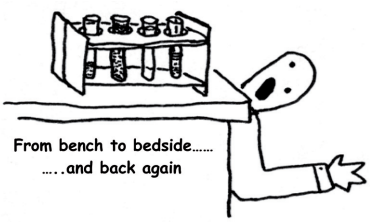


NCS Winter meeting Research Symposium, Jan 30th 2009

Abstracts

Mitral regurgitation quantified by three-dimensional (3D) echocardiography- a comparison with Magnetic Resonance Imaging (MR).

Thomas R. Skaug, Torbjørn Hergum, Brage H. Amundsen, Hans Torp, Bjørn Olav Haugen. Dept. of Circulation and Medical Imaging, NTNU.

Purpose

To calculate the Vena Contracta Area (VCA) and quantify mitral regurgitation by MULDO (MULtibeam hprf Doppler) and compare it with MR.

Methods

We isolated the Doppler signal from the mitral jet using MULDO. The Nyquist limit was near the peak velocity of the jet. The power of the Doppler signal is proportional to the amount of blood in the sample volume. The VCA was found by summing the Doppler power from multiple beams within the vena contracta region and compensating for the attenuation and geometry by a reference beam within the jet. The regurgitant volume (MULDO-RV) was calculated as the product of VCA and the VTI of the regurgitant jet by CW Doppler. The regurgitant volume by MR (MR-RV) was calculated as the difference between left ventricular stroke volume and ascending aortic stroke volume.

Materials

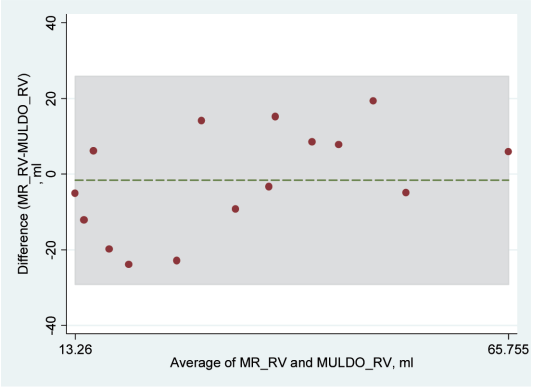
In 21 patients with mitral regurgitation grade 1 to 4, six patients with mild regurgitations were excluded due to artefacts and poor MULDO results.

Results

The VCA was measured from 12 to 52 mm^2, MULDO-RV 12,4 to 62,8 ml (mean 33,9 ml) and MR-RV 7,5 to 68,7 ml (mean 32,3 ml). There was moderate correlation (R=0,63) between VCA and MR-RV. R between MULDO-RV and MR-RV was 0,73. Also see the BA Plot.

Conclusion

There is an expected overestimation of mild regurgitations, and it can be difficult to place the Region of Interest correctly. There is moderate agreement between MULDO-RV and MR-RV after exclusion of poor MULDO results.



Septal placement of RV electrodes - a single center experience

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Background

Traditionally, ventricular pacing has been achieved by right ventricular apical pacing (RVAP). However several studies have shown an increased incidence of atrial fibrillation, heart failure and death. This has given interest to alternative pacing sites. Most studied is pacing from the right ventricular outflow tract (RVOT). Compared to the inverted vector of RVAP, RVOT pacing gives a depolarization that imitates the normal one. Consideration has been made concerning the stability and function of RVOT-leads.

Methods

In our institution RVOT as preferred pacing site has been used since January 2005 . In this study we analysed the safety and electrical measurements at implant and at 3 months follow-up in the ICD-population of 162 patients with RVOT-leads.

Results

There has been no dislocation, perforation or need for revision of any leads. The lead measurements at implant and 3 months FU has been for the intrinsic cardiac signal (R-wave) 10.7 ± 5 mV and 11.4 ± 4.8 mV, for the impedance 716 ± 172 ohms and 532 ± 110 ohms and for the threshold 0.8 ± 0.3 V and 0.7 ± 0.3 V at 0.4 ms.

In 130 ICD-implantations the initial defibrillation-threshold-testing has been carried out successfully with a 10-16 Joule safety-margin. In one patient reversing of the shocking polarity and in another patient deactivation of the SVC-coil was required to obtain an adequate safety-margin.

Conclusion

In our population of ICD-patients placement of the ventricular lead in the RVOT seems to be a safe alternative with adequate sensing-, pacing- and defibrillation threshold.

Pathological Motion of the Inter-ventricular Septum in Left Bundle-Branch Block; Electromechanical or Reversal of the Trans-septal Pressure Gradient?

Ola Gjesdal, Espen W. Remme, Anders Opdahl, Helge Skulstad, Kristoffer Russell, Erik Kongsgard, Otto A. Smiseth, Thor Edvardsen

Objective

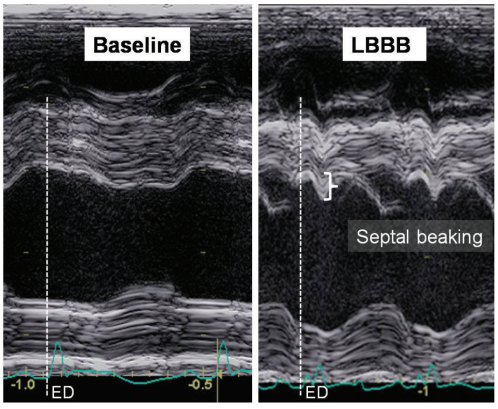
Septal beaking (SB) is seen in LBBB as abrupt leftward pre-ejection displacement of septum followed by paradoxical rightward motion during early ejection, and has been suggested as predictor of successful CRT-treatment. It has been attributed to end-diastolic reversal of the LV-to-RV transseptal pressure gradient (TSG), but can also be explained by early septal contraction unopposed by the later activated lateral wall. Our study aimed to investigate the role of these potential mechanisms.

Methods

In 8 anesthetized dogs with LV and RV micromanometers we measured myocardial segment-lengths by sonomicrometry or M-mode echocardiography, and intra-myocardial bipolar ECG. LBBB was induced by RF-ablation and load was changed by caval- (CC) and aortic constriction (AC). SB was quantified as percent shortening of end-diastolic septal-to-lateral diameter.

Results

Induction of LBBB increased QRS duration from 72±2 to 122±2 ms (±SEM, $p<0.01$). SB became distinct during LBBB and was associated with early-systolic stretching in the lateral wall. AC and CC significantly altered ventricular pressures and TSG; reduction in TSG was associated with increasing SB, but SB was present in LBBB even in the presence of high TSG. LV pressure-dimension loops revealed shortening against rising LV pressure during SB, with counterclockwise rotation of the pressure-dimension coordinates.



Conclusion

Induction of LBBB resulted in SB. SB reflects active contraction of early activated myocardium in the septum. Reduction and reversal of TSG may contribute to SB by causing a left-ward septal shift. Therefore, active myocardial contraction and passive septal displacement appear to contribute to SB.

Chromogranin B: a novel myocardium-regulated biomarker in experimental and clinical heart failure

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Background

Chromogranin B (CgB) has recently been found closely associated with myocardial hypertrophy *in vitro*. However, whether CgB is upregulated in experimental and clinical heart failure (HF) is currently unknown.

Methods

In a post-myocardial infarction (MI) HF mouse model animals were evaluated by echocardiography before being sacrificed one week post-MI. CgB protein levels in different organs were evaluated by Western blotting (WB) and radioimmunoassay (RIA). Circulating CgB levels were measured with the same RIA as used for evaluating tissue protein levels. In clinical HF 80 patients recruited mainly from an ambulatory HF clinic were compared to 20 age- and gender-matched control subjects.

Results

Myocardial CgB protein levels were markedly increased in the non-infarcted part of the LV in HF animals (WB: 110 %, p= 0.005, RIA: 37 %, p< 0.001). CgB correlated closely with animal lung weight (r= 0.76, p< 0.001) and LV mass (r= 0.69, p= 0.001). In contrast, CgB levels did not increase in other tissues investigated. Circulating CgB levels were also increased in HF animals (HF animals vs. sham: 1.44 ± 0.12 vs. 1.02 ± 0.07 nmol/L, p= 0.003) and in patients with established HF of mainly moderate severity (HF patients vs. control: 1.69 ± 0.03 vs. 1.52 ± 0.05 nmol/L, p=0.007).

Conclusion

CgB is identified as a new myocardium-regulated protein during HF development and may potentially be an interesting novel cardiovascular biomarker.

Tnf-alpha antagonists improve arterial stiffness in patients with rheumatoid arthritis and related arthropathies

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Objective

It has been suggested that the chronic inflammatory state of rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) contributes to accelerated atherosclerosis. The aim of this study was to evaluate the effect of treatment with TNF-α antagonists on arterial stiffness in patients with RA, AS and PsA.

Methods

35 patients (RA=17, AS=12 and PsA=6) who started with anti-TNF-α therapy (adalimumab=16, etanercept=13, infliximab=6) and a non-treatment group of 25 patients (RA=12, AS=9 and PsA=4) underwent measurements of aortic Pulse Wave Velocity (aPWV) and Augmentation Index (AIx) at baseline and after 3 months (Sphygmocor). Patients in the non-treatment group had the same

indications for anti-TNF-α therapy, but had to postpone their initiation due to positive Mantoux-test or planned operations.

Results

Patients who started anti-TNF-α therapy had a significant decrease in aPWV (-0.50 m/s) whereas the patients in the control group had no change (+0.05 m/s, p=0.002 for between group changes). Between group differences for AIx were not observed (change +0.1% and -0.44%, p=0.48). As expected, a significant reduction in CRP and DAS28 for the RA patients was observed in the treatment group, but we did not find significant correlations between change in aPWV and CRP in the entire treatment group (r=0.13, p=0.43) and between change in aPWV and DAS28 in the RA group (r=-0.15, p=0.60).

Conclusion

These findings indicate that anti-TNF-α therapy improves functional parameters of early atherosclerosis in patients with RA, AS and PsA.

Exercise training induces left ventricle hypertrophy in MLP$^{-/-}$ mice

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Objectives

Maximal oxygen uptake (VO_{2max}) is closely linked to cardiomyocyte contractile function and stroke volume. Regular physical activity is known to improve cardiac function and stroke volume. Mice with a congenital knockout for muscle LIM protein (MLP$^{-/-}$), is a well known model of cardiac dysfunction and reduced contractility. Our working hypothesis was that the response to exercise training is altered in MLP$^{-/-}$ mice.

Methods

33 mice were included. Wildtype (WT) mice served as controls. An eight-week high-intensity training program included 8 min intervals at 85-90% of VO_{2max}, interspersed with 2 min at moderated intensity, 1 hour, 5 days a week. Animals were either subjected to training or remained sedentary. Echocardiography was performed before and after training program. VO_{2max} and maximum running speed (RS) were measured weekly. Postmortal analysis included histology and proteinexpression.

Results

VO_{2max} and RS increased in both trained MLP$^{-/-}$ and WT mice during the program. WT increased VO_{2max} by 33%, and RS by 55%, and MLP$^{-/-}$ by 8% and 32% respectively.

Heartweight increased in MLP$^{-/-}$ (P=0.025), and heartweight/tibialength by 11% in MLP$^{-/-}$ (P<0.05), independent of training. Training increased left ventricle mass in both MLP$^{-/-}$ and WT (P<0.05). Echocardiography showed increased anterior and posterior wall thicknesses in trained MLP$^{-/-}$ (P<0.05), compared to sedentary mice. No changes in left ventricle dimensions were recorded in control mice.

Conclusions

MLP$^{-/-}$ mice shows reduced increase in VO_{2max} compared to WT controls after eight weeks of training. Anterior and posterior wall thicknesses increased by training in MLP$^{-/-}$ mice. However, cardiac dysfunction could not be demonstrated.

A black cat crossing your path signifies that the animal is going somewhere.
Groucho Marx

Training effects on skeletal muscle calcium handling in chronic heart failure (CHF) patients and controls

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Background

CHF patients typically complain about increased skeletal muscle fatigability. We have previously reported that in contrast to normal muscle, reduced intracellular calcium release was not related to fatigue development in CHF rats and hypothesize that training might affect intracellular calcium cycling differently in muscles from patients with CHF as compared with healthy controls (HS).

Methods

Before and after six weeks of one legged knee extensor training biopsies were taken from vastus lateralis bilaterally and analyzed both for Ca^{2+} handling proteins and the capability of sarcoplasmic reticulum (SR) vesicles to take up, retain and release calcium.

Results

Peak power of the trained leg was 14 and 10% greater than in the untrained leg in CHF and HS respectively. For the HS group training resulted in a higher Ca^{2+} release rate and lower leak in the trained leg associated with a tendency of increased RyR content with reduced phosphorylation level. In the CHF patients Ca^{2+} uptake rate was higher in the untrained leg but Serca levels were unchanged and ser16 phosphorylation of the PLB monomer paradoxically reduced. In the trained leg of CHF patients RyR content was reduced without associated changes of either Ca^{2+} leak or release rate.

Conclusions

Training in HS has effect on SR Ca^{2+} leak and release, but in CHF patients training is achieved without such changes. Thus, calcium handling seems not to be the site of increased fatigability in CHF.

High-Intensity Interval Training May Reduce in Stent Restenosis Following Percutaneous Coronary Intervention with Stent Implantation

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Aims

The objective of this study was to evaluate the effect of regular high-intensity interval training on in-stent restenosis following percutaneous coronary intervention (PCI) for stable or unstable angina.

Methods and Results

We prospectively randomized 40 patients after PCI with implantation of a bare metal stent (n=30) or drug eluting stent (n=32) to a 6 months supervised high-intensity interval exercise training program (n=20) or to a control group (n=20). At six months restenosis, measured as in-segment late luminal loss of the stented coronary area was smaller in the training group (0.21±0.39 mm) compared to the control group (0.55±0.41 mm, p=0.01). Reduction of late luminal loss in the training group was consistent with both stent types. Peak oxygen uptake increased in the training and control group by 17.6% and 0.5%, respectively (p<0.01). Flow-mediated dilation improved 6.5% in the training group and 0.3% in the control group (p=0.01).

Conclusions

Regular high-intensity interval exercise training was associated with a significant reduction in late luminal loss in the stented coronary segment independent of stent type implanted. This effect was associated with increased aerobic capacity and improved endothelium dependent vasodilation.

Reverse Remodeling of the Left Ventricle during the Early Phase after Relief of Pressure Overload in a Mouse Model

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Background

Due to pressure overload, aortic stenosis (AS) induces concentric myocardial remodeling with hypertrophy, fibrosis and reduced cardiac function. Aortic valve replacement (AVR) is the treatment for AS. Patients with excessive remodeling carry a particular operative risk. AVR leads to reverse remodeling, with regression of hypertrophy and fibrosis. The mechanisms regulating reverse remodeling remain unknown.

Aim

To study reverse remodeling after relief of pressure overload in a mouse model of aortic banding-debanding.

3Materials & Methods

We have established a novel banding-debanding model in mice. Myocardial gene expression was examined using Affymetrix microarray 4 weeks following aortic banding and 3 days after debanding. Regulation of functional gene groups was assessed using the topGO software.

Results

Aortic banding increased left ventricular weight by 44 %, with reduction to sham level by 14 days after debanding. The gene ontology group: "extracellular matrix structural constituent" and in particular the collagen genes were most significantly regulated following debanding. These genes were up-regulated after aortic banding and reduced back to sham levels 3 days after debanding. Myocardial collagen content was 2.3-fold increased after banding, but remained 1.6-fold and 1.7-fold increased at 3 and 7 days following debanding. We were not able to identify any possible active mediators regulating reverse remodeling. However, it seems that the balance between pro- and anti-remodeling factors is shifted in favour of anti-remodeling factors following debanding.

Conclusion

Even though regression of extracellular matrix gene expression was the most significant alteration, collagen protein content remained increased. We could not identify any potential active mediators regulating reverse remodeling.

BNP and CNP increase cGMP in different functional compartments in failing hearts

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Background

Natriuretic peptides (NPs) are used as biomarkers in heart failure (HF) as they increase with severity of disease. Furthermore, NPs have direct cardiac effects through NPR-A (BNP, ANP) and NPR-B (CNP) receptors. Thus, nesiritide (recombinant BNP) is used in the treatment of acute decompensated HF. CNP elicits a negative inotropic response through cGMP and protein kinase G (PKG), but the role of CNP in HF is incompletely understood.

Methods & Results

In this study we address the role of phosphodiesterase (PDE) 2, 3 and 5 in the regulation of the negative inotropic response to CNP and BNP in left ventricle from Wistar rats with HF. In a concentration-dependent manner, CNP and BNP both increased cGMP levels, but only CNP caused

a negative inotropic response. This response was reduced by the cGMP antagonist Rp-8-Br-PET-cGMP (3μM), demonstrating PKG involvement. The presence of a PDE3- (1μM cilostamide) or a PDE5-inhibitor (0.1μM sildenafil) caused only a marginal cGMP increase to CNP, whereas a PDE2-inhibitor (10μM EHNA) caused a large cGMP increase to CNP in cardiomyocytes. Despite this, only PDE3-inhibition caused an increased negative inotropic response to CNP. A negative inotropic response to BNP (300nM) was not revealed even in the presence of combined PDE2, 3 and 5-inhibition.

Conclusion

cGMP signalling is compartmentalized in the failing heart. In contrast to NPR-A signalling, NPR-B mediates phosphorylation of proteins involved in Ca^{2+}-handling and contraction. This indicates different roles of BNP and CNP in the pathophysiology of HF.

Levosimendan exerts its inotropic effect mainly or exclusively by inhibition of PDE3

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Background & Aim

Levosimendan is a novel inotropic drug used in the treatment of decompensated heart failure, and elicits inotropic responses by two mechanisms; calcium-sensitization and phosphodiesterase (PDE) 3 inhibition. Characterizing the relative importance of these two mechanisms with respect to contractility is relevant, as agents that elevate cAMP levels, such as milrinone and dobutamine, increase mortality in long-term treatment of HF patients. Thus the aim of the study was to single out each component and to characterize their relative importance in generating a positive inotropic response.

Methods & Results

Concentration-response curves of levosimendan on failing human ventricular strips, revealed a positive inotropic response, with a maximum increase of 26% above control at 10^{-5} M levosimendan. In addition, lusitropic effects were elicited, a typical finding for PDE3 inhibition accentuating the cAMP-PKA-pathway In the presence of the PDE3 inhibitor cilostamide, added in advance, the positive inotropic effect of levosimendan was nearly abolished, indicative of the importance of the PDE3-inhibitory component of levosimendan in generating a positive inotropic response.

Further experiments on the beta-adrenergic system in human and rat ventricular strips showed that levosimendan caused a significant shift of the concentration-response curve of isoproterenol to lower concentrations of agonist in the same way as cilostamide. In experiments done in the presence of cilostamide, levosimendan failed to cause a further shift to lower concentrations of isoproterenol. Thus, the main component responsible for the shift is the PDE3 inhibition by levosimendan.

Conclusion

The results demonstrate a dominating PDE-inhibitory mechanism of levosimendan with respect to increased contractility.

Long term results after intracoronary injection of autologous mononuclear bone marrow cells in acute myocardial infarction. The ASTAMI study

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Background

In the ASTAMI study, patients with acute anterior wall STEMI successfully reperfused with acute PCI on LAD, were randomized to intracoronary injection of autologous mononuclear bone marrow cells (mBMC, n=50) or control

(n=50). No significant effects on LV volumes, EF or infarct size were found by SPECT, MRI or echocardiography after 6 months. We performed a 3 year follow-up to ensure safety and evaluate long term effects of this new treatment modality.

Methods

Patients were re-assessed 3 years after randomization. Adverse events, clinical status and the SF-36 quality of life survey were recorded. MRI, echocardiography, exercise testing and blood biochemistry analyses were performed.

Results

Clinical outcome was for mortality (number of patients, mBMC:control) 1:1, recurrent AMI 1:2, hospitalization for heart failure 2:1, revascularizations 14:12, severe arrhythmias 2:1 and stroke 1:1. NYHA- (p=0.89) and CCS- scores (p=0.16) did not differ. On repeated echocardiography, the groups had similar changes in LVEDV (p=0.39), LVEF (p=0.87) and WMSI (p=0.48). On MRI, change in LVEF (p=0.18), LVEDV (p=0.60) and infarct size (p=0,37) did not differ. Infarct size decreased significantly in both groups. Exercise capacity and quality of life improved to a similar extent in both groups. Blood biochemistry, including pro-BNP (median [interquartile range]): 23.5 [11-46] vs. 23 [12-34], p=0.96, revealed no differences.

Conclusion

Intracoronary mBMC therapy in acute MI appears safe, but has no significant beneficial effect on the predefined endpoints during 3 years follow-up when compared to best medical treatment.

Recombinant CTGF causes preemptive conditioning of the heart towards ischemia/ reperfusion injury

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Background & aim

Previous studies from our laboratory have shown that hearts from transgenic mice with cardiac-restricted overexpression of CTGF have increased tolerance towards ischemia-reperfusion injury. The purpose of this study was to investigate to what extent recombinant CTGF elicits preemptive conditioning of the heart and activation of protective signalling mechanisms.

Methods

Secreted recombinant human CTGF were purified from media of transfected HEK293 cells by sequential heparin-Sepharose and S-Sepharose chromatography.

Mouse hearts were subjected to Langendorff-perfusion *ex vivo* using constant perfusion pressure. Heart rate, coronary flow, and left ventricular developed pressure were recorded. 10 min prior to ischemia, CTGF were added to the perfusion solution. The hearts were perfused for 10 min with Krebs-Henseleit containing 75 nmol/L CTGF. After 40 min of no-flow ischemia, perfusion was resumed for 1 hour in Krebs-Henseleit without CTGF. Primary cultures of adult mouse cardiac myocytes were prepared by retrograde perfusion with collagenase.

Results

Hearts that received CTGF recovered faster during reperfusion, generated significantly higher LV developed pressure and acquired smaller infarct size than control hearts (26±4% vs. 39±3% of left ventricular transverse sectional area in CTGF-perfused hearts vs. control hearts, respectively; mean±SEM of n=8 in each group; $P<0.05$). CTGF caused phosphorylation of the AKT/GSK-3β salvage pathway with ensuing inhibition of GSK-3β.

Conclusions

Recombinant CTGF recapitulates the findings from transgenic mice with cardiac-restricted overexpression of CTGF and provides evidence for a direct cardioprotective effect of CTGF on cardiac myocytes.

Het-potet-loven

Jo mer presserende det er å få tatt en beslutning, desto større er sjansen for at det nedsettes en hurtigarbeidende komité som bruker år på å avgi innstilling

Circulating cytokine levels heart failure are etiology-dependent

Vistnes M[1,2], Wæhre A[1,2], Sjaastad I[1,2,3], Nygård S[1,2,4], Andersson K B[1,2], Husberg C[1,2], Christensen G[1,2]. [1]Institute for Experimental Medical Research, Ullevål University Hospital, Oslo, Norway, [2]Center for Heart Failure Research, University of Oslo, Norway, [3]Department of Cardiology, Ullevål University Hospital, Oslo, Norway, [4]Department of Mathematics, University of Oslo, Norway

Background

Heart failure (HF) is associated with altered levels of circulating cytokines, but the use of cytokines as diagnostic and prognostic biomarkers or therapeutic targets is not applicable today. The purpose of this study was to examine whether circulating cytokine levels vary depending on the etiology and type of HF.

Methods

The serum levels of 25 cytokines were quantified in four experimental murine models of heart disease; banding of the ascending aorta (AB) or the pulmonary artery (PB), myocardial infarction (MI) and a cardiomyopathy model with inducible cardiomyocyte-specific knockout of the sarco(endo) plasmatic reticulum Ca^{2+}-ATPase (SERCA2 KO). The mice were classified with or without HF based on echocardiographic criteria and necropsy measurements. Circulating cytokines were quantified by Luminex technology or ELISA in serum samples obtained after one week of AB, PB and MI, and at four or seven weeks after induced SERCA2 excision.

Results

In AB mice, no increases in cytokine levels were found. Only IL-18 showed increased level in MI mice. Several cytokines showed decreased levels in HF following AB and MI. On the other hand, in mice with right ventricular overload following PB or SERCA2 KO there were extensive alterations with increased levels of several cytokines.

Conclusions

Our findings show that circulating levels of cytokines are highly dependent on the etiology of the HF. Increased serum levels of cytokines were found almost excludingly in the models with increased right ventricular afterload, indicating that systemic congestion gives rise to increased levels of cytokines in the circulation.

Increased production of CXCL16 in experimental and clinical heart failure; a possible role in extracellular matrix remodeling

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Background

Although both experimental and clinical studies indicate a role for inflammation in the development of myocardial failure, knowledge about the production and functional role of the different inflammatory actors in heart failure (HF) remains incomplete. Based on its combined role in inflammation and vascular remodeling, we hypothesized a role for CXCL16 in the pathogenesis of HF.

Methods and Results

Our main findings were: (i) Patients with chronic HF (n=188) had significantly raised plasma levels of CXCL16 as compared with healthy controls (n=20), that significantly correlated with the degree of disease severity. (ii) Left ventricular (LV) tissue from patients with severe HF (n=8) showed enhanced production of CXCL16 compared to non-failing LV (n=6) as assessed by Western blotting. (iii) In mice exposed to pressure overload we found enhanced CXCL16 mRNA levels in the LV, with particularly high levels in those with decompensated hypertrophy. In mice with post-myocardial infarction (post-MI) HF, expression of CXCL16 was increased both in the infarcted and the non-infarcted areas of LV 3 and 7 days after coronary ligation, indicating early onset of increased CXCL16 production. The increase in CXCL16 in the tissue at 7 days post-MI was associated with increased CXCL16 levels both in cardiomyocytes and in non-cardiomyocytes (i.e., endothelial cells and fibroblasts). (iv) *In vitro* experiments showed that CXCL16 induces enhanced protein synthesis in neonatal rat cardiomyocytes, and promotes proliferation and matrix metalloproteinase (MMP) activity in myocardial fibroblasts accompanied by a significant increase in gelatinolytic activity. Furthermore, CXCL16 induced increased MMP activity in cardiomyocytes, primarily reflecting increased MMP-2 levels. (v) Using specific inhibitors in cell experiments, we showed that the effect of CXCL16 on fibroblasts involved activation of the c-Jun N-terminal kinases.

Conclusion

We demonstrate enhanced myocardial expression of CXCL16 in both experimental and clinical HF. The combined effect of CXCL16 on cardiomyocytes and myocardial fibroblasts suggest a role for CXCL16 in extracellular matrix remodeling and ultimately also in the development of HF.