

## Cardiology 2019: Aggressive neo-intimal hyperplasia is associated with increased TNF- $\alpha$ mRNA expression in a pig animal coronary grafting model

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Atherosclerosis is a chronic vascular and inflammatory disease condition that results in thickening and hardening of the affected blood vessels. Different risk factors contribute to the cause of atherosclerotic cardiovascular disease and increasing evidence implicates the immune system. Clinically, the patient could be asymptomatic depending on the stage of the atherosclerotic process and the duration of the diseased condition; on the other hand the patient may show severe symptoms as in acute coronary syndrome, and treatment could be conservative or interventional as in balloon and stenting angioplasty or surgery as in coronary bypass grafting. Intimal hyperplasia (thickening of the intimal vascular layer) will support the foundation of the atherosclerotic process and later on the progression of the formation of atheromatous plaque, and starts as early as few hours following coronary bypass surgery, and progress within the first one month postoperatively. In this study, we hypothesized that TNF- $\alpha$  mRNA expression levels were directly dependent on the severity of atherosclerosis to test our hypothesis. Seven, 4 months old, 35 kilogram, Yorkshire Gross domestic swine supplied from Yeazel and Co.(Wolverton,OH,USA) were proposed to be used in this study. Our pigs animal model, are planned to be subjected to coronary bypass surgery. The implanted vessels to be harvested at different time points 0 hour, 1 hour, 3 hours, 1 day, 4 days, 1 week and 2 weeks to calculate the development of intimal hyperplasia at vein to artery versus artery to artery implantation sites, based on the intimal area/ total circumference area (RI) ratio. Our expected results may be helpful to show that TNF- $\alpha$  mRNA expression and the development of the neo-intimal hyperplasia in providing the evidence of a direct pro-inflammatory cytokine signaling link between the biomechanical forces on the vessel wall and the remodeling response. We are expecting that anastomosis of a vein graft to an artery will result in acute induction of intimal hyperplasia and expression of the TNF- $\alpha$  mRNA with an early increase within the first few hours, peaking at the first week post operatively. This expression could be augmented by different factors including the accelerated intimal hyperplasia. The expected high levels of TNF- $\alpha$  mRNA associated with the aggressive development of the intimal hyperplasia at the venous side of the anastomosis could be similar to human studies. The proposed study could be an important step for better understanding the pathogenesis of re-stenosis and the aggressive development of neo-intimal hyperplasia in association with the expression of TNF- $\alpha$  mRNA at the vein-artery anastomosis site which is different and much less on the

artery-artery site of anastomosis accompanied by a dramatic expected decline in the TNF- $\alpha$  mRNA expression on the arterial side. In conclusion, the study proposed that aggressive neo-intimal hyperplasia in animal pig model can develop early, and is associated with increased recruitment of macrophages capable of expressing TNF- $\alpha$  mRNA producing TNF- $\alpha$ . The above results may guide us to the use of arterial graft conduits in humans (total arterial revascularization) using the different arterial conduits as left and right internal mammary arteries, radial artery and others which could even be helpful in preventing the progression of the atherosclerotic process in the native coronary arteries. Thus, it becomes rather obvious that part of the disease management and therapeutic approach entails the modulation of the innate immune responses to lipoproteins.

Two weeks after establishing the AV fistula, marked changes in gene expression were observed in the venous limb, mRNA expression of MCP-1 and PAI-1 were markedly increased, 15-fold and 10-fold, respectively, in the venous segment of the AV fistula as compared to expression of these genes in the sham-operated rats; thus expression of a prototypic proinflammatory chemokine (MCP-1) and a procoagulant, proinflammatory gene (PAI-1) was vigorously induced. Expression of ET-1 mRNA was also increased threefold in the AV fistula whereas TGF- $\beta$ 1 mRNA was markedly suppressed 2 weeks after establishing the fistula

We believe that the development and validation of a large animal model of venous neo-intimal hyperplasia and venous stenosis in the setting of arteriovenous grafts is an important first step toward (1) achieving a better understanding of the pathogenesis of venous stenosis and venous neo-intimal hyperplasia in arteriovenous PTFE grafts, and (2) testing out novel interventions for the treatment of this condition (we have already obtained some very positive results with external beam radiation in this model [37]). Finally, clinical dialysis access grafts could be an ideal model for novel local therapies (such as radiation), in view of their superficial location (away from vital organs) and easy access to both the patient (in dialysis three times a week) and the graft (dialysis needles are placed within 3 to 4 cm of the site of lesion). We hope that our validated pig model of VNH and venous stenosis will provide a major impetus to the nephrology and vascular surgery communities, for the development and testing of novel local therapies for the management of hemodialysis vascular access dysfunction.

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