P5708 | BEDSIDE
Alterations of monocyte subsets in chronic heart failure patients in association with changes in epigenetic regulation

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Chronic heart failure (CHF) is closely with associated altered inflammatory responses. Their mechanisms has not been fully elucidated, but there is support for the notion that the specific subsets of monocytes may play a crucial role. Here we aimed to investigate whether CHF is associated with alterations of distribution of different monocyte subsets, namely classical CD14++CD16-, intermediate CD14++CD16+, and non-classical CD14+CD16++. Classical monocytes are involved in phagocytosis and resolution of inflammation, a minor subset of macrophage-like CD16-positive monocytes (mostly non-classical) is capable of driving and modulating inflammatory processes by secretion of TNFα, tissue factor or ACE. Moreover, we attempted to explain these changes by investigating epigenetic regulation.

We performed a clinical and immunologic analysis of 29 CHF patients and 34 healthy age and gender matched controls. Abovementioned monocyte subsets were analyzed by flow cytometry. Methylation of 94 proinflammatory genes in nuclear blood cells was assessed using restrictase digestion based assay. In 8 CHF and 14 control serum samples, circulating microRNA regulating inflammatory reactions were assessed (miR-20a. miR-21, miR146a, miR199), using RT-PCR.

We demonstrated that monocytes of CHF patients are significantly enriched in non-classical subset as compared to healthy subjects [6.76% (4.16-9.87) vs. 3.57% (2.48-5.27), respectively; $p<0.001$]. Similarly, although to a lesser extent, CHF patients presented with greater frequencies of intermediate monocytes [13.2% (6.76-36.1) vs. 8.01% (4.63-15.1), p=0.013]. In contrast, percentages of classical monocytes were significantly less in CHF patients than in healthy controls [70.6% (42.4-80.1) vs. 83.1% (77.0-87.1), respectively; $p<0.001$]. Median level of methylation of proinflammatory genes was higher in patients with CHF 0.4% vs 0.09%, with particular methylation increase of Mapk1 (100% vs 0), IL17 receptor A (25% vs 2%) and NFATc3 (10.1% vs 0.6%) genes. Interestingly, CD14 was severely hypermethylated in controls (99.8%) and much less in CHF (50%). CHF patients had lower serum expression of miR-146a (55.8% of controls) and miR-20a (10.5% of controls) and higher of miR199a (221% of controls) and miR-21 (344% of controls).

Our data indicate that CHF is associated with accumulation of more mature immunomodulatory monocyte subsets. The observed phenotype may be result of epigenetic effects of blood cells and altered expression of circulation miRNA. Based on our results we could hypothesize that all monocyte subsets are closely implicated in inflammatory processes due to CHF

P5709 | BEDSIDE
Cardiac transthyretin (ATTR) amyloidosis - clinical and echocardiographic findings from the largest single cohort worldwide

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Purpose: Cardiac transthyretin (ATTR) amyloidosis, also known as senile systemic/cardiac amyloidosis, is a rarely diagnosed late onset progressive cardiomyopathy. Clinical features and outcome data have been characterised only in small groups of patients. Various observations suggest that it may in fact be far more common, and several promising specific new therapies, including transthyretin stabilizers and RNA inhibitors, are now in clinical development. Our aim here was to review and better characterise the clinical features of the disease in a large single centre series.

Methods: More than 200 patients have been diagnosed at our UK tertiary centre during the past 5 years, comprising the largest cohort worldwide. Analyses of clinical data and echocardiography performed at our centre in the first 155 patients are presented here, and will be updated to include all cases prior to the ESC Congress. Survival was estimated using Kaplan-Meier analysis.

Results: The number of new patients has increased year on year, from 16 in 2007 to 60 in 2012. Of 155 patients, 144 were male (93%). Median age at diagnosis was 77 yr (IQ range 72-81) and at death was 81 yr (IQ range 77-84). Twenty three patients (15%) were younger than 70 yr at diagnosis. Forty five patients have died. Median survival was 51.2 months (95% CI 40.9 to 67.5). Sixty seven (43%) patients had atrial fibrillation at diagnosis. Median serum NT-pro BNP at diagnosis was 329pmol/L (IQ range 208-658), and serum Troponin-T was elevated in 131 (86%) patients. Transthoracic echocardiography showed median EF of 48% (IQ range 40-55), median IVSd 1.7cm (IQ range 1.5-1.8) and median LVPWd 1.7cm (IQ range 1.5-1.8). Median E/E' was 15.7 (IQ range 12.2-19.3), lateral S' TDI 0.05m/s (IQ range 0.04-0.06) and septal S' TDI 0.04 m/s (IQ range 0.03-0.05).

Conclusions: Cardiac ATTR amyloidosis is a cause of heart failure with preserved EF that typically affects older men, but it does occur in women and younger patients. The clinical phenotype is rather non-specific, and although concentric LV wall thickening and reduced longitudinal systolic function with moderate to severe diastolic dysfunction in association with elevated cardiac biomarkers are characteristic, the range of echocardiography findings was wide. Many recent referrals were prompted following CMR, which had strongly suggested amyloid infiltration in most cases. These observations, coupled with the promise of specific new therapies in the near future, encourage a high index of suspicion for cardiac ATTR amyloidosis among older patients with heart failure and preserved EF.

P5710 | BEDSIDE
Effects of everolimus conversion from mycophenolate mofetil on cardiac allograft vasculopathy in heart transplant recipients

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Background: Use of EVL may reduce the progression of cardiac allograft vasculopathy (CAV) in primary HTx recipients. Our basic immunosuppression protocol is triple therapy with a calcineurin inhibitor (CNI; ciclosporin or tacrolimus), mycophenolate mofetil (MMF), and prednisolone (PSL). In HTx recipients with CAV progression and/or renal dysfunction, we generally convert from MMF to EVL and reduce CNI administration. However, the efficacy of EVL for CAV is unknown.

Purpose: We investigated the effects of everolimus (EVL) for vessel remodeling in maintenance heart transplant (HTx) recipients in regard to vessel volume changes, and lumen and plaque volumes.

Methods: Seventy-two patietns who underwent heart transplantation from July 1997 to December 2012 at our institution were followed, of whom 15 were converted to EVL from MMF after a mean 2.4 years. Those patients underwent serial 3-dimensional intravascular ultrasound analysis of the first 50 mm of the left anterior descending coronary artery before EVL conversion and again after 12 months. As a control group, 30 patients matched for baseline year and who received our basic immunosuppression therapy were compared in regard to vessel volume changes, and lumen and plaque volumes.

Results: The mean baseline maximal intimal thickness (MIT) and baseline plaque volume in the EVL group were significantly greater than in the control group (1.29 ± 0.45 vs 0.71 ± 0.45 mm, 137.70 ± 74.12 vs. 59.42 ± 43.43 mm^3, $p<0.05$). CAV progression was significantly suppressed in the EVL group as compared with the control group [Δmaximal intimal thickness -0.11 ± 0.32 vs. 0.07 ± 0.24 mm (p=0.05), Δplaque volume -13.41 ± 41.38 vs. 9.43 ± 28.10 mm^3 (p=0.06)]. The EVL group also had kept lumen volumes and suppressed the progression of max stenosis rate (Δlumen volume 8.78 ± 52.13 vs. -32.04 ± 80.15 mm^3, Δmax stenosis rate -5.65 ± 8.95% vs 1.75 ± 7.66%, $p<0.05$).

Conclusion: Conversion to EVL from MMF suppressed CAV progression and reduced the degree of luminal narrowing in HTx recipients.

P5711 | BEDSIDE
Ischemia-modified albumin levels in patients with acute decompensated heart failure treated with dobutamine or levosimendan: IMA-HF study

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Purpose: Ischemia-modified albumin (IMA) is a very sensitive biomarker of myocardial ischemia before necrosis. However, data about IMA levels specifically in patients with heart failure (HF) are still lacking. Dobutamine (DOB) is known to increase myocardial oxygen consumption, and thereby may precipitate myocardial ischemia and myocyte damage. In contrast to DOB, levosimendan (LEVO) does not increase myocardial oxygen demand and therefore is thought to have cardio protective properties. So, we aimed to evaluate 1-) serum IMA concentrations in acute decompensated HF and 2-) the effects of DOB and LEVO treatments on IMA levels.

Methods: This prospective multicenter study was performed at the five independent sites. Fifty-nine patients admitted to participating centers with NYHA III-IV acute decompensated HF and LVEF <35% were enrolled in this study. Blood samples for IMA measurements were obtained from all patients at baseline and 24 h after the initiation of HF therapy. 18 patients were treated with guidelines-recommended HF therapy with oxygen, diuretic, vasodilators (control group), 18 patients received an additional 24-h infusion of LEVO with a loading dose of 12 μg/kg over 10 min followed by a continuous infusion of 0.2 μg/kg/min (LEVO group) and 23 patients had DOB treatment with a continuous infusion of 10 μg/kg/min for 24-h in addition to optimal pharmacologic therapy (DOB group). A single serum specimen was also collected from 32 apparently healthy individuals. IMA concentrations were measured by albumin cobalt binding colorimetric assay and results were given as absorbance units (AU).

Results: In patients with acute decompensated HF, mean serum concentration of IMA was found to be significantly higher than those of apparently healthy population (0.894 ± 0.23 AU vs 0.379 ± 0.08 AU, $p<0.0001$). Overall, IMA levels significantly decreased after 24-h of the initiation of appropriate HF therapy (0.894 ± 0.23 AU and 0.832 ± 0.18 AU, $p<0.013$). Furthermore, IMA levels were

also found to significantly decrease in control group (1.041±0.28 vs 0.884±0.15 AU, p<0.041), in LEVO group (0.771±0.18 vs 0.728±0.18 AU, p<0.046) and also in DOB group (0.892±0.18 vs 0.820±0.13 AU, p<0.035).
Conclusions: This study suggested for the first time that patients with acute decompensated HF had elevated levels of IMA when compared to healthy controls and appropriate HF therapy significantly reduced serum IMA levels. The findings of this study also demonstrated that both DOB and LEVO treatments did not increase in IMA levels, suggesting lower potential in inducing myocardial ischemia when used in recommended doses.

P5712 | BENCH
Predict value of circulating endothelial progenitor cells in patients with moderate-to-severe chronic heart failure due to coronary artery disease

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Background: Recent evidence has defined that circulating Endothelial Progenitor Cells (EPCs) might have a pivotal role in the presence of atherosclerosis, chronically diseased vessels or following acute vascular injury. Previous studies have shown decreased numbers of EPCs both in established Coronary Artery Disease (CAD) and in patients with increased burden of cardiovascular risk.
The aim of this study was to evaluate predict value of circulating EPCs in chronic heart failure patients with documented CAD.
Methods: 118 moderate-to-severe Chronic Heart Failure (CHF) subjects (62 male, left ventricular ejection fraction = 42.68% [95 confidence interval (CI) = 35%-54%]) aged 46-68 years with angiographic documented stable CAD and 25 healthy volunteers were enrolled to the study. Vessel-wall and plaque geometrical and compositional parameters were measured on contrast-enhanced CT angiography. CAD severity was graded by calculating Gensini score index. Immunostaining and Flow Cytometric Technique (FCT) were used for predicable distinguish cells subsets depended on expression of CD14, CD34, Tie-2, CD45, and VEGFR2. 10,000 events were analyzed from each tube. Mononuclear cells were cultured for functional analysis (CFUs) after FCT.
Results: Analysis of obtained outcomes have been shown a significantly decreasing of the total CFU count and also circulating CD34+ subsets level: CD34+ CD45- VEGFR2+, and CD34+ CD45- Tei-2+ VEGFR2+ cells in CHF patients when compared with healthy volunteers. The relationship between Gensini score index and CD34+ CD45- Tei-2+ VEGFR2+ was determined by negative linear regression (R=-0.68; P=0.006). No relationship was seen with CD34+ subsets cells and volume of intramural calcium in coronary plaques. CD34+ CD45- Tei-2+ VEGFR2+ and CD34+ CD45- VEGFR2+were significantly higher in patients with first and second quartiles of Gensini score index when compared with those who have top quartiles of one (adjusted odds ratio (OR) = 5.32 [95% CI = 2.7-11.50]; P=0.008). Results did not change after adjustment for age, sex, body mass index, smoke, hypercholesterolemia, arterial hypertension, NYHA functional class of CHF and previous myocardial infarction (β=0.490, 95% CI=0.32-1.16, P=0.240).
Conclusions: A reduction in circulating EPCs defined as CD34+ CD45- VEGFR2+, and CD34+ CD45- Tei-2+ VEGFR2+ subsets cells in ischemic CHF patients. These findings can be taken into consideration as supporting of hypothesis about predict value of such cellular biomarkers with potential vascular repair capacity in evaluation of CAD severity in patients with CHF.

P5713 | BEDSIDE
The Incidence of morphological left ventricular noncompaction in Churg-Strauss syndrome

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Purpose: Left Ventricular Noncompaction (LVNC) is a type of hereditary cardiomyopathy characterized by a pattern of prominent trabecular meshwork and deep intertrabecular recesses, caused by insufficiency of normal endomyocardial morphogenesis. Although isolated LVNC was thought to be rare, the reports of adult LVNC have been increasing in accordance with the echocardiographic definition.
Methods and results: Among consecutive 18 cases of Churg-Strauss Syndrome (CSS), Left Ventricular (LV) systolic dysfunction was observed in 5 cases. All of the 5 cases exhibited eosinophilic myocarditis and LV systolic function have recovered to normal range without the findings of LVNC in 3/5 cases. The remaining 2 cases, though satisfied the echocardiographic definition of LVNC in the course of recurrent eosinophilic myocarditis with decompensated heart failure during the tapering of corticosteroids in spite of no preceding evidence of LVNC. In one of these 2 cases (Figure 1), "pathological" LVNC, i.e., a non-compacted layer could not be observed microscopically in the excised full-layer myocardium obtained through the left ventriculectomy, regardless of "morphological" LVNC in echocardiographic observations.

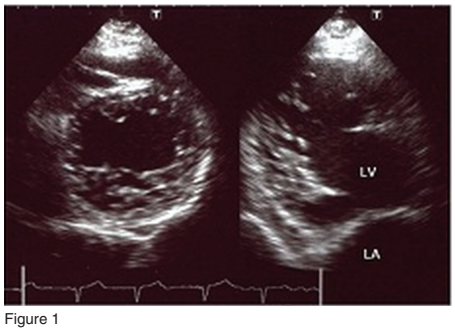

Figure 1

Conclusions: The diagnosis of LVNC must be cautiously made in cases of CSS with persistent or relapsed inflammation of the myocardium and endocardium. LVNC must be diagnosed not only by morphological evaluation but also through comprehensive assessment including clinical background and etiology.

P5714 | SPOTLIGHT 2013
Cardiac involvement in Churg-Strauss syndrome and granulomatosis with polyangiitis (Wegeners)

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Purpose: To investigate the prevalence of cardiac involvement in a large population of ambulatory Churg-Strauss syndrome (CSS) and granulomatosis with polyangiitis (Wegener's: WG) patients.
Methods: A total of 50 patients aged 59±11 years with CSS in remission and 40 patients aged 60±11 with WG in remission (diagnosis-to-enrolment interval resp. 4.0±4.5 and 4.6±5.4 years; P=0.45) who were previously unaware of cardiac involvement were compared with 50 randomly selected age- and sex-matched control subjects, using clinical evaluation, electrocardiography (ECG), echocardiography and cardiac magnetic resonance imaging (CMR). Control subjects without previous cardiac disease and ≤2 cardiovascular (CV) risk factors were randomly selected from our cardiology out-patient clinic.
Results: Age, sex and CV risk factors showed no significant difference between the three groups. Detailed cardiac evaluation revealed a high prevalence of echocardiographic defects and ECG abnormalities in both CSS and WG patients (Table 1). CMR in CSS (n=41) and WG (n=26) subjects revealed cardiac manifestations in respectively 20 (49%) and 11 (42%) patients (P=0.60), with wall motion abnormalities in respectively 16 (39%) and 6 (23%), fibrosis in 9 (22%) and 5 (19%), endocardial defect in 1 (2%) and 1 (2%), and pericardial effusion in 2 (5%) and 1 (2%). In patients with CMR available, echocardiography could detect cardiac involvement in CSS patients with a sensitivity of 60% and specificity of 81%, whereas sensitivity and specificity in WG patients was respectively 36% and 83%. Absence of ECG abnormalities did not exclude cardiac involvement, since abnormalities could still be detected in 18% of CSS and 25% of WG patients.

Clinical findings in CSS, WG and control

	CSS (n=50)	Wegeners (n=40)	Control (n=50)	A vs B	B vs C	A vs C
Echocardiography abn (no. of patients)	22 (44%)	12 (30%)	3 (6%)	NS	0.002	<0.001
Wall motion abnormalities	16 (32%)	6 (15%)	2 (4%)	0.05	0.07	<0.001
Valvular abnormalities	3 (6%)	2 (5%)	1 (2%)	NS	NS	NS
Pericardial effusion	2 (4%)	1 (3%)	0 (0%)	NS	NS 7 NS	
Pulmonary hypertension	2 (4%)	1 (3%)	0 (0%)	NS	NS	NS
Endocardial defects	2 (4%)	1 (3%)	1 (2%)	NS	NS	NS
ECG abnormalities	27 (55%)	14 (35%)	6 (12%)	0.05	0.009	<0.001

Values are number (%) of patients. CSS, Churg-Straus Syndrome.

Conclusion: These results demonstrate a high prevalence of cardiac involvement in WG and even more so in CSS patients. Systematic cardiac evaluation including detailed imaging is required to properly identify both CSS and WG patients with cardiac involvement.

P5715 | BENCH
Anchored cAMP signalling in progression from hypertrophy to heart failure in a rat model of pressure overload

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Introduction: Pathophysiological progression to Heart failure (HF) occurs in different phases starting with onset of hypertrophy. During this progression alterations in the adrenergic drive are vital and affect both electrical remodeling and associated arrhythmias (early phases), and structural remodeling (later phases). The reasons for altered efficacy of protein kinase A (PKA) signaling are still rather incomplete. Here we identify alterations in the PKA-AKAP (A kinase anchoring protein) interaction profile during transition to HF using a rat model of pressure overload, and relate this to arrhythmia vulnerability and deterioration of contractile performance.