Cardiac adrenergic control and atrial fibrillation

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Abstract. Atrial fibrillation (AF) is the most common cardiac arrhythmia, and it causes substantial mortality. The autonomic nervous system, and particularly the adrenergic/cholinergic balance, has a profound influence on the occurrence of AF. Adrenergic stimulation from catecholamines can cause AF in patients. In human atrium, catecholamines can affect each of the electrophysiological mechanisms of AF initiation and/or maintenance. Catecholamines may produce membrane potential oscillations characteristic of afterdepolarisations, by increasing Ca^{2+} current, $[Ca^{2+}]_i$ and consequent Na^+-Ca^{2+} exchange, and may also enhance automaticity. Catecholamines might affect reentry, by altering excitability or conduction, rather than action potential terminal repolarisation or refractory period. However, which arrhythmia mechanisms predominate is unclear, and likely depends on cardiac pathology and adrenergic tone. Heart failure (HF), a major cause of AF, causes adrenergic activation and adaptational changes, remodelling, of atrial electrophysiology, Ca^{2+} homeostasis and adrenergic responses. Chronic AF also remodels these, but differently to HF. Myocardial infarction, and AF, cause neural remodelling that also may promote AF. β-adrenoceptor antagonists (β-blockers) are used in the treatment of AF, mainly to control the ventricular rate, by slowing AV conduction. β-blockers also reduce the incidence of AF, particularly in HF or after cardiac surgery, when adrenergic tone is high. Furthermore, the chronic treatment of patients with β-blockers remodels the atria, with a potentially anti-arrhythmic increase in the refractory period. Therefore, the suppression of AF by β-blocker treatment may involve an attenuation of arrhythmic activity that is caused by increased $[Ca^{2+}]_i$, coupled with effects of adaptation to the treatment. An improved understanding of the involvement of the adrenergic system and its control in basic mechanisms of AF under differing cardiac pathologies might lead to better treatments.

Keywords: Atrial fibrillation; Adrenergic; Catecholamine; Beta-blocker; Arrhythmia mechanism; Calcium; Action potential; Remodeling

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with an estimated prevalence in the general population of 0.4-1% (Fuster et al. 2006). AF affects primarily the elderly, e.g., 4.6% of people aged >65 years, and 7.1% of those >85 years (Murphy et al. 2007). Symptoms include palpitations, dizziness, fatigue, chest pain and dyspnoea. Moreover, AF substantially increases the risk of stroke, heart failure (HF) and death (Fuster et al. 2006). Pharmacological therapy is the mainstay of treatment. However, current anti-arrhythmic drugs for AF prevention have limited efficacy and considerable potential for adverse effects. The autonomic nervous system has a profound influence on the occurrence of AF, and a predominance of activity of either the adrenergic (sympathetic) (Dimmer et al. 1998) or cholinergic (parasympathetic) (Bettoni et al. 2002) branches can promote AF. Furthermore, AF may be generated and maintained by a variety of electrophysiological mechanisms (Workman et al. 2008), and a change in autonomic activity is expected to affect each differently. This review focuses on the effects of adrenergic stimulation and antagonism on the electrophysiological mechanisms of AF, and on their modulation by atrial remodelling from cardiac disease and drug treatment. The effects of adrenergic modulation are wide ranging, complex and species- and cardiac chamber-dependent, so studies of human atrium are highlighted where available.

The cardiac adrenergic system

The cardiac adrenergic system comprises adrenergic nerves, hormones and receptors. Pre-ganglionic adrenergic neurons of the spinal cord, sympathetic trunk, cervical ganglia and cardiac plexuses synapse with post-ganglionic neurons. Those penetrate the myocardium along coronary arterial pathways, terminating on cardiac myocytes and vessels of all chambers (Kawashima 2005). Adrenergic stimulation results in the release of the adrenergic hormones, catecholamines, including noradrenaline (norepinephrine) from post-ganglionic nerve terminals, and adrenaline (epinephrine) from the adrenal medulla. Catecholamines bind to and activate cell surface adrenoceptors, including the α, β_1, β_2 and β_3 subtypes, all of which are present in human atrium (Mary-Rabine et al. 1978; Hedberg et al. 1985; Chamberlain et al. 1999). Their independent stimulation has complex and sometimes opposing effects on atrial function, and the net response to catecholamine stimulation depends on catecholamine type and relative adrenoceptor subtype density and sensitivity, which may vary with disease.

What is the evidence for involvement of the adrenergic system in AF?

In patients, heart rate variability studies indicated an increased level of adrenergic, relative to cholinergic, activity in the minutes preceding the onset of AF (Dimmer et al. 1998; Coccagna et al. 1997). However, increased cholinergic activity, perhaps following increased adrenergic activity (Bettoni et al. 2002) also generated AF. Infusion of isoprenaline (isoproterenol, ISO), a mixed β-receptor agonist, produced AF in 5% of patients with no history of AF, and in 84% of patients with paroxysmal AF, in a dose-dependent manner (Oral et al. 2008). In dogs, adrenaline (Sharifov et al. 2004) or ISO (Kiss et al. 2004; Sharifov et al. 2004) produced AF, and ISO facilitated acetylcholine-induced AF (Sharifov et al. 2004). Electrical stimulation of pulmonary vein (PV) autonomic nerves produced rapid PV arrhythmic activation, abolished by the β_1-antagonist (β_1-blocker) atenolol (Patterson et al. 2005). Furthermore, increased atrial adrenergic innervation was associated with chronic AF in patients (Gould et al. 2006). Propranolol (a mixed β-blocker) reduced the incidence of burst pacing-induced sustained atrial tachyarrhythmia (AT) associated with HF in dogs (Stambler et al. 2003). Moreover, several β-blockers are effective in suppressing AF in patients with various heart diseases (Lopez-Sendon et al. 2004). It is reasonable to infer, therefore, that adrenergic stimulation may be involved in the initiation and/or maintenance of AF. However, it is unclear how adrenergic stimulation or antagonism affect the various electrophysiological mechanisms of AF or, indeed, which of these mechanisms predominate.

Electrophysiological mechanisms of AF initiation and maintenance

The majority of atrial premature beats that trigger (initiate) AF originate from focal (focussed) ectopic (away from the sinoatrial (SA) node) electrical activity in or near the PVs. For example, in patients with drug-resistant paroxysmal AF, 94% of ectopic foci that initiated spontaneous AF were located, using multi-electrode catheter mapping, to the PVs (Haissaguerre et al. 1998). The electrophysiological mechanism of the trigger is often considered to be either abnormal automaticity (AA) or triggered activity. AA is the premature firing of action potentials due to increased pacemaking, i.e. accelerated diastolic, phase 4, membrane depolarisation. It is favoured by an increase in diastolic inward, depolarising, ion currents such as the funny current (I_f) and potentially the L-type Ca^{2+} (I_{CaL}) and Na^+-Ca^{2+} exchanger ($I_{Na/Ca}$) currents. It is also favoured by a decrease in outward, hyperpolarising, currents such as the delayed rectifier K^+ currents, of

which there are various types, having either ultra-rapid (I_{Kur}), rapid (I_{Kr}) or slow (I_{Ks}) activation kinetics. Triggered activity is premature firing due to oscillations in membrane potential following an action potential upstroke, i.e. afterdepolarisations. Those may be delayed (DADs), which occur after full repolarisation. They are favoured by high heart rates and excessive intracellular Ca^{2+} (Ca^{2+}_i) loading. That can result in a transient inward current carried by $I_{Na/Ca}$, as 1 Ca^{2+} is extruded in exchange for 3 Na^+. Alternatively, they may be early afterdepolarisations (EADs), which occur during repolarisation. Those are favoured by low heart rates, increases in the action potential duration (APD) in the voltage range at which I_{CaL} can reactivate, or by abnormalities in I_{Na} activation or inactivation. Once initiated, AF may be maintained by single or multiple wavelet intra-mural reentry. Reentry is rapid circuitous activation caused by unidirectional conduction block. It is favoured by premature beats, increased spatial heterogeneity of electrical activity, and a decrease in the circuit length, the wavelength. For example, a premature impulse may divide at a functional or anatomical obstacle, with one wavefront being blocked at refractory, i.e., inexcitable tissue. The other may activate adjacent tissue with a short effective refractory period (ERP), circulate the obstacle and reenter the previously inexcitable tissue provided that the wavelength, the product of ERP and conduction velocity, is shorter than the available conduction path (Workman et al. 2008). A reduced ERP may result from early availability of the Na^+ channel current (I_{Na}) due, e.g., to shortening of the terminal phase of repolarisation of the action potential. Slowed conduction may result from decreased excitability, increased intercellular fibrosis or reduced intercellular gap junction current (I_{gap}). Myocardial tissue capable of supporting reentry is sometimes termed a reentrant “substrate”, i.e., having structural or functional characteristics predisposing to reentry, perhaps resulting from pathological remodelling. It should be noted, however, that a pathological predisposition to sustained non-reentrant activity (AA and/or triggered activity) could also constitute, or contribute to, a substrate for AF. Furthermore, the focal trigger of AF in the PVs could be either micro-reentrant, triggered or abnormally automatic (Haissaguerre et al. 1998). Whether reentrant or non-reentrant mechanisms predominate is under debate (Wit et al. 2007), and likely depends on, e.g., the underlying cardiac pathology and autonomic tone. The effects of changes in adrenergic activity on each of the reentrant and non-reentrant mechanisms should, therefore, be considered when attempting to understand how adrenergic modulation affects the initiation and maintenance of AF.

Effects of adrenergic stimulation on pacemaking

In the natural pacemaker, the SA node, adrenergic stimulation accelerates phase 4, shortening diastole, thus increasing heart rate. Multiple ion current mechanisms have been proposed. In rabbit SA node, β-stimulation increased I_f, associated with a positive shift in its activation voltage (Barbuti et al. 2007), and accelerated the deactivation of I_{Kr} and I_{KS} (Lei et al. 2000); each potentially accelerating phase 4. β-stimulation also increases SA nodal I_{CaL} and peak $[Ca^{2+}]_i$, potentially enhancing phase 4 via increased $I_{Na/Ca}$ (Bers 2008). The atrium is not normally a pacemaker, although isolated tissues obtained from patients undergoing cardiac surgery may activate spontaneously. Right atrial (RA) pectinate muscles sometimes featured a "single pacemaker", and adrenaline transiently decreased, then markedly increased, its rate (Trautwein et al. 1962). Specialised conducting fibres from human RA were identified by their pacemaker activity after ceasing stimulation, and adrenaline increased phase 4 and automatic rate (Mary-Rabine et al. 1978). A similar effect of adrenergic stimulation was observed in other human studies (Mary-Rabine et al. 1980; Levi et al. 1981), as well as in healthy animal atria (Davis 1975; Ono et al. 1995). Specialised pacemaker-type cells, similar to those normally found in SA node, have been identified in patients' PVs (Perez-Lugones et al. 2003). Pacemaker activity was found in rabbit PV isolated cells, which was enhanced by ISO (Chen et al. 2002). However, it is unclear whether pacemaking or AA occur in either PV or atrium *in-vivo*, or whether such activity could arise from adrenergic stimulation.

Can adrenergic stimulation cause afterdepolarisations in human atrium?

Adrenergic stimulation produces several types of arrhythmic electrical activity in human atrial isolated tissues or cells, that are distinct from the production of regular automaticity or the acceleration of automatic rate. In unstimulated, quiescent RA muscle strips, adrenaline produced "bizarre" action potentials of "various shapes, durations and frequencies", some with "distinct second spikes" (Sleator et al. 1964) (Figure 1*a*). ISO produced "DADs" or "triggered activity" in unstimulated RA "specialized fibers" (Wang et al. 2006). Adrenaline produced "DADs" immediately after cessation of physiological-rate stimulation in RA trabeculae (Yeh et al. 1992). In RA isolated cells stimulated at physiological rate, ISO caused action potentials to be interrupted frequently by low amplitude, usually sub-threshold, transient depolarisations, termed "cellular arrhythmic depolarisations" (CADs) (Redpath et al. 2006) (Figure 1*b*). They could occur after repolarisation, during repolarisation or after a CAD, and may represent DADs, EADs or AA. Adrenergic stimulation also

produced “arrhythmic contractions” in human RA appendages (Kaumann et al. 1993), although electrical activity was not studied. Therefore, adrenergic stimulation produced arrhythmic electrical activity in each of four studies that could be found on human atrial isolated tissues or cells. For such activity to qualify as a DAD, its amplitude should increase and its coupling interval decrease in proportion with an increasing stimulation rate (Wit et al. 2007), as demonstrated in canine atria with adrenaline (Johnson et al. 1986). However, in none of these human atrial studies were potential DADs qualified in that way. Which type of non-reentrant activity is produced by adrenergic stimulation in human atrium remains unclear.

[Insert Figure 1]

Can adrenergic stimulation affect atrial reentry?

Reported effects of adrenergic stimulation on atrial reentry wavelength are rather discordant. In the absence of arrhythmias, wavelength change has been assessed by measuring ERP and conduction velocity. In patients, intravenous ISO increased wavelength, associated with suppression of extrastimuli-induced repetitive atrial firing, by causing a marked increase in conduction velocity and only a small change in ERP (Shimizu et al. 1994a). However, an absence of change in atrial wavelength in dogs (Rensma et al. 1988), or an increase due to ERP-prolongation in rabbits (Smeets et al. 1986) also were reported. In patients with atrial flutter, ISO decreased the arrhythmia cycle length, primarily by slowing conduction, thus potentially promoting reentry (Stambler et al. 1996). ISO also sustained reentrant circuits in PVs, but without changing conduction velocity (Arora et al. 2003). In diseased atria that are partially depolarised, adrenergic stimulation might inhibit reentry, by increasing excitability and overcoming conduction block. For example, in tissues from patients with RA enlargement, slow-rate ectopic foci fired independently of the pacing stimuli, revealing conduction block between driven and ectopic cells. Adrenaline hyperpolarised the maximum diastolic potential (MDP), and abolished the ectopic foci by electrically connecting them to the driven cells (Gelband et al. 1977). However, since adrenergic stimulation increases I_{CaL}, this could potentially promote reentry in tissues which remain sufficiently depolarised to keep I_{Na} inactive, by generating slowly conducted Ca^{2+}-dependent action potentials. Atrial reentry and AF can result from wavelength decrease associated with reduction of ERP, as demonstrated with acetylcholine (Rensma et al. 1988). There are few studies of effects of adrenergic stimulation on human atrial ERP, with a report of a small (5%) decrease (Shimizu et al. 1994a) and of no change (Redpath et al. 2006). There are several studies, however, of effects of adrenergic stimulation on human atrial action potential terminal repolarisation, a major determinant of the ERP.

Effects of adrenergic stimulation on human atrial action potentials

Adrenergic stimulation is generally considered to shorten myocardial terminal repolarisation, as shown in canine ventricle, with a reduction in the APD at 95% repolarisation (APD_{95}) in isolated tissues (Volders et al. 2003) and cells (Stengl et al. 2006) (Figure 2*ai*). In human ventricle, however, adrenergic stimulation may lengthen, rather than shorten, terminal repolarisation, since in isolated tissues or cells, APD_{95} was markedly prolonged by noradrenaline or ISO in three of four available studies (Eckel et al. 1982; Mitchell et al. 1986; Koumi et al. 1995) (Figure 2*aii*), and by adrenaline in two of three tissues in the other study (Yeh et al. 1992). It should be noted, however, that these preparations were from patients who were undergoing cardiac surgery, and the associated myocardial diseases and drug treatments could affect the responses to adrenergic stimulation. In undiseased human ventricular tissues, adrenaline had no effect on repolarisation already prolonged by dofetilide (Jost et al. 2005), but effects of adrenergic stimulation alone were not studied. In human atrium, by contrast with ventricle, terminal repolarisation is usually unaffected by adrenergic stimulation. Of the six available reports in isolated tissues or cells, five showed no significant effect of adrenaline or ISO on APD_{90} (Sleator et al. 1964; Gelband et al. 1977; Kecskemeti et al. 1985; Yeh et al. 1992; Redpath et al. 2006) (e.g. Figure 2*aiii & iv*), and one showed a marked increase in APD_{90} (Li et al. 1997). Species differences in effects of adrenergic stimulation on atrial terminal repolarisation should be noted, however, with shortening in dog (Liang et al. 1985; Yeh et al. 2007), and lengthening in guinea pig (Yoshimoto et al. 1998) and rat (Webb et al. 1956). The MDP and action potential maximum upstroke velocity, which can affect conduction velocity and hence reentry, also were unaffected by adrenergic stimulation, in normally polarised human atrial tissues (Gelband et al. 1977; Kecskemeti et al. 1985). However, the action potential plateau, phase 2, was markedly elevated by adrenergic stimulation in several reports, reflected by increased APD_{50} (Kecskemeti et al. 1985; Li et al. 1997; Redpath et al. 2006). For example, 50 nM ISO approximately doubled APD_{50} in human atrial cells (Redpath et al. 2006) (Figure 2*aiv*). The available human atrial studies, taken together, do not support an effect of adrenergic stimulation that could substantially affect reentry via action potential terminal repolarisation. However, the plateau elevation has the potential to promote afterdepolarisations, either by increasing APD in the voltage range at which I_{CaL} can reactivate and thus cause EADs (Bers 2008), or by its association with increased Ca^{2+}_i loading and DADs. To understand the mechanisms by which adrenergic stimulation elevates the action potential plateau,

without affecting terminal repolarisation, we need to know which ion currents are affected in human atrium by adrenergic stimulation, and also how these currents interact.

[Insert Figure 2]

Effects of adrenergic stimulation on human atrial ion currents

The atrial action potential plateau amplitude is determined largely by the magnitude of I_{CaL} (Figure 2*b*). This is an inward cationic, i.e. depolarising, current and its agonism and blockade elevate and lower the plateau, respectively, as shown using Bay K 8644 (Yue et al. 1997) or nifedipine (Workman et al. 2001). Adrenergic stimulation has consistently been shown to increase human atrial I_{CaL}, often more than 2-fold, e.g. (Ouadid et al. 1995; Pelzmann et al. 1995; Li et al. 1997; Van Wagoner et al. 1999; Christ et al. 2004; Redpath et al. 2006; Greiser et al. 2007) (Figure 2*b*). The biophysical mechanism is an increase in the open probability of available I_{CaL} channels, resulting from an increase in their open time and a decrease in their closed time. The signalling mechanism involves phosphorylation of I_{CaL} channels by protein kinase A (PKA). That is activated by increased adenylyl cyclase-dependent cyclic AMP (cAMP), which results from the stimulation of GTP regulatory proteins due to the binding of catecholamines to β-receptors. I_{CaL} may be moderately increased by high stimulation rates, due to slowing of current decay: so-called high frequency-induced upregulation (HFIUR). Since HFIUR was potentiated by ISO in human atrial cells (Piot et al. 1996), the increase in I_{CaL} by adrenergic stimulation may be potentiated at the high atrial rates encountered during AF. The influence of I_{CaL} on the action potential is normally balanced partly by the transient outward K^+ current (I_{TO}). However, I_{TO} was unaffected by ISO in human atrium (Su et al. 1994) and should not, therefore, alter the influence of I_{CaL} to elevate the plateau. Chloride currents (I_{Cl}) also may contribute to early repolarisation. However, ISO had inconsistent effects on human atrial I_{Cl}, with either an increase (Tsai et al. 2001) or no change (Sakai et al. 1995) in $I_{Cl.cAMP}$, or no change in $I_{Cl.swell}$ (Sato et al. 1998). Reports of effects of adrenergic stimulation on other mechanosensitive currents (Stiber et al. 2009) in human atrium could not be found. The increased voltage resulting from the increase in I_{CaL} may enhance the activation of delayed rectifier K^+ currents, with a potential shortening influence on terminal repolarisation. However, the relative magnitudes, and contributions to repolarisation, of I_{Kur}, I_{Kr} and I_{KS} in human atrium are incompletely understood. I_{Kr} and I_{KS} were relatively small or present in only a minority of cells (Wang et al. 1994; Schaffer et al. 1998), but this might reflect disruption of these currents by the requisite "chunk" method of cell isolation (Yue et al. 1996), and in intact atrial tissue, I_{Kr} blockade may prolong APD_{90} (Wettwer et al. 2004). Adrenergic stimulation

may increase both I_{Kr} (Heath et al. 2000) and I_{KS} (Volders et al. 2003), but human atrial data are lacking. Altered plateau voltages resulting from changes in I_{Kur} also may affect terminal repolarisation via I_{Kr} and I_{KS} (Wettwer et al. 2004), and adrenergic stimulation increased I_{Kur} in human atrium (Li et al. 1996; Su et al. 1994). Therefore, the net contribution of adrenergic stimulation-induced changes in I_{Kur}, I_{Kr} and I_{KS} to human atrial terminal repolarisation is unclear. Several additional currents contribute to terminal repolarisation in human atrium, including the inward rectifier K^+ currents I_{K1} and I_{KACh}, the Na^+, K^+ pump current (I_p), $I_{Na/Ca}$, and possibly ATP-sensitive K^+ current (I_{KATP}) (Workman et al. 2008). ISO increased I_{KACh} in canine atrium (Yeh et al. 2007), yet it may affect neither I_{K1} nor I_{KACh} in human atrium (Voigt et al. 2009). Human atrial I_p has been measured directly in only a single study (Workman et al. 2003a), but adrenergic stimulation was not studied. However, the hyperpolarisation caused by rewarming of human atrial tissue, considered to be due to I_p reactivation, was unaffected by adrenaline (Rasmussen et al. 1985). $I_{Na/Ca}$ was increased by ISO in cat atrium (Zhou et al. 1993), but human atrial data are lacking. I_{KATP} was increased by ISO in cat ventricle, from ATP_i depletion rather than a direct effect (Schackow et al. 1994), but atrial data are lacking. I_{Na} was reduced by ISO in human atrium (Lee et al. 1990). However, any conduction-slowing influence of that might be outweighed by an opposing increase in I_{gap} (Salameh et al. 2006). I_f is consistently increased by β-stimulation in human atrium, associated with a positive shift in its activation voltage, e.g. (Hoppe et al. 1998; Lonardo et al. 2005). However, whether such an increase could lead to atrial arrhythmias from AA is uncertain (Workman et al. 1998), because of the rather negative activation voltage of I_f relative to atrial MDP, and the small current size under physiological $[K^+]_o$. Mathematical modelling should help to clarify the relative contribution of these ion current changes to the altered action potential shape under adrenergic stimulation. However, the weight of currently available evidence, summarised in Figure 2*b*, suggests that in human atrium the plateau is elevated primarily by I_{CaL} increase, and that an associated increase in I_{Kur}, with little or no direct effect on other repolarising currents, results in no net change in terminal repolarisation. The contrasting changes in terminal repolarisation seen in some other species and in ventricle may result in part from differing magnitudes of the various delayed rectifier current components. Moreover, the prominent increase in I_{CaL} has important implications for Ca^{2+}_i homeostasis and arrhythmogenesis.

Effects of adrenergic stimulation on atrial Ca^{2+}_i and its contribution to arrhythmogenesis

The flow of Ca^{2+} into myocardial cells via I_{CaL} during systole causes contraction by triggering a marked increase in $[Ca^{2+}]_i$, by the opening of sarcoplasmic reticulum (SR) Ca^{2+} release channels (ryanodine receptors, RyR); so-called Ca^{2+}-induced Ca^{2+}-release (CICR). During relaxation, Ca^{2+} is returned to the SR by the SR Ca^{2+} pump (SERCA). The amplitude of the transient rise in $[Ca^{2+}]_i$ is influenced in part by the amplitude of I_{CaL}. Adrenergic stimulation increases the Ca^{2+}_i transient and accelerates its decline, by causing the phosphorylation of various proteins including I_{CaL} channels and phospholamban (PLB) (Bers 2002). There is probably only a minor contribution in the steady state from phosphorylation of RyR (Eisner et al. 2009). The phosphorylation of PLB reduces its inhibitory effect on SERCA, thus increasing Ca^{2+}_{SR} uptake, and is the dominant cause of accelerated Ca^{2+}_i decline under β-stimulation. The faster Ca^{2+}_{SR} uptake also contributes to an increased Ca^{2+}_{SR} content, thus increasing Ca^{2+}_{SR} availability for CICR, and coupled with increased I_{CaL}, is the main determinant of the increased Ca^{2+}_i transient under adrenergic stimulation (Bers 2002). Ca^{2+}_i homeostasis differs between atrium and ventricle (Dobrev et al. 2008). Atrial cells lack a fully developed transverse tubule network and, in contrast to ventricular cells, in which Ca^{2+} influx increases $[Ca^{2+}]_i$ uniformly, the Ca^{2+} wave arises in the cell's periphery, propagating to the centre. The Ca^{2+}_i transient was also smaller in atrium, and Ca^{2+}_{SR} content substantially larger (Walden et al. 2009). In human atrial cells, β-stimulation increased the Ca^{2+}_i transient amplitude (Hatem et al. 1995), as reported in atria of other species (Mackenzie et al. 2004; Danson et al. 2005; Coutu et al. 2006). In rat atrial cells which displayed primarily peripheral Ca^{2+}_i transients, β-stimulation produced large transients in central regions (Mackenzie et al. 2004). β-stimulation also increased atrial diastolic $[Ca^{2+}]_i$ (Danson et al. 2005), and might enhance a diastolic Ca^{2+}_{SR} leak, as shown in rabbit ventricle (Curran et al. 2007). β-stimulation could elevate Ca^{2+}_{SR} content and $[Ca^{2+}]_i$ sufficiently to cause propagating waves of CICR, which may increase Ca^{2+} extrusion via $I_{Na/Ca}$ sufficiently to produce DADs (Eisner et al. 2009). Furthermore, increased $[Ca^{2+}]_i$ may enhance pacemaker activity, by increasing $I_{Na/Ca}$ (Bers 2008), thus potentially causing AA. Adrenergic stimulation caused DADs in canine atrial fibres, but Ca^{2+}_i was not studied (Johnson et al. 1986). ISO promoted spontaneous Ca^{2+}_i transients in canine atrial and PV cells, but action potentials were not studied (Coutu et al. 2006). Focal ectopic beats that were preceded by rises in $[Ca^{2+}]_i$ were produced by perfusing canine atria with ryanodine plus ISO, but ISO alone was not studied (Chou et al. 2005). It is conceivable that adrenergic stimulation in human atrium could

increase the Ca^{2+}_i transient, Ca^{2+}_{SR} content and diastolic $[Ca^{2+}]_i$ sufficiently to cause DADs or AA, but more studies are required to clarify that.

Independent stimulation of adrenoceptor subtypes

The effects of adrenergic stimulation on atrial rhythm, pacemaking, propensity to spontaneous depolarisations, reentry, and action potentials were demonstrated using both combined β- and α-stimulation with adrenaline, and β-stimulation only, with ISO. Effects of adrenaline and ISO, sometimes compared within studies, largely conformed, suggesting a prominent involvement of β. However, for human atrial ion currents or Ca^{2+}_i, β-stimulation only was used, except in one study (Christ et al. 2004). Moreover, adrenoceptor subtypes can mediate different, sometimes opposing (Li et al. 1996; Yeh et al. 2007) effects, that may also vary with cardiac disease. Independent β_1- and β_2-stimulation has been studied using ISO plus selective β-subtype blockers. In canine atrium, whilst only ~25% of β-receptors were β_2, ~50% of the effect of ISO to decrease APD_{75} was via β_2 (Liang et al. 1985). In human atrium, however, although up to 55% of β-receptors are β_2 (Hedberg et al. 1985), ISO did not affect APD_{75} (Redpath et al. 2006). β_2-stimulation increased human atrial I_{CaL} (Skeberdis et al. 1997) and I_f (Lonardo et al. 2005), although the I_f increase was greater with β_1- than β_2-stimulation. Nevertheless, the electrophysiological effects of independent β_2-, or indeed β_1-, stimulation in human atrium are largely unknown. β_3-stimulation had no effect on mouse atrial contraction (Oostendorp et al. 2000), but no human atrial studies were found. In ventricle, β_3-stimulation moderately affected APD (Gauthier et al. 1996; Bosch et al. 2002), probably via I_{KS} (Bosch et al. 2002) which may have limited involvement in human atrium. However, since β_3-stimulation can affect I_{K1} (Scherer et al. 2007), I_{CaL} and Ca^{2+}_i (Cheng et al. 2001), its potential to contribute to atrial adrenergic electrophysiological responses should not be overlooked. Myocardial effects of α-stimulation are multiple, complex and species-, chamber- and α-subtype-dependent. In human atrium, an α-agonist increased APD (Sato et al. 1995). That is consistent with effects of phenylephrine to inhibit I_{K1} (Su et al. 1994; Voigt et al. 2009), I_{KACh} (Voigt et al. 2009) and I_{Kur} (Li et al. 1996). However, the APD increase could also involve an increase in the Ca^{2+}_i transient (Jahnel et al. 1992), although data are lacking in human atrium. Furthermore, α-stimulation may increase inositol (1,4,5)-trisphosphate ($InsP_3$), and $InsP_3$ can cause Ca^{2+}_i release, particularly in atrium, in which $InsP_3$ receptors are prevalent (Bers 2002). However, the rate and extent of Ca^{2+}_i release is much lower

via $InsP_3$ than CICR (Bers 2002). α-, by contrast with β-, stimulation, did not produce DADs or EADs in canine ventricle (Priori et al. 1990), but whether it would in human atrium is unknown.

Heart failure causes AF, atrial remodelling and sympathetic activation

AF is usually associated with cardiac disease, such as coronary artery disease, valve disease, hypertension, myocardial infarction (MI), or HF. These, and AF, can cause chronic adaptational changes, i.e. remodelling, of atrial structure and function, including adrenergic responses, as well as increasing adrenergic tone. Each disease may, therefore, influence an involvement of the adrenergic system in the development of AF in a variety of ways. HF is a major cause of AF, and both systolic and diastolic ventricular dysfunction were independently associated with increased risk of AF (Tsang et al. 2002). Severe HF was associated with an ~70% increase in plasma noradrenaline (Bolger et al. 2002). However, the maximum concentration reached, 2.7 nM, was ~75-fold lower than was half-maximally effective at increasing I_{CaL} (Christ et al. 2004). Therefore, a promotion by HF of adrenergically-mediated atrial arrhythmic activity involving, e.g. I_{CaL} increase, may require a localised catecholamine accumulation. HF can predispose to atrial arrhythmic activity by remodelling atrial electrophysiology and Ca^{2+}_i homeostasis. In dogs, chronic ventricular tachypacing-induced congestive HF (CHF) increased atrial ERP and APD and produced spontaneous depolarisations (Stambler et al. 2003; Yeh et al. 2008). This was associated with various ion current changes including decreased I_{TO}, I_{CaL} and I_{KS} and increased $I_{Na/Ca}$, whilst I_{K1}, I_{Kr} and I_{Kur} were unaffected (Li et al. 2000). CHF also increased atrial diastolic $[Ca^{2+}]_i$, the Ca^{2+}_i transient, and Ca^{2+}_{SR} content, associated with "spontaneous Ca^{2+} transient events" (Yeh et al. 2008). Ca^{2+}_i changes could be caused partly by the APD increase, and partly by increased CaMKII-phosphorylation of PLB potentially enhancing Ca^{2+}_{SR} uptake (Yeh et al. 2008). It has been suggested (Lehnart et al. 2004) that chronic adrenergic activation in HF may cause hyperphosphorylation of RyRs and a consequent increased diastolic leak of Ca^{2+}_{SR}. However, leaky RyRs are unlikely to be sufficient, in the steady state, to cause Ca^{2+}_i waves and DADs via $I_{Na/Ca}$, because of compensatory changes of Ca^{2+}_{SR} content (Eisner et al. 2009). Nevertheless, CHF-induced atrial arrhythmic activity may involve RyRs, since it was abolished by RyR blockade in dogs (Stambler et al. 2003; Yeh et al. 2008). Such arrhythmic activity might be potentiated by increased adrenergic tone, e.g., via increased phosphorylation of I_{CaL} and PLB, although this awaits investigation. Human atrial electrophysiological changes have been associated with CHF or left ventricular systolic dysfunction (LVSD). Whilst the data are

often compounded by variability in patients' disease states and drug treatments (Workman et al. 2008), LVSD has been independently associated with a reduction in the atrial cellular ERP (Workman et al. 2009). In that study the ERP correlated positively with the LV ejection fraction (Workman et al. 2009), which is a significant predictor of AF (Tsang et al. 2002). Such ERP decrease, which contrasts with the ERP increase in canine CHF, might predispose to reentry by decreasing the wavelength. The ionic mechanisms are unclear, although an associated reduction in I_{TO} (Workman et al. 2009) might be involved. I_{K1}, I_{CaL} and the sustained outward current (I_{SUS}; predominantly I_{Kur}) were unaffected. I_{KS}, a likely major contributor to the APD increase in canine CHF, may be minimally involved in human atrium. Other atrial currents such as $I_{Na/Ca}$, constitutively active (CA) I_{KACh}, I_{Na}, I_p, and stretch-activated currents, as well as Ca^{2+}_i, and afterdepolarisations, remain to studied in human HF (Workman et al. 2008). The expression of atrial HCN2 and HCN4 (encode I_f) was increased in human HF (Stillitano et al. 2008), but atrial I_f was not measured. Some human atrial responses to adrenergic stimulation have been studied, although the data were equivocal. The effect of ISO to increase I_{CaL} or HFIUR was attenuated (Ouadid et al. 1995; Piot et al. 1996), unchanged (Workman et al. 2009) or potentiated (Dinanian et al. 2008) in patients with HF or LVSD, and contractile responses to ISO were attenuated (Harding et al. 1990). An attenuated β-response may involve impaired β-receptor function or signalling, or a reduction in receptor density, as shown in atria of patients with end stage HF (Steinfath et al. 1992) or pigs with CHF (Roth et al. 1993). Furthermore, HF may preferentially downregulate β_1, in atrium, depending on the cause of HF (Steinfath et al. 1992), and that could result from chronic adrenergic stimulation (Brown et al. 1992). β_3 density was not studied in atrium, although this was increased in ventricle (Moniotte et al. 2001). The multiple, complex and interacting influences of HF on the involvement of the adrenergic system in the development of AF are, therefore, yet to be resolved.

AF causes AF and atrial remodeling

Once AF occurs, a persistence of the rapid atrial activation causes atrial electrophysiological remodelling that promotes AF. This includes a reduction in the atrial ERP, AF cycle length and reentry wavelength (Workman et al. 2008). Chronic AF in patients was associated with a decreased atrial ERP and RA conduction velocity, increased ERP dispersion (Kojodjojo et al. 2007) and decreased atrial isolated tissue or cellular ERP (Workman et al. 2001) or APD_{90} (Bosch et al. 1999; Workman et al. 2001; Wettwer et al. 2004; Pau et al. 2007). In dogs, chronic rapid atrial rate also decreased APD_{90} in isolated PVs (Chen et al. 2000;

Cha et al. 2005), and either enhanced (Chen et al. 2000) or did not enhance (Cha et al. 2005) the ability of PVs to produce arrhythmic activity. The atrial ion current changes are different in chronic AF than in HF or LVSD (Workman et al. 2008; Workman et al. 2009), with an increased I_{K1} and CA I_{KACh}, and a markedly decreased I_{CaL} and I_{TO}. I_p was unchanged (Workman et al. 2003a); data on I_{Kur} and I_{KATP} are equivocal; and several other currents remain to be studied (Workman et al. 2008). These include I_{Kr} and I_{KS}, whose activation could be enhanced by action potential-triangulation in chronic AF (Workman et al. 2001). Rapid atrial rate also remodels Ca^{2+}_i homeostasis. In canine cultured atrial cells, chronic rapid stimulation reversed the elevation in both diastolic $[Ca^{2+}]_i$ and Ca^{2+}_i transient that had resulted from shorter periods of stimulation. This was probably via decreased CICR, due to transcriptional downregulation of I_{CaL} (Qi et al. 2008). AF-remodelling of Ca^{2+}_i in human atrium is only poorly understood. Ca^{2+}_i sparks, which reflect Ca^{2+} release from single clusters of RyRs, were either increased (Hove-Madsen et al. 2004) or unchanged (Liang et al. 2008) in frequency, and increased (Liang et al. 2008) or unchanged (Hove-Madsen et al. 2004) in duration. The frequency of Ca^{2+}_i waves was increased in both studies, and Ca^{2+}_{SR} content was unchanged. Chronic AF also increased PKA phosphorylation of RyR (Vest et al. 2005). The effects of adrenergic stimulation on Ca^{2+}_i were not studied in AF-remodelled atrium. Moreover, AF without HF may not change catecholamine levels in patients (Berglund et al. 1990). Nevertheless, chronic AF has consistently been shown to be associated with a potentiated effect of ISO to increase human atrial I_{CaL} (Van Wagoner et al. 1999; Skasa et al. 2001; Christ et al. 2004; Greiser et al. 2007). This contrasts with an attenuated effect of 5-hydroxytryptamine (5-HT) on I_{CaL} (Pau et al. 2007), despite both acting via cAMP. The kinase/phosphatase balance can affect I_{CaL} in human AF without altered channel transcription or translation (Christ et al. 2004). Since β- (unlike 5-HT-) receptor expression was unchanged in AF (Grammer et al. 2001), the potentiated I_{CaL} response to adrenergic stimulation might involve altered signalling, perhaps via CaMKII (Christ et al. 2004). Chronic AF was also associated with an attenuated effect of α-stimulation to decrease human atrial I_{K1} and I_{KACh} (Voigt et al. 2009). The lack of change in atrial Ca^{2+}_{SR} content associated with chronic AF, in contrast to the increase by HF, might suggest a lower susceptibility to any adrenergically-mediated arrhythmic activity than in HF. However, that remains to be investigated. Furthermore, AF-remodelling may interact with HF-remodelling (Workman et al. 2008), but no studies of adrenergic stimulation in that setting could be found.

Atrial neural remodelling by MI and by chronic AF

Atrial adrenergic nerves can be modified by myocardial diseases associated with AF, and also by persistent rapid atrial activation; so-called neural remodelling. For example, ventricular MI in dogs increased the atrial density and spatial heterogeneity of both tyrosine hydroxylase, which stains adrenergic nerves, and growth-associated protein, which stains for nerve sprouting; axonal regeneration. This may have resulted from injury of atrial nerves passing through the ventricle (Miyauchi et al. 2003). Chronic AT in dogs caused a spatially heterogeneous atrial adrenergic hyperinnervation, an increased atrial tissue noradrenaline concentration, and nerve sprouting (Jayachandran et al. 2000; Chang et al. 2001). Comparable changes were associated with chronic AF in humans, including hyperinnervation and increased tissue noradrenaline (Gould et al. 2006). Increases in atrial tissue adrenergic innervation and associated catecholamines, particularly of a spatially heterogeneous nature, may favour reentry and/or non-reentry.

Clinical use of β-blockers in AF: when and how is adrenergic control effective?

In patients with AF, β-blockers are used mainly to prevent the rapidly activating atria from stimulating the ventricles at excessively high rates. The mechanism is a slowing of atrioventricular (AV) nodal conduction, associated with increased AV nodal ERP and AH interval (Prystowsky 1988). This probably involves an anti-adrenergic effect on I_{CaL}, which is the main inward current in AV node (Workman et al. 1999). β-blockers can also prevent AF, convert it to sinus rhythm, or maintain sinus rhythm after it is restored, depending on β-blocker type and cardiac pathology (Lopez-Sendon et al. 2004). For example, in patients with CHF, β_1-blockade substantially reduced the incidence of AF (Van Veldhuisen et al. 2006). In patients with LVSD following MI, carvedilol, a β_1-, β_2- and α_1-antagonist, also substantially reduced the incidence of AF/atrial flutter (McMurray et al. 2005). β-blockers reduced the incidence of AF following cardiac surgery (Mathew et al. 2004; Workman et al. 2006), and post-surgery β-blocker withdrawal increased it (Mathew et al. 2004). Carvedilol was more effective than a β_1-blocker (Haghjoo et al. 2007), perhaps by decreasing I_{Kur} and I_{TO} (Deng et al. 2007). A β_1-blocker also caused a moderate reduction in the incidence of paroxysmal AF (Steeds et al. 1999) or of relapse into AF after electrical or pharmacological cardioversion (Kuhlkamp et al. 2000). Acute β-selective blockade has little or no effect on atrial electrophysiology in the absence of catecholamines (Wit et al. 1975), and catecholamine levels were not affected by β-blockade in patients

(Bolger et al. 2002). Therefore, the relatively high efficacy of β-blockers to prevent AF associated with elevated adrenergic tone, as occurs in, e.g. CHF (Bolger et al. 2002) or post-surgery (Engelman et al. 1983), suggests an anti-adrenergic suppression of pro-arrhythmic effects of catecholamines. The electrophysiological mechanisms are likely to be multiple. For example, a reduction by atenolol of cAMP-stimulated I_{CaL} in human atrial cells (Mewes et al. 1993) might suppress arrhythmic activity that involves increased CICR. A similar mechanism might account for an acute effect of propranolol to suppress either noradrenaline-induced AA in canine atrial fibres (Davis 1975), or AT in a CHF-remodelled atrium that produced spontaneous depolarisations (Stambler et al. 2003). A reduction of ISO-stimulated I_{Kur} by propranolol in human atrial cells (Li et al. 1996) is consistent with its acute effect to moderately increase atrial APD_{90} and ERP in patients (Shimizu et al. 1994b). That might moderately increase wavelength, although acute propranolol did not affect wavelength in canine atrium (Rensma et al. 1988), or ERP in AF-remodelled goat atrium (Wijffels et al. 1997). Furthermore, an acute suppression by atenolol of autonomic nerve stimulation-induced PV arrhythmic activity in dogs, might involve inhibition of AA or reentry, as well as afterdepolarisations (Patterson et al. 2005). Moreover, atrial anti-arrhythmic effects of β-blockers may also involve another type of electrophysiological remodelling: that from the long term drug treatment.

Atrial remodelling by chronic β-blocker treatment

The long term use of β-blockers causes adaptive changes in, e.g., atrial electrophysiology, contraction and adrenoceptors, which may contribute to the effects of these drugs on AF. Such "pharmacological remodelling" (Workman et al. 2003b) was originally demonstrated in rabbits (Raine et al. 1981). Treatment with either a β_1- or a mixed β-blocker increased APD in atrium (Figure 3*a*) and ventricle; maximally after six days in atrium (Raine et al. 1981). This was an adaptation to the treatment, not effects due to the presence of the drugs, because the APD was recorded at a sufficient time after the last dose for the drugs to have been eliminated from the body. That was confirmed in plasma and tissue samples (Raine et al. 1980). Subsequent studies in atrial cells from patients in sinus rhythm showed that β_1-blocker treatment for ≥ 7 days was associated with an increased APD_{90} and ERP (Workman et al. 2003b; Redpath et al. 2006; Workman et al. 2006) (Figure 3*b*), and a decreased I_{TO} (Workman et al. 2003b; Marshall et al. 2009) and I_{K1} (Marshall et al. 2006). [Insert Figure 3] The atrial ERP correlated with β-blocker dose (Workman et al. 2008). The I_{TO}

reduction, as found also in atrial cells from rabbits treated with carvedilol (Cao et al. 2006), did not involve altered voltage-dependency, kinetics or channel expression (Marshall et al. 2009). I_{CaL} did not change, either in amplitude (Workman et al. 2003b; Pau et al. 2003; Redpath et al. 2006; Workman et al. 2006; Pau et al. 2007), activation voltage-dependence (Redpath et al. 2006), single channel gating (Klein et al. 2003) or expression (Grammer et al. 2001). That is consistent with a lack of change in APD_{50} (Workman et al. 2003b; Redpath et al. 2006). I_{SUS} also was unaffected (Workman et al. 2003b; Marshall et al. 2006). The human atrial electrophysiological changes most likely reflect an adaptation to the treatment also, because recordings were made in the presumed absence of residual β-blocker (cells had been isolated and washed) and the APD_{90} and ERP increases were independent of various clinical covariables (Workman et al. 2003b; Workman et al. 2006). No reports on atrial Ca^{2+}_i were found, but chronic β_1-blockade in mice increased a HF-impaired ventricular Ca^{2+}_i transient (Bartholomeu et al. 2008). Catecholamine-induced arrhythmic contractions in human atrial muscles were exacerbated by β-blocker therapy (Kaumann et al. 1993), probably not involving any altered I_{CaL} response to β-stimulation (Redpath et al. 2006). Nevertheless, human atrial β-receptors, perhaps predominantly β_1, were upregulated by β-blocker therapy (Hedberg et al. 1985; Michel et al. 1988), possibly related to a reduction in adrenergic nerve activity (Raine et al. 1977). The β-blocker-remodelling of atrial APD_{90} and ERP might be expected to increase reentry wavelength and thus contribute to anti-fibrillatory actions of β-blockers. However, the net effect of β-blockers in patients undergoing treatment is likely to include anti-adrenergic effects in an atrium remodelled by the chronic treatment, as well as by underlying cardiac disease.

Concluding remarks, and potential future directions

The evidence in this review suggests that AF that is caused by adrenergic stimulation results, in large part, from a promotion of atrial arrhythmic activity involving increased I_{CaL} and Ca^{2+}_i, rather than from any effect on action potential terminal repolarisation or ERP. The suppression of AF by treatment with β-blockers is likely to involve attenuation of such arrhythmic activity, potentially coupled with an ERP-prolonging adaptation to the treatment; so-called pharmacological remodelling. It is hoped that an improved understanding of the involvement of the adrenergic system and its control in basic mechanisms of AF under differing cardiac pathologies will lead to better pharmacological treatments. However, there are numerous

and wide gaps in our knowledge, particularly pertaining to human atrium, which suggest avenues for further research. For example, what are the predominant PV and atrial electrophysiological mechanisms of AF initiation and maintenance in different cardiac diseases? Could adrenergic stimulation increase atrial Ca^{2+}_i sufficiently to cause AA or DADs in patients, and how would HF and chronic AF affect such responses? Does adrenergic stimulation substantially influence human atrial I_{Kr} or I_{KS}? What is the relative involvement of α- and β-subtypes in human atrial arrhythmogenic responses to adrenergic stimulation, and does carvedilol's marked ability to suppress AF post-MI involve α_1-antagonism? What are the molecular mechanisms of atrial pharmacological remodelling by chronic β-blockade, and how are they affected by cardiac diseases? Future therapeutic strategies for adrenergic control of AF may include non-pharmacological interventions. However, radiofrequency ablation of atrial ganglionated plexi, sites rich in adrenergic and cholinergic neurons, may not be as efficacious as other ablation procedures (Katritsis 2008). Despite continuous improvement of ablation techniques, pharmacological therapy is the mainstay of treatment for AF. New anti-AF drugs in development include "atrial-selective compounds", and "multi-channel blockers" such as dronedarone (Ehrlich et al. 2009). This drug's anti-adrenergic activity may be expected to contribute to its anti-arrhythmic efficacy.

Figure legends

Figure 1. Arrhythmic electrical activity produced by adrenergic stimulation in human atrium. Action potentials recorded from human right atrial isolated tissue (*a*) and myocyte (*b*) in the absence (control) or presence of adrenaline or isoprenaline (ISO). Myocyte stimulated at 75 beats/min. Circles: spontaneous depolarisations; one occurring just before stimulus spike (←). Calibration bars: 50 mV (vertical), 200 ms (horizontal). Based on data in (Sleator et al. 1964) (*a*) and (Redpath et al. 2006) (*b*) with permission from American Physiological Society, and Elsevier, respectively.

Figure 2. Species- and cardiac chamber-dependent effects of adrenergic stimulation on action potentials and ion currents. *a*, Action potentials from dog (i) and human (ii) left ventricular myocyte, and from human right atrial tissue (iii) and myocyte (iv). C: control, ISO: isoprenaline, A: adrenaline, W: washout, HMR: HMR1556 (I_{KS} blocker), ET: endothelin. Calibrations: 25 mV, 100 ms. Based on data in (Stengl et al. 2006) (i), (Koumi et al. 1995) (ii), (Yeh et al. 1992) (iii), and (Redpath et al. 2006) (iv) with

permission from Oxford University Press, American Society for Clinical Investigation, S. Karger AG, Basel, and Elsevier, respectively. *b*, Simulated time courses of main human atrial ion currents (defined in text) determining action potential (top trace) shape. Ordinate scales equalised for all currents <0.5 pA/pF. All traces derived from mathematical model (Courtemanche et al. 1998) using CESE Pro 1.4.8 software (Simulogic Inc., Halifax, Canada). Arrows indicate reported effect of ISO on currents.

Figure 3. Remodelling of atrial action potentials by chronic β-blocker treatment. *a*, Action potentials (dotted) in right atrium isolated from a rabbit not treated (control) or treated (chronic β-blocker) for 24 days with metoprolol. *b*, Action potentials and effective refractory period (↔) recorded in an atrial cell obtained from a patient not treated (upper panel) or treated (lower) with a β-blocker. Calibrations: 50 mV, 100 ms. Based on data in (Raine et al. 1981) (*a*) and (Workman et al. 2003b) (*b*) with permission from Wolters Kluwer Health/Lippincott, Williams & Wilkins, and Oxford University Press, respectively.

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Figure 1

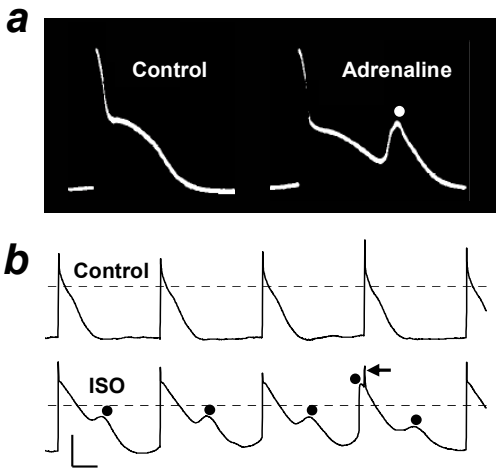

Figure 3

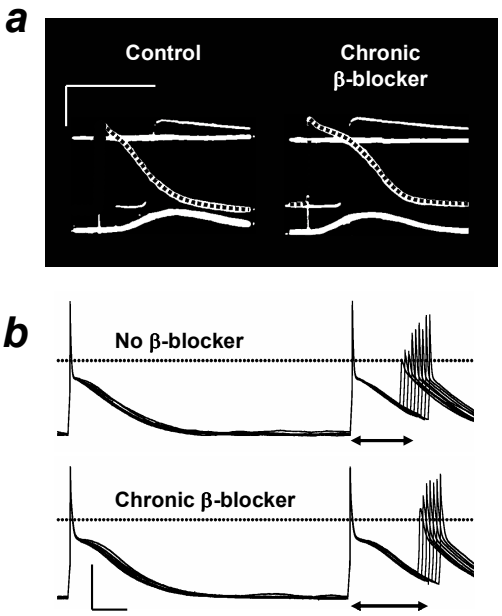

Figure 2