Effects of human atrial ionic remodelling by β-blocker therapy on mechanisms of AF: a computer simulation

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Abstract

Aims: Atrial anti-arrhythmic effects of β-adrenoceptor antagonists (β-blockers) may involve both a suppression of pro-arrhythmic effects of catecholamines, and an adaptational electrophysiological response to chronic β-blocker use; so-called "pharmacological remodelling". In human atrium, such remodelling decreases the transient outward (I_{to}) and inward rectifier (I_{K1}) K^+ currents, and increases the cellular action potential duration (APD) and effective refractory period (ERP). However, the consequences of these changes on mechanisms of genesis and maintenance of atrial fibrillation (AF) are unknown. Using mathematical modelling, we tested the hypothesis that the long-term adaptational decrease in human atrial I_{to} and I_{K1} caused by chronic β-blocker therapy, i.e., independent of acute electrophysiological effects of β-blockers, in an otherwise un-remodelled atrium, could suppress AF.

Methods and results: Contemporary, biophysically detailed human atrial cell and tissue models, were used to investigate effects of the β-blocker based pharmacological remodelling. Chronic β-blockade-remodelling prolonged atrial cell APD and ERP. The incidence of small amplitude APD alternans in the CRN model was reduced. At the 1D tissue level, β-blocker-remodelling decreased the maximum pacing rate at which APs could be conducted. At the 3D organ level, β-blocker-remodelling reduced the life span of re-entry scroll waves.

Conclusion: This study improves our understanding of the electrophysiological mechanisms of AF suppression by chronic β-blocker therapy. AF suppression may involve a reduced propensity for maintenance of re-entrant excitation waves, as a consequence of increased APD and ERP.

Keywords: Arrhythmia; atrial fibrillation; ion channel; β-blockers; computer simulation.

Condensed abstract: The atrial anti-arrhythmic effects of K^+ current suppression due to chronic β-blocker-therapy were computationally evaluated using contemporary mathematical descriptions of cell electrophysiology, and tissue models. The observed increase in cellular action potential duration and effective refractory periods may be the mechanism which attenuates re-entry life span, contributing to suppression of atrial fibrillation.

What's New?

- β-blockers have anti-arrhythmic effects involving suppression of catecholamine-induced after-depolarisations. However, a less well understood effect of β-blockers is the adaptational electrophysiological remodelling (AER) resulting from long term β-blocker treatment of patients.
- In human atrium, AER, by prolonging refractory period could, in theory, suppress atrial re-entry, but effects of AER on re-entry have not been investigated previously.
- This study implemented multi-scale models of human atria to investigate the functional impacts of β-blocker-induced AER on atrial electrical activity.
- At the cellular level, AER prolonged atrial action potential duration and effective refractory period.
- At the tissue level, AER reduced the propensity to re-entry genesis, decreased the maximum excitation rates of atrial activity, increased the meandering region of re-entry, and reduced re-entry life-span.
- This study provides mechanistic insights into the anti-arrhythmic effects of β-blockers.

1. Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia, affecting 1-2% of the general population [1]. Currently available anti-arrhythmic drugs are moderately effective and safe, and an improved understanding of their action on atrial electrophysiology is warranted [2, 3]. β-adrenoceptor antagonists (β-blockers) are used in AF treatment, mainly to control the ventricular rate by slowing atrio-ventricular conduction [2, 4]. Some clinical studies showed that β-blockers can prevent AF, convert it to sinus rhythm, or maintain sinus rhythm after it is restored [5, 6], and these drugs are most effective when adrenergic tone is high [6]. AF from adrenergic stimulation is caused, in large part, by the effect of catecholamines to elevate intracellular Ca^{2+} that promotes arrhythmogenic action potential (AP) after-depolarisations. β-stimulation is known to increase human atrial I_{CaL} and I_{Kur}, and to elevate intracellular Ca^{2+} by a combined increase in I_{CaL} and sarcoplasmic reticular Ca^{2+} content [6]. The main mechanism of the anti-arrhythmic effects of β-blockers is generally accepted to involve suppression of such intracellular Ca^{2+}-dependent after-depolarisations. However, an additional, less well understood and potentially anti-arrhythmic mechanism of β-blockers is an adaptational electrophysiological response to long-term β-blocker use; so called "pharmacological remodelling" [6, 7]. Such pharmacological remodelling features an increase in the atrial AP duration (APD) and effective refractory period (ERP), as shown in rabbits [8], and subsequently in atrial myocytes isolated from patients in sinus rhythm [7, 9, 10]; with ERP-prolongation correlating with β-blocker dose [11]. This ERP-prolongation could, in theory, contribute an atrial anti-arrhythmic, or a sinus rhythm-maintaining, effect, by lengthening the minimum wavelength required for re-entry, because re-entry wavelength = ERP x conduction velocity. The main ion current mechanisms underlying the increased APD and ERP in human atrium probably include a decrease in the density of the transient outward (I_{to}) and/or inward rectifier (I_{K1}) K^+ currents [7, 12, 13]; with L-type Ca^{2+} (I_{CaL}) and ultra-rapid delayed rectifier K^+ (I_{Kur}) currents unaffected by chronic β-blockade [7, 9, 10, 12, 14, 15]. However, the consequences of these ion current changes for the maintenance of re-entry are unknown.

This question is difficult to address experimentally because of a lack of specific I_{to} and/or I_{K1} blockers. For example, the best available I_{to} blocker, 4-AP, inhibits I_{Kur} at ≥ 40-fold lower concentration than I_{to} [16], and I_{Kur} is large in human atrium [16]. Whereas these currents are distinguishable under voltage-clamp by their voltage dependence and kinetics, the pharmacological investigation of effects of their independent block on AP morphology and re-entry is hampered by such lack of specificity. However, this question is highly amenable to mathematical and computational investigation. Mathematical modelling has already proven useful in helping to clarify likely mechanisms of changes in human atrial APs [17, 18] and spiral [19 20] and scroll wave [20, 21] re-entry due to ion current or structural changes resulting from chronic AF. However, such models have not yet been used to investigate electrophysiological mechanisms of changes in APs and re-entry characteristics resulting from chronic β-blocker therapy. Our aim, therefore, was to use mathematical modelling to test the hypothesis that

the long-term adaptational decrease in human atrial I_{to} and I_{K1} caused by chronic β-blocker therapy, i.e., independent of acute electrophysiological effects of β-blockers, in an otherwise un-remodelled atrium, could suppress AF by inhibiting re-entry by increasing ERP. The Methods are detailed in the online Supplementary Materials.

2. Results

Three biophysically detailed models of human atrial cell APs, by Courtemanche et al. [22] (CRN), Grandi et al. [18] (Grandi), and Koivumaki et al. [23] (KT) were used. Abbreviations: g_{K1}: conductance of I_{K1}; g_{to}: conductance of I_{to}; RP: resting potential; AP: action potential; dV/dt_{max}: maximum upstroke velocity of AP; OS: overshoot of AP; APD: AP duration; ΔAPD: change of APD; APDr: APD restitution; DI: diastolic interval; ERP: effective refractory period; PCL: pacing cycle length; CV: conduction velocity; CVr: CV restitution; VW: vulnerability window; LS: life span of re-entry. All numerical results from cell to 3D simulations are summarised in Table 1.

2.1 Effects of β-blocker remodelling on single atrial cell APs

The effects of chronic β-blocker remodelling on atrial cell APs and major ion currents are shown in Figure 1. β-blocker induced ion channel remodelling prolonged APD_{90} in the cell models (CRN by 18%; Grandi by 30%; and KT by 27%). Such a prolongation of APD_{90} is in agreement with our experimental data from human atrial cells, in which chronic β-blockade increased APD_{90} by 19-28% [7, 10, 14]. Whereas APD_{30} was prolonged in Grandi (15%) and KT (15%) due to β-blockade, it was reduced in CRN (6%). The resting potential was shifted positively by 2 to 5 mV in the cell models, consistent with the effect of β-blockade to decrease $I_{K1.}$ The amplitudes of I_{to} and I_{K1} were reduced, while those of I_{CaL} were largely unaffected, during the AP (Figure 1). AP clamp simulations (Supplementary Figure S2) showed similar results to those obtained from the cell model simulations, with a reduced I_{K1} and I_{to} whereas I_{CaL} was reduced during the AP under β-blockade in the Grandi and KT models. There was a marginal increase of I_{CaL} in the CRN model's I_{CaL} under β-blockade conditions. AP triangulation (Table 1) showed that the CRN model has a type 1 AP morphology, while the Grandi model's high AP triangulation reflects a type 3 AP morphology. Triangulation was found to be increased under β-blocker remodelled conditions as compared to control by 43% (CRN), 41% (Grandi), and 30% (KT). β-blockade increased AP triangulation significantly indicating the prolonging effects on atrial repolarisation. The results of g_{K1} and g_{to} parameter sensitivity analyses are shown in Supplementary Figure S3. Reduction of g_{K1} caused substantial prolongation of APD_{90} in all the models. APD_{30} was either prolonged (CRN), or remained largely unaffected (Grandi and KT models), due to a reduction of g_{K1}. Contrary to experimental findings [18], a reduction of g_{to} caused APD_{90} and APD_{30} to be reduced in the CRN model. The Grandi and KT models showed a prolongation of APD due to reduced g_{to}. When g_{to} was increased, APD (APD_{30} as well as APD_{90}) reduced in all three models.

2.2 Effects of β-blocker remodelling on atrial cell APDr and ERP

S1-S2 APDr (Figure 2) shows that β-blocker remodelling increased APD_{90} at slow pacing rates (i.e. large diastolic interval, DI) in all cell models. APD_{30} was abbreviated in the CRN model, while it was prolonged in the Grandi and KT models, due to β-blocker remodelling. β-blocker remodelling reduced the APDr maximum slopes in the CRN and Grandi models. In the KT model, β-blocker remodelling increased the APDr maximum slope. Thus, the action of β-blocker remodelling was to reduce the maximum slope of APD_{90} APDr, at least in the CRN and Grandi models. Irrespective of maximum APDr slopes, all models showed that β-blocker remodelling prevented atrial excitation electrical activity at fast pacing rates (i.e. small diastolic interval, DI), which are close to the rate of atrial excitations seen in AF. ERP (Figure 2) of single atrial cells was substantially increased by β-blocker remodelling. For slow pacing rates (PCL = 1 s), the ERP increased by 24% (CRN), 31% (Grandi), and 18% (KT) due to β-blocker remodelling. Whereas the CRN and KT models were found to sustain faster pacing rates (approx. PCL ~ 290 ms) under both conditions, the Grandi model AP sustained a minimum PCL of 500 ms under control and 760 ms under remodelled conditions. Dynamic APDr showed the CRN model to sustain small amplitude APD alternans (of both APD_{90} and APD_{30}) for PCLs at values between 295 and 410 ms (Figure 3). The KT model showed larger amplitude APD_{30} alternans at PCL values between 200 and 263 ms. APD_{90} in this PCL range (200-263 ms, KT model) could not be computed as the AP did not achieve 90% repolarisation. In the CRN model, β-blockade significantly reduced the amplitude of APD alternans, as illustrated in Figure 3 and Supplementary Figure S5. At a PCL of 350 ms, the measured APD alternans amplitudes was 6.2 ms at 90% repolarisation (ΔAPD_{90}) and 3.7 ms at 30% repolarisation (ΔAPD_{30}) under control conditions, both of which were reduced to less than 0.15 ms under the β-blockade condition. In the KT model, β-blockade had negligible effect on APD alternans (Figure 3 and Figure S5). However, as Figure 3 shows, β-blockade prevented atrial excitation of APs at faster pacing rates (PCL < 320 ms for CRN, and PCL < 247 ms [at APD_{30}] for KT). Alternans were not observed in the Grandi model.

2.3 Effects of abrupt change of pacing rates in cell models

The APD_{90} adaptation dynamics under control and β-blocker conditions are shown in Figure 4. The results of fitting a mono-exponential curve are given in Table S1. Under abrupt change of pacing from 1 Hz to 1.67 Hz, β-blockade reduced the APD_{90} slow adaptation time constant by 15% (CRN and Grandi). Thus, the effect of β-blocker remodelling was to increase the atrial cell's ability to adapt rapidly to an abrupt increase in pacing rate. The β-blocker remodelling did not have any significant effect on the APD_{90} adaptation time constant in the KT model.

2.4 1D rate dependent conduction properties, vulnerability window, tissue ERP

CV restitution data (Figure 4) showed that at slow pacing rates (DI ~ 1 s), successive propagations in the CRN and KT models had a CV similar to solitary wave CV. However, in the Grandi model, the CV of propagations due to S2 stimuli had a significant and inverse dependence on the pacing rate. β-

blocker remodelling prevented the conduction of atrial excitation waves at high pacing rates. The computed maximum pacing rate for sustained excitation propagation was reduced in all three models; by 9.6% (CRN), 26.6% (Grandi), and 13.7% (KT) in the β-blocker remodelling condition.

The wavelength of excitation propagation was calculated from 1D simulations (Table 1). At slow pacing rates, the β-blocker remodelling increased the excitation propagation wavelength. However, at fast pacing rates, β-blocker remodelling did not affect the wavelength (Table 1). The alterations of wavelength in the Grandi model due to β-blockade were small, reflecting the models rate adaptation capability.

Unidirectional conduction block of a premature extrasystole can lead to initiation of AF by formation of re-entry [24-26]. The time window within which unidirectional conduction block occurs in response to a premature stimulus applied to the refractory tail of a previous excitation wave is termed the temporal vulnerability window (VW). Temporal VW (Supplementary Figure S4, and Table 1) was increased in CRN and Grandi models, while it was reduced in the KT model, due to β-blockade. The temporal VW simulations also allowed estimation of tissue ERP. Tissue ERP was defined as the shortest coupling interval of a premature stimulus (during VW simulations) that elicited propagation in the 1D atrial strands. The action of β-blockade was to increase tissue ERP in all models (CRN by 8%; Grandi by 19.6%; and KT by 10%).

2.5 Scroll wave propagation in 3D organ model

Further simulations were performed to investigate the effects of β-blocker remodelling on atrial tissue's re-entrant excitation waves. The 3D atrial organ simulations are illustrated in Figure 5. Under control conditions, the re-entrant waves became trapped to a model boundary and thus became persistent (CRN), or continued as meandering mother rotors (Grandi and KT) throughout the whole period of simulation (5 s). Under β-blocker conditions, the re-entrant waves self-terminated at 0.35 s and 0.5 s, respectively, in the CRN and Grandi models, due to the wave front reaching the opening of the superior vena cava as illustrated in Figure 5.

In the KT model, re-entrant excitation wave in the β-blocker remodelling condition was persistent for the duration (5 s) of the simulation. However, the re-entrant waves meandered over larger areas as compared to the control condition. In addition, the excitation rate of localised atrial action potentials was also decreased by β-blocker remodelling.

The total simulation time for 5 s of electrical activity was about 4 hours in each case of the simulations.

3. Conclusions and Discussion

3.1 Key findings

The key finding was that computer simulation of human atrial I_{to} and I_{K1}-remodelling by chronic β-blocker therapy, independent of acute electrophysiological effects of β-blockers, revealed

electrophysiological mechanisms that may contribute to the atrial anti-arrhythmic actions of these drugs. Thus, we showed, in mathematical models of single atrial cells and 3-D tissues, that the reduction in I_{to} and I_{K1} could reduce the propensity for initiation and maintenance of re-entrant excitation waves, as a consequence of an increased APD, ERP and atrial excitation wavelength, as well as a suppression of atrial alternans.

Reducing the repolarising currents I_{K1} and I_{to} prolonged the APD_{90} in all three cell models. This added weight to the idea that the APD increase observed experimentally is caused by the decrease in these two currents. The effects of β-blocker remodelling were also to increase cell and tissue ERP, consistent with experimental data from human atrial cells [7, 9, 10]. The maximum slope of APDr has been proposed as a possible index to quantify tissue's propensity to arrhythmic events [27], and that was reduced by the β-blocker remodelling. A reduced occurrence of alternans at cellular level may contribute to reducing the human atrial tissue's propensity to dynamic heterogeneity [28]. In simulations, the β-blocker-induced K^+ current remodelling reduced the amplitude of APD alternans in the CRN model, though did not affect alternans behaviour in the KT model. In our simulations, the effect of blocking K^+ currents on AP alternans was small. This may be due to the primary mechanisms of alternans being in the coupling between intracellular Ca^{2+} and AP dynamics [29 30], and that blocking I_{to} and I_{K1} does not significantly affect this coupling. Consideration of the effects of acute β-blockade on I_{CaL} and SERCA concurrent with K^+ current remodelling will more fully quantify the effects of β-blockers on atrial APs and alternans behaviour and warrants future studies. The K^+ current remodelling did, however, reduce the cell models' abilities to sustain high rates of AP excitations (i.e. at PCL <320 ms in CRN and <247 ms in KT) and might be expected, therefore, to inhibit AP excitation at the fast rates normally encountered during AF [31]. The observed stimulation failure at high rates due to β-blockade suggests a cellular mechanism which may contribute to the anti-arrhythmic effects of β-blockers. The adaptation of atrial APs to abrupt changes of pacing rate was seen to be more pronounced under β-blockade conditions as compared to control. This suggests an anti-arrhythmic effects of β-block remodelling, as a previous study showed that a slower rate of APD adaptation can lead to EAD formation in a ventricular cell model [32]. Dependence of AP excitation on pacing rate has been argued to give rise to dynamical conduction block at the tissue level independent of spatial heterogeneity [33]. Therefore, an increased rapid adaptation to an altered pacing rate by β-blockade may reduce the propensity to AF initiation. Such cell level AP adaptation correlates with tissue level heart rate (HR) adaptation, which when protracted has been suggested to be a pro-arrhythmic risk factor [34]. The CVr simulations showed that β-blocker remodelled tissue had a reduced propensity to sustain electrical propagations at faster pacing rates. CVr also showed that the Grandi model has a large CV adaptation. In the Grandi model, the excitations elicited by the S2 stimulus has appreciably smaller CV, possibly due to the strong influence of the slow intracellular Ca^{2+} dynamics on electrical properties in the Grandi model. The CV adaptation of the Grandi model may be due to

the strong coupling between the (faster) membrane ionic currents and the (slower) intracellular ionic dynamics. Thus at fast pacing rates, sufficient depolarising currents (e.g. I_{Na}) required for the propagation of a wave may not be available.

The prolonged ERP due to β-blocker remodelling led to termination of 3D spiral waves (CRN and Grandi) and a reduced rate of localised excitation in all models. Our results agree with the K^+ current block-mediated increase of spiral wave meander reported by Comtois et al. [35]. The triangular but long ERP APs typical of atrial cells may also provide other mechanisms to prevent initiation of such spiral waves.

Grandi et al. [18] and Workman et al. [11] helped show that the major ionic currents implicated in the maintenance of AF include some of those central to the present study. Indeed, the involvement of I_{K1} and I_{to} changes in arrythmogenesis have also been explored in previous mathematical modelling studies for atria and ventricles [17, 19, 36, 37]. Zhang et al. [17] used two human atrial cell models to demonstrate that an increase of I_{K1} reduces cell APD dramatically. This work was subsequently extended, in a multi-scale study [21], which showed that such I_{K1} increase was pro-arrhythmic. The other repolarising current central to this study, I_{to}, has been implicated in explaining the type 1 APs in human atrial cells [22]. Although APD in the CRN model is abbreviated by I_{to} suppression (Supplementary Figure S3), Pandit et al. [19] have shown that suppression of I_{to} leads to re-entrant wave disorganisation and termination. That observation may be due in part to the small APD abbreviation in their model (by 10% due to a 50% block of I_{to}) which still allows the CRN type re-entrant wave self-termination. The responses to I_{to} reduction in the Grandi and KT models are consistent with a recent dynamic-clamp study [13], in which a progressive selective I_{to} decrease prolonged early and late repolarisation in human atrial cells (Supplementary Figure S3), and may better suit the demonstration of re-entrant wave self-termination due to I_{to} suppression.

3.2 Limitations of the study

1) Some limitations of the CRN, Grandi and KT models have been discussed elsewhere [18, 22, 23]. Of note, our simulations show that the KT AP is more triangular and shorter than our experimental observations [7, 12]. 2) In our multi-cellular models, electrical and spatial homogeneity was assumed, whereas human atria are electrically and spatially heterogeneous [38]. 3) Inter-cellular coupling was modelled to give a CV of 0.3 mm/ms, whereas the CV in atria has been estimated over a wide range of values [39]. 4) Whilst studies in human atrial cells showed that chronic β-blocker therapy in patients significantly remodelled I_{to} and I_{K1}, and not I_{CaL} or I_{Kur} [7, 9, 10, 12-15], no quantitative data are available on other currents (e.g. I_{KACh}, $I_{Na/Ca}$, I_{Kr}, I_{KCa}), or $[Ca^{2+}]_i$, and so their potential remodelling by chronic β-blocker therapy should not be excluded. Adrenergic stimulation or β-blockade may also affect gap junction function or expression [40 41] and thereby alter intercellular propagation. 5) This study sought to simulate only the long-term adaptational changes in ion currents by chronic β-blocker therapy, i.e., independent of acute electrophysiological effects of β-blockers, and future studies may attempt to

model the combination of the chronic and acute effects. 6) The effect of β-blockade to slow the sino-atrial node and thus heart rate was not incorporated in the model, and although atrial cellular ERP prolongation by chronic β-blockade occurs after adjusting for heart rate [7], future modelling studies could compare effects of chronic β-blockade on re-entry characteristics at different sinus rates. 7) The ion current data used to inform the present mathematical models were obtained from studies of patients who were taking β_1-selective blockers, thus excluding those taking other β-blockers such as propranolol (β_1/β_2-blocker), sotalol ($\beta_1/\beta_2/I_{Kr}$ blocker) or carvedilol ($\beta_1/\beta_2/\alpha_1$-blocker). The effects of chronic non-β_1-selective therapy on human atrial cellular electrophysiology are unknown. However, in line with the present data, 24 days treatment of rabbits with propranolol prolonged atrial tissue APD_{90} [8], and 8 weeks carvedilol prolonged atrial cell APD_{90} [42]. 8) Whereas human atrial cellular ERP prolongation has been correlated with β_1-blocker dose [11], only limited data are available on I_{to} or I_{K1} at different doses, so dose-dependency of the β-blocker effect on ion currents was not modelled here. 9) Since atrial APD and ERP may be shortened in "vagal" forms of AF, as well as by remodelling from chronic AF or LVSD [3], APD-prolongation from chronic β-blocker therapy might be predicted to attenuate or oppose such shortening. However, experimental data from human atrial cells under such conditions are lacking, and effects of chronic β-blocker therapy under conditions of increased vagal tone or myocardial disease were not modelled in the present study. 10) We acknowledge that in clinical practice and in the guidelines, class 1C and class 3 drugs are the preferred choice for interrupting AF or for the maintenance of sinus rhythm. Nevertheless, an improved understanding of the mechanisms of action of anti-arrhythmic drugs from any class, as gained in the present theoretical study on class II drugs, may aid the search for improved drug treatments for the prevention of AF.

3.3 Conclusion and clinical significance

In patients, suppression of AF by treatment with β-blockers likely involves the combined action of 1) acute attenuation of pro-arrhythmic effects of adrenergic-stimulation (after-depolarisations resulting from increased I_{CaL} and $[Ca^{2+}]_i$) and 2) an ERP-prolonging adaptation to the long-term treatment; so-called pharmacological remodelling [6]. The present study improves our understanding of the electrophysiological mechanisms and consequences of the pharmacological remodelling-induced ERP increase. Thus we show, with mathematical modelling of single cells and 3-D tissues, that the anti-arrhythmic effect of chronic β-blockade in human atria probably involves a reduced propensity for initiation and maintenance of spiral wave re-entry, as a consequence of an increased APD and ERP and a suppression of alternans, due to reduced I_{K1} and I_{to}.

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References

[1] McManus DD, Rienstra M, Benjamin EJ. An update on the prognosis of patients with atrial fibrillation. *Circulation* 2012; **126**: e143-6.

[2] Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010; **31**: 2369-429.

[3] Workman AJ, Smith GL, Rankin AC. Mechanisms of termination and prevention of atrial fibrillation by drug therapy. *Pharmacol Ther* 2011; **131**: 221-41.

[4] Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012; **33**: 2719-47.

[5] Lopez-Sendon J, Swedberg K, McMurray J, Tamargo J, Maggioni AP, Dargie H, et al. Expert consensus document on beta-adrenergic receptor blockers. *Eur Heart J* 2004; **25**: 1341-62.

[6] Workman AJ. Cardiac adrenergic control and atrial fibrillation. *Naunyn Schmiedebergs Arch Pharmacol* 2010; **381**: 235-49.

[7] Workman AJ, Kane KA, Russell JA, Norrie J, Rankin AC. Chronic beta-adrenoceptor blockade and human atrial cell electrophysiology: evidence of pharmacological remodelling. *Cardiovasc Res* 2003; **58**: 518-25.

[8] Raine AE, Vaughan Williams EM. Adaptation to prolonged beta-blockade of rabbit atrial, purkinje, and ventricular potentials, and of papillary muscle contraction. Time-course of development of and recovery from adaptation. *Circ Res* 1981; **48**: 804-12.

[9] Redpath CJ, Rankin AC, Kane KA, Workman AJ. Anti-adrenergic effects of endothelin on human atrial action potentials are potentially anti-arrhythmic. *J Mol Cell Cardiol* 2006; **40**: 717-24.

[10] Workman AJ, Pau D, Redpath CJ, Marshall GE, Russell JA, Kane KA, et al. Post-operative atrial fibrillation is influenced by beta-blocker therapy but not by pre-operative atrial cellular electrophysiology. *J Cardiovasc Electrophysiol* 2006; **17**: 1230-8.

[11] Workman AJ, Kane KA, Rankin AC. Cellular bases for human atrial fibrillation. *Heart Rhythm* 2008; **5**: S1-6.

[12] Marshall GE, Russell JA, Tellez JO, Jhund PS, Currie S, Dempster J, et al. Remodelling of human atrial K(+) currents but not ion channel expression by chronic beta-blockade. *Pflugers Arch* 2012; **463**: 537-48.

[13] Workman AJ, Marshall GE, Rankin AC, Smith GL, Dempster J. Transient outward K+ current reduction prolongs action potentials and promotes afterdepolarisations: a dynamic-clamp study in human and rabbit cardiac atrial myocytes. *J Physiol* 2012; **590**: 4289-305.

[14] Pau D, Workman AJ, Kane KA, Rankin AC. Electrophysiological effects of 5-hydroxytryptamine on isolated human atrial myocytes, and the influence of chronic beta-adrenoceptor blockade. *Br J Pharmacol* 2003; **140**: 1434-41.

[15] Pau D, Workman AJ, Kane KA, Rankin AC. Electrophysiological and arrhythmogenic effects of 5-hydroxytryptamine on human atrial cells are reduced in atrial fibrillation. *J Mol Cell Cardiol* 2007; **42**: 54-62.

[16] Wang Z, Fermini B, Nattel S. Sustained depolarization-induced outward current in human atrial myocytes. Evidence for a novel delayed rectifier K+ current similar to Kv1.5 cloned channel currents. *Circ Res* 1993; **73**: 1061-76.

[17] Zhang H, Garratt CJ, Zhu J, Holden AV. Role of up-regulation of IK1 in action potential shortening associated with atrial fibrillation in humans. *Cardiovasc Res* 2005; **66**: 493-502.

[18] Grandi E, Pandit SV, Voigt N, Workman AJ, Dobrev D, Jalife J, et al. Human atrial action potential and Ca2+ model: sinus rhythm and chronic atrial fibrillation. *Circ Res* 2011; **109**: 1055-66.

[19] Pandit SV, Berenfeld O, Anumonwo JM, Zaritski RM, Kneller J, Nattel S, et al. Ionic determinants of functional reentry in a 2-D model of human atrial cells during simulated chronic atrial fibrillation. *Biophys J* 2005; **88**: 3806-21.

[20] Aslanidi OV, Al-Owais M, Benson AP, Colman M, Garratt CJ, Gilbert SH, et al. Virtual tissue engineering of the human atrium: Modelling pharmacological actions on atrial arrhythmogenesis. *European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences* 2012; **46**: 209-21.

[21] Kharche S, Garratt CJ, Boyett MR, Inada S, Holden AV, Hancox JC, et al. Atrial proarrhythmia due to increased inward rectifier current (I(K1)) arising from KCNJ2 mutation--a simulation study. *Prog Biophys Mol Biol* 2008; **98**: 186-97.

[22] Courtemanche M, Ramirez RJ, Nattel S. Ionic mechanisms underlying human atrial action potential properties: insights from a mathematical model. *Am J Physiol* 1998; **275**: H301-21.

[23] Koivumaki JT, Korhonen T, Tavi P. Impact of sarcoplasmic reticulum calcium release on calcium dynamics and action potential morphology in human atrial myocytes: a computational study. *PLoS Comput Biol* 2011; **7**: e1001067.

[24] Qu Z, Garfinkel A, Weiss JN. Vulnerable window for conduction block in a one-dimensional cable of cardiac cells, 1: single extrasystoles. *Biophys J* 2006; **91**: 793-804.

[25] Colman MA, Aslanidi OV, Kharche S, Boyett MR, Garratt CJ, Hancox JC, et al. Pro-arrhythmogenic Effects of Atrial Fibrillation Induced Electrical Remodelling- Insights from 3D Virtual Human Atria. *J Physiol* 2013.

[26] Kharche S, Adeniran I, Stott J, Law P, Boyett MR, Hancox JC, et al. Pro-arrhythmogenic effects of the S140G KCNQ1 mutation in human atrial fibrillation - insights from modelling. *J Physiol* 2012; **590**: 4501-14.

[27] Qu Z, Weiss JN, Garfinkel A. Cardiac electrical restitution properties and stability of reentrant spiral waves: a simulation study. *Am J Physiol* 1999; **276**: H269-83.

[28] Gilmour RF, Jr., Gelzer AR, Otani NF. Cardiac electrical dynamics: maximizing dynamical heterogeneity. *J Electrocardiol* 2007; **40**: S51-5.

[29] Lugo CA, Cantalapiedra IR, Penaranda A, Hove-Madsen L, Echebarria B. Are SR Ca content fluctuations or SR refractoriness the key to atrial cardiac alternans?: insights from a human atrial model. *Am J Physiol Heart Circ Physiol* 2014.

[30] Blatter LA, Kockskamper J, Sheehan KA, Zima AV, Huser J, Lipsius SL. Local calcium gradients during excitation-contraction coupling and alternans in atrial myocytes. *J Physiol* 2003; **546**: 19-31.

[31] Gong Y, Xie F, Stein KM, Garfinkel A, Culianu CA, Lerman BB, et al. Mechanism underlying initiation of paroxysmal atrial flutter/atrial fibrillation by ectopic foci: a simulation study. *Circulation* 2007; **115**: 2094-102.

[32] Pueyo E, Husti Z, Hornyik T, Baczko I, Laguna P, Varro A, et al. Mechanisms of ventricular rate adaptation as a predictor of arrhythmic risk. *Am J Physiol Heart Circ Physiol* 2010; **298**: H1577-87.

[33] Fox JJ, Riccio ML, Drury P, Werthman A, Gilmour RF. Dynamic mechanism for conduction block in heart tissue. *New Journal of Physics* 2003; **5**: 14.

[34] Grom A, Faber TS, Brunner M, Bode C, Zehender M. Delayed adaptation of ventricular repolarization after sudden changes in heart rate due to conversion of atrial fibrillation. A potential risk factor for proarrhythmia? *Europace* 2005; **7**: 113-21.

[35] Comtois P, Kneller J, Nattel S. Of circles and spirals: bridging the gap between the leading circle and spiral wave concepts of cardiac reentry. *Europace* 2005; **7 Suppl 2**: 10-20.

[36] Seemann G, Sachse FB, Weiss DL, Ptacek LJ, Tristani-Firouzi M. Modeling of IK1 mutations in human left ventricular myocytes and tissue. *Am J Physiol Heart Circ Physiol* 2007; **292**: H549-59.

[37] Dong M, Niklewski PJ, Wang HS. Ionic mechanisms of cellular electrical and mechanical abnormalities in Brugada syndrome. *Am J Physiol Heart Circ Physiol* 2011; **300**: H279-87.

[38] Seemann G, Hoper C, Sachse FB, Dossel O, Holden AV, Zhang H. Heterogeneous three-dimensional anatomical and electrophysiological model of human atria. *Philos Transact A Math Phys Eng Sci* 2006; **364**: 1465-81.

[39] Weber FM, Luik A, Schilling C, Seemann G, Krueger MW, Lorenz C, et al. Conduction velocity restitution of the human atrium--an efficient measurement protocol for clinical electrophysiological studies. *IEEE Trans Biomed Eng* 2011; **58**: 2648-55.

[40] Salameh A, Dhein S. Adrenergic control of cardiac gap junction function and expression. *Naunyn Schmiedebergs Arch Pharmacol* 2011; **383**: 331-46.

[41] Dhein S, Rothe S, Busch A, Rojas Gomez DM, Boldt A, Reutemann A, et al. Effects of metoprolol therapy on cardiac gap junction remodelling and conduction in human chronic atrial fibrillation. *Br J Pharmacol* 2011; **164**: 607-16.

[42] Cao F, Huang CX, Wang T, Li X, Jiang H, Bao MW. Effects of carvedilol on rabbit atrial cell electrophysiology. *Heart Rhythm* 2006; **3 (Supp 1)**: S178.

Figure legends

FIGURE 1 Simulated AP and ion current profiles under control and β-block induced remodelling conditions using the CRN (column A), Grandi (column B) and KT (column C) models. Top row shows AP, middle row I_{K1}, third row shows I_{to}, and bottom row shows I_{CaL} profiles.

FIGURE 2 Cellular S1-S2 APDr and ERP restitution curves computed from the CRN (Column A), Grandi (Column B), and KT (Column C) cell models. Top panels show APD_{90} restitution curves, middle panels show APD_{30} restitution curves, while bottom panels show ERP restitution curves.

FIGURE 3 Alternans manifested by bifurcation of dynamic APD restitution curves in CRN (left hand panels) and KT (right hand panels) cell models. APD_{90} and APD_{30} panels show absolute values of APD at 90% and 30% repolarisation and their maximal and minimal values when alternans occurs. ΔAPD_{90} and ΔAPD_{30} panels show the absolute differences between the maximal and minimal APDs (i.e., alternans amplitudes) under control and β-blockade conditions.

FIGURE 4 Effects of abrupt change of PCL on APD_{90} and CVr in CRN (column A), Grandi (column B) and KT (column C) models. *Top panels:* The cell models were paced under control and β-block induced remodelling conditions for 500 beats at 1 Hz pacing, followed by 500 beats at 1.67 Hz (PCL = 600 ms) pacing, and finally followed by 1 Hz pacing for 500 beats. The APD_{90} adaptation during the 1.67 Hz pacing was fitted for slow AP adaptation rates. *Bottom panels:* CVr in 1D models under control (gray lines) and β-blockade (solid black lines) conditions.

FIGURE 5 Re-entrant waves in 3D atria models. Row wise panels show results for each of the three models under control and β-block induced remodelling conditions. A: Representative frames from the 3D simulations are shown in the first 3 columns, with arrows indicating approximate path of scroll waves to inferior vena cava (IVC) model boundary. B: Period of localised excitation.

Table

Table 1. Summary of the multi-scale numerical results under β-block-induced remodelling and control conditions.

Quantity	CRN (β-blocker, Control)	Grandi (β-blocker, Control)	KT (β-blocker, Control)	Text section
Cell simulations				
APD_{90} (ms) (Expt. data [7, 12]: β-blocker: 238 ms; non-β-blocker: 186)	355.4, 302.8	433.0, 334.2	299.2, 238.1	2.1
APD_{30} (ms)	139.8, 148	76.1, 66.2	30, 26.5	2.1
dV/dt_{max} (mV/ms)	203.6, 206.7	101.2, 108.7	53.6, 55.54	2.1
OS (mV)	37.6, 36.03	9.5, 28.5	38.7, 36.1	2.1
RP (mV)	-77.8, -81.2	-68.6, -73.4	-75.9, -77.2	2.1
triangulation (mV/ms)	4.6, 3.2	8.8, 6.1	5.9, 4.6	2.1
S1-S2 APDr max. slope	0.97, 1.2	0.88, 2.8	1.9, 1.2	2.2
ERP (ms)	432, 347	850, 650	375, 318	2.2
Alternans PCL range (ms)	295-410, alternans suppressed	Alternans not observed	200-263, alternans suppressed	2.2
Slow time constant of APD adaptation (ms)	258, 217	96, 111	257, 255	2.3
1D simulations				
1D maximum pacing rate (Hz)	2.8, 3.1 (9.6%)	2.2, 3 (26.6%)	4.4, 5.1 (13.7%)	2.4

1D wavelength of propagation (mm), low PCL	124, 105	55.6, 55.7	106.6, 83.3	2.4
1D wavelength of propagation (mm), fast PCL (ms)	35.4 (350), 36.1 (317)	21.4 (464), 22.9 (329)	15.3 (227), 12.6 (195)	2.4
Temporal VW (ms)	12.7, 10.1	24, 18.8	11.5, 15.8	2.4
Tissue ERP (ms)	399.4, 370.5 (8%)	433.8, 362.7 (19.6%)	263.2, 215.0 (10%)	2.4
3D re-entry simulations				
Re-entry LS (s)	0.4, > 5	0.5, > 5	> 5 s in both cases	2.5
Average re-entry period (ms)	< 150, 360	< 250, 635	380, 290	2.5