding "paced only"-groups but with additional dexamethasone medication (dosage like DO). Dexamethasone was chosen for our experiments due to its lacking mineralocorticoid action [11]. After 7 days, animals were anesthetized for removal of the heart. Single myocytes were isolated from left atrium by enzymatic dissociation. Cell isolation, patch clamp experiments (bath and pipette solutions, patch clamp protocols, data handling) are described in detail in a previous publication of our group [2]. Electrical remodeling of L-type calcium channel $I_{Ca,L}$ and accordingly transient outward potassium current I_{to} is considered to be most important in pathophysiology of human atrial

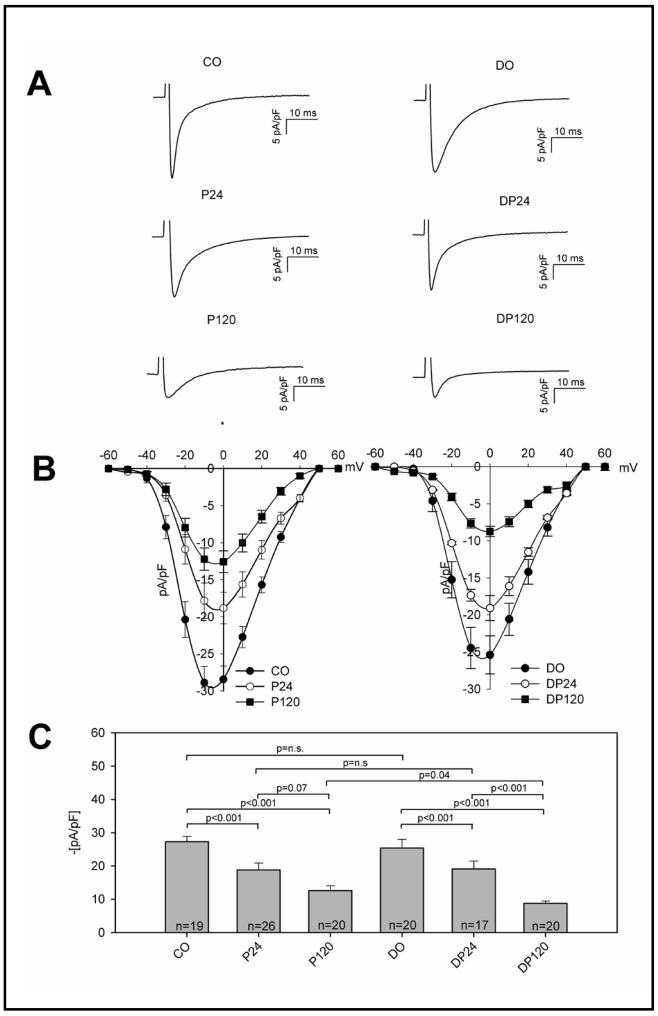

Fig. 1. (A) Typical recordings of each group exemplarily at 0 mV. $I_{Ca,L}$ was elicited by depolarizing (200 ms) the cell from a holding potential of -80 mV to test potentials between -40 mV and +50 mV. (B) IV-relation of the currents. (C) Current densities at a test potential of 0 mV. n = number of cells patched in each group. *p < 0.05, **p < 0.01, ***p < 0.001, n.s. = non-significant.

	$I_{Ca,L}$ CO	P24	P120	DO	DP24	DP120
voltage-dependent activation						
n	19	26	20	20	17	20
$V_{h,act}$ *[mV]*	-24.8±0.6	-21.1±0.5	-25.2±0.7	-22.1±0.3	-20.8±0.3	-20.8±0.8
κ_{act} *[mV]*	4.9±0.5	5.3±0.5	5.5±0.6	4.8±0.3	5.4±0.3	5.7±0.7
voltage-dependent inactivation						
n	14	22	12	17	14	17
$V_{h,inact}$ *[mV]*	-39.1±0.4	-35.2±0.3	-36.8±0.9	-35.2±0.3	-34.2±0.3	-35.8±0.3
$_{inact}$ *[mV]*	-4.0±0.4	-5.0±0.3	-6.0±0.8	-4.9±0.2	-5.1±0.2	-4.9±0.3
Time constants of recovery from inactivation						
n	10	16	5	14	13	15
$\tau_{recovery}$ *[ms]*	95.7±12.6	84.0±14.3	80.6±15.5	82.7±14.0	87.3±13.9	70.8±17.2
Time constant of inactivation						
n	20	26	20	21	17	20
$\tau_{inactivation,\ fast}$ *[ms]*	23.6±1.9	19.6±2.5	24.4±2.1	19.7±1.6	18.5±1.2	25.1±3.4
$\tau_{inactivation,\ slow}$ *[ms]*	5.5±0.4	4.1±0.4	6.3±0.4	4.9±0.5	4.4±0.5	5.7±0.6
test potential [mV]	0	0	0	0	0	0

	I_{to} CO	P24	P120	DO	DP24	DP120
voltage-dependent activation						
n	20	21	26	25	18	22
$V_{h,act}$ *[mV]*	19.8±0.8	23.2±1.4	19.8±0.9	23.0±1.1	18.2±1.1	17.5±0.9
κ_{act} *[mV]*	17.7±0.8	20.1±1.3	18.1±0.8	17.0±1.0	17.7±1.0	17.5±0.8
voltage-dependent inactivation						
n	11	15	13	17	11	15
$V_{h,inact}$ *[mV]*	-21.2±2.3	-20.1±2.5	-26.1±1.0	-25.0±1.4	-26.1±1.2	-21.5±1.6
$_{inact}$ *[mV]*	-19.0±2.0	-20.1±2.2	-12.8±0.9	-15.5±1.3	-11.4±1.1	-13.3±1.4
Time constants of recovery from inactivation						
n	7	7	9	6	5	10
$\tau_{recovery,\ fast}$ *[ms]*	479.4±44.9	318.5±43.3	310.8±41.8	505.6±60.7	399.4±45.7	663.2±69.0
$\tau_{recovery,\ slow}$ *[ms]*	3586.6±611.6	3289.3±977.6	2085.2±334.9	2449.3±604.7	4723.8±1033.1	2495.8±638.4
Time constant of inactivation						
n	20	21	26	25	18	22
$\tau_{inactivation,\ fast}$ *[ms]*	11.8±0.8	16.9±1.2	14.8±0.8	11.9±0.9	12.5±0.7	11.7±0.5
test potential [mV]	50	50	50	50	50	50

Table 1. Biophysical properties of $I_{Ca,L}$ and I_{to} . n= number of cells patched. $V_{h,inact}$ and $V_{h,inact}$ = half-activation and half-inactivation voltages. κ_{act} and κ_{inact} = slope factors for activation and inactivation. $\tau_{recovery}$ = time constants of recovery from inactivation. $\tau_{inactivation}$ = time constants of inactivation.

fibrillation [12], therefore we focused on these currents in our experiments. Data are expressed as mean±SEM. Statistical comparison between groups was performed by two way repeated measures ANOVA/ Holm-Sidak t-test.

Results

Cell Size

There was no statistical significant difference of the cell capacitance (and consecutively cell size) between the groups (CO: 45.9±2.4 pF [n=40], P24: 51.7±2.7 pF [n=47], P120: 53.8±4.2 pF [n=46], DO: 49.6±2.6 pF [n=46], DP24: 56.0±5.8 pF [n=35], DP120: 65.1±4.6 pF [n=42]).

Effects on $I_{Ca,L}$

Effects of dexamethasone and/or rapid atrial pacing on $I_{Ca,L}$ are illustrated in Fig. 1. Atrial tachypacing was associated with a significant decrease in current densities [2]. For example at a test-potential of 0 mV, densities averaged -27.3±1.6 pA/pF in CO-group (n=19) vs. -18.8±2.1 pA/pF after 24 hours of rapid atrial pacing (n=26, p<0.001

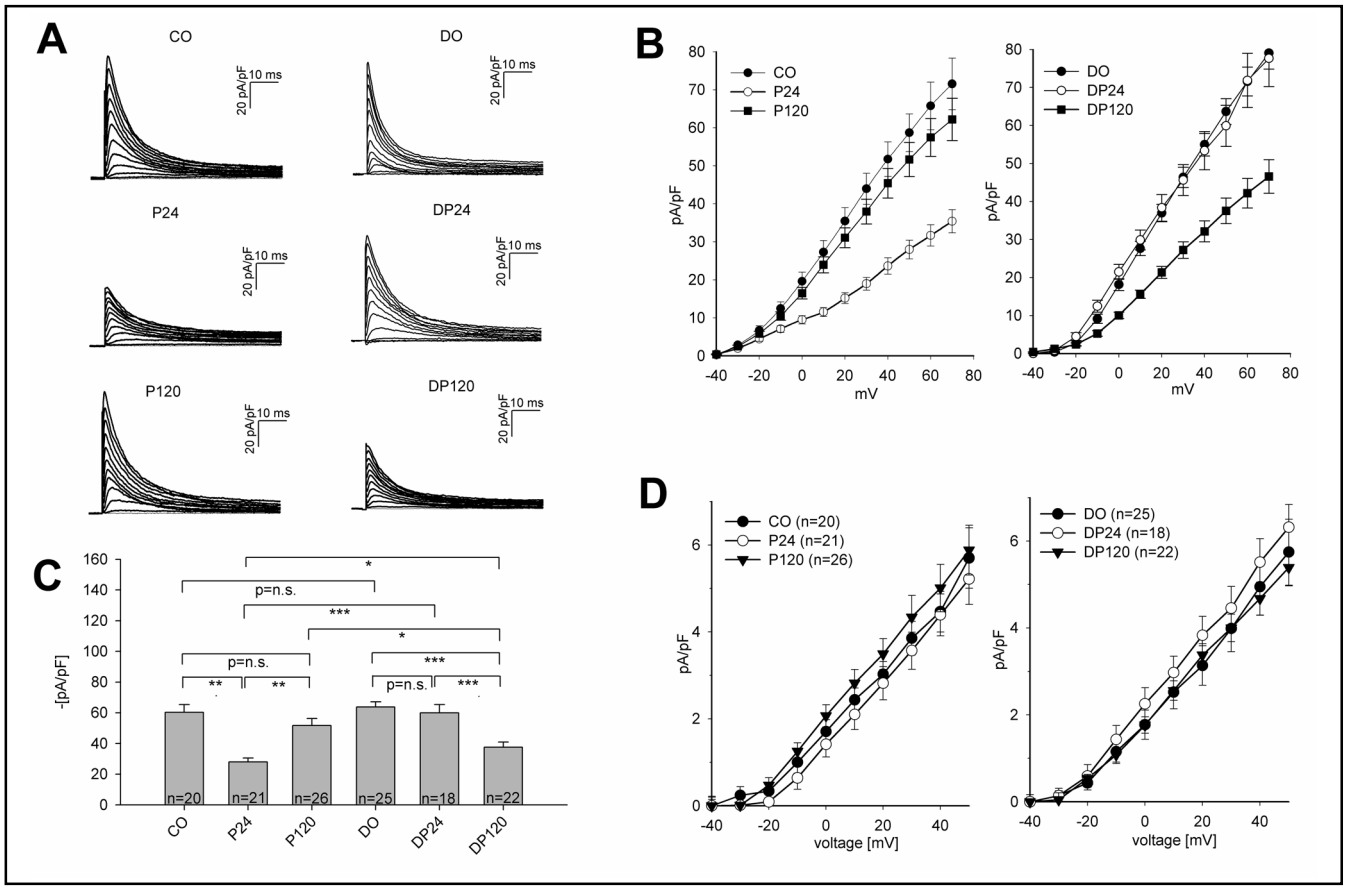

Fig. 2. (A) Typical recordings of each group. Currents were recorded upon depolarizing the cell (200 ms) from a holding potential of -80 mV to various test potentials between -40 mV and +70 mV after a pre-pulse to -40 mV (30 ms) to inactivate I_{Na}. I_{sus} was defined as the remaining steady-state current after decline of the peak current and was measure at the end to the 200 ms test-pulse. (B) IV-relation of I_{to} current densities. (C) I_{to} current densities at a test potential of +50 mV. *p < 0.05, **p < 0.01, ***p < 0.001, n.s. = non-significant. (D) IV-relation of I_{sus} current densities.

CO vs. P24) and -12.6±1.5 pA/pF after 120 hours (n=20, p<0.001 CO vs. P120) (Panel 1C). Dexamethasone alone had no effect on $I_{Ca,L}$ (DO: -26.0±2.6 pA/pF, n= 20, p=n.s. CO vs. DO). When dexamethasone-treated animals also underwent atrial tachypacing, pacing-induced reduction of $I_{Ca,L}$ was still observed after 24 hours (DP24: -19.1±2.4 pA/pF, n=17, p<0.001 DP24 vs. DO) and was even augmented after 120 hours compared to untreated but tachypaced animals (DP120: -8.8±0.7 pA/pF, n=20, p<0.001 DO vs. DP120, p<0.05 P120 vs. DP120). No significant changes of voltage dependent activation, voltage dependent inactivation, recovery from inactivation and time constants of inactivation were observed in each group (Table 1).

Effects on I_{to}

Rapid atrial pacing for 24 hours resulted in a remarkable reduction of I_{to} (Fig. 2A-2C). At a test-potential of +50 mV, current density was reduced from 60.3±5.4 pA/pF (CO, n=20) to 28.0±2.5 pA/pF (n=21, p<0.01 CO vs. P24). However, after 120 hours of atrial tachypacing, current density almost returned to initial values: 51.7±4.5 pA/pF (P120, n=26, p=n.s. CO vs. P120) [2]. Dexamethasone alone did not alter I_{to} (DO: 63.7±3.4 pA/pF, n=25, p=n.s. DO vs. CO). Pacing-induced remodeling of I_{to} was influenced by dexamethasone: when animals were pre-treated, no significant reduction of I_{to} after 24 hours of rapid atrial pacing was observed (DP24: 58.8±5.4 pA/pF, n=18, p=n.s. DO vs. DP24). However, after 120 hours, I_{to} current density was significantly reduced (DP120: 37.5±3.4 pA/pF, n=22, p<0.001. DO vs. DP120). Biophysical properties of I_{to} were not different in each group (Table 1).

Effects on I_{sus}

I_{sus}, defined as the remaining steady state current after decline of peak I_{to}, was not altered neither by rapid atrial pacing nor by dexamethasone pre-treatment (CO:

5.7±0.7 pA/pF [n=20], P24: 5.2±0.6 pA/pF [n=21], P120 5.9±0.6 pA/pF [n=26], DO 6.5±0.8 pA/pF [n=25], DP24 5.7±0.8 pA/pF [n=18], DP120 5.4±0.4 pA/pF [n=22], test-potential +50 mV) as shown in Fig. 2D.

Discussion

Cell Capacity

Cell capacity as a correlate of cell size did not differ significantly between the groups. As a greater cell size is one aspect of tachycardia-induced structural remodeling which chronologically occurs later in comparison to electrical remodeling [13], this observation might indicate that structural remodeling is - if started at all - not very advanced yet after such short pacing periods performed in our study.

Pacing- induced alterations of atrial ion currents

In longer tachypaced animals as well as in patients with chronic AF, a reduction of $I_{Ca,L}$ and I_{to} can be found [1, 12, 14-16]. The experiments of our group indicate that - at least in rabbit - time course of early I_{to} remodeling due to rapid atrial pacing seems to be more complex ("multiphasic") than just a straight downregulation of current density. Furthermore short term atrial tachypacing for 120 h already reduced $I_{Ca,L}$ to a similar extent as in chronic AF but later existence of a likewise multiphasic time course of $I_{Ca,L}$ remodeling can also not be excluded [2]. Pacing-induced alterations of $I_{Ca,L}$ and I_{to} including potential molecular mechanisms are discussed in detail in previous publications of our group [2, 7, 17, 18].

In rabbit atrium, I_{sus} is generated by at least two components [19]. I_{Kur}, which is one component of I_{sus}, seems to exist only in human atrial but not in ventricular myocytes [20-22] and therefore is considered to be a potentially interesting drug target [16] although literature concerning AF-associated changes of I_{Kur} is inconsistent [14]. Consistent to our results, Dun et al. also report of lacking alterations of I_{sus} in various regions of the rabbit atrium after intermittent atrial burst pacing for 3 hours [19]. Anyhow, absence of pacing-induced (and lately also of dexamethasone-induced) changes of I_{sus} might be of functional importance in atrial fibrillation: As derived from a computer model of human action potential [23], the role of this current depends strongly on action potential morphology and is increased with the more triangular action potentials that occur in sustained AF [12].

Effects of dexamethasone on atrial ion channels and their tachycardia-induced alterations

In our study, dexamethasone treatment alone had no effect on $I_{Ca,L,}$ I_{to} and, respectively, I_{sus}. Dexamethasone could not prevent tachycardia-induced downregulation of $I_{Ca,L}$ and after 120 hours of atrial tachypacing, downregulation was even augmented compared to untreated animals. Expected tachycardia-induced reduction of I_{to} was first prevented by dexamethasone treatment after 24 hours but then subsequently occurred after 120 hours. This observation suggests a "delay" of I_{to} remodeling after DPT but has to be confirmed in further studies with longer pacing intervals. Finally, I_{sus} was not affected by dexamethasone.

$I_{Ca,L}$ is increased after pre-treatment with dexamethasone in rat [24] and mice [25] neonatal ventricular myocytes. Wang et al. also described a reduction of I_{to} after dexamethasone pre-treatment in mice neonatal ventricular myocytes [25]. Controversial results of our study might be due to species- and tissue -specific (atrial vs. ventricular myocytes [26]) molecular composition and, respectively, regulation of $I_{Ca,L}$ and I_{to}. Lack of dexamethasone effect on atrial I_{sus} is in agreement with previous publications [25, 27].

Basal current density of each ion channel is mediated each by a complex interaction between various signalling cascades changing ion channel expression in the cell membrane and/or influencing their biophysical properties. In turn, these signalling cascades are susceptible to atrial tachypacing [1, 14, 16, 28-31] as well as to steroids [32-35]. Therefore, it is difficult to say without further ado and without being too speculative which potential molecular mechanisms are responsible for the observed time-dependent effects of dexamethasone in our experiments. Even more complicated, dexamethasone or steroids in general influence many other regulation mechanisms like - to name only a few - for instance systemic inflammation, oxidative stress, blood pressure, blood potassium levels or acid-base homeostasis [36]. Since dexamethasone was applied systemically, alterations of atrial ion currents may therefore not be due to "direct" effects on the atrium or, respectively, atrial ion channels but also because of secondary alterations of other systemic regulatory systems. Summarized, further experiments are needed to clarify potential mechanisms of the at the moment only observational alterations of atrial ions channels and their tachycardia induced alterations by a dexamethasone treatment.

Correlation to in-vivo electrophysiology

Shiroshita-Takeshita et al. examined the effects of a non-selective glucocorticoid-receptor agonism with prednisone on tachycardia-induced electrical remodeling in vivo [37]. In AF, atrial effective refractory period (AERP) as an *in vivo* parameter for tachycardia-induced electrical remodeling is shortened [13]. After 2 days of atrial tachypacing, AERP in dogs treated with prednisone was not yet reduced as normally expected due to atrial tachycardia but then - after 7 days - tended to decrease slightly but not to that extent as in untreated tachypaced animals. Despite fundamental differences of unequal animal models, these observations are in good agreement with our results on the ionic level: In dogs, pacing-induced shortening of AERP is mediated by reduction of $I_{Ca,L}$ and I_{to} [38] which is consistent with tachycardia-induced changes of these currents in our model. Time course of ion channel remodeling in our experiments (preserved downregulation of $I_{Ca,L}$, potential "delay" of I_{to} downregulation) is also in accordance with the described time course of the more moderate AERP reduction in prednisone-treated dogs in comparison to untreated animals: Although tachypacing-induced downregulation of I_{to} has complex but relatively small effects on human an canine atrial action potential duration (APD) in a mathematical model of atrial myocytes [23] and therefore functional importance of prevention of I_{to} downregulation is not fully clarified, insights from this model also showed that absolute impact of I_{to} on APD (and consecutively on AERP) is much more pronounced in early phases of AF (after 2 days of tachypacing: less reduced $I_{Ca,L}$, more "sinus rhythm-like" action potential) compared to later phases (after 5-7 days of tachypacing: totally decreased $I_{Ca,L}$, "remodeled" action potential).

Non-uniform remodeling of atrial refractoriness plays an important role in increasing atrial vulnerability to AF induction and duration of induced AF [39]. As expression of I_{to} is very heterogeneous in different regions of the atrium [40], tachypacing-induced region-specific I_{to} remodeling might be at least partly responsible for this non-uniformity [19, 41, 42]. Therefore, it can be speculated that influence of glucocorticoid-receptor agonism on I_{to} remodeling might be one possible mechanism of suppressed AF-promoting effect of atrial tachypacing described by Shiroshita-Takeshita in dogs [37]. However, it has to be considered that Shiroshita-Takeshita et al. used prednisone in their study (considerable mineralocorticoid effect [11]) whereas we used dexamethasone (negligible mineralocorticoid effect [11]), so mineralocorticoid effects might be additionally responsible for the observations of their study in dogs.

Potential limitations

As already discussed above, individual time-course of the alterations of current densities obtained in our experiments induced by atrial tachypacing as well as by dexamethasone treatment are finally the result of a complex interaction between atrial tachypacing and/ or dexamethasone treatment on various signaling cascades which modify the expression of the ion channels or their biophysical regulation. Thus, in turn, denotation of changes of single ion channels must always be interpreted in context of the complex atrial (electro-) physiology as a whole. One cannot exclude that functional importance of the affection of I_{to} downregulation by dexamethasone is annihilated by effects on other determinants of atrial electrophysiology. In summary, net effect of our observation has to be further evaluated, for example by measuring of action potentials or other parameters which describe atrial *in-vivo* electrophysiology as a whole. In addition, dexamethasone effects on markers of oxidative stress and accordingly inflammatory response possibly associated with atrial tachycardia (for example leucocytes in atrial tissue, serum-CRP) have to be evaluated. Finally, rapid pacing model might not represent clinical AF in all aspects.

Conclusions

In our animal model of early tachycardia-induced atrial electrical remodeling, dexamethasone influenced tachycardia-induced alterations of atrial I_{to} and $I_{Ca,L}$. Our experiments give evidence that - amongst other anti-inflammatory action - impact of dexamethasone on ion currents and their tachycardia-induced alterations might also play a role in treatment/ prevention of AF with steroids.

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