was similar in RIPC and sham groups both at rest (22.3±1.8 vs. 22.2±1.55 mfi; p=0.91) and following ADP stimulation (26.1±1.1 vs. 26.3±1.5 mfi; p=0.74). As shown in the table, compared to controls, RIPC was associated with a lower spontaneous and ADP-induced MPA formation and platelet CD41 expression both during the procedure and 24 hours later.
Conclusion: Our data show that RIPC before RF catheter ablation for AF significantly reduces the increased platelet reactivity associated with the procedure.

P4110 | BEDSIDE
Epicardial fat is associated with the level of endothelial dysfunction in patients with atrial fibrillation

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Background: Epicardial adipose tissue (EAT) is associated to atrial fibrillation (AF) burden and outcome after AF ablation. We intended to determine whether global or local EAT is associated with systemic and/or left atrial (LA) inflammation and endothelial dysfunction in AF patients.
Methods: Total, atrial, and ventricular EAT volume (EATtotal, EATatrial, EATventricular) were measured by multislice cardiac CT in 49 patients with paroxysmal (PAF, n=25) or persistent AF (PeF, n=24). Periatrial epicardial fat thickness at the esophagus (LA-ESO) and thoracic aorta (LA-ThA) were also measured. Vascular endothelial growth factor (VEGF), interleukin-8 (IL-8), soluble intercellular adhesion molecule 1 (sICAM-1), transforming growth factor-β1 (TGF-β1), and von Willebrand Factor (vWF) levels were measured in peripheral and LA blood samples obtained during catheterization during AF ablation.
Results: Patients with PeF had higher EATatrial ($P<0.05$) and LA-ESO (P=0.04) than patients with PAF. VEGF, IL-8, and TGF-β1 were not associated with EAT. In contrast, after adjusting for LA volume and body mass index, higher LA-ThA was significantly associated with higher sICAM-1 and vWF levels, both in peripheral blood ($P<0.05$) and in LA ($P<0.05$). Similar results were found with LA-ESO. Body mass index, EATtotal and EATventricular were not associated with sICAM-1 and vWF. In the subset of patients with persistent AF, all periatrial EAT thickness variables were independently associated with LA vWF ($p<0.05$). Greater EATatrial also tended to be associated with higher LA vWF.
Conclusions: Periatrial epicardial fat showed a significant positive association with increased biomarkers of endothelial dysfunction. This association appears particularly strong in patients with persistent AF. No such associations were found when considering body mass index or total amount of EAT. These results suggest that local EAT rather than regional or total adiposity may modulate endothelial dysfunction in patients with AF.

P4111 | BENCH
Inhibition of aldosteronsynthase regulates miR-21 during atrial fibrillation in mice

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Introduction: Early studies have suggested that torasemide may influence fibrosis in the left ventricle by antialdosteronergic effects. The role of torsemide for structural remodeling during atrial fibrillation (AF) is unknown.
Methods and results: 8 month old transgenic mice with cardiac overexpression of Rac1 GTPase (RacET) which develop spontaneous AF are characterized by increased atrial fibrosis, increased protein expression of the profibrotic cytokine connective tissue growth factor (CTGF, 257±77%), the key enzyme of collagen crosslinking lysyl-oxidase (LOX, 195±24%) and the fibrosis regulator microRNA-21 (miR-21, 252±43%) compared to wildtypes (WT). Long-term treatment with torsemide (10mg/kg/day) for 8 months prevented atrial fibrosis in RacET as well as the upregulation of CTGF (62±18%), LOX (124±23%) and miR-2 (68±7%) compared to vehicle, whereas Rac1 expression and activity was unaffected.
Mineralcorticoide receptor expression was not altered by torsemide. There was no change of blood pressure but a significant reduction of heart rate in torsemide treated RacET associated with a reduced prevalence of atrial fibrillation (38% RacET+Tora vs. 70% RacET). Interestingly, in vitro studies of V97MZ cells (lung fibroblasts without endogenous aldosteronsynthase) transfected with humam aldosteronsynthase (CYP11B2) showed that torsemide inhibited CYP11B2 activity by 75±1.8%, most likely through a competitive inhibition of CYP11B2 by binding of torsemide to the heme binding site of CYP11B2 through its nitrogen ring.
In order to test the underlying mechanism, primary neonatal cardiac fibroblasts were stimulated with angiotensin II (Ang; 1μM; 3 hours) and preincubated with or without the CYP11B2 specific inhibitor SL 242. SL 242 (1μM; 24 hours) reduced the expression of CTGF, LOX and miR-21 whereas Rac1 expression and activity was unaffected. All effects are significant with $p<0.05$.
Conclusion: Torsemide treatment was associated with inhibition of aldosteronsynthase (CYP11B2), preventions of atrial fibrosis and reduced the prevalence of atrial fibrillation in RacET mice. These effects were mediated through reduced expression of the profibrotic regulators CTGF, LOX and miR-21.

P4112 | BENCH
The mineralocorticoid receptor promotes pro-fibrotic remodeling in atrial fibrillation

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Purpose: We studied the role of the mineralocorticoid receptor (MR) for the signalling that promotes atrial fibrosis.
Methods and results: Left atrial myocardium (LA) of patients with atrial fibrillation (AF) had increased hydroxyproline content (425±103%) compared to patients matched for atrial size in sinus rhythm (SR). AF patients showed similar expression of MR but had increased expression of 11β hydroxysteroid dehydrogenase type 2 (11β-HSD2; 376±115%), a glucocorticoid inactivating enzyme providing minderalocorticoid access to MR. Hydroxyproline in LA correlated with upregulated 11β-HSD2, connective tissue growth factor (CTGF) and secreted protein acidic and rich in cysteine (SPARC). In cultured cardiac fibroblasts, aldosterone increased hydroxyproline expression (244±46%), which was completely prevented by BR-4628, a dihydropyridine-derived non-steroidal and selective MR antagonist, and by spironolactone. Aldosterone and TGF-β enhanced the expression of CTGF (207±34% and 176±22%, respectively), and BR-4628 as well as spironolactone prevented these effects. Compared to control, CTGF expression was diminished with either BR-4628 or spironolactone treatment (59±17% and 51±155%, respectively). The Rho kinase inhibitor Y-27632 decreased both aldosterone and TGF-β induced CTGF upregulation (52±15% and 95±8%, respectively), whereas the RhoA activator CN03 increased CTGF expression (206±28%). This effect persisted after BR-4628 or spironolactone pre-treatment. CTGF and aldosterone increased lysyl oxidase (LOX) expression (194±19% and 272±37%, respectively). The aldosterone but not the CTGF effect was reduced by MR antagonists indicating that CTGF induces LOX expression downstream of the MR. Aldosterone elevated miR-21 expression (415±120%) and suppressed the miR-21 target Sprouty-1 (43±8%), both effects were prevented by BR-4628 and spironolactone. All reported effects are significant with $p<0.05$.
Conclusions: Mineralocorticoid receptor signalling through hydroxyproline, CTGF, LOX and miR-21 contributes to pro-fibrotic remodeling. Inhibition of the MR pathways may therefore represent a target for the prevention of fibrosis which is a substrate for atrial fibrillation.

P4113 | BEDSIDE
The effects of ranolazine on paroxysmal atrial fibrillation in patients with coronary artery disease

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Purpose: The impact of ranolazine, an anti-ischemic agent with antiarrhythmic properties, on Paroxysmal Atrial Fibrillation (PAF) in patients with Coronary Artery Disease (CAD) remains unclear. Pacing devices can be useful tools for disclosing even asymptomatic PAF. Purpose of this study is to assess the effect of ranolazine on atrial fibrillation (AF), in patients with CAD, PAF and a dual-chamber pacemaker.
Methods: We studied 74 patients with CAD, PAF, and sick sinus syndrome or atrio-ventricular block, treated with pacemakers capable to detect PAF episodes. The total time in AF, AF burden, and the number of PAF episodes within the last 6 months before enrolment in the study, mean AF duration per episode, and the QTc interval were initially assessed. Subsequently, patients were randomized into additional treatment with ranolazine (375 mg twice daily) or placebo. Following six months of treatment, all parameters were reassessed and compared to those before treatment.
Results: Ranolazine was associated with shorter total AF duration (81.56±45.24 hours versus 68.71±34.84 hours, p=0.002), decreased AF burden (1.89±1.05% versus 1.59±0.81%, p=0.002), and shortened mean AF duration (1.05±0.41 hours versus 0.92±0.35 hours, p=0.01). In the placebo group no such differences were observed. In both groups, no significant differences in the number of PAF episodes and QTc duration were observed.

	Ranolazine-Group (n=36)			Control-Group (n=36)		
	Baseline	6 months after	p value	Baseline	6 months after	p value
Total time in AF (hr)	81.56±45.24	68.71±34.84	0.002	80.28±43.20	81.40±42.54	0.57
Mean AF episode duration (hr)	1.05±0.41	0.92±0.35	0.01	1.12±0.43	1.11±0.40	0.53
AF burden (%)	1.89±1.05	1.59±0.81	0.002	1.86±1.00	1.88±0.99	0.57
No. of AF episodes	77.33±36.12	75.53±33.13	0.61	71.56±30.92	72.39±26.99	0.66
QTc (msec)	462.44±9.71	463.81±10.18	0.21	462.22±9.06	461.67±9.64	0.64