Atrial cellular electrophysiological changes in patients with ventricular dysfunction may predispose to AF

Short title: Human atrial cellular electrical changes in LVSD

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Conflicts of interest

No author has a conflict of interest.

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Abstract

Background. Left ventricular systolic dysfunction (LVSD) is a risk factor for atrial fibrillation (AF), but the atrial cellular electrophysiological mechanisms in humans are unclear. **Objective.** To investigate whether LVSD in patients who are in sinus rhythm (SR) is associated with atrial cellular electrophysiological changes which could predispose to AF. **Methods.** Right atrial myocytes were obtained from 214 consenting patients in SR who were undergoing cardiac surgery. Action potentials or ion currents were measured using the whole-cell-patch clamp technique. **Results.** The presence of moderate or severe LVSD was associated with a shortened atrial cellular effective refractory period, ERP (209±8 ms; 52 cells, 18 patients *vs* 233±7 ms; 134 cells, 49 patients; $P<0.05$); confirmed by multiple linear regression analysis. The LV ejection fraction (LVEF) was markedly lower in patients with moderate or severe LVSD (36±4%, $n=15$) than in those without LVSD (62±2%, $n=31$; $P<0.05$). In cells from patients with LVEF≤45%, the ERP and action potential duration at 90% repolarisation were shorter than in those from patients with LVEF>45%, by 24 and 18%, respectively. The LVEF and ERP were positively correlated ($r=0.65$, $P<0.05$). The L-type calcium ion current, inward rectifier potassium ion current, and sustained outward ion current was unaffected by LVSD. The transient outward potassium ion current was decreased by 34%, with a positive shift in its activation voltage, and no change in its decay kinetics. **Conclusion.** LVSD in patients in SR is independently associated with a shortening of the atrial cellular ERP, which may be expected to contribute to a predisposition to AF.

Keywords

Human; Left ventricular systolic dysfunction; Ejection fraction; Sinus rhythm; Atrial fibrillation; Electrophysiological remodelling; Isolated myocyte; Effective refractory period; Action potential duration; Ion current.

Introduction

Atrial fibrillation (AF) and congestive heart failure (CHF) frequently co-exist, and left ventricular systolic dysfunction (LVSD) may increase AF risk.[1] The mechanisms of this predisposition to AF likely involve interacting adaptational changes, or remodelling, of atrial structure and electrical, mechanical, metabolic and neurohumoral activities. AF generation and maintenance may each involve atrial reentrant and non-reentrant electrical activity. Reentry is promoted by a shortening of the wavelength, due to a reduction in either the effective refractory period (ERP), conduction velocity, or both. Atrial cellular electrical remodelling in patients with persistent AF features a shortening of the ERP, which is considered to facilitate reentry in these patients.[2] It is conceivable that, in patients who are in sinus rhythm (SR), a predisposition to AF in those with LVSD might involve an associated reduction in the atrial cellular ERP. However, the available data are scarce and conflicting, and often compounded by variability in patients' disease states and drug treatments.[3] In atrial cells isolated from patients with CHF, the action potential duration at 90% repolarisation (APD_{90}), an important determinant of ERP, was either increased,[4] unchanged[5,6] or, when recorded at relatively high stimulation rate, shortened.[5] A shortening,[6] or no change,[4] in atrial cell APD_{50} were also reported. However, the ERP has not been measured in atrial cells from patients with CHF or LVSD,[3] and also remains to be correlated with the left ventricular ejection fraction (LVEF), an important index of LVSD and predictor of AF.[7] Furthermore, the pattern of ionic remodelling in CHF or LVSD in human atrium also is presently unclear.[3] For example, the L-type Ca^{2+} current (I_{CaL}) was either decreased[8,9] or unchanged,[5,10] with either slowed[5] or unchanged[8] kinetics, and had either an increased[9] or decreased[8,10] response to β-adrenergic stimulation. Studies of human atrial K^+ currents have shown increased transient outward current (I_{TO}), with no change in its voltage-dependence or decay, but with enhanced reactivation;[6] a decreased inward rectifier (I_{K1});[4] and an unchanged ultra-rapid delayed rectifier.[6]

The aims of this study, therefore, were two-fold. First, to investigate whether LVSD and reduced LVEF in patients who were in SR and undergoing cardiac surgery correlate with a shortening of atrial cellular ERP, which could contribute to a predisposition to AF. Second, to clarify the pattern of any accompanying ionic remodelling, by comparing various ion currents and their voltage- and time-dependent characteristics between patients with and without LVSD.

Methods

Right atrial appendage tissue was obtained from 214 consenting patients who were in SR and undergoing cardiac surgery. Procedures were approved by the institutional research ethics committee. Atrial cells were isolated as described previously.[2] Action potentials and ion currents were recorded using the whole-cell-patch clamp technique. Cells were superfused at 35-37^{o}C with a physiological solution containing (mM): NaCl (130), KCl (4), $CaCl_2$ (2), $MgCl_2$ (1), glucose (10) and HEPES (10); pH 7.4, with Cd^{2+} (0.2 mM) added for some cells, to block I_{CaL} when recording K^+ currents. Either the perforated or conventional ruptured patch configuration was used. The proportion of cells in which the perforated patch was used (64%) was not different between the groups under comparison. The constituents of the pipette solutions used for the different types of recordings are as detailed previously.[11] Action potentials were stimulated with 5 ms current pulses of 1.2x threshold, at 75 beats/min (bpm) while injecting a small, constant current (set at the start of threshold measurement to clamp the maximum diastolic potential (MDP) to -80 mV, 1-2 min after attaining whole-cell).[2,11-13] The cellular ERP was then measured using a standard S_1-S_2 protocol. Ion currents were recorded by voltage-clamping. I_{K1} was stimulated with linear voltage ramps from -120−+50 mV at 24 mV/s, or with 500 ms pulses (0.2 Hz) increasing from -120−+50 mV in 10 mV steps, from a holding potential (HP) of -50 mV. I_{TO} and the sustained outward current, I_{SUS}, were stimulated with 100 ms pulses (0.33 Hz), from -40−+60 mV, from a -50 mV HP. I_{SUS} was measured as end-pulse current, and I_{TO} as peak outward minus end-pulse current. I_{CaL} was stimulated with 250 ms pulses (0.33 Hz), from -30−+60 mV, from an HP of -40 mV.

Details of each patient's clinical characteristics and drug treatments were obtained from the medical records, post-surgery. All patients were in SR on the day of surgery, confirmed from a pre-surgery 12 lead ECG. An ECG was also available for the preceding day in 206 of 214 patients, and all confirmed SR. Patients were excluded if they had a documented episode of AF at any time pre-surgery, if they were taking digoxin or a non-β_1-selective β-blocker, or if their β_1-blocker-treatment had started later than 7 days pre-surgery. Each patient was designated as having either "no LVSD", "mild LVSD", "moderate LVSD" or "severe LVSD", from qualitative reports of assessments in the patient's case record. The LVEF was obtained, in a subset of 58 patients, from either echocardiography (52%), radionuclide ventriculography (26%) or contrast ventriculography (22%).

Statistical methods

Univariate measurements were compared between pairs of various subgroups of patients using 2-sided, 2-sample unpaired Student's *t*-tests. Categorical data were compared using a χ^2-test. All univariate electrophysiological data are expressed as cell means±1 standard error (SE), unless otherwise stated. Multiple linear regression analysis was used to further investigate relationships between the presence of LVSD and various electrophysiological measures, adjusted in a mixed effects linear model with the subject as a random effect, according to 10 covariates. Analyses were performed retrospectively, using "SAS PROC MIXED" in SAS 9.1.3 software (SAS Inst, USA). The group of patients with moderate or severe LVSD (19% of total) was used for statistical comparisons of cellular electrophysiology against patients with no LVSD whenever patient *n* permitted and unless otherwise stated, to maximise analysis sensitivity. All available information was incorporated. Therefore, the tables and statistical models are sometimes based on different numbers of subjects, reflecting some missing data for some covariates. $P<0.05$ was regarded as statistically significant.

Results

Patients' characteristics

The patients' clinical characteristics and drug treatments are shown in Table 1. The majority (91%) suffered from angina and underwent CABG surgery. Valve surgery (AVR or MVR) was performed with or without CABG in 15% of patients. 36% of patients had mild, moderate or severe LVSD, and 19% had moderate or severe LVSD. The majority of patients with LVSD had a history of MI and were taking an ACEI or ARB.

[Insert Table 1]

Changes in atrial cellular ERP and capacity associated with LVSD

Atrial cells from patients with moderate or severe LVSD had a significantly shorter ERP than those from patients without LVSD (Figure 1*A*). The resting potential (V_m) before current-clamp was similar in patients with moderate or severe LVSD to no LVSD (-20±2 *vs* -17±1 mV, $P>0.05$). During current-clamp, the holding current and MDP (taken during ERP-recording) also were similar between these groups (0.72±0.05 *vs* 0.68±0.03 pA/pF, and -82±1 *vs* -81±0 mV, respectively; $P>0.05$ for each). There

were no significant differences in other action potential measurements. In a sub-group of 37 patients for whom left atrial (LA) size was available, the LA was larger in patients with LVSD (4.4±0.2 cm, n=7) than in those without (3.8±0.1 cm, n=30; P<0.05). The ERP was similar in cells from patients with LA size≤ 4 cm (clinically recognised as normal[14]), at 245±22 ms, to those with LA>4 cm, at 256±36 ms (P>0.05), and there was no significant correlation between LA size and ERP (P>0.05). The right atrial (RA) size was not available, though RA cell capacity was increased in LVSD (Figure 1*C*). The incidence of chronic β_1-blocker use (which is associated with ERP-prolongation[11,12]) in patients from whom ERP was recorded, was 67% in those with moderate or severe LVSD *vs* 59% in those without LVSD (P>0.05). ERP-shortening associated with LVSD was maintained when patients were sub-analysed by chronic β_1-blockade. In non-β-blocked patients, ERP was 179±13 ms in 27 cells from 8 patients with mild, moderate or severe LVSD *vs* 212±9 ms in 47 cells from 20 patients with no LVSD (P<0.05). Furthermore, in patients who underwent CABG-only (excludes all AVR, MVR, ASDR & VSDR), the magnitude of change in ERP and capacity associated with moderate or severe LVSD was largely maintained: ERP=213±10 *vs* 241±8 ms, P>0.05 (0.053); capacity=85±2 *vs* 77±1 pF, P<0.05). Finally, ERP-shortening associated with LVSD was confirmed by multiple linear regression analysis, adjusting for 10 covariates considered to be of particular importance (Table 2).

[Insert Figure 1]

[Insert Table 2]

Correlation between LVEF and atrial cellular electrophysiology

Within the sub-group of 58 patients whose LVEF was available, the qualitative assessment of increasing severity of LVSD was associated with a progressive and significant reduction in LVEF, compared with that recorded in patients without LVSD (Figure 2*A*). In patients with LVEF≤ 45% (a clinically accepted threshold for LVSD[14]), the APD_{90}, but not APD_{75} or APD_{50}, was significantly shorter than in patients with LVEF>45%, by 18% (Figure 2*B*), and the ERP was significantly shorter, by 24% (Figure 2*C*). Furthermore, the action potential maximum upstroke velocity (dV/dtmax) was significantly greater in patients with LVEF≤ 45%, by 11%, than in patients with LVEF>45% (Figure 2*D*). The holding current was similar between these groups (0.67±0.06 *vs* 0.60±0.04 pA/pF, P>0.05), and there were no significant differences in other action potential measurements. There was a significant correlation (Spearman rank correlation test) between patients' atrial cellular ERP and

LVEF, with ERP shortening with decreasing LVEF (Figure 2*E*). However, there was no significant correlation between dV/dtmax and LVEF with this test (P>0.05). There was also no correlation between LVEF and holding current (P>0.05), nor between ERP and dV/dtmax (P>0.05, n=49 cells).

[Insert Figure 2]

Changes in atrial K^+ currents associated with LVSD

Atrial cells from patients with LVSD had a significantly lower peak I_{TO} density (at +60 mV) than patients without LVSD, by 34% (Figure 3*A&B*). This reduction was maintained when patients were sub-analysed by chronic β_1-blockade (itself associated with I_{TO}-decrease[12]). In β_1-blocked patients, I_{TO} was 7.4±1.0 pA/pF in 15 cells from 9 patients with LVSD of any designation *vs* 10.0±0.6 pA/pF in 38 cells from 23 patients with no LVSD (P<0.05). LVSD was associated with significant I_{TO}-reduction at all voltages between +20 and +60 mV (Figure 3*C*). Furthermore, the voltage of half-maximal activation ($Vact_{50}$), assessed from Boltzmann relations, was significantly more positive, by 5 mV, in patients with LVSD (Figure 3*D*). The-time course of I_{TO} inactivation was bi-exponential. There was no significant difference in the time constant (τ) or amplitude (A) of either phase of inactivation, measured at +60 mV, between patients with and without LVSD (Figure 3*E*). Peak I_{SUS} was similar in cells from patients with LVSD (9.1±1.3 pA/pF; n=15 cells, 8 patients) to those without (10.3±0.6 pA/pF; n=72 cells, 31 patients, P>0.05). Peak I_{K1} was not significantly different between patients with and without LVSD (Figure 3*F&G*). This pattern of K^+ current changes was maintained in the sub-group of CABG-only patients: I_{TO}=8.3±1.2 *vs* 12.7±0.7 pA/pF, P<0.05; $Vact_{50}$=30±4 *vs* 25±1 mV, P<0.05; with I_{SUS} and I_{K1} again unaltered (P>0.05).

[Insert Figure 3]

Atrial I_{CaL} characteristics associated with LVSD

Peak I_{CaL} density (at +10 mV) was similar in cells from patients with and without LVSD (Figure 4*A&B*). This similarity was maintained in the CABG-only sub-group: -6.0±0.5 *vs* -5.4±0.3 pA/pF, P>0.05. I_{CaL} also was not significantly different between patients with LVEF≤ 45% (-4.7±0.5 pA/pF; n=51 cells, 13 patients) and >45% (-5.7±0.5 pA/pF; n=54 cells, 15 patients, P>0.05). I_{CaL} was not different at any voltage, between patients with and without LVSD (Figure 4*C*), and $Vact_{50}$ also was similar (Figure 4*D*). I_{CaL} decay was bi-exponential, and both time constants and amplitudes of decay, measured at +10 mV, were similar between patients with and without LVSD (Figure 4*E*). In a sub-

group of cells, the magnitude of increase in peak I_{CaL} in response to acute superfusion with either isoproterenol or 5-hydroxytryptamine at near-maximally effective concentrations[13,15] was assessed. There was no significant difference between cells from patients with and without LVSD in the response to either drug (Figure 4*F*&*G*).

[Insert Figure 4]

Discussion

Left ventricular systolic dysfunction in patients who were in SR was independently associated with shortening of their atrial isolated cellular ERP. Previous reports of associations between atrial cell APD, an important determinant of ERP, and human CHF or LVSD are equivocal, likely due to differing experimental conditions and/or clinical characteristics of patients studied.[3,4,6] For example, APD_{90} was longer in cells from explanted, than from donor, hearts,[4] but not different[6] or shortened[5] between LVEF<45% and >60%, despite action potential plateau depression.[4,6] A comparison of the present data with those studies is difficult, however, since they included cells with resting potentials of -50 mV or more positive[4,6] which would have relatively slow responses, or patients with chronic AF.[4] Furthermore, whilst AF accompanies a number of pathologies, the present cohort was dominated by coronary artery disease. In a single clinical study, CHF was associated with a moderate (≤ 10%) atrial ERP-lengthening at rates ≥ 100 bpm, but lower, physiological, rates were not studied.[16] The relevance of the measurement of the ERP and APD_{90} in isolated cells is supported by the demonstration that human chronic AF was associated with shortening of either, or both parameters in atrial isolated cells,[2,15,17] as in atrial isolated tissues,[17,18] and RA appendages *in-vivo*.[19] The present ERP-shortening associated with LVSD may be expected, therefore, to contribute to a shortened atrial ERP *in-vivo*, and consequently, a shortened reentrant wavelength. On the other hand, LVSD was associated with an increase in dV/dtmax, which might oppose wavelength-shortening, by increasing conduction velocity. However, the dV/dtmax increase was smaller (11%) than the ERP decrease (24%) and, moreover, should increase conduction velocity by only 4%, according to a mathematical model of a cardiac fibre.[20] The combined observed ERP and dV/dtmax changes should, therefore, shorten the wavelength by ~20%.

The consequence of such wavelength-shortening, in the atria of patients in SR with LVSD, would be an increased propensity to reentry. Consistent with that, atrial wavelength-shortening that was produced either by drugs[21] or chronic AF,[22] increased the vulnerability to induction of AF. Furthermore, CHF or LVSD may cause additional atrial electrophysiological changes that may predispose to AF, particularly in the presence of a shortened wavelength. CHF promoted afterdepolarisations in canine atrial cells,[23,24] possibly from $[Ca^{2+}]_i$-overload[24] and enhanced Na^+/Ca^{2+} exchanger current,[25] which might produce triggered activity *in-vivo* and facilitate the initiation of reentry. Elevated sympathetic tone, which may accompany CHF, could promote such activity. However, the present experiments with isoproterenol suggest that this would not involve an altered I_{CaL} response to β-stimulation. CHF also causes fibroblasts and collagen to accumulate between fibres or cells of both atria,[26] associated with disturbed local conduction, perhaps facilitating microreentry.[26] Any associated cellular uncoupling may be expected to have a greater influence on conduction velocity than the present change in dV/dtmax,[20] which would result in a correspondingly greater reduction in wavelength and predisposition to AF. Furthermore, atrial fibrosis and susceptibility to AF may persist in CHF after the reversal of ionic remodelling.[27]

The ionic changes we found in LVSD and which might, therefore, have contributed to the atrial ERP-shortening, were a reduction in I_{TO}, in line with the shift in its activation voltage. Previous reports of changes in human atrial I_{TO} associated with cardiac disease include a reduction with atrial dilation[28] and an increase with LVSD.[6] However, the latter may have been compounded by the lower proportion of patients treated with β-blockers in the LVSD group,[6] since such treatment is associated with decreased I_{TO} in human atrium.[12] A decreased atrial I_{TO} is also a consistent feature of the canine model of CHF.[25,29] However, it is unknown what effect a reduction in I_{TO} might have on the human atrial action potential, due to a lack of availability of specific I_{TO} blockers. Mathematical modelling suggested either a shortening or lengthening of APD_{90}, depending on which of two human atrial models (which had differing baseline I_{TO}) was studied.[30] Furthermore, either shortening or lengthening of atrial APD_{90} occurred in a canine model, depending on the initial level of I_{TO}.[31] In that model, in support of a link between the present reduction in I_{TO} and APD_{90}, a complex coupling of I_{TO} with I_{CaL} was reported such that I_{TO} reduction shortened APD_{90} by reducing the driving force and amplitude of I_{CaL}, secondary to phase 1 suppression.[31] The absence of change in I_{K1} was consistent with studies of

CHF in dogs,[25,29] although a decrease was reported in 3 patients with CHF.[4] Furthermore, the absence of change in I_{SUS} was consistent with both a human[6] and canine[25] study. The lack of change in I_{CaL} was consistent with two reports of human LVSD,[5,10] although a decrease was also reported, in two others.[8,9] In the more recent study,[9] I_{CaL} decrease was independently associated with both decreased LV function and mitral valve disease. However, a comparison with the present data is difficult due to differing overall clinical characteristics of the patients between the two studies (e.g., a higher incidence of valvular disease in the Dinanian study[9]), and is also potentially compounded by the differing recording temperatures and $[Ca^{2+}]_i$-buffering conditions used. The unaltered I_{CaL} voltage-dependence and decay were in line with the majority of reports.[5,8] The action potential dV/dtmax depends predominantly on Na^+ conductance, determined by Na^+ current (I_{Na}) availability, in turn dependent on Na^+ channel characteristics and diastolic voltage.[20] I_{Na} was not measured here, so the mechanism of dV/dtmax increase associated with LVSD is unknown. However, any contributory changes in I_{Na} availability potentially arising from altered density or time- or voltage-dependence of activation or inactivation would have been independent of diastolic voltage, since this was ~-80 mV in all cells. Increased dV/dtmax could arise from the I_{TO} reduction, since it has been suggested[32] that this current's rapid activation may oppose I_{Na} during phase 0.

The resolution of the ionic mechanisms of the action potential and ERP changes will require measurement of additional currents, as well as $[Ca^{2+}]_i$-handling characteristics,[3] in future studies. Nevertheless, we demonstrate here that the overall pattern of atrial ionic remodelling associated with LVSD is clearly different from that already associated with human chronic AF,[3] in which both I_{CaL} and I_{TO} were markedly decreased, and I_{K1} was increased. In line, a disparate pattern of atrial ionic remodelling was also demonstrated in dogs between chronic ventricular tachypacing (VTP)-induced CHF and chronic atrial tachypacing.[29] Furthermore, the present work highlights species- and/or ventricular pathology-dependent differences in atrial ionic remodelling, and the importance of obtaining clinical data. In particular, I_{CaL} was clearly unchanged in the present study, yet moderately decreased in canine VTP-induced CHF.[25,29] The slow delayed rectifier (I_{KS}) also was decreased in canine CHF,[25,29] perhaps contributing to an increase in APD or ERP in some studies of that model[23,24,29] (though ERP was unchanged in others[26,33]), yet the contribution of I_{KS} to human atrial ERP may be negligible.

Limitations of the study

1: The enzymatic isolation of myocytes from atrial appendage tissue is recognised to depolarise V_m. We current-clamped V_m to overcome this and prevent I_{Na} inactivation. However, whilst un-clamped V_m was similar in patients with and without LVSD, V_m *in-vivo* may vary with pathology, with the potential to affect ERP in clamped cells. 2: LV function was assessed qualitatively or quantitatively, rather than uniformly for all patients. 3: The possibility of asymptomatic AF having been missed cannot be excluded.

Clinical implications

The clinical implications of the present data are that the treatment of patients who have LVSD and are in SR, with drugs that prolong ERP, might be expected to attenuate an atrial cellular electrophysiological predisposition to AF. In support, amiodarone and dofetilide, the only anti-arrhythmic agents currently recommended for maintenance of SR in patients with AF and CHF,[1] each prolong ERP, including in electrically-remodelled atria.[34,35] Furthermore, amiodarone reduces the occurrence of new-onset AF in CHF.[1] Renin-angiotensin-aldosterone system (RAAS) inhibitors also reduce new-onset AF in CHF, as may β-blockers.[1] RAAS inhibitors may inhibit conduction abnormalities caused by structural remodelling, rather than altering ERP,[33] but the effect of β-blockers may involve atrial ERP-prolongation, as demonstrated in atrial cells from patients in SR.[11,12] Furthermore, in patients with LVSD post-MI, the non-selective β-blocker carvedilol exerted a powerful atrial anti-arrhythmic effect, even in patients already taking an ACEI.[36]

Conclusion

The present work contributes to the understanding of the pattern of atrial cellular electrophysiological changes associated with, and potentially caused by, LVSD in patients who underwent cardiac surgery. The cellular ERP-shortening, which might contribute to a predisposition to AF, may represent a potential therapeutic target for maintaining SR in patients with LVSD.

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Table 1. Patients' characteristics

	LVSD none		LVSD any		LVSD mod/sev	
	n	%	*n*	%	*n*	%
Patient details						
Total	138	-	76	-	40	-
Male	97	70	62	82	33	83
Age (years)	63±1	-	62±1	-	63±2	-
Heart rate (bpm)	63±1	-	64±2	-	64±2	-
Drug						
$Beta_1$-blocker	90	65	52	68	28	70
ACEI or ARB	63	46	51	67*	29	73*
CCB	58	42	27	36	14	35
Statin	111	80	66	87	33	83
Disease						
Angina	124	90	70	92	36	90
History of MI	38	28	51	67*	31	78*
History of HT	81	59	38	50	18	45
Diabetes	14	10	13	17	7	18
Operation						
CABG only	114	83	66	87	34	85
AVR only	11	8	5	7	4	10
CABG + AVR	8	6	4	5	2	5
MVR only	1	1	1	1	0	0
CABG + MVR	2	1	0	0	0	0
ASDR only	1	1	0	0	0	0
VSDR only	1	1	0	0	0	0

Values are numbers of patients (*n*, and % of total) with selected clinical characteristics, except for age and heart rate (means±SE), in groups of patients with and without LVSD. "Any"=mild, moderate or severe. ACEI=angiotensin converting enzyme inhibitor. ARB=angiotensin receptor blocker. CCB=calcium channel blocker. MI=myocardial infarction. HT=hypertension. CABG=coronary artery bypass graft surgery. AVR=aortic valve replacement. MVR=mitral valve replacement. ASDR=atrial septal defect repair. VSDR=ventricular septal defect repair. *=$P<0.05$ *vs* LVSD none.

Table 2. Multiple linear regression analysis of atrial cellular electrophysiology

EP variable	Patient *n*		Estimated change in EP with LVSD mod/sev	95% confidence interval	*P*
	LVSD none	LVSD mod /sev			
ERP	49	18	-26 ms	-49−-3	0.027
APD_{90}	54	21	-20 ms	-49−+9	0.17
APD_{50}	54	21	+4 ms	-5−+13	0.36
dV/dtmax	54	21	+4 V/s	-20−+28	0.76
I_{TO}	40	6	-3.2 pA/pF	-7.5−+1.0	0.14
I_{TO} $Vact_{50}$	39	5	+5 mV	-2−+13	0.15
I_{CaL}	73	19	-0.1 pA/pF	-1.6−+1.5	0.92
I_{K1}	40	10	+0.4 pA/pF	-0.9−+1.7	0.57
Capacity	135	38	+6 pF	-1−+13	0.074

Estimated changes in electrophysiological (EP) variables associated with LVSD, adjusting for the covariates: age, sex, β-blocker-treatment, ACEI/ARB-treatment, CCB-treatment, history of MI, history of HT, valve replacement surgery, diabetes, and heart rate.

Figure legends

Figure 1

Change in ERP and capacity of atrial cells from patients with LVSD. *A*. Representative, superimposed action potentials stimulated by the 7th and 8th of a train of current pulses, S_1, followed by responses to a premature, S_2, in a cell from a patient with no LVSD (upper trace) and moderate/severe LVSD (lower). ERP (bar)=longest S_1−S_2 which failed (↘) to produce an S_2 response of amplitude>80% of S_1. Mean±SE ERP (*B*) and capacity (*C*) of cells from patients with no LVSD (□; *n*=134 cells, 49 patients for ERP, and 535 cells, 135 patients for capacity) and moderate/severe LVSD (■; *n*=52 cells, 18 patients for ERP, and 152 cells, 38 patients for capacity). *=*P*<0.05 *vs* □.

Figure 2

Associations and correlations between LVEF, LVSD and atrial cellular electrophysiology. *A*. Mean±SE LVEF in patients with no LVSD (□; *n*=31) *vs* mild (*n*=12), moderate (*n*=11) and severe (*n*=4) LVSD (■). Comparison of APD at 50, 75 and 90% repolarisation (*B*), ERP (*C*) and dV/dtmax (*D*) between patients with LVEF>45% (horizontal stripes; *n*=27-38 cells, 10-13 patients) and ≤45% (diagonal stripes; *n*=22-26 cells, 7-8 patients). *=*P*<0.05; NS=not significant, *vs* LVEF>45%. *E*. Correlation between LVEF and ERP. Points are means of cell data from individual patients (*n*=49 cells, 17 patients).

Figure 3

Changes in atrial K^+ currents associated with LVSD. I_{TO} recordings (*A*), peak density (*B*), current-voltage relationships (*C*), $Vact_{50}$ (*D*) and decay kinetics (*E*) in no LVSD (□; *n*=72-81 cells, 38-40 patients) and moderate/severe LVSD (■; *n*=11-12 cells, 5-6 patients). I_{K1} recordings (*F*) and density at -120 mV (*G*) in no LVSD (□; *n*=99 cells, 40 patients) and moderate/severe LVSD (■; *n*=20 cells, 10 patients).

Figure 4

I_{CaL} characteristics in atrial cells from patients with and without LVSD. I_{CaL} recordings (*A*), peak density (*B*), current-voltage relations (*C*), $Vact_{50}$ (*D*) and decay kinetics (*E*) in no LVSD (□; *n*=167-222 cells, 61-73 patients) and moderate/severe LVSD (■; *n*=36-65 cells, 12-19 patients). Comparison of stimulatory effects on I_{CaL} of isoproterenol (ISO; 50 nM) (*F*) and 5-hydroxytryptamine (5-HT; 10 μM) (*G*) between no LVSD (□; *n*=45 cells, 19 patients for ISO; 37 cells, 23 patients for 5-HT) and moderate/severe LVSD (■; *n*=12 cells, 6 patients for ISO; 10 cells, 5 patients for 5-HT).

Figure 1

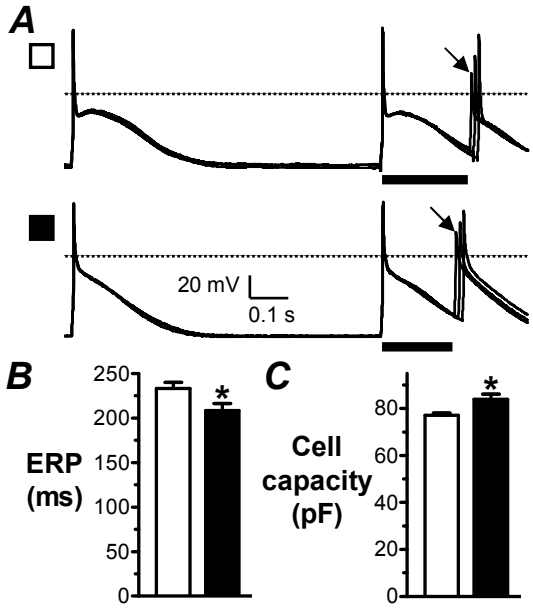

A
20 mV
0.1 s
B
ERP
(ms)
250
200
150
100
50
0
*
C
Cell
capacity
(pF)
80
60
40
20
0
*

Figure 2

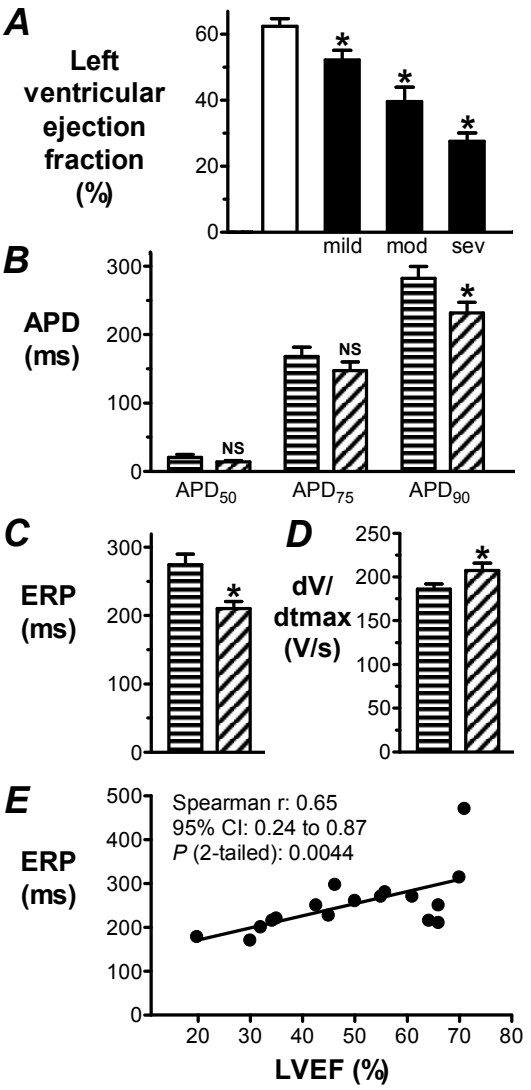

A
Left ventricular ejection fraction (%)
60
40
20
0
mild
mod
sev
B
APD (ms)
300
200
100
0
NS
NS
APD50
APD75
APD90
C
ERP (ms)
300
200
100
0
D
dV/ dtmax (V/s)
250
200
150
100
50
0
E
ERP (ms)
Spearman r: 0.65
95% CI: 0.24 to 0.87
P (2-tailed): 0.0044
500
400
300
200
100
0
20
30
40
50
60
70
80
LVEF (%)

Figure 3

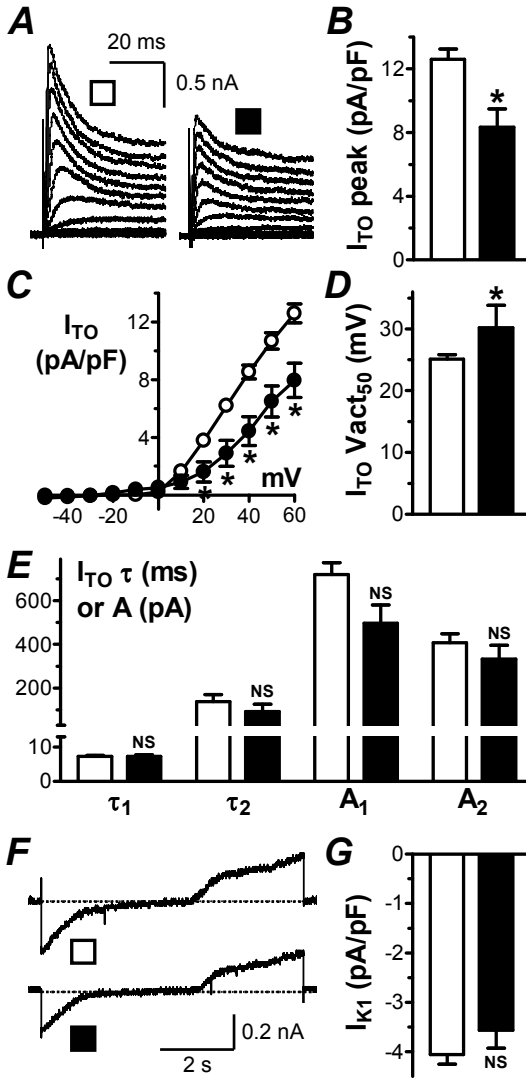
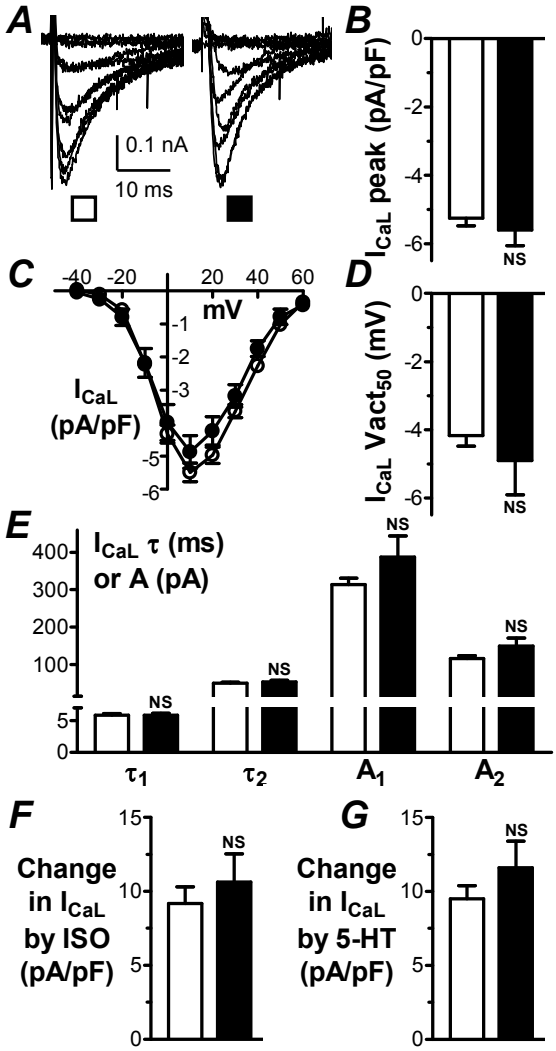

A
20 ms
0.5 nA
B
I_{TO} peak (pA/pF)
12
8
4
0
*
C
I_{TO} (pA/pF)
12
8
4
mV
-40
-20
20
40
60
D
I_{TO} $Vact_{50}$ (mV)
30
20
10
0
E
I_{TO} τ (ms) or A (pA)
600
400
200
10
0
NS
τ_1
τ_2
A_1
A_2
F
0.2 nA
2 s
G
I_{K1} (pA/pF)
0
-1
-2
-3
-4
NS

Figure 4


A
0.1 nA
10 ms
B
I_{CaL} peak (pA/pF)
0
-2
-4
-6
NS
C
-40 -20 20 40 60
mV
-1
-2
-3
-5
-6
I_{CaL} (pA/pF)
D
I_{CaL} $Vact_{50}$ (mV)
0
-2
-4
-6
NS
E
I_{CaL} τ (ms) or A (pA)
400
300
200
100
5
0
NS
NS
NS
NS
τ_1
τ_2
A_1
A_2
F
Change in I_{CaL} by ISO (pA/pF)
15
10
5
0
NS
G
Change in I_{CaL} by 5-HT (pA/pF)
15
10
5
0
NS