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

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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 This study sought to investigate whether LVSD in patients who are in sinus rhythm (SR) is associated with atrial cellular electrophysiological changes that 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 left ventricular 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% repolarization 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 were 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 remodeling; Isolated myocyte; Effective refractory period; Action potential duration; Ion current.

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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 remodeling, 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, caused by a reduction in either the effective refractory period (ERP), the conduction velocity, or both. Atrial cellular electrical remodeling 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 are 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% repolarization (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 remodeling 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 un-

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changed,[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 twofold: 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, and second, to clarify the pattern of any accompanying ionic remodeling 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°C to 37°C with a physiological solution containing (in 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 1.2× threshold, at 75 beats/min while injecting a small, constant current (set at the start of threshold measurement to clamp the maximum diastolic potential [MDP] to −80 mV, 1 to 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 to +50 mV at 24 mV/s, or with 500 ms pulses (0.2 Hz) increasing from −120 to +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 to +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 to +60 mV, from an HP of −40 mV.

Details of each patient's clinical characteristics and drug treatments were obtained from the medical records after surgery. All patients were in SR on the day of surgery, confirmed from a presurgery 12-lead electrocardiogram (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 presurgery, 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 presurgery. 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 *t*-tests. Categorical data were compared using a χ^2 test. All univariate electrophysiological data are expressed as cell means ± 1 standard error, 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 Institute Inc., Cary, North Carolina). 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 maximize 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

Patient characteristics

The patients' clinical characteristics and drug treatments are shown in Table 1. The majority (91%) suffered from angina and underwent coronary artery bypass graft (CABG) surgery. Valve surgery (aortic valve replacement [AVR] or mitral valve replacement [MVR]) was performed with or without CABG in 15% of patients. Thirty-six percent 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 angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.

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 1A). 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 subgroup of 37 patients for whom left atrial (LA) size was available, the LA was larger in