1163-115 Traditional Risk Factors Are Associated With Regional Left Ventricular Dysfunction in Asymptomatic Individuals: The Multi-Ethnic Study of Atherosclerosis (MESA)

Boaz D. Rosen, Mohammed Saad, Steve Shea, Khurram Nasir, Thor Edvardsen, Michael Jerosch-Herold, Shenghan Lai, David A. Bluemke, Joao AC Lima, Johns Hopkins Hospital, Baltimore, MD

Background: Coronary artery disease (CAD) is the main cause of LV dysfunction in USA and Europe. Hence, LV dysfunction may begin as a regional process that eventually progresses to global dysfunction. We hypothesized that different risk factors for CAD would be related to regional LV dysfunction in asymptomatic individuals.
Methods: MESA is a large multicenter study focused on subclinical cardiovascular disease among individuals aged 45-84 years. We evaluated global and regional LV function by MRI tagging in 841 participants. Peak midwall systolic circumferential strain (Ecc) was analyzed by Harmonic Phase Imaging (HARP). Ecc below the 5th percentile was used as an index of regional dysfunction in three coronary territories: left anterior descending (LAD), circumflex (LCX) and right (RCA). Logistic regression was used to study the relationship between Ecc and traditional risk factors.
Results: After adjustment for age and gender, significant associations were noted between elevated diastolic blood pressure (DBP), and presence of abnormal Ecc. Odds ratios of having abnormal Ecc in the presence of DBP>=90mmHg were 3.5-5.2 in each of the coronary regions, (p<0.05). Percentage of individuals with abnormal Ecc in RCA region was 4.1%, 5.9% and 26.7% in individuals with DBP<85, 85-89 and >=90 mmHg (p<0.01). A similar pattern was seen in other coronary territories, and also in the presence of increased total and LDL cholesterol. Existence of more than one risk factor was associated with a substantially higher proportion of participants with abnormal Ecc. In individuals with DBP<85 mmHg and cholesterol <200 mg%, 4.3% of the individuals had abnormal Ecc-RCA, in the presence of either increased cholesterol or DBP, corresponding percentages were 3.9% and 7.8%, respectively. When both risk factors existed, the percentage of individuals with abnormal Ecc increased to 24.4% (<0.01). Similar findings were seen in the other regions. A similar pattern was noted when increased DBP and other risk factors.
Conclusions: Classic risk factors, especially increased DBP are associated with regional LV dysfunction in asymptomatic individuals. This association is stronger when more than one risk factor is involved.

1163-116 Neurohormones but Not Adrenomedullin Correlate With Left Ventricular Structure in Patients With Heart Failure: Results From an EARTH Substudy

Jens P. Hellermann, Tatsuo Shimosawa, Frank Ruschitzka, Kurt Quitzau, Inder Anand, Thomas F. Luescher, University Hospital Zurich, Zurich, Switzerland

Background: Adrenomedullin (ADM), mainly produced in cardiovascular tissue in response to shear stress and stretch, has been proposed as marker for left ventricular (LV) dysfunction in patients with heart failure (HF). Yet, data on longitudinal changes in ADM serum concentrations and their relation to changes in LV-volume and function in patients with HF are scarce.
Methods: In 642 patients with moderate to severe HF, plasma levels of ADM, brain natriuretic peptide (BNP), atrial natriuretic peptide (ANP), and big endothelin (B-ET-1) at baseline and after 6 months follow-up were measured. LV-enddiastolic volume index (LVEDVI), ejection fraction (EF), LV-mass index and wall stress were assessed with MRI. Spearman`s Rho correlations were performed to assess longitudinal changes in the relationship between ADM and LV-volume and function changes as well as clinical baseline variables.
Results: There was no association between ADM and clinical variables like BMI, sex or NYHA class at baseline. ADM was highly correlated with age (P = 0.0220), B-ET-1 (P < 0.0001) and BNP (P = 0.0006) levels at baseline and at follow-up. ANP and BNP were significantly and positively correlated with changes in LVEDVI, LV-Mass Index and LV-Wall Stress but not ADM. In patients treated with darusentan, an endothelin$_A$ antagonist and an ACE inhibitor or ARB, a negative correlation between ADM and LV-Wall Stress was observed (Rho = -0.1753, P = 0.0241) compared to patients without ACE inhibitor or ARB (Rho = 0.1693, P = 0.5133). Conclusions: In this so far largest dataset of longitudinal follow-up in patients with HF, ADM appears not to be correlated with clinical variables except age nor LV-volume or function. Neurohormones BNP and ANP are best related to changes in LV-volumes, but not LV function. ACE inhibitors and endothelin receptor antagonist neutralized their effect on ADM serum concentration. Thus, ADM is not a useful marker for monitoring HF.

1163-117 Prognostic Value of Development of Atrial Fibrillation in Outpatients With Heart Failure: Data From the Italian Network on Congestive Heart Failure (IN-CHF Registry)

Gianna Fabbri, Samuele Baldasseroni, Maurizio Marini, Francesca Coppi, Anna Gentile, Lucio Gonzini, Marco Gorini, Franco Ingrilli, Aldo P. Maggioni, The IN-CHF Investigators, ANMCO Research Center, Florence, Italy

BACKGROUND: Atrial fibrillation (AF) is the most frequent arrhythmia in patients (pts) with heart failure (HF) and is related with an adverse prognosis. The development of AF in HF may worsen clinical profile. However, it is not completely understood whether new onset of AF is a more severe prognostic determinant than the presence of chronic AF.
AIM: To examine whether HF pts with presence, or occurence of AF, have a poorer prognosis, compared to pts with sinus rhythm.
METHODS: We studied 4710 HF outpts from the IN-CHF registry, followed for two years. Pts were stratified in three groups: A) synus rhythm at baseline and at 1 year (3776 pts, 80.2%), B) synus rhythm at baseline and AF at 1 year (159 pts, 3.4%), C) AF at baseline and at 1 year (775 pts,16.4%). Two year mortality and hospitalization rates were assessed for all pts.
RESULTS: Table shows the characteristics of groups at entry.
Two years mortality (A=5.3%, B=17.8%, C=7.2%) and hospitalisation rates (A=32.1%, B=61.0%, C=36.9%) were higher in B than in C and A, p<.0001. Adjusted analysis confirms that development of AF in pts with HF is independently related to an adverse outcome both in terms of mortality (B group: HR 3.0, CI 95% 1.9-4.5; C group: HR 1.4, CI 95% 0.9 -1.9 vs A) and hospital admissions (B group: HR 3.0, CI 95% 2.1- 4.2; C group: HR 1.1, CI 95% 0.9-1.3 vs A).
CONCLUSIONS: Pts with new onset AF have a markedly reduced survival compared with those with chronic or without AF. These findings suggest that AF is associated with a worse outcome early after its development.

	A	B	C	p
Age (mean±SD), yrs	62±12	67±9	67±10	<.0001
NYHA III-IV, %	22	33	33	<.0001
Ischemic etiology, %	42	38	21	<.0001
Ejection fraction >40%, %	24	27	33	0.0005
Anemia (Hb <12mg/dL), %	12	20	12	0.05
Creatinine >2.5 mg/dL, %	2	5	1	0.02
Beta-blockers yes, %	23	14	15	<.0001
ACE-inhibitors yes, %	84	75	80	0.0002
Amiodarone yes, %	20	30	16	<.0001

1163-118 Alcohol Consumption and Cardiac Structure and Function in American Indians: The Strong Heart Study

Marcello Chinali, Giovanni de Simone, Thomas K. Welty, Elisa T. Lee, Lyle G. Best, Barbara V. Howard, Richard B. Devereux, Weill Medical College of Cornell University, New York, NY

Background. Chronic alcohol intake has been considered as a possible cause of cardiomyopathy. However, it has been recently reported that alcohol consumption is not associated with increased risk for congestive heart failure, even among heavy drinkers. This study was designed to assess the relation between alcohol intake and preclinical cardiac abnormalities in the population of the Strong Heart Study.
Methods. We studied 3,310 middle-aged to elderly participants of the study (age 59.6 ± 7.8 years, 63.8% women, 54.5% obese, 45.6% hypertensive, 47.5% diabetics), without prevalent cardiovascular disease. Participants were divided into groups according to the amount of self-reported alcohol intake. Quantities of alcoholic beverages were converted to number of drinks (1 drink = 12oz of beer, 4 oz of wine or 1 shot of hard liquor). All participants underwent clinical, laboratory and echocardiographic examination.
Results. Participants were divided in 1,147 never drinkers (N), 1,387 former drinkers (FD; defined as no alcohol for at least 12 months), and 776 drinkers (404 were light drinkers (LD)>4 drinks/week, 220 were moderate drinkers (MD) 4 to 12 drinks/week, and 157 were heavy drinkers (HD)>12 drinks/week). Drinking was more frequently associated with male gender, younger age, and higher diastolic blood pressure (p for trend all <0.01). Similar prevalence of diabetes, hypertension and obesity was found in all five groups (for all p=ns). All three drinking groups showed higher values of left ventricular diameter, cardiac output and aortic root diameter as compared with both the never and the former drinkers (all p<0.05). After controlling for clinical covariates there was no significant difference in left ventricular structure among the five groups. However, HD was still associated with increased aortic root diameter and higher cardiac output compared to both never and former drinkers (p for both <0.01).
Conclusion. In a middle-aged to elderly population of American Indians, mild to moderate alcohol consumption is not associated with preclinical cardiac abnormalities. However, heavy drinking is independently associated with increased aortic root diameter and increased cardiac output.

1163-119 Changes of Inflammatory Cytokines and Uric Acid in Patients With Severe Chronic Heart Failure: A COPERNICUS Substudy

Stefan D. Anker, Aidan P. Bolger, Andrew JS Coats, Hugo A. Katus, Michael B. Fowler, Milton Packer, for the COPERNICUS Study Group, NHLI, London, United Kingdom, Applied Cachexia Research, Berlin, Germany

It is not known, whether changes in inflammatory cytokines and serum uric acid (UA) relate to prognosisin in patients chronic heart failure (CHF), and whether the prognostic benefits of carvedilol are related to such changes.
Methods: In 204 randomly selected patients (age 62±1y, LVEF: all <25%, BMI 26.6±0.3 kg/m^2, female: 22%) participating in the Eurpean arm of the COPERNICUS study, we evaluated plasma levels of tumor necrosis factor alpha (TNF), soluble TNF receptor-1 (sTNFR1), interleukin (IL-6), IL-1 receptor antagonist (IL-1RA) and serum UA at baseline (BL) and after 115±6 days follow-up (FU, n=185).
Results: Mean levels of cytokines and UA are shown in the table. At BL, UA correlated with sTNFR1 (r=0.29, p<0.0001, n=203) and IL-6 (r=0.26, p=0.001, n=154). During FU, 29 deaths were observed in this cohort (12-month mortality 15.4%). Adjusting for age, gender, BMI and treatment, UA (p<0.03), but none of the cytokines predicted prognosis. Considering changes of parameters vs subsequent survival, only increases in IL-1RA (p<0.04) and UA (p<0.03) independently related to poor prognosis. An increase of UA by 1 mg/dL (i.e. 60 µmol/L) related to 39% higher mortality (95%CI 4-87%).
Conclusion: The beneficial effects of carvedilol in CHF are not dependent on plasma

levels of inflammatory cytokines or serum uric acid or their changes. Serum uric acid and its changes independently predict poor prognosis in CHF, more acurately than do plasma cytokines.

Table (for changes over time between drugs: all p>0.2)

Time point	TNF	sTNFR1	IL-6	IL1-RA	Uric Acid
	(pg/mL)	(pg/mL)	(pg/mL)	(pg/mL)	(mg/dL)
Carvedilol-BL	2.20±0.14	1575±79	3.25±0.30	400±25	7.26±0.24
Carvedilol-FU	2.13±0.22	1615±72	3.53±0.32	406±27	7.47±0.23
Placebo-BL	1.92±0.11	1589±59	3.26±0.25	410±39	7.24±0.23
Placebo-FU	1.96±0.26	1621±80	3.84±0.32	409±30	7.11±0.25

1163-120 Complement Activation in Patients With Congestive Heart Failure

Suhua Wu, Hong Ma, Yugang Dong, Jiangui He, Huiying Ye, Yujun Zhong, First Affiliated Hospital, Sun Yet-Sen University, Guangzhou, People's Republic of China

Background Increasing evidence suggests that complement may play a role in the pathogenesis of myocardial damage secondary to ischemia and reperfusion, but the role of complement in congestive heart failure is at present unclear. **Objectives** To determine whether the complement system is activated and its relationship to clinical outcomes in patients with congestive heart failure (CHF). **Methods** The plasma levels of products of complement activation C4d (classic pathway), Bb (alternative pathway), 3bc (final common pathway) and C5b-9 (terminal complement complex) were measured by enzyme-linked immunosorbent assay(ELISA) method in forty-four patients with CHF and sixteen normal age and sex matched volunteers. The left ventricular ejection fractions of all patients were measured by electron beam computed tomography (EBCT). Forty-one patients with CHF were followed up for 13±3 months to determine the combined clinical outcomes (hospitalization with worsening heart failure or death). **Results** Our major finding were (1) The plasma levels of C4d, Bb, C3bc and C5b-9 in patients with CHF were significantly higher than those in normal volunteers. (2) Significantly more of the patients with highest levels of C5b-9 (highest 50th percentile) had worse left ventricular function and adverse clinical outcomes compared with the patients with lowest levels of C5b-9 (lowest 50th percentile). **Conclusions** We have observed an activation of complement system and an association between high levels of C5b-9 and adverse clinical events in patients with CHF. Our findings suggested that complement might be added to the list of possible therapeutic targets.

1163-121 Prognostic Role of Neutrophil and Lymphocyte Counts in Heart Failure: Results From Val-HeFT

Inder S. Anand, Joseph Yen, Viorel G. Florea, Allen Hester, Robert Glazer, Roberto Latini, Aldo Maggioni, Jay N. Cohn, Veterans Affairs Medical Center and University of Minnesota, Minneapolis, MN

Background. Lymphocyte and neutrophil counts predict cardiovascular events in patients with coronary artery disease. Their role in heart failure (HF), however, is not known. We evaluated the prognostic value of baseline (BL) neutrophil and lymphocyte counts on mortality and first morbid event (M&M;) in the Valsartan Heart Failure Trial (Val-HeFT).
Methods and Results. Blood counts were measured at BL and during follow-up. Cox proportional hazards analysis was made for all cause mortality and M&M; with BL neutrophil and lymphocyte counts, classified by median and quartile (Q) groupings and used as independent variables in separate analyses. Patients with high BL neutrophil counts and low BL lymphocyte counts had more advanced HF. Both neutrophil and lymphocyte counts were significant multivariate predictors of mortality and M&M; when analyzed as continuous, dichotomized or Q variables. Whereas, higher neutrophil count was associated with greater mortality and M&M;, higher BL lymphocyte count was associated with a lower mortality and M&M;. Relative risk (RR) for neutrophils was 1.315 (95% CI 1.172 – 1.458; p=0.00016) and for lymphocytes 0.789 (95% CI 0.644 – 0.934, p=0.00131). Comparison of RRs and 95 % CIs with other dichotomized (> vs < median) multivariate predictors of mortality in descending order of p-value is shown in Table.
Conclusions: High BL neutrophil and low BL lymphocyte counts are important predictors of outcomes in HF, suggesting a possible role of inflammation in the progression of HF.

Variable	BNP	NYHA, III and IV	LVIDD/ BSA	Uric Acid	Neutrophils	Plasma Renin Activity	Beta Blocker Use	Lymphocytes	Norepinephrine	Age, >65 yrs	Ischemic etiology	Creatinine
Relative Risk	1.906	1.398	1.354	1.357	1.315	1.324	0.754	0.789	1.272	1.260	1.208	1.206
95% CI	1.748, 2.065	1.257, 1.539	1.211, 1.497	1.206, 1.508	1.172, 1.458	1.177, 1.471	0.597, 0.910	0.644, 0.934	1.125, 1.419	1.113, 1.407	1.059, 1.357	1.053, 1.358
p-Value	<0.00001	<0.00001	0.00003	0.00007	0.00016	0.00018	0.0004	0.00131	0.00132	0.00216	0.0123	0.01701

1163-122 Does Wider QRS Reflect Heart Failure Severity?

Teresa De Marco, Michael B. Higginbotham, Leslie A. Saxon, Sudha Balasubramanian, Patrick Yong, Elyse Foster, University of California San Francisco, San Francisco, CA, Guidant Corporation, St. Paul, MN

Background: A wide QRS is used as a surrogate measure of ventricular dysynchrony for selecting cardiac resynchronization therapy candidates. It is not clear if prolonged QRS correlates with other baseline measures such as left ventricular structure, systolic function, exercise tolerance, and heart failure symptoms.

Methods: Patients participating in the VENTAK® CHF/CONTAK® CD Biventricular Pacing Study were included in this retrospective analysis. Correlation of baseline QRS was calculated for each of the following baseline parameters: left ventricular ejection fraction (LVEF), LV internal dimension, systole (LVIDs), peak oxygen consumption (peak VO_2), six-minute walk distance (6MWD), quality of life (QOL; Minnesota living with heart failure questionnaire) and NYHA class.
Results: At implant the study population consisted of 83% males, mean age 66 ± 10 years, NYHA II (33%), III (58%), IV (9%), mean LVEF 21±7%, mean QRS width 158 ± 28 ms. Baseline QRS significantly correlated with baseline LVEF, LVIDs, peak VO_2, 6MWD but not with QOL and NYHA Class.
Conclusions: Widening of the QRS is significantly associated with measures of heart failure severity including greater LV dimension, lower LVEF and reduced exercise tolerance but does not correlate with measures of symptomatic status. If these findings can be confirmed, then the degree of QRS prolongation in heart failure patients may serve as an inexpensive and reliable surrogate indicator of these measures of heart failure severity.

Variable	N	Correlation	P-value
LVEF at Baseline	500	-0.17	<0.01
LVIDs at Baseline	420	0.27	<0.01
Peak VO2 at Baseline	382	-0.11	0.03
6 MWD at Baseline	438	-0.12	0.02
QOL at Baseline	457	0.03	0.59
NYHA at Baseline	465	0.08	0.10

1163-123 Relationship Between Plasma C-Reactive Protein Concentration on Admission and Long-Term Outcome in Unselected Hospitalized Heart Failure Patients

Colin Berry, Karen Hogg, Karen Stevenson, John Norrie, John J. McMurray, University of Glasgow, Glasgow, United Kingdom

Background: Although systemic inflammation is recognised in heart failure (HF) its importance in relation to outcome is uncertain. Plasma c-reactive protein (pCRP) concentration is typically elevated in inflammatory conditions and is recognised as a marker of systemic inflammation.
Methods: We studied all index emergency admissions with HF to one University hospital (which provides exclusive acute medical care to the local urban district) during the year 2000. Echocardiography was undertaken by a single operator. Reduced LVSF was defined as an ejection fraction of <40%. Hematological and biochemical data (from the initial blood samples taken on the day of admission) were obtained from hospital electronic records. Information on death was obtained from the national record linkage database for all patients.
Results: 528 consecutive first admissions with HF were identified. The median follow-up was 693 days (range 1 - 978 days). Median (interquartile range) pCRP concentration was 16 (5, 183) mg/L, and 65% of patients had an elevated (> 10 mg/L) pCRP concentration. 45% and 35% of patients had a pCRP concentration greater than 20 and 30 mg/L, respectively. Univariate predictors of an elevated pCRP concentration included hemoglobin, hematocrit, white cell count (WCC), platelet count, serum creatinine concentration and plasma fibrinogen, sodium and albumin concentrations. On multivariate analysis, predictors (odds ratio, 95% CI) of pCRP concentration included WCC (1.9 [1.4, 2.9]), fibrinogen count (1.9 [1.3, 2.6]), and albumin (0.7 [0.5, 0.9]). pCRP concentration was an independent predictor of in-hospital survival (Cox proportional hazard ratio (HR) 0.2 per SD (61 mg/L); 95% CI 0.1,0.6, P=0.001), and long-term mortality (CRP per SD, HR 1.4; 95% CI 1.2 -1.7; P <0.001).
Conclusion: Systemic inflammation, indicated by an elevated pCRP concentration, is very common in hospitalized HF patients, and predicts long-term adverse outcome. That CRP is an independent predictor of mortality suggests that this protein may have harmful effects.

1163-124 Improvement in Autonomic Dysfunction Manifested by Altered Heart Rate Variability, T-Wave-Alternans and Norepinephrine by Long-Term Exercise in Chronic Heart Failure

Robert M. Nechwatal, Michael Horn, Uwe Scharf, Bettina Mochalski, Ulrike Lachenmeyer, Christiaan Barnard Klinik, Dahlen, Germany

Background: In recent years exercise training has become an established therapy for patients with stable chronic heart failure. However there is a paucity of data on the effects of long term training on autonomic dysfunction. Methods: 100 patients with DCM and CHD were randomized to an exercise (n=50, mean age:49,9+-9,3,mean ejection fraction (EF) 33,3+-5,7%)or to a control group (n=50, mean age:54,7+-11,3,EF: 32,4+-5,3%).Patients underwent six 20 minute supervised training sessions per week at a VO2 of 60% VO2peak. Before and after the six month study period exercise testing with respiratory gas exchange, heart rate variability in the time domain on holter monitoring, norepinephrine plasma values and T-wave alternans testing were performed. Results:See Table.VO2AT: oxygen uptake at the anaerobic threshold. *: p<0,05 **: p<0,01 vs pre-training.id: indeterminate. 10 patients in the exercise group and 2 in the control group did not complete the protocol: one of each group died unassociated with exercise, one of