Pathohistological Rational in new treatment modalities

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Since the introduction of percutaneous coronary balloon angioplasty, restenosis has remained the most challenging problem facing interventional cardiologists. Stenting has reduced the need for clinically driven repeat revascularization, but has far from eliminated it. Recently animal models have been criticized for not being representative of what is seen in clinical studies in man at 6 month. One obvious explanation is that humans have an underlying atherosclerotic process, which usually manifests in the fifth or sixth decade of life, whereas balloon-injury in the pig, is usually performed in normal arteries of juvenile animals.

How do we reconcile differences between clinical and experimental studies? One possible explanation for the conflicting results among species is that there is a differential rate of healing. This differential rate of healing may be proportional to the longevity of the species. Humans have a life span of >70 years (72.8 years males and 79.6 years females). In contrast, pigs have a life span of 16 years, and rabbits 5-6 years. Human coronary arteries take longer to heal following injury than normal pig or rabbit arteries. Histologic studies of stented human arteries show a persistence of platelet and fibrin up to 14 and 30 days, respectively, following balloon injury and stenting [12]. Inflammatory polymorphonuclear leukocytes and macrophages are present at 1 to 3 days following stenting and persist for more than 3-months. T-lymphocytes appear at 2 to 3 weeks and may persist beyond 6-months. Smooth muscle cells, the main cellular component of the restenotic lesion, usually appear 14 days following stenting. The extracellular matrix composed initially of proteoglycans and type III collagen, is gradually replaced by collagen type I between 6 and 12 months. In general, human coronary arteries take approximately 6 months for complete healing following stenting, compared to the pig coronary and rabbit iliac arteries which heal at about 1 month, with deposition of collagen type I taking 3 to 6 months.

In contrast the pig coronary arteries show platelet/fibrin deposition almost immediately following stent placement with inflammatory cell infiltration commencing soon after and peaking between 3 to 5 days. Endothelization also begins and is almost complete by 7 to 14 days. Smooth muscle cell proliferation is seen from 3 to 14 days but peaks at 7 days with extracellular matrix formation (proteoglycans and collagen III deposition) being completed by 28 days. 80% of arteries are fully healed by 1 month. Therefore it should not be surprising that studies in animals and man do not parallel each other.

The new modality of drug coated stents (rapamycin, paclitaxel, and actinomycin-D) is being currently touted as the next revolution in reducing rates of restenosis following stenting. Preliminary results at 6 months from the RAVEL (rapamycin, Cordis J&J) and ASPECT (paclitaxel, CooK) trials have shown a 0% and 4% restenosis, respectively. Why do these drugs lead to a significant reduction in restenosis? Both the drugs are known to act on the cell cycle and reduce the rate of cell proliferation however, rapamycin has the added benefit of also inhibiting T lymphocyte activation and proliferation to antigenic and cytokine (Interleukin 2, 4, 15) stimulation. Paclitaxel is a novel microtubular agent that promotes the assembly of microtobules from tubulin dimers and stabilizes microtubules by preventing depolarization. The microtubule network is essential for the interphase and mitotic cellular function in the cell cycle. Paclitaxel also prevents migration of smooth muscle cells in a dose dependent manner. Actinomycin-D has been shown to have antineoplastic and cytotoxic effects by binding DNA and inhibiting RNA synthesis, respectively.

Animal studies in the pig and rabbit coronary and iliac arteries respectively have shown neointimal inhibition at one month. However, the beneficial effects of all three drugs are associated with presence of fibrin deposition occupying 30 to 70% of the neointima. Paclitaxel and actinomycin D are also associated with greater inflammatory infiltrate. Thus showing some delay in healing of the neointima with all three drugs. It is not surprising that once the drug is fully eluted from the stent the vessel begins to heal and long-term studies in animals (3 to 6 months) would be negative for reduction in neointima; which has been shown for rapamycin and paclitaxel eluting stents. Therefore the statement has been made that animal models are not predictive of clinical results. When really because of differences in the ability of the vessel to repair in animals and man are the real reasons for the difference and that it is not surprising that 6 month studies are positive in man as they correspond to one month in normal animal arteries. However, long-term studies (1 to 2 years) in man must be performed to determine if there is a catch-up phenomenon as seen in animals.