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

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Background: Recent studies indicated increased plasma oxypurine (hypoxanthine/xanthine/uric acid) levels as an independent risk factor for worsened heart failure, suggesting oxypurine 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, without influencing collagen content/subtype or cross-linking. Here we tested whether AII+P (n=7) enhances AMP catabolism to increase cardiac nucleoside/oxypurine and diastolic stiffening, assessing the ability of MMPI to prevent these changes.

Results: AII+P raised diastolic chamber stiffness and end-diastolic pressure ~100% and markedly activated gelatinases MMP-9 and MMP-2 (abundance and in situ assays). With AII+P, ATP declined while AMP catabolites increased: nucleotides (inosine, adenosine) raised from 254±84 to 1700±363 nmol/g (p<0.005), and oxypurines from 100±20 to 666±236 nmol/g (p<0.01) while antioxidant levels (glutathione) significantly declined. However, MMPI did not mitigate AII+P-induced oxidative stress (MDA = 6.1±1.3).

Conclusions: Diastolic stiffness is associated with a rise in myocardial content of AMP-breakdown byproducts (i.e. nucleotides and oxypurines). 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.

870-4 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

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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. Each rat received 10 million cells (12% neonatal cardiomyocytes (n=22), 5×10⁶ cells each). At 2 or 6 weeks, the graft site on the aorta was exposed and fixed for histologic 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, displayed spontaneous rhythmic beating at the graft site, with no evidence of thrombosis or aneurysm formation. In the aorta group, the inter-aortic pressure was comparable between the cell group and the control group, which was significantly higher than of the control group.

Conclusion: This study presents a new approach to the development of an auxiliary circulatory pump using immature cardiac cells for local myocardial support.

870-5 Uncovering Human Cardiac Myocyte Progenitor Cells for Myocardial Regeneration

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Background: The failure to identify and culture human cardiac progenitor cells has reinforced the idea that the heart is a terminally differentiated organ, with little or no capacity for self renewal. Increasing evidence suggests baseline levels of myocyte loss in the human myocardium require sustainable myocyte renewal for cardiac homeostasis. We investigated whether cardiac progenitor cells can be cultured from the human myocardium.

Methods: Cells derived from cultured human right atrial tissue explants (RATs) were depleted of fibroblast surface antigen (FSA) positive cells using immunomagnetic beads. The resultant 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.

Results: Human atrial myocardial tissue explants produce a heterogeneous cell population amongst which are small highly proliferating cells, expressing markers of cardiac differentiation (CXs/NKx-2.5, GATA-4, alpha-sarcomeric actinin, cardiac myosin heavy chain together with the cell cycle antigen Ki-67. In addition the cells also express c-KIT and MDR-1 denoting stem cell properties. At 9-12 weeks in culture they fuse to form rod like multinucleate cells similar to those previously described as myocytes.

Conclusions: Our study shows for the first time that there is a potential for self renewal of the human myocardium involving cardiac progenitor cells and that cardiac stem cells can be cultured. This has major implications in the study of stem cell biology and the development of cell therapy for myocardial regeneration.

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

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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≤35%. 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. Device 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. Analysis assessed whether infarct location predicted the degree of reverse remodeling after 6 months of CRT. RESULTS: Significant reductions in LVEDV and LVESV were observed in pts with anterior and inferior infarction (IM) or septal infarction (SI) at 6 months of CRT but not in pts with lateral infarction (LI).}

872-2 Heart Failure: Resynchronization Therapy

Wednesday, March 10, 2004, 8:30 a.m.-10:00 a.m.
Morial Convention Center, Room 260

872-2-1 ORAL CONTRIBUTIONS

Morial Convention Center, Room 260

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