Initially the main differences in in-hospital evolution and clinical outcome between patients with new onset AF and sinus rhythm were analyzed. Afterwards a comparison among the three groups was performed.
Results: Patients from Group I were older (66.6 vs. 60.4 years, p=<0.001). Gender distribution was similar in both groups. No differences were observed in previous cardiac disease between the two groups. Regarding to comorbidities, chronic renal failure (17.7% vs. 9%, p=0.017) was more frequent in Group I. Coagulase-negative staphylococci and S.aureus were the most frequently isolated microorganisms in both groups without differences between them. Heart failure (53.2% vs. 35.3%, p=0.003) at admission was more frequent in Group I, although moderate to severe valvular insufficiency was similar between the groups (p=0.475). There were no differences in vegetation size and periannular complications between the two groups.
During hospitalization, persistent signs of infection, septic shock (p=0.235), acute renal insufficiency (26.6% vs. 17.4% vs. 20.7%, p=0.131) and systemic embolisms (12.7% vs. 11.8% vs. 10.7%, p=0.820) were similar between the three groups. The need of surgery was similar between the three groups (51.9% vs. 59.4% vs. 58.1%, p=0.454), while mortality was higher in patients from Group I (44.7% vs. 22.8% vs. 33.8%, p=0.01). Those patients with new onset AF who developed heart failure showed an even higher mortality (p=0.042), suggesting a synergistic relation between them. In the multivariate analysis, new onset AF was an independent risk factor for heart failure (OR 2.92, CI (95%) 1.53-5.59, p<0.001) and mortality (OR 1.67, CI (95%) 1.01-3.09, p=0.04).
Conclusions: Patients with IE who present with de novo AF at the time of IE diagnosis are older than those who do not. The occurrence of new onset AF was an independent risk factor for heart failure and mortality and thus, of worse prognosis.

PULMONARY HYPERTENSION FROM BENCH TO BEDSIDE

P4322 | BEDSIDE
Persistent pulmonary hypertension after mitral valve replacement: analysis of the importance of pre-implantation pulmonary pressures

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Purpose: Persistent pulmonary hypertension (P-PH) after mitral valve replacement (MVR) leads to an increased risk of morbidity and mortality. We sought to determine the influence of systolic pulmonary artery pressure (sPAP) before surgery on the appearance of P-PH.
Methods: Patients undergoing MVR between January 2005 and December 2007 were analyzed. We excluded those with an available follow up shorter than 3 months. PH was diagnosed if sPAP estimated by doppler-echocardiography was >40 mmHg.
Results: A total of 111 patients with an average age of 61.3 years were studied. 67.6% were women and the most frequent etiologies were rheumatic and degenerative valvular disease (46.8% each). Intermedium sized-prostheses were implanted in most cases. No differences were found before the implant between age, gender, etiology of mitral disease and rates of atrial fibrillation among patients who underwent surgery with or without PH; however patients affected by PH before the implant had smaller body surface area. The type (mechanical of biological) and size of prostheses used in the implant were not different, but patients affected by PH before the surgery had higher rates of significant tricuspid regurgitation (TR) and underwent tricuspid annuloplasty more frequently.
After MVR, P-PH was present in 42,3% of patients after 12.6 months of mean follow up. P-PH was more frequently observed in elderly and female patients, in those with severe degrees of PH before surgery, and significant tricuspid regurgitation (≥3). On multivariable analysis, more severe degrees of PH before surgery (OR: 1.761; p=0.03) and significant TR (OR: 1.739; p=0.01) were independent predictors of P-PH after MVR. Surgical factors related to P-PH were prosthesis size and tricuspid annuloplasty. Both, tricuspid annuloplasty (OR: 0.345; p=0.025) and the implant of a smaller prosthesis (OR: 0.656; p=0.004) were independent predictors of P-PH after MVR.
Conclusion: MVR was associated with high prevalence of P-PH after mid term follow up. Both PH and significant TR before surgery were independent predictors of P-PH. Our data points out that MVR should be planned before the development of PH and greater TR. Smaller prosthetic size is also a risk factor for P-PH and bigger prostheses are desirable when possible.

P4323 | BEDSIDE
Effective regurgitant orifice area is an independent predictor of pulmonary hypertension in patients with aortic valve stenosis

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Purpose: Pulmonary hypertension (PHT) is frequently associated with aortic stenosis (AS) and can lead to a poor prognosis and more severe symptoms. The pathophysiological role of mitral regurgitation (MR) as a determinant of PTH is well established in other clinical models, as in heart failure with reduced ejection fraction (EF). However, some uncertainty persists in aortic stenosis patients. In this study a quantitative assessment of aortic valve area (AVA) and MR is prospectively performed to reveal their relation with PHT.
Methods: Consecutive patients with aortic flow velocity >2.5 m/s form the study population. End-diastolic (EDV) and end-systolic left ventricular volumes and left atrial (LA) volume are measured. Longitudinal shortening velocity, early and late lengthening velocities are assessed. Effective regurgitant orifice area (ERO) and regurgitant volume (RV) are obtained with PISA method. Systolic pulmonary artery pressure (S-PAP) is calculated adding the right atrial pressure to the tricuspid regurgitation pressure gradient.
Results: 113 consecutive patients are included; mean age is 79±8 years, EF 55±15%, NYHA 2.2±0.9, indexed AVA 0.56±0.18 cm^2/m^2, ERO 0.09±0.08 cm^2. 84 (74%) patients present MR, and among these 48 (42%) show ERO<0.10 cm^2. S-PAP result to be significantly different in the group of patients with ERO≥0.10 cm^2 compared to the groups with ERO 0-0.10 cm^2 and with ERO=0 cm^2 (mean S-PAP values in the 3 groups are 50±12 mmHg, 42±9 mmHg and 37±7 mmHg respectively; p<0.0001). At univariate analysis S-PAP correlates with VTD (R=0.37; p<0.0001), EF (R= -0.23; p=0.01), E (R=0.43; p<0.0001), E/E' (R=0.37; p<0.0001), LA volume (R=0.39; p<0.0001) and in particular with ERO (R=0.47; p<0.0001). There is no association between S-PAP and indexed AVA or mean gradient. In a multivariate regression model ERO (p=0.005) and VTD (p=0.03) remain associated with S-PAP, while E/E' and EF lose significance. When LA volume is added to the model, ERO remains the only variable significantly associated with S-PAP (p=0.02).
Conclusions: ERO results an independent predictor of PHT in patients with even mild MR and a wide range of aortic stenosis severity. This relation is not influenced by other variables commonly associated with LA pressure overload, such as E/E' or LA volume. This might reveal additional pathophysiological links of PHT in this context.

P4324 | BENCH
Characterization of intrinsic diastolic properties of the right ventricle. Importance of geometry-driven elastic restoring forces on rapid filling

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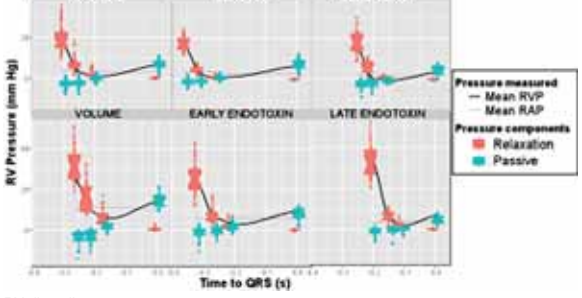
Fully characterization of right ventricular (RV) diastolic function is still a challenge. In early diastole, RV generates negative pressure but the mechanisms underlying RV suction remain unclear. Classical methods of pressure-volume (PV) data analysis fail to decouple relaxation from elastic recoil in early filling. We aimed to assess the contribution of elastic recoil to RV filling and determine its relationship with RV geometry.
Methods: 13 pigs were instrumented with a conductance-pressure catheter in RV. 3D echo images and PV data during transient cava occlusion were obtained after inotropic modulation, volume overload and endotoxin induced RV failure. Indices of RV diastolic function were obtained decoupling relaxation from passive diastolic pressure using previously validated algorithm. 3D RV inner surface meshes were analyzed computing septum curvature indices.
Results: Passive restoring forces generated suction in all phases contributing to rapid filling (Figure). Inotropic modulation didn't alter passive diastolic properties. Beta-blockade partially blunted passive suction (Pp -0.8±1.4 vs. -2.2±1.7 mmHg, P<.05) modifying operative volumes. Despite severe RV overload, maintenance of suction late after endotoxin infusion was possible by shifting the passive PV relationship to the right, so that equilibrium volume (V0) increased from 31±9 ml to 46±16 ml (P<.001). Changes in V0 correlated with the degree of septal curvature. In turn the latter was related to the transmural pressure gradient (P<.001).



RV diastolic pressure components.

Conclusions: Diastolic suction is generated by elastic restoring forces and is a major determinant of RV filling even during acute overload. Septal bulging towards

the LV preserves RV diastolic suction. For the first time, these aspects of diastolic function can be analyzed in vivo.

P4325 | BENCH
Long-term oral B3-agonist treatment reduces pulmonary vascular resistance and improves right ventricular function in a swine model of chronic postcapillary pulmonary hypertension

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Purpose: There are few therapies available for pulmonary hypertension (PH), particularly no specific therapy has demonstrated a consistent effect in postcapillary PH. Our purpose was to assess the effect of long-term oral treatment with a B3-adrenoceptor (B3-AR) agonist on pulmonary vascular resistance (PVR) and right ventricular (RV) function in chronic postcapillary PH.
Methods: Eight pigs with chronic postcapillary PH generated by surgical banding of the inferior pulmonary vein were randomized to oral treatment with a B3-agonist (Mirabegron 50 mg/12h for 14 days) or placebo. Right heart catheterization (RHC) and cardiac magnetic resonance (CRM) were performed at baseline and at the end of the treatment period. Pulmonary vascular resistance (PVR) was measured in Wood units by RHC. Changes in RHC and CMR parameters were compared between groups using Student T or Wilcoxon test.
Results: Baseline characteristics were well balanced between groups (table). After 14 days of treatment, subjects randomized to B3-agonist showed a significant reduction in PVR and an improvement in RV-arterial coupling and RV ejection fraction. No significant changes were observed in heart rate and systemic blood pressure.

Baseline characteristics and changes in the treatment group and placebo group

	Baseline characteristics			Change		
	Control (N=4)	B3-agonist (N=4)	P	Control (N=4)	B3-agonist (N=4)	P
Weight	41.9±8.4	37.9±12.3	0.61	7.4±2.4	11.6±1.9	0.033
HR (bpm)	79.5±13.8	83.5±8.4	0.64	–4.0±23.2	13.8±8.5	0.229
Mean systemic BP (mmHg)	100.0±8.5	93.8±5.9	0.27	1.2±16.0	0.5±8.7	0.937
Mean PAP (mmHg)	37.5±3.3	35.8±3.1	0.47	8.0±16.5	1.2±1.5	0.447
Indexed PVR (WU/m^2)	5.8±0.9	6.2±1.2	0.58	2.2±2.2	–1.2±0.6	0.027
Cardiac index (L/min/m^2)	5.4±1.1	4.5±0.2	0.24	–0.8±1.2	1.1±0.4	0.030
RV end-systolic volume (ml/m^2)	41.6±8.5	40.6±17.8	0.93	8.1±8.7	–3.5±2.5	0.042
RV ejection fraction (%)	58.5±6.5	53.6±4.1	0.25	–3.8±6.8	5.7±1.7	0.036
RV-arterial coupling (Ea/Emax)	0.69±0.17	0.59±0.16	0.42	0.08±0.16	–0.16±0.07	0.029

Conclusion: Long-term oral therapy with a B3-AR agonist significantly reduced PVR and improved RV performance in a translational experimental large-animal model of chronic PH. The absence of significant changes in heart rate and systemic blood pressure confers a good safety profile.

P4326 | BENCH
Airway delivery of AAV1.SERCA2a ameliorates vascular resistance and right ventricular performance in a preclinical model of postcapillary pulmonary hypertension

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Background: Recent evidence indicates that defective calcium homeostasis in vascular smooth muscle cells is a key contributing factor to excessive cell proliferation and disease progression in pulmonary hypertension (PH). Decreased sarcoplasmic reticulum ATPase pump (SERCA2a) lung expression has been described in human pulmonary arterial hypertension and experimental monocrotaline-induced PH in rodents, where its normalization through adeno-associated virus serotype 1 (AAV1) mediated gene transfer had regressive effects in vascular remodeling and improvement in pulmonary hemodynamics. In postcapillary PH, the role of SERCA2a downregulation and its potential as a therapeutic target remains unknown.
Aims: 1) To analyze the relationship between distal vascular remodeling and lung SERCA2a protein expression chenges in a large animal model of postcapillary PH, and 2) assess the beneficial effects of AAV1-SERCA2a gene transfer using a novel airway aerosolized delivery technique.
Methods: A post-capillary model of PH was created in swine by surgical restrictive banding of 2 pulmonary veins. After 8 weeks, animals were randomized to airway delivery of 10^{13} viral genomes using an intratracheal aerosolizer (n=5) or saline (n=5), and reevaluated 8 weeks later. A sham-operated group (n=4) served as control. Invasive pulmonary hemodynamics and right ventricular function (RVEF) and remodeling by MRI were assessed before randomization and at the final follow up 8 weeks later.
Results: Compared to the sham group, postcapillary PH animals showed significant arterial wall remodeling as assessed by increased medial thickness in small distal pulmonary arteries (<300 μm) along with increased indexed vascular resistance (PVR), and SERCA2a protein levels were decreased by 48% (p=0.036). SERCA 2a gene tranfer halted the progressive increase in PVR (mean[SD] change 6.3[6.1] vs -0.1[2.6] wood units/m^2 in saline vs SERCA-treated, respectively, p=0.047) assessed by invasive right heart catheterization. Furthermore MRI revealed preservation of RVEF after SERCA 2a gene transfer (mean[SD] change -13 [8] vs +0.1[9] % units, in saline vs SERCA-treated, respectively, p=0.048).
Conclusions: In a clinically relevant large animal model of postcapillary PH, SERCA2a protein downregulation was associated with distal arterial wall thickening and high PVR. AAV-mediated SERCA2a overexpression using a novel aerosolized delivery resulted in beneficial hemodynamic effects and improved cardiac function.

P4327 | BENCH
The novel endothelin receptor antagonist, Macitentan, improves right ventricular energetics and function in the Sugen5416/hypoxia rat model of severe pulmonary artery hypertension

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Purpose: Pulmonary artery hypertension (PAH) is characterized by vascular changes causing increased pulmonary resistance and eventual right heart failure (RHF). Altered myocardial substrate utilization may be associated with RHF, however these changes have not yet been well characterized. The aim of this study was to evaluate in vivo the right ventricular (RV) function, and RV glucose and fatty acid metabolism in an animal model of PAH using non-invasive positron emission tomography (PET). The effect of the novel endothelin receptor antagonist (ERA) treatment, Macitentan, was also investigated on the development of PAH and RV energetics.
Methods: Male Sprague-Dawley rats (n=11) weighing 150-200 g received a single injection (20mg/kg) of Sugen5416, a vascular endothelial growth factor receptor2 inhibitor, followed by three weeks of chronic hypoxia (10% O2). The rats were then randomized to treatment or no treatment with Macitentan (25 mg/kg daily) beginning five weeks post Sugen injection. Five and eight weeks post Sugen injection, substrate utilization was serially assessed with 2-[18F]fluoro-2-deoxyglucose (FDG) and 4-[18F]fluoro-6-thia-heptadecanoate (FTHA) PET scans for glucose and fatty acid metabolism respectively, and reported as a standardized uptake value (SUV). This data was correlated with in vivo functional measurements with echocardiography and multi gated acquisition scans.
Results: The Sugen-hypoxia (SuHx) model resulted in a progressive increase in RV FDG uptake over 8 weeks (SUV baseline: 1.80, PAH week 5: 3.81, PAH week 8: 3.69, $p<0.05$ between baseline and PAH week 8). RV FTHA uptake significantly increased from baseline to week 5 with the SuHx model (SUV baseline: 1.50, PAH week 5: 2.97, $p<0.05$). Macitentan significantly decreased RV/LV FDG uptake (SUV PAH week 8 untreated: 1.09 vs. PAH week 8 treated: 0.66, $p<0.05$). This was associated with improved RV ejection fraction (PAH week 8 untreated: 53.15% vs PAH week 8 treated: 73.22%, $p<0.01$) and with an improvement in pulmonary artery pressures measured by pulmonary artery acceleration time (PAH week 8 untreated: 17.32 ms vs. PAH week 8 treated: 24.38 ms, $p<0.001$)
Conclusion: PAH is associated with metabolic changes in the RV, characterized by increased fatty acid and glucose utilization with a proportionally greater increase in glucose uptake, likely representing increased glycolysis. Macitentan attenuated RV/LV FDG uptake and significantly improved RV function and hemodynamics. Clinical studies evaluating the link between metabolic and functional alterations in the RV and the effects of therapy are warranted.

P4328 | BENCH
Intratracheal administration of prostacyclin analog-incorporated nanoparticles ameliorates the development of monocrotaline-induced pulmonary artery hypertension in rats

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Background: Nanoparticles (NPs) have been used as a novel delivery system for transport of drug to target organs. NPs are taken up by target organ because of their small size. Drug release from NPs is controlled according to the NP composition. Thus, drug-incorporated NPs for local delivery might optimize the efficacy and minimize the side effects of drugs. Intravenous prostacyclin improves long-term survival in patients with pulmonary arterial hypertension (PAH). However, intravenous prostacyclin causes flashing, headache and catheter-related infections. We investigated the effects of intratracheal administration of prostacyclin analog-incorporated NP (Pro-NP) in a rat model of PAH.
Methods: Rats were received a single intratracheal administration of PBS, FITC-NP or Pro-NP 14 days after monocrotaline injection. Hemodynamics, right ventricular (RV) hypertrophy and pulmonary artery muscularization were assessed 28 days after monocrotaline injection. We examined survival rates after single administration of PBS or Pro-NP.
Results: After single administration, Pro-NP significantly decreased RV pressure (Pro-NP: 63±15 mmHg, FITC-NP: 87±13 mmHg, PBS: 84±11 mmHg) (Figure