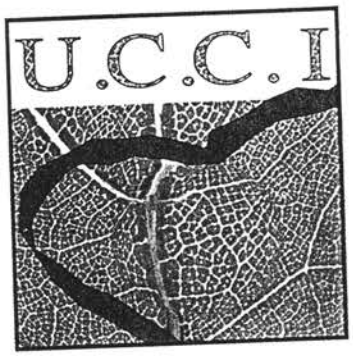

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In-Vitro Models of Human Carotid Atheromatous Disease

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INTRODUCTION: WHY IN-VITRO MODELS ?

Endovascular therapy using balloon dilatation, stent application, or both appear currently to be interesting therapeutic alternatives to surgical CEA[1,2,3,4,5,6]. Nevertheless, as stated by different councils, this emerging new endovascular technologies should be further developed and standardized prior to widespread use[7,8]. In-vitro methodology with realistic human vascular models exhibit reproducible test conditions for medical device evaluation and comparison as well as for medical training and provide therefore an ideal environment for preclinical experimentation. The lack of biological conditions excludes of course compatibility testing, however, for the benefit of avoiding unnecessary and expensive animal use and the advantage of providing clean and directly visible "endovascular" conditions, in-vitro models are welcome to overcome initial clinical learning curves while training for endovascular treatment.

METHODS OF MODEL CONSTRUCTION

An exact reproduction of the vascular lumen was obtained using a corrosion method[9]. After cannulation, the cervical vessels of non fixed human specimen were injected with methylmethacrylate to create a normal cast of the carotid artery and its branches. This was obtained by using a mixture of methylmethacrylate (Beracryl, Troller, Switzerland) and barium sulfate powder (HD-200 plus, Lafayette, USA)[9]. The mixture was injected under fluoroscopic control after flushing of the arterial tree with a 5% glucose solution. Potential alteration of the vascular morphology due to excessive injection pressure was avoided by using continuous fluoroscopic control to interrupt the filling procedure prior to vascular over dilatation[10]. Once filled, the specimen was immersed in a 15% solution of potassium hydroxide at 40 degrees Celsius, until complete dissolution of the surrounding soft and bony tissues was achieved. The remaining solid corrosion cast (Fig. 1) was then simplified by removing small branches. In a next step, using dentistry copy techniques, wax copies of the cast were obtained (ELASTRAT, Switzerland). Such wax copies exhibited dimensions which are identical to the initial corrosion[10]. A wax copy was then used as a form to mold soft or rigid, normal or pathological vascular models[11]. For soft models, silicone was applied in thin layers by painting manually on the wax copies. During the drying process, the models were placed in a 3-D rotator machine to avoid uneven distribution of the wet silicone coating. For solid models, the wax copies were immersed in a box filled with liquid silicone. Once the silicone was completely dried, the models were heated (80 C°) in order to drain the wax and to free the vascular lumen according to the ancient and well known principle of "lost wax technique".

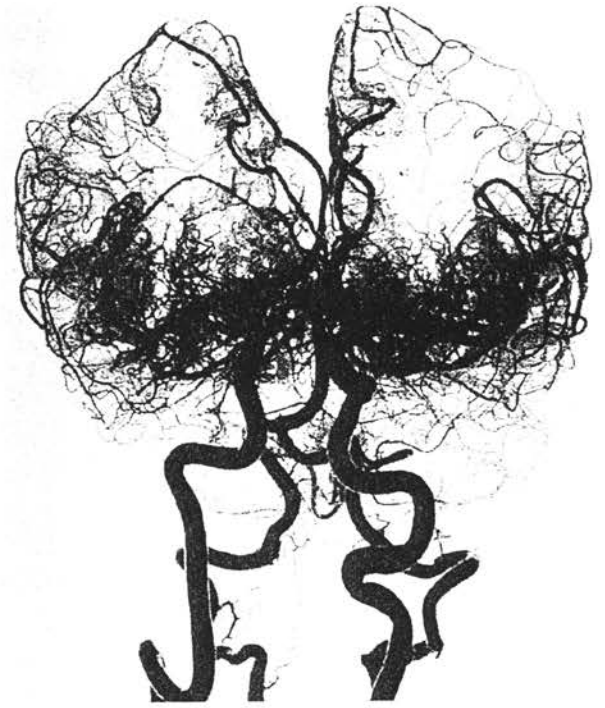

Figure 1. Solid corrosion cast of human cerebral arteries.

SIMULATION OF CAROTID ATHEROMATOUS DISEASE - A MODEL STENOSIS TO MATCH THE PLAQUE MORPHOLOGY

Models matching plaque morphology can be obtained by wax copies of diseased arteries or by modifying wax copies of normal arteries. Such models, rigid or soft, provide exact copies of a specific stenosis, however, when used for endovascular dilatation procedures, remain not dilated due to their elastic memory. Therefore, these models appear useful for imaging techniques and hemodynamic studies only, and are of limited use for endovascular treatment simulation.

SIMULATION OF CAROTID ATHEROMATOUS DISEASE - A MODEL STENOSIS TO DILATE

Best results were obtained by creating soft and thinwalled silicone models with uneven wall thickness. Secondary circular constrain using a

breakable thread tied around the model at the level of desired stenosis, created a more or less excentric and irregular stenosis. The morphologic aspect of the stenosis was observed to be in relation with the type of ligature, the lumen surface characteristics and the model wall thickness (fig. 2). Such simulations of stenosis allow for release of the outer constrain by pre- or post-dilatation procedures or by introduction of self-expandable stents in dependence of the quality of the thread used.

SIMULATION OF NORMAL VISCOELASTIC WALL PROPERTIES

To create biomechanically, physically and anatomically accurate in-vitro models exhibiting wall properties of normal human carotid arteries, we mixed silicone with variable degrees of mineral powder additives (titan, talc, silice). The mixtures were applied in two to seven layers, producing a thin silicone coat. The visco-elastic wall properties of the models were then evaluated and compared with values known from normal human carotid arteries. For evaluation, the models were connected to a systolo - diastolic pump producing flow and pressure curves in physiological ranges. The vascular fluid pressure was monitored and the external vessel diameter was measured using piezoelectric probes. The physical and biomechanical parameters (pulsatility, radial force, compliance, elasticity and stiffness) of the different models were calculated[12, 13] and compared to results obtained in an earlier study from normal human carotid arteries[14] using the same method of evaluation on fresh, non-fixed human carotid material. Two different types of models, the RTV-121(3 layers) and Silgard-184 (mixed with Titan, 2 layers) exhibited viscoelastic properties close to normal human carotid arteries at physiological pressure ranges of 140/80 mmHg (Fig. 3). Their wall, however, was very thin and the models proved to be too fragile for use with most endovascular devices. There role may be interesting for specific studies such as e.g. evaluation of hemodynamic impact of a stent.

SIMULATION OF THE CIRCULATION

All the models can be connected to any circulation system using fluids of different viscosities and involving a pump systems to produce flow and pressure changes to simulate variable or constant flow conditions in the in-vitro model. Changes in distal resistance can be obtained by using adaptable outflow constraints.

COMPATIBILITES WITH MEDICAL IMAGING

The models exhibited excellent compatibility with all current medical imaging methods, including magnetic resonance imaging, computed tomography, digital subtraction angiography, ultrasound and intravascular ultrasound. Of particular interest may be the good translucency of certain model types (ELASTRAT, Switzerland), allowing for direct visual control avoiding the need of using medical image equipment during evaluation or training. Photographic documentation or video recording of devices within the model may easily be obtained.

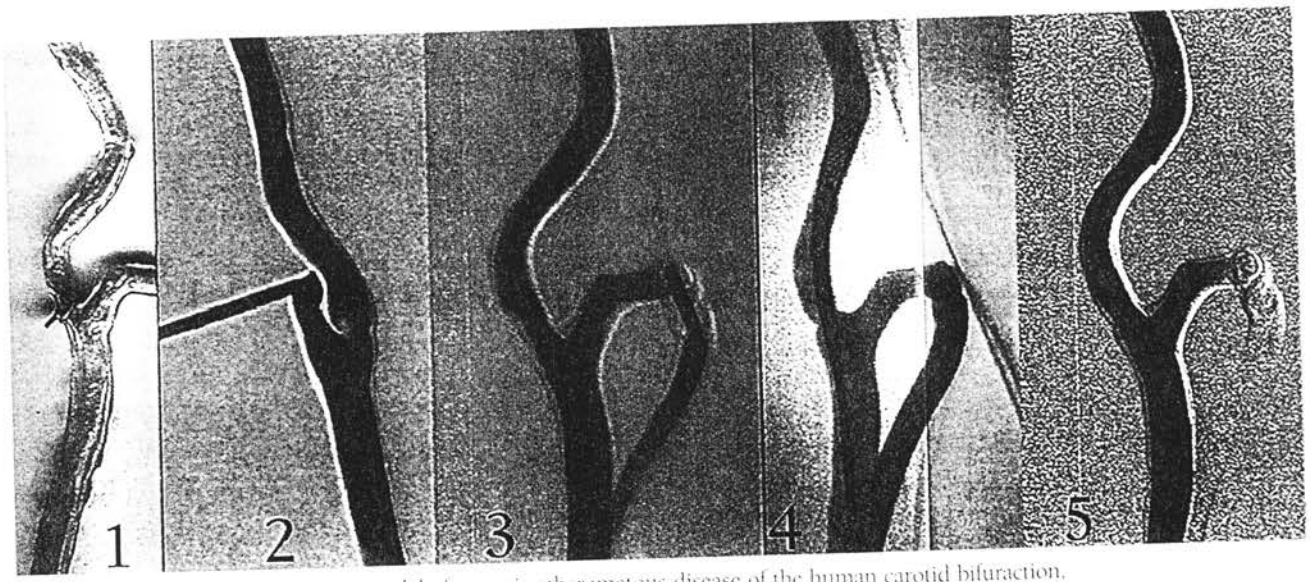

Figure 2. Soft and dilatable in-vitro model of stenotic atheromatous disease of the human carotid bifuraction.

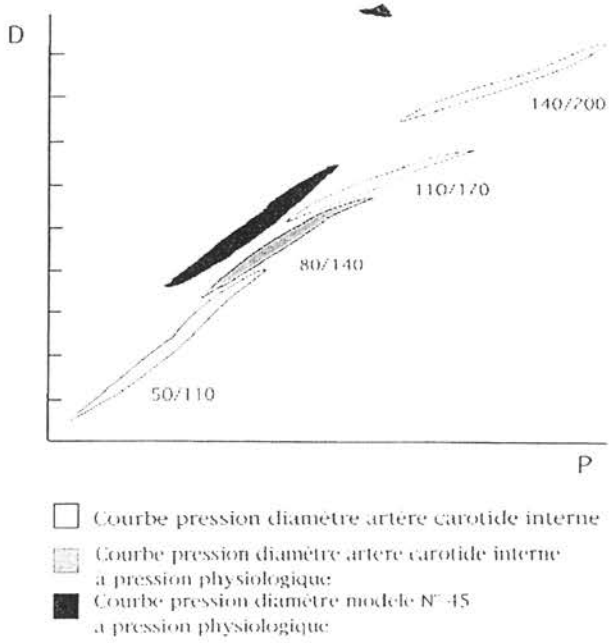

Figure 3. Mechanical properties of a soft model with simulation of normal wall characteristics.

PRECLINICAL EVALUATION FOR REGULATORY PURPOSES

The models have been used and accepted for preclinical device evaluation for Ce-marking.

AN EXAMPLE OF ENDOVASCULAR TECHNIQUE EVALUATION: CAN USE OF A DISTAL PROTECTIVE BALLOON AVOID POTENTIAL EMBOLIZATION TO THE INTERNAL CAROTID ARTERY TERRITORY?

To evaluate controversial arguments in favor or against use of distal protection, we evaluated the distal protection technique by temporary balloon occlusion of the ICA using a triple coaxial system[6] and quantified the potential to remove emboli positioned within the dilated stenotic area of an internal carotid artery (ICA) on in-vitro models. Using a triple coaxial system, a self expandable stent (Wallstent, Schneider, Switzerland) was deployed below the temporary protective occlusion of the ICA (Fig. 4). Subsequently, emboli were introduced through microcatheters into the proximal aspects of the ICA below the protective balloon to simulate plaque debris. A range of sizes and numbers of particles were used for this purpose. To evaluate the efficacy of the different elements of the cleaning procedure, aspiration and flushing at different levels below the occlusion balloon protection system were performed. For this purpose, the aspirated, flushed or remaining amount of particle emboli were counted after collection in separate filters. Aspiration or flushing occured at a range of pressures and fluid volumes, and with the tip of the coaxial 9F catheter positioned at a variety of levels. To evaluate the impact of flushing fluid volumes and to avoid reflux to the aortic arch, a model of aortic arch including the cervical vessels was constructed (Fig. 5, ELASTRAT, Switzerland). Simulating pulsatile flow and blood viscosity, circulating fluid consisting of 2/3 water and 1/3 of glycerine was used at average pressures of 120 mmHg. The flow was regulated at 100 cc/min in the external carotid artery, similar to normal physiological conditions[15]. The potential of debris reflux was evaluated using an ICA protective occlusion at midcervical level and applying different flush rates through the 9F coaxial catheter with the catheter tip positioned at levels 1) close to the balloon (high-H), 2) at the origin of internal carotid artery (low-L), and 3) in an intermediate position (middle-M). The optimal flush flow was observed to be at 2 cc/sec (Fig. 6), with reflux occuring to the vertebral artery (Fig. 7) for flush rates superior to 2.5 cc/sec injected for a total volume of 40 cc.

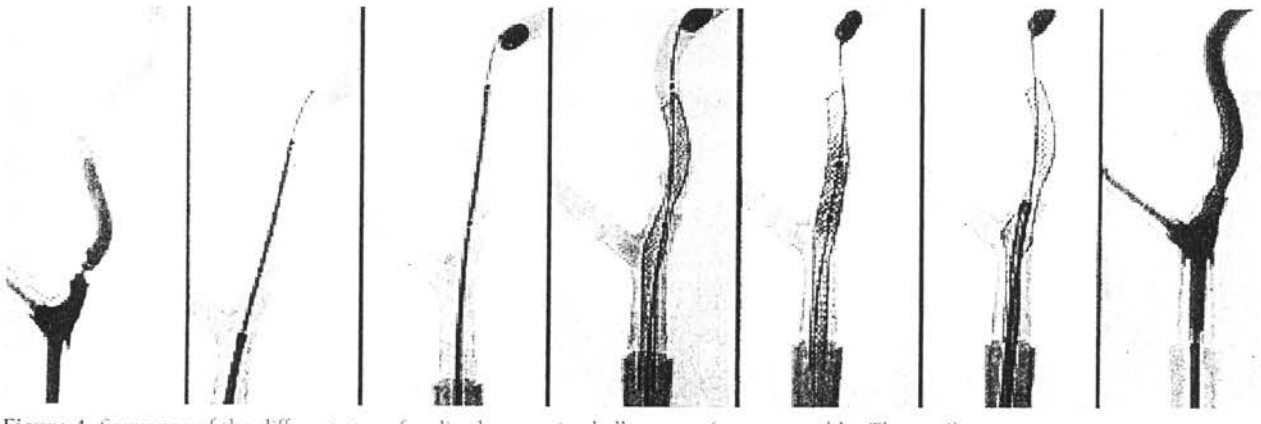

Figure 4. Sequence of the different steps for distal protective balloon use (system used by Theron J).

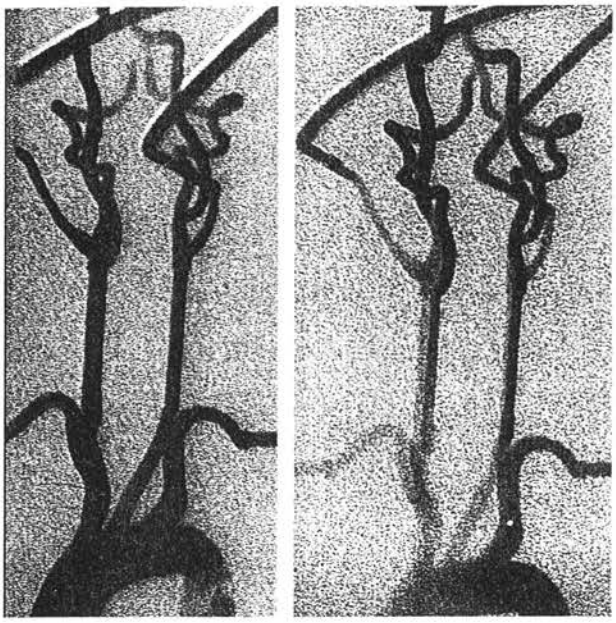

Figure 5. DSA of a model of aortic and cranio-cervical vessels realized as a combination of two solid in-vitro models (ELASTRAT, Switzerland).

Efficiency evaluation of aspiration (60 cc) and flushing (2cc/sec for a total of 20 sec) at different levels below the distal balloon protection revealed, that use of a distal protective balloon with flushing at the bifurcation level allowed to recover 83% to 100% of the emboli with an average of 92.2 %. With the tip of the 9F catheter placed close to the protective balloon, the efficacy of the cleaning procedure was measured 93.7% to 100% with a average of 98.2%. Using two flushes at different levels following measurements were made With a first flush through the 9F catheter with its tip next to the protective balloon and the second at the origin of the carotid internal artery, 93.3% to 99.3% of the particles were removed. Using an inversed sequence with a first proximal and a second distal flush, the debris removal was measured to be 99.8% to 100%, this even when high number of particle (201 to 420) were used. In conclusion, the in-vitro model allowed to demonstrate the potential to protect the brain from distal migration of plaque

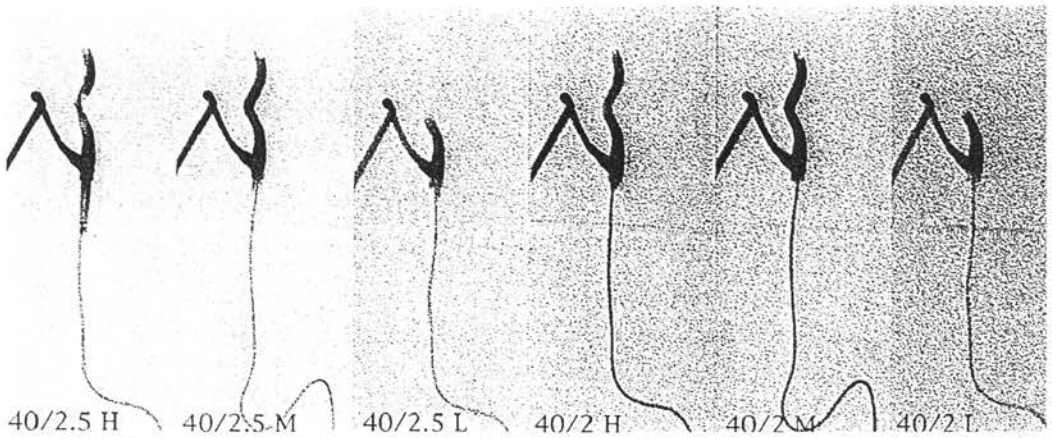

Figure 6. Cleaning the space below a protective balloon system in a model as in Fig. 5 with the coaxial 9F catheter tip in high (H), middle (M) and low (L) position in regard to the protective balloon. The figure shows a DSA of flush visualized by contrast material using a power injection pump. Note that injection rates of a 40 cc total at 2 cc/sec exhibited no reflux to the aortic arch whereas injection rates of 2.5 cc/sec showed beginning reflux into the common carotid artery.

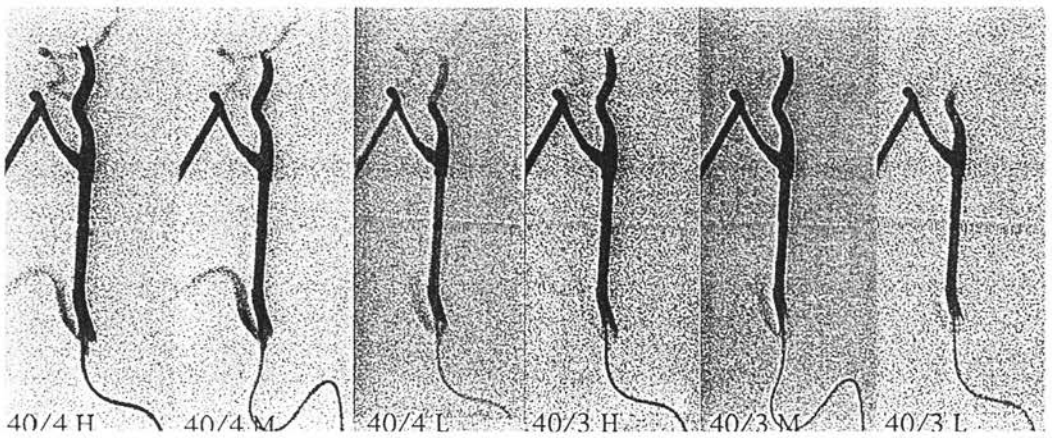

Figure 7. Same conditions as described in Figure 6 with flush injection rates of 3 and 4 cc/sec showing reflux down to the level of the aortic arch.

debris by using a distal protective balloon system (Theron[6]), when correct catheter position and flush rates are used.

CONCLUSION

Transparent vascular in-vitro models made of silicone are highly reproducible and are anatomically correct in their dimensions, when copied from human vascular systems. The wall characteristics can be constructed rigid, soft and even equivalent to viscoelastic properties of normal human carotid arteries, what might be of interest for hemodynamic studies. Stenotic lesions can be simulated in their morphologic and mechanical aspects. The models are compatible with all current imaging techniques. The in-vitro models provide very good conditions for preclinical evaluation of medical devices and medical training to shorten the clinical learning curve and to reduce animal experimentation.

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