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DESIGN AND EVALUATION OF TISSUE ENGINEERED ARTERIES

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Background

Tissue engineered vascular substitutes have the potential to be used for treatment of clinically advanced atherosclerotic disease. Design considerations for a tissue engineered vascular substitutes include physiologic levels of flow, low thrombogenicity, and adaptation to changes in flow demands. Some of these attributes may be evaluated using less expensive bench top methods before proceeding to in vivo testing. We have recently developed several methods for determining flow, thrombogenicity, and adaptation in tissue engineered arteries.

Experimental methods

An *ex vivo* perfusion organ culture system has been designed to mimic the hemodynamic environment of arteries, including the shear stress produced by lumen blood flow, the tensile stress produced by blood pressure, and the axial stretch. Tubular segments of porcine carotid arteries are cultured with pulsatile perfusion of DMEM supplemented with calf serum under mimic *in vivo* pressure and flow.

Vessel integrity and viability is demonstrated by histology using H&E staining, MTT staining. Physiologic contractility and tone is assayed using norepinephrine (NE), acetylcholine (ACh) and sodium nitroprusside (SNP).

Results

Results show that the paramount prototypic tissue engineered vascular substitute, a fresh artery, can remin viable for seven days in our test organ culture system. Histological evaluation demonstrates a morphologically intact artery with no elastin or ECM degradation in amount or architecture. The cultured arteries maintain viable mitochondria by MTT staining. The smooth muscle produced basal tone in the artery is intact and responds to mechanical and pharmacological agonists. There is a strong diameter response to NE, ACh, and SNP. The diameter contraction and relaxation is geneerally greater than ~16% in response to NE and ACh.

Further, our quantitative assessment indicates that the cultured artery is undistinguishable from a fresh artery by a battery of seven different quantitative measurements.

Discussion

The organ culture system developed at GTEC can be used to study many biomechanical and biochemical responses of natural arteries. The advantages of this bench top artery organ culture system include well-defined environment, and precise, consistent, and independent control of the hemodynamic parameters. It is also convenient for continuous observation and accurate measurement.

This organ culture system could serve as a standard test system for tissue engineered arteries before *in vivo* animal tests. Some of these tests are:

1. Mechanical behavior of new vascular grafts, e.g. the dynamic response to pressure or flow including pressure-diameter relation and burst pressure under physiologic conditions.
2. Active responses of the vascular cells in tissue engineered arteries. e.g. the responses of EC and SMC to agonists norepinephrine (NE), acetylcholine (ACh).
3. Short-term response of the new vascular grafts to hemodynamic changes including the preconditioning effect.
4. Responses to varies biochemical factor like calcium and lipid transportation,

This study address many of the Design - Validation issues which would be required to produce a Tissue Engineered Vascular Substitute. The bench tests described in our study have been validated on natural arteries and may be used on tissue engineered vascular substitutes for design optimization studies and as data in support of an FDA submission.