P4324 | BENCH
Characterization of intrinsic diastolic properties of the right ventricle. Importance of geometry-driven elastic restoring forces on rapid filling
C. Perez Del Villar Moro1, J. Bermejo1, D. Rodriguez-Perez2, R. Yotti1, P. Martinez-Legazpi1, Y. Benito1, J.C. Antoran2, M.M. Desco2, J.E. Ortuno4, F. Fernandez-Aviles1, 1University General Hospital Gregorio Maranon, Department of Cardiology, Madrid, Spain; 2Department of Mathematical Physics and Fluids, Facultad de Ciencias, Universidad Nacional de Educaci, Madrid, Spain; 3Mechanical and Aerospace Engineering Department, University of California San Diego, La Jolla, United States of America; 4Universidad Politecnica de Madrid. Departamento de Ingenieria Electronica, Madrid, Spain
Fully characterization of right ventricular (RV) diastolic function is still a challenge. RV geometry, RV diastolic function and pressure-volume (PV) 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. The pathophysiological role of mitral regurgitation (MR) as a determinant of RV function was evaluated. Results: MR was observed in all 13 animals, MR grade varied from mild to severe. MR grade and annular area were significantly correlated. Despite that, significant gradients were not observed in any of the animals.
Conclusions: From these results, MR is not enough to explain RV dysfunction. Other mechanisms, such as RV geometry, should be considered.

New insights in infective endocarditis / Pulmonary hypertension from bench to bedside

P4323 | BEDSIDE
Effective regurgitant orifice area is an independent predictor of pulmonary hypertension in patients with aortic valve stenosis
G. Benfari1, A. Rossi2, P. Faggiano3, S. Nistri4, G. Cioffi5, C. Vassanelli1
1Cardiology, 2Section of Cardiology, University of Verona, Verona, 3Section of Cardiovascular Disease, University of Brescia, Brescia, 4CMSR Veneto Medica, Altavilla Vicentina, 5Villa Bianca Hospital, Trento, Italy
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 PHT is well established in other clinical models, as in heart failure with reduced ejec-
tion 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 thickening 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 tri-
cuspid regurgitation pressure gradient.
Results: 113 consecutive patients are included: mean age is 79±8 years, EF 55±15%, NYHA 2.2±0.09, indexed AVA 0.56±0.18 cm²/m², ERO 0.09±0.08 cm², 84 (74%) patients present MR, and among these 48 (42%) show ERO>0.10 cm². S-PAP result to be significantly different in the group of patients with ERO>0.10 cm² compared to the groups with ERO<0.10 cm² and with ERO=0 cm² (mean S-PAP values in the 3 groups are 50±12 mmHg, 42±5 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<0.0001), E/E' (R=0.37; p<0.0001), LA volume (R=0.39; p<0.0001) and in particular with ERO (R=0.57; p<0.0001). The new association between S-PAP and ERO was superior to the association between S-PAP and E/E' or LA volume. When LA volume is added to the model, ERO remains the only variable signifi-
cantly 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 influ-
enced 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.

P4322 | BEDSIDE
Persistent pulmonary hypertension after mitral valve replacement: analysis of the importance of pre-implantation pulmonary pressures
S. Briongos Figuero1, J.L. Moya Mur1, A. Garcia Lledo2, T. Centella Gomez1, J.L. Zamorano Gomez1, G. Benfari1, A. Rossi2, P. Faggiano3, S. Nistri4, G. Cioffi5, C. Vassanelli1
1Cardiology, 2Section of Cardiology, University of Verona, Verona, 3Section of Cardiovascular Disease, University of Brescia, Brescia, 4CMSR Veneto Medica, Altavilla Vicentina, 5Villa Bianca Hospital, Trento, Italy
Purpose: Persistent pulmonary hypertension (P-PH) is frequently associated with aortic valve disease. In turn the latter was related to the transmural pressure gradient (P<0.18). When LA volume is added to the model, ERO remains the only variable signifi-
cantly 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 influ-
enced 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.

P4323 | BEDSIDE
Effect of regional suction on ventricular filling
J. Martínez-Delclòs1, C. Sánchez-Romero1, A. García-Lledo2, T. Centella-Gómez3, J.L. Zamorano-Gómez1
1Cardiology, 2Section of Cardiology, University of Verona, Verona, 3Section of Cardiovascular Disease, University of Brescia, Brescia
Purpose: 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. P-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%). Mean estimated sPAP values in the 3 groups are 50

Conclusions: In this setting the knowledge of sPAP values ≥ 40 mmHg identifies patients at high risk for sPAP rise after surgery. Both PH and significant TR before surgery were independent predictors of sPAP rise (OR: 1.739; p=0.01) and significant TR (OR: 1.761; p=0.03) were independent predictors of ERO rise (R=0.47; p<0.0001). AVA or mean gradient. In a multivariate regression model ERO (p=0.005) and P-PH was more frequently observed in elderly and female patients, in patients who underwent surgery with or without PH; however patients affected by PH before the implant had smaller body surface area. The type (mechanical or biological) and size of prosthesis 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: 0.658; 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 prosthesis are desirable when possible.
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


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 (CMR) 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

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>-0.4 ± 0.2</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>8 ± 4</td>
</tr>
<tr>
<td>Mean systemic BP (mmHg)</td>
<td>8 ± 4</td>
</tr>
<tr>
<td>Mean P(A-V) (mmHg)</td>
<td>8 ± 4</td>
</tr>
<tr>
<td>Indexed PVR (WU/m2)</td>
<td>8 ± 4</td>
</tr>
<tr>
<td>Cardiac index (L/min/m2)</td>
<td>8 ± 4</td>
</tr>
<tr>
<td>RV ejection fraction (%)</td>
<td>8 ± 4</td>
</tr>
<tr>
<td>RV arterial coupling (Ea/Emax)</td>
<td>8 ± 4</td>
</tr>
</tbody>
</table>

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

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

K. Drozd1, Y. Deng1, B. Jiang1, J. Lockwood1, S. Thorn1, D. Stewart2, R.S. Beanlands1, R.S. Dekemp1, J. Dasilva1, L.M. Milenicz1, 1University of Ottawa Heart Institute, Ottawa, Canada; 2The Ottawa Hospital, Ottawa, Canada

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 been well characterized. The purpose 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 RHF 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 receptor-2 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]fluorodeoxyglucose (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: 8 weeks of Sugen-hypoxia (PHx) 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 (SUHVAPAH 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 mmHg vs PAH week 8 treated: 12.68 mmHg, p<0.05).

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 administration 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
Intraarterial administration of protocyclin analog-incorporated nanoparticles ameliorates the development of monocrotaline-induced pulmonary artery hypertension in rats

S. Akagi1, K. Nakamura2, H. Matsubara2, H. Ito1, 1Okayama University, Department of Cardiovascular Medicine, Okayama, Japan; 2Okayama Medical Center, National Hospital Organization, Okayama, Japan

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. Intraarterial protocyclin improves long-term survival in patients with pulmonary arterial hypertension (PAH). Intraarterial protocyclin causes flushing, headache and catechol-related infections. We investigated the effects of intraarterial administration of protocyclin analog-incorporated NP (Pro-NP) in a rat model of PAH.

Methods: Rats were received a single intraarterial administration of PBS, FITC-NP or Pro-NP 14 days after monocrotaline administration. Hemodynamics, right ventricular (RV) hypertrophy and pulmonary artery muscularization were assessed after monocrotaline administration. 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)