However, the molecular mechanisms by which IBD predisposes some patients to cardiovascular diseases remain elusive.
Purpose: This project aims to identify epigenetic mechanisms by which experimental colitis epigenetically remodels adult heart to impair cardiac function.
Methods: To induce colonic inflammation in adult rats, we administered dextran sodium sulfate (DSS, 3% in drinking water) for 3 cycles of 7 days each, with intermittent 2-week intervals of normal drinking water. Seven days after the last cycle of DSS, echocardiography was performed to evaluate cardiac function and all animals were euthanised for tissue collection.
Results: Ultrasound revealed that left ventricular ejection fraction (LVEF) was significantly reduced after 3 cycles of DSS (77.9% vs 65.7%, $P<0.01$), whereas LV mass was markedly increased (107.1 vs 147.8, $P<0.05$). Serum B-type natriuretic peptide (BNP) was significantly upregulated by DSS (487 vs 221 pg/ml, $P<0.05$), suggesting that colitis impedes heart function. To assess epigenetic remodelling, total RNA was extracted from individual heart and miRNA arrays were performed. We found that 30 miRNAs, including miR-423-5p, a potential biomarker for heart failure, were significantly elevated, whereas 38 miRNAs were significantly downregulated. Real-time PCR analyses confirmed the elevation of miR-1-3p, let-7d-3p, and miR-423-5p by DSS colitis. Since miR-1-3p targets brain-derived neurotrophic factor (BDNF), which regulates cardiac contraction force and protects against cardiac dysfunction, we evaluated BDNF levels. Serum BDNF was significantly decreased in animals receiving DSS (96.5 vs 5.7 pg/ml, $P<0.05$). BDNF mRNA levels were also significantly downregulated in the heart by DSS colitis ($P<0.05$), suggesting that epigenetic downregulation of BDNF may contribute to cardiac impairment. To determine the role of BDNF in regulating cardiac function, we created a cardiac-specific conditional BDNF knockout mouse line. Cardiac function and disease susceptibility to DSS are being evaluated. We also carried out an intervention study with aspirin in this DSS rat model. Supplementation of aspirin in drinking water (0.01%) ameliorated the decreases of LVEF and serum BDNF as well as the increases of LV mass, miR-1-3p, and serum BNP in DSS-treated animals.
Conclusions: Chronic colitis causes epigenetic remodelling, including marked changes in miRNA expression profiles, in adult heart. We are now pursuing the in-depth mechanisms by which epigenetic modifications contribute to cardiac impairment, via the repression of BDNF.
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BIOMARKERS

P4759
Myocardial fibrosis is reflected by two novel biomarkers of collagen formation in patients with cirrhosis: results from a prospective study with advanced cardiac MRI

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Background and aims: Cardiac dysfunction is often seen in patients with advanced cirrhosis. Diffuse myocardial fibrosis (DMF) seems to play an important role in the underlying pathophysiology of cirrhotic cardiomyopathy. Thus, the myocardial extracellular volume (ECV), which reflects the degree of myocardial fibrosis as assessed by cardiac MRI seems to be increased in cirrhosis and associated with liver and cardiac dysfunction. Upregulation of collagen production and deposition in the heart is the main feature of DMF. Elevated biomarkers of collagen formation indicate an ongoing process of fibrogenesis. PRO-C3 has previously proven to be a marker of hepatic fibrosis in patients with different liver diseases and PRO-C6 has been associated with adverse outcomes in kidney failure. Our aim was therefore to evaluate the association between presence of DMF as assessed by cardiac MRI with ECV quantification and circulating levels of two novel biomarkers of collagen type III and type VI formation.
Methods: Sixty-three stable cirrhotic patients underwent a cardiac MRI with ECV quantification, ECG including QTc interval, clinical and biochemical assessments. Formation of collagen type III and type VI was assessed in serum by means of enzyme-linked immunosorbent assays (PRO-C3 and PRO-C6, respectively), measuring the concentration of the pro-peptides of the two collagens, which are cleaved and released in circulation during maturation of newly synthesized collagen molecules.
Results: PRO-C3 and PRO-C6 were increased in serum of the investigated patients in comparison to the assay normal range (mean (2.5–97.5 percentile) PRO-C3: 54.3 (11.2–147.2) vs. 12.1 (6.7–22.2) ng/ml, $p<0.0001$ and mean (2.5–97.5 percentile) PRO-C6: 14.5 (5.1–34.7) vs. 8.0 (4.9–12.2) ng/ml, $p<0.0001$). Moreover, there was a positive correlation of both markers to ECV (PRO-C3: r=0.33 p=0.016; PRO-C6: r=0.39 p=0.005) and QTc (PRO-C3: r=0.314, p=0.016; PRO-C6: r=0.343, p=0.008). When dividing the patients in two groups according to the median myocardial ECV level (31%), levels of both markers were significantly more elevated in patients in the high ECV group (PRO-C3 p=0.031; PRO-C6 p=0.003).
Conclusion: In stable cirrhotic patients, PRO-C3 and PRO-C6 are associated with increased myocardial ECV, which reflects DMF. In addition, the association of the biomarkers to the prolonged QTc interval suggests that increased cardiac fibrosis is involved in the electrophysiological abnormalities in cirrhosis. The novel biomarkers of collagen formation may therefore be valuable in the investigation of presence and pathophysiology of cardiac dysfunction in cirrhosis.

P4760
Age-related changes in the biomechanics of left ventricular twist are associated with accumulation of advanced glycation end-products and replicative senescence

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Introduction: The biomechanics of contraction changes with advancing age both in diastole and in systole. Such changes contribute to the development of heart failure with a preserved ejection fraction in the elderly. Left ventricular (LV) twist is the circumferential motion of the apex with respect to the base of the heart and has an important role in LV ejection and filling. We examined the biomechanics of age-related changes in LV twist by determining a broad spectrum of LV rotation parameters in different age groups, using speckle tracking echocardiography (STE). Formation glucose-dependent cross-links of collagen, termed advanced glycation end products (AGEs) can accumulate with age and increase myocardial stiffness. The purpose of this study was to investigate the changes in LV twist in relation with glycation and a marker of replicative senescence such as telomere length.
Methods: 2-D speckle tracking analysis was performed on 194 healthy non-obese volunteers aged 40 to 88 years without history of cardiovascular disease, diabetes, regular use of medication and significant deviations by 12-lead electrocardiogram. LV rotation parameters, systolic twist were measured using off-line analysis program QLAB (Advanced Ultrasound Quantification Software Release 8.1.2 (Philips). In 29 subjects (15%) image quality was insufficient for STE analysis. Methylglyoxal (MG) is a byproduct of glucose metabolism and an inducer of AGEs. Concentration of MG in serum was determined using HPLC with UV detector. Telomere length was measured in leukocyte (LTL) by real-time quantitative polymerase chain reaction.
Results: The subjects were 68.04±6.57 years old, 36% were men. With increasing age, apical rotation ($P<0.05$), time to apical rotation ($P<0.05$) and twist ($P<0.001$) increased, whereas basal rotation ($P<0.01$), time to basal rotation ($P<0.01$), and rotational deformation delay (defined as the difference of time to basal rotation and apical rotation) ($P<0.05$) decreased. LTL was associated with age (β=-0.026, P=0.015), LV systolic twist (r=-0.761, P=0.03) and apical rotation (r=-0.690, P=0.002). MG was related with age (r=0.866, $p<0.001$). In multivariate regression MG was associated with LV twist (β=0.518, P=0.03), apical (β=0.128, P=0.005) and basal (β=-0.136, P=0.001) rotation. Increased MG was observed in 85% of people with increased LV twist and apical rotation, and in 78% of people with decreased basal rotation. Older subjects with higher MG and shorter telomeres length had more pronounced changes in the biomechanics of LV twist.
Conclusions: Our findings suggest that age-related increase of LV twist, apical rotation and decrease of basal rotation are associated with accumulation AGEs, significant contributing factors in heart aging. Changes in these parameters of STE are related to marker of replicative senescence – shortening of telomere length.

P4761
Genetic risk variants for heart failure onset and progression do not improve prediction of mortality beyond established prognostic neurohormonal and echocardiographic markers

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Background: Genome-wide association studies and candidate gene studies have identified genetic risk variants associated with the onset and progression of heart failure.
Purpose: This study aimed to investigate whether genetic risk variants for heart failure onset and progression can improve prediction of mortality in heart failure patients, beyond established prognostic markers.
Methods: We genotyped 11 genetic variants identified from genome-wide association or candidate gene studies in two independent heart failure cohorts and investigated associations with neurohormone levels, echocardiographic indices and survival (discovery cohort, recruited from 1997–2000, 4 years follow-up, n=451; validation cohort, recruited from 2010–2014, median 2.6 years follow-up, n=900). Genotyping was performed for variants located at 1p36, 3p22, 10q22, 10q26, 15q13, 20p12 and within 3 genes of the renin-angiotensin system. To investigate a potential mechanism through which these variants may influence heart failure onset or progression, we tested associations between each variant and levels of gene expression in the left ventricle using Affymetrix microarrays, in 106 heart transplant patients and 108 heart donors with no history of cardiovascular disease.
Results: In the discovery cohort, we found that variants located at 3p22