Metalloproteinase Inhibition Prevents Diastolic Stiffening, AMP-Breakdown, and Oxyypurine Accumulation in Accelerated Heart Failure

Nazzareno Paolocci, Barbara Tavazzi, Roberto Biondi, Yehezkel A. Gluzband, Mariangela Amorini, Carlo G. Tocchetti, Sonia Donzelli, Michael T. Crow, Giuseppe Lazzarino, David A. Kass, Johns Hopkins Medical Institutions, Baltimore, MD, University of Catania, Catania, Italy

Background: Recent studies indicated increased plasma oxyppurine (hypoxanthine/xanthine/uric acid) levels as an independent risk factor for worsened heart failure, suggesting oxyppurine output role for diastolic dysfunction.

Methods: We used a canine model of enhanced diastolic failure (1 week AII infusion + subacute tachypacing; 250 bpm for 48 hrs; AII+P), displaying pronounced diastolic stiffening and markedly elevated cardiac MMP activity. MMP inhibition (MMPI) prevents diastolic stiffening, without influencing collagen content subtype or cross-linking. Here we tested whether MMPI + P (n=7) enhances AMP catabolism to increase cardiac nucleoside/ oxyppurine and diastolic stiffening, assessing the ability of MMPI to prevent these changes.

Results: All+P raised diastolic chamber stiffness and end-diastolic pressure ~100% and markedly activated gelatinases MMP-9 and MMP-2 (and in situ assays). With All+P, ATP declined while AMP catabolites increased: nucleotides (inosine, adenosine) raised from 254±84 to 1700±363 nmol/g (p<0.005), and oxyppurines from 1000±20 to 66±7 67 nmol/g (p<0.001). MMP inhibition (PD-166730, 5 mg/kg/day; n=9) prevented diastolic stiffening as well as MMP-9 and -2 activation, and countered the rise in both nucleotides (804±35 to 39±0.02 All+P) and oxyppurines (597±27, p<0.01 vs All+P; MMPI directly inhibited in vitro AMP deaminase activity in a dose-dependent manner but did not affect other steps of the purine catabolism cascade. In All+P hearts hallmarksa of oxidative stress were evident: malondialdehyde (lipid peroxidation index) raised from 0.31±0.1 (controls) to 6.7±2.3 mmol/g (p=0.01) while antioxidant levels (ascorbate and reduced glutathione) significantly declined. However, MMPI did not mitigate All+P-induced oxidative stress (MDA = 6.1±1.3).

Conclusions: Diastolic stiffening is associated with a rise in myocardial content of AMP-breakdown byproducts (i.e. nucleotides and oxyppurines). MMP inhibition fully prevents diastolic stiffening by limiting this accumulation, directly interfering with AMP catabolic activities (i.e. AMP deaminase), independently from the extent of cardiac oxidative stress.

Survival, Differentiation, and Contractility of Immature Cardiac Cells Implanted Into the Outer Wall of Aorta in Rats as a Step in the Development of an Auxiliary Circulatory Pump

Wangye Dai, Sharon Hale, Robert A. Kloner, The Heart Institute, Good Samaritan Hospital, University of Southern California, Los Angeles, CA

Purpose: We proposed to build an auxiliary circulatory pump by implanting neonatal cardiac cells into the wall of aorta in rats. As a first step, we investigated the survival, differentiation, and contractility of immature cardiac cells implanted into the wall of the abdominal aorta.

Methods: Cardiomyocytes from neonatal Fischer rats (both sexes) were injected into the outer wall of the abdominal aorta at a site 3 mm above the take-off of the renal arteries in female Fischer rats. Rats were injected on day 16 from the day of birth. The volume of injection was 2-4 μL. Confocal microscopy identified three steps: (1) medium only (n=22); (2) neonatal cardiomyocytes (n=22), 5×10^5 cells each. At 2 or 6 weeks, the graft site on the aorta was exposed and fixed for histological and immunohistochemical examination.

Results: At 2 weeks after transplantation, 7 out of 10 aortas in the cell group, but none of 10 in the medium only group (2-4 μL), displayed multinucleate cells similar to those previously described as myotubes. As a second step, we performed flow cytometry to assess the cell renewal potential for myotubes and myocytes. The FSA negative fraction was assessed for cells expressing markers of cardiac differentiation using flow cytometry and confocal microscopy as well as for stem cell markers and the cell cycle antigen Ki-67.

Conclusion: Recent studies indicated increased plasma oxyppurine (hypoxanthine/xanthine/uric acid) levels as an independent risk factor for worsened heart failure, suggesting oxyppurine output role for diastolic dysfunction.

872-1 Reverse Remodeling With Cardiac Resynchronization Therapy Varies With Infarct Location: Analysis of Echocardiographic Data From the MIRACLE Trial

Martin St. John Sutton, Tad Flapped, Thomas J. Mullen, Kathryn Hilipsich, Edward Chinchky, University of Pennsylvania Medical Center, Philadelphia, PA, Medtronic, Inc, Minneapolis, MN

Reverse remodeling has been reported in moderate to severe heart failure (HF) patients (pts) with ventricular dysynchrony after cardiac resynchronization therapy (CRT). This analysis assessed whether Infarct location predicted the degree of reverse remodeling after 6 months of CRT. METHODS: The MIRACLE study enrolled NYHA Class III/IV HF pts with ventricular dysynchrony and LVEF=25%. All pts were implanted with an InSync atrial synchronous biventricular pacing system. AV delay was individually optimized and pts were randomized to no pacing (control) or to CRT. Doppler echocardiograms were analyzed by a core laboratory. Left ventricular end diastolic volume (LVEDV), LV end systolic volume (LVESV), LV ejection fraction (LVEF), and mitral regurgitation color flow jet area (MR) were calculated. Infarct location was determined using a 16 segment model. Anterior infarction (AMI) was defined as akinesis in at least 3 anterior-apical segments and inferior infarction (IMI) defined as akinesis in at least 3 postero-inferior segments. Changes in LV remodeling were quantified and compared between the AMI and IMI groups after 6 months of CRT. RESULTS: Significant reductions in LVEDV and LVESV...