Introduction: The prevalence of left atrium (LA) thrombi in atrial fibrillation (AF) has been reported up to 10%. We tried to correlate LA/LA appendage (LAA) thrombus detection with possible clinical predictors, in warfarin treated patients.
Methods: A cohort of 430 study patients (mean age of 60.3±9.8 years;), all in oral anticoagulant (OAC) and undergoing pulmonary vein isolation (PVI) was assessed with transesophageal echo (TEE). In 10/430 (2.3%) an LA thrombus was found despite therapeutic OAC (mean INR 2.6±0.6 over the previous 4 weeks). Two study groups were then identified: 1) T-positive group = with LAA thrombus. 2) T-negative group = without LAA thrombus.
Results: The T-positive patients had higher CHADS score (1.5±0.7 versus 0.7±0.8; p=0.004), a lower LVEF (54.7±9.5 % versus 60.2±7.4; p=0.02), and a larger LA size (LA diameter: 56±12.2 mm versus 46±6.5 mm, p=0.000). A higher percentage of them were over 75 years old. A greater LA size (OR 1.15 95% C.I. 1.05-1.2; p=0.03) predicted LAA thrombus in the multivariate model. In further 42/430 (9.8%) patients an LA spontaneous echo-contrast (SEC) was detected. Thus, cumulatively 52/430 (12.1%) study patients were found to have both LAA thrombi or SEC. The LA size continued to predict also both the thrombi and SEC presence (OR 1.14 95% C.I. 1.07-1.2; p=0.000).
Conclusions: We found a 2.3% prevalence of LA thrombus (up to 12.1% when SEC was also considered) in AF patients. The thrombus was present despite on-target warfarin prevention. The LA enlargement predicted warfarin failure.

PO3-70

REVERSE REMODELING OF LEFT ATRIUM AFTER CATHETER ABLATION OF ATRIAL FIBRILLATION: 1 YEAR FOLLOW-UP ECHOCARDIOGRAPHIC DATA

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Introduction: Although it has been known that radiofrequency catheter ablation (RFCA) of atrial fibrillation (AF) induces reverse remodeling of atrium, its mechanism has not been evaluated yet.
Methods: We included 156 patients with AF (male 78.1%, 56.3±10.7 years old, paroxysmal AF 66.7%) who underwent RFCA, and compared pre-procedural and post-RFCA 1-year follow-up echocardiography.
Results: 1. AF catheter ablation significantly reduces left atrium (LA) size (pre 42.1±5.8mm vs. post 39.1±5.5mm, p<0.001) and improves left ventricle (LV) ejection fraction (pre 63.1±8.0% vs. post 65.9±6.5%, p<0.001) during 1 year follow-up. 2. When we compared the patients with reduced LA size (n=114) and those without LA reverse remodeling(n=42), baseline LA size (with 42.9±5.9mm vs. without 39.8±4.6mm, p=0.002), LV size (end diastolic dimension: with 51.0±4.1mm vs. without 49.2±3.5mm, p=0.012, and end systolic dimension: with 34.7±4.5mm vs. without 33.0±3.2mm, p=0.024), mitral E velocity (with 0.74±0.20 m/sec vs. without 0.65±0.14 m/sec, p=0.007), and E/E (with 10.4±4.0 vs. without 8.4±2.5, p=0.002) were greater in patients with reverse remodeling than those without reverse remodeling. 3. The early recurrence rate within 3 months of ablation was lower (27.0% vs. 45.2%, p=0.031) in patients with LA reverse remodeling. However, late recurrence rate (with 21.6% vs. without 33.3%, p=0.135) or duration of RF energy delivery (with 5598.7±1842.9sec vs. without 5549.9±1692.5sec, p=0.881) were not different between 2 groups.
Conclusions: AF catheter ablation improves LV systolic function and induces LA reverse remodeling. LA reverse remodeling was more significant in patients with high pre-ablation E/E', and LA enlargement, suggesting ventricular diastolic dysfunction, and that could be potentially associated with high AF burden or early recurrence. In pateints with mild-moderate diastolic dysfunction, AF catheter ablation is effective on LA reverse remodeling.

PO3-71

QUANTITATIVE ANALYSIS OF ISOLATION AREA AND RHYTHM OUTCOME AFTER CIRCUMFERENTIAL PULMONARY VEIN ANTRUM ISOLATION IN PATIENTS WITH PAROXYSMAL ATRIAL FIBRILLATION

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Introduction: We sought to investigate the relationship between the size of the left atrial (LA) isolated surface area (ISA) after pulmonary vein antrum isolation (PVAI) for paroxysmal atrial fibrillation (AF) and rhythm outcome after a 12 month follow up. PVAI is an established therapy for patients with paroxysmal AF. However, the influence of the size of ISA on rhythm outcome is unclear.
Methods: One-hundred-one consecutive patients with paroxysmal AF (mean age 59 ± 11 years, median AF history 36 (24; 96) months, mean LA size 42 ± 6 mm) underwent placement of circumferential lesions around the ipsilateral pulmonary vein (PV) pairs at the antral level aiming at complete electrical PV isolation. The ISA was defined as the proportion of total isolated antral surface area (IASAtotal) excluding the PVs to the sum of the IASAtotal and the LA posterior wall (LAPW) surface area taking into consideration the individual antral anatomy. All surface areas were assessed using a special software tool of the NavX system (St. Jude Medical, Inc., St. Paul, Minnesota). Patients were arbitrarily divided into four groups according to ISA (Group I: <50%, group II: 50 to 60%, group III 60 to 70%, group IV 70% and more).
Results: ISA was 59.2±11.6% in all patients. In subgroup analysis, ISA was 42.8±4.2% in group I (n=23), 54.2±3.0% in Group II (n=23), 64.3±3.0% in group III (n=33), and 73.9±3.6% in group IV (n=22), respectively. After a 12 month follow-up, 74% of patients in group I, 78% of patients in group II, 97% of patients in group III, and 100% of patients in group IV were free from AF and/or atrial macro-re-entrant tachycardia (MRT) on serial 7-day-Holter-ECG-recordings after a single procedure without antiarrhythmic drug treatment. In Kaplan-Meier analysis, recurrence rate was significantly lower in group III and group IV, respectively, as compared to group I (p<0.03 for both comparisons). No statistically significant difference could be found between group I and group II (p=0.6). According to receiver-operator characteristic curve analysis, the optimal cutoff value of ISA was 55%.
Conclusions: After 12 months, a larger ISA was associated with a significantly lower AF / MRT recurrence rate. ISA >55% might serve as a predictor for long-term success after PVAI.

PO3-72

PROPAFENONE RECEPTORS IN KIR2.X CHANNELS

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Introduction: Increase of the inward rectifying K+ current (IK1) plays a key role in the establishment of fast and stable reentries

of spiral electrical waves (rotors) and fibrillation dynamics. Therefore, cardiac inward rectifier Kir2.x channels underlying IK1 are putative targets for the control of fibrillatory arrhythmias. However, data on the pharmacological properties of Kir2.x channels are scarce.
Methods: We studied the effects of propafenone (P), a class Ic antiarrhythmic drug, on human Kir2.1, 2.2, and 2.3 channels transiently expressed in CHO cells and on human IK1 recorded in myocytes isolated from right atrial appendages. Currents were recorded using the patch-clamp technique.
Results: P produced dual effects (increasing and decreasing) on Kir2.1 channels whereas only blocking effects were produced on Kir2.2 and 2.3 channels. At low concentrations (10 nM-1 μM) P significantly increased the mean open time and the open probability of Kir2.1 channels by decreasing the affinity of the channel for intracellular polyamines. These P increasing effects critically depend on its interaction with Cys311 located at the HI-loop of the cytoplasmic domain of the channel. At the equivalent position Kir2.2 and Kir2.3 channels exhibit an alanine which explains the Kir2.1-specificity of the P increasing effects. At concentrations above the therapeutic range (5-50 μM) P significantly decreased the Kir2.x unitary current amplitude, an effect which was abolished by the mutation of two arginines conserved in the three Kir2.x channels (Arg228 and 260 in Kir2.1). P binding to these residues allosterically decreased the Kir2.x channel affinity for phosphatidylinositol 4,5-bisphosphate (PIP2), an essential modulator of Kir2.x channel activity, which ultimately decreases the current. On human atrial IK1 only the P inhibitory effects were produced.
Conclusions: Kir2.1 channels exhibit two P binding sites, the high affinity site being responsible for the P increasing effects. The low affinity site, also located in the cytoplasmic domain, is present in all Kir2.x channels and is allosterically coupled to the PIP2 binding. Thus, P blocks Kir2.x channels by decreasing the channel affinity for PIP2 which represents a novel and specific blocking mechanism.

PO3-73

KIR2.X INTERACTS WITH PROTEIN PHOSPHATASE 1 AND ASSEMBLES IN A HYPOPHOSPHORYLATED STATE IN CARDIAC MYOCYTES

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Introduction: The inward rectifier potassium (Kir) current, IK1, plays a key role to maintain resting membrane potential and to augment terminal repolarization of the action potential. Four distinct Kir2 inward rectifiers (referred to collectively as Kir2.x) have been identified, and Kir2.1, Kir2.2 and Kir2.3 are expressed in cardiac myocytes. Kir2.x subunits can function as heterotetramers, and the heteromeric assemblies of Kir2.1/2.2 and Kir2.1/2.3 channels are observed in native cardiac myocytes. Kir2.x function can be regulated by its associated proteins as well as protein kinase-mediated phosphorylation. Ion channel assembly can be a dynamic process but whether and how Kir2.x assembles dynamically in native cardiac myocytes is unknown.
Methods and Results: Cell lysates were prepared from isolated mouse ventricular cardiomyocytes with a Langendorf preparations. Western blot was used to detect Kir2.x with specific anti-Kir2.x antibody. Co-immunoprecipitation (Co-IP) assay was carried out by using anti-Kir2.1 antibody. We found that the size of Kir2.x, especially Kir2.2 and Kir2.3 were shifted with multiple bands larger than their expected size of ~50KD in the cell lysates from isolated cardiomyocytes. The size shift of Kir2.x was abrogated by pre-incubation of the lysates with protein phosphatase. Interestingly, only sizes ~50KD of Kir2.2 and Kir2.3 were detected in the anti-Kir2.1 immunoprecipitants. Moreover, the intensities of Co-IP'd Kir2.2 and Kir2.3 were increased in the cell lysates pre-treated with protein phosphatase compared to that of non-treatment. In addition, protein phosphatase 1 (PP1) was detected in the anti-Kir2.1 immunoprecipitants with anti-PP1 antibody; and Calyculin A, the PP1 inhibitor, prolonged action potential duration in cardiac myocytes.
Conclusion: Our data suggested that Kir2.x assembles in a hypophosphorylated state, and that PP1 interacts with Kir2.x and possibly modulates their assembly in native cardiac myocytes.

PO3-74

MECHANISMS OF DELAYED INTRAVENTRICULAR CONDUCTION IN HEART FAILURE

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Introduction: About one-third of heart failure (HF) patients have left bundle branch block and resynchronization therapy is beneficial. We have investigated possible mechanisms in a rabbit model of left-sided volume and pressure overload.
Methods: HF was induced by destruction of aortic valve and banding of abdominal aorta. The ECG was recorded from anaesthetized sham-operated and HF rabbits at week 8, before and after autonomic blockade. Free-running Purkinje fibres in the 2 ventricles were collected and RNA was extracted and reverse transcribed to produce cDNA. Quantitative PCR was carried out to measure the abundance of different ion channel and Ca2+-handling transcripts.
Results: Echocardiography revealed an increase in the LV internal diameter (in diastole) from 1.49±0.03 to 2.16±0.07 cm (n=6/8; P<0.001) and a decrease in LV fractional shortening from 41.3±1.4 to 25.5±3.2 % (n=6/8; P=0.002). Micro-CT imaging as well as visual inspection showed hypertrophy of the Purkinje fibres. Following autonomic blockade, there was an increase in the PR interval from 68.5±0.9 to 83.9±2.9 ms (n=7/9; P=0.001) and the QRS duration from 38.4±2.0 to 48.2±2.9 ms (n=7/10; P<0.05). This suggests that there is delayed His-Purkinje conduction in the HF model. In the LV Purkinje fibres from the HF group, we found significant downregulation of many ion channel mRNAs, including mRNAs for funny channels (HCN1 by 66%, HCN4 by 82%), Na+ channels (Nav1.5 by 51%), Ca2+ channels (Cav1.2 by 63%, Cav1.3 by 90%), K+ channels (Kv1.5, ERG, KvLQT1, Kir2.1, Kir3.1, Kir6.2 and SUR2a by 48-93%), Ca2+- handling proteins (RYR2, SERCA2 and NCX1 by 55-62%) and connexins (Cx40 by 50%, Cx43 by 49%). The change in HCN4 appears to have been driven by a significant downregulation in the transcription factor, Tbx3, by 70%. In the RV Purkinje fibres, fewer differences were observed.
Conclusions: We propose that remodelling of ion channels etc. in left His-Purkinje network may occur in response to LV dilatation and consequent stretching of the His-Purkinje tissue, particularly given that stress/stretch is thought to play a role in Purkinje fibre differentiation. Strategies to limit acute ventricular dilatation may be worthwhile in preventing long-term LV dysfunction in HF.