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Feasibility of a Percutaneously Deployed Clip to Create and Maintain an Interatrial Communication

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Background: In many instances of congenital heart disease there is a necessity of mixing of blood from the right and left atria. A number of techniques have been described to create, enlarge or maintain a passage to allow for this mixing. We investigated the effect of a simple clip that can be placed during an interventional procedure to create and maintain a channel between the left and right atria.

Methods: Fifteen juvenile pigs (5 acute and 10 chronic) were used weighing 35-45 kg. Following anesthesia and ventilation, transseptal puncture was performed. A simple 6 winged nitinol clip was deployed through an 8F system under intracardiac echocardiographic (ICE) guidance. At full expansion the clip provided a 6mm aperture. Flow was confirmed by ICE. Follow up and pathological analysis was performed at 4 hours -12 weeks. All animals were treated with aspirin and plavix until sacrifice. Intraprocedural heparin was administered to a target ACT of >200secs.

Results: All acute animals demonstrated excellent patency by ICE at 4 hours. The 5 acute animals demonstrated neat 6 mm apertures in the device. Four devices were occluded at sacrifice (2 at 3 weeks, one each at 6 and 8 weeks). Animals sacrificed at 2, 4, 8 and 12 weeks had patent apertures, however of decreasing diameters due to progressive endocardial ingrowth. The mean ACT at implant appeared lower in the occluded (122±43secs) than that of the patent cases (191±93secs).

Conclusions: A simple clip for the creation and maintenance of interatrial communication is feasible and effective in the short term. A combination of early occlusion probably due to thrombus formation and late closure due to endocardial growth limited its effectiveness in this study. Improved design, increased initial aperture and medical therapy would likely remedy some of these issues.

Completely Bioabsorbable Salicylate-Based Sirolimus-Eluting Stent: In-Vivo Intravascular Imaging in Pig Coronary Artery Implants

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Background: Recent advances in bioabsorbable stent technology have contributed to awakened interest in their role as alternatives to current metallic drug-eluting stents. We sought to evaluate a novel, fully bioabsorbable sirolimus-eluting stent (SES) synthesized entirely from salicylic-acid polymer, in a clinically relevant animal model.

Methods: Bioabsorbable balloon-expandable stents (n=32) were implanted in pig coronaries using quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) to optimize stent apposition. Dose density of sirolimus was 8.3 μg/mm stent length with *in-vitro* studies demonstrating elution over 30 days and complete stent degradation in 9-12 months. Animals underwent QCA and IVUS restudy and were terminated at 7, 14, 30, 90, and 180 days for histologic assessment. Optical coherence tomography (OCT) was also performed for the 90- and 180-days samples.

Results: All stents were deployed successfully without notable mechanical difficulties. No edge dissection or vasospasm was observed during implant. No stent migration was observed at any time. Angiographic diameter stenosis (DS) was 20±16%, 24±4%, and 23±17%, at 1, 3, and 6 months, respectively. In parallel, IVUS showed good apposition of the stent to the vessel wall with DS of 21±9%, 25±7%, and 18±3%; and area stenosis (AS) of 35±13%, 33±7%, and 32±4% at 1, 3, and 6 months, respectively. OCT demonstrated good apposition of the stent with DS of 28±7% and 20±6%, and AS of 37±10% and 33±13% at 3 and 6 months, respectively. OCT showed reduction of stent thickness by 23% from 3 to 6 months. Histologic analysis confirmed these in-vivo findings and revealed a favorable healing process of absorbable stent incorporation into the arterial wall, without excessive thrombotic or inflammatory reactions.

Conclusions: This study shows favorable vascular compatibility and efficacy for a novel fully bioabsorbable salicylate-based SES. This device has good mechanical performance during deployment and stays well-apposed to the vessel wall at long term follow-up. These initial results are highly encouraging and support progress into more extensive preclinical studies as well as early clinical testing.

Differential Predictive Power of Endothelial Progenitor Cell Phenotypes in Acute Coronary Syndromes

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Background: Endothelial progenitor cells (EPCs) originate from hemapoietic stem cells, and can transform into mature endothelial cells and participate in new vessel formation in ischemic tissue by angiogenesis. EPCs are a heterogeneous group of cells that can be characterized by the expression of surface markers, such as CD34, CD133, and KDR in various combinations and currently, precise phenotype definition is lacking. Previous studies have shown that reduced numbers of EPCs as measured by Colony Forming Units in cell culture or by CD34+KDR+ phenotype count as assessed by flow cytometry analysis constitute a predictor of cardiovascular risk.

Objective: We sought to determine which phenotype combination of EPC (CD34+KDR+/ CD34+CD133+/CD133KDR+) correlates best with adverse cardiovascular outcome in a cohort of patients with acute coronary syndrome (ACS).

Methods and results: Peripheral blood mononuclear cells were isolated by Ficoll density-gradient from 76 consecutive patients with with acute coronary syndrome (ST-elevation MI, NSTEMI and unstable AP) who underwent coronary angiography in our institution. Samples were incubated with stained monoclonal antibodies for CD34, CD133, and VEGFR2. Circulating number of EPCs of various phenotype combinations (CD133+CD34+, CD133+VEGFR2+, CD34+VEGFR2+), were determined by FACS analysis. Telephonic follow-up each 6 months was performed for a maximum period of 24 months. The primary end point was a combination of censored mortality and recurrent ACS events.

***Results*:** During the follow-up period, there were 7 deaths, 3 occurring within less than a month of initial PCI. We did not find a significant correlation between any of the EPC phenotype combinations and the primary endpoint, but we did find a weak albeit statistically significant correlation between CD133+KDR+ cells and recurrent ACS.

Conclusion. Our results can be explained by the inherent difficulty in using a very small number of cells as a biomarker in addition to the relatively small number of patients enlisted. Given the positive correlation between CD133+KDR+cells (but not the two other phenotype combinations) and recurrent ACS, it seems the various EPC phenotypes cannot be used interchangeably. Further studies enrolling more patients should be performed in order to explore the relative value of various EPC phenotypes in predicting cardiovascular outcomes.

Differentiation of Mesenchymal Stem Cells Derived from Human Embryonic Stem Cells to Endothelial Cell

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Mesenchymal stem cells (MSC) derived from human embryonic stem cells (hESC) can give rise to cells from a number of mesodermal lineages, such as bone, cartilage, fat, skeletal muscle, and hematopoietic lineages but have not yet been demonstrated to differentiate into endothelial cells. In this study, we purified MSC from hESC by a novel approach employing retroviral vectors to transduce the hESC, and showed that these cells can differentiate to cells with multiple endothelial cells markers. We took advantage of the different molecular handling of genes transferred by MMLV-based retroviral vectors by hESC and MSC. While hESC efficiently silence genes transferred by MMLV-based retroviral vectors, MSC do not silence the transferred genes. We transduced hESC with MMLV-based retroviral vectors encoding VEGF and neomycin phosphotransferase. After gene transfer we used G418 in the culture media. hESC died under G418 regiment due to transgene silencing while MSC that differentiated from hESC survived G418 selection and differentiated to cells with multiple endothelial markers such as VE-cadherin, vWF, and tie-2. The differentiated cells formed a robust capillary-like network when seeded on Matrigel.
We conclude that hESC-derived MSC can be derived to differentiate to endothelial cells and that this process can help in studying the differentiation and maturation of endothelial cells.