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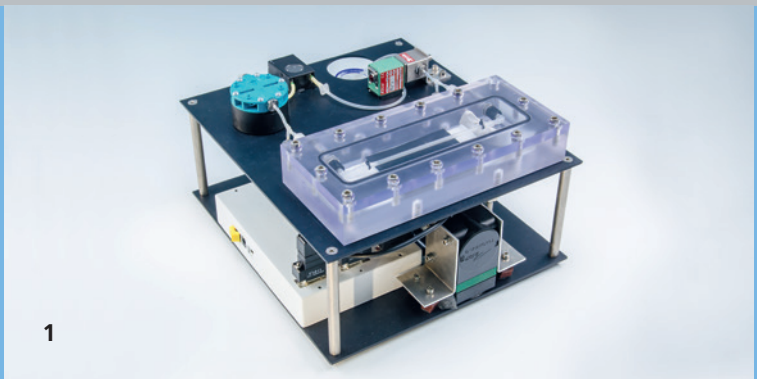


1 *Automated closed loop perfusion system*

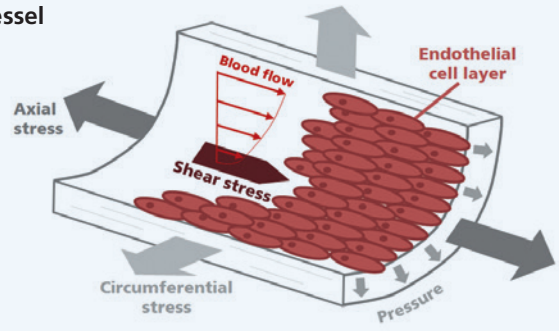
PERFUSION TOOLKIT FOR ENDOTHELIAL CELLS

Introduction

The blood vessel system is key for the absorption and distribution of active substances and gases in the human body. Almost all substances are transported via blood vessels where they have to pass the vascular endothelial layer to reach the organs. The vascular cells are exposed to permanent mechanical forces, including the fluidic shear stress by the blood flow and the bending stress by stretching of the vascular wall caused by the pulsating pressure. Amongst other processes cell division and signaling were influenced by these hemodynamic conditions.

Fraunhofer IMM developed in cooperation with Frankfurt University of Applied Sciences a toolkit for *in vitro* investigation of the vascular endothelial layer. It allows the analysis of endothelial cells, which were cultivated on flexible substrates and under physiological condition including all relevant mechanical forces.

Schematic of forces in a blood vessel



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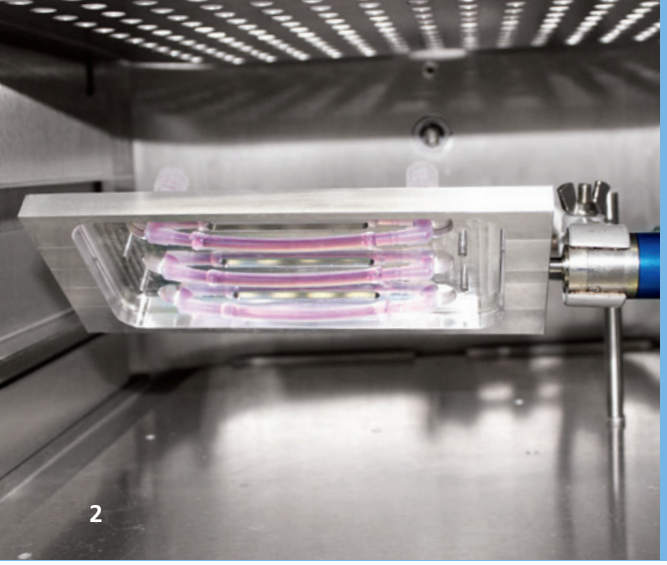

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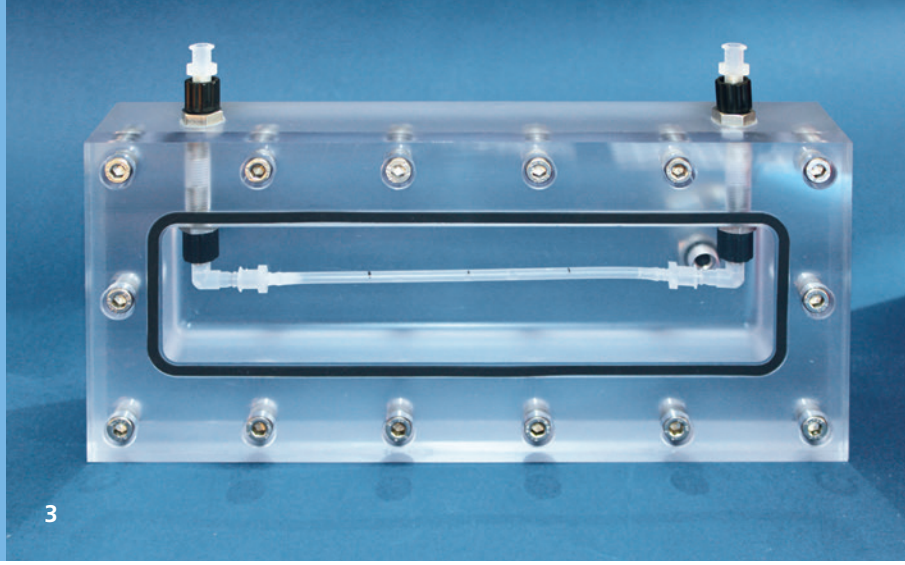

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Key components

The perfusion toolkit for endothelial cells comprises two key components:

1. Artificial blood vessel substrates:
Various materials are used for the construction of a blood vessel model system, built from different types of (stretchable) materials and variously functionalized via different methods. Feasible substrates are:

- Highly flexible plastic materials for specific applications, e.g. with special optical properties for microscopic investigation.
- Biocompatible collagen material with characteristics mimicking the vascular environment.

2. Instruments for running the experiments with the artificial blood vessel substrates.
Two different types are available:

- *3D cell cultivation module:*
  With this module seeding processes for the initialization of the cell layer can be established to achieve a confluent endothelial cell layer on the entire circular inner surface of tubular substrates by rotation. Multiple tubular substrates can be processed in parallel.
- *Automated closed loop perfusion system:*
  It allows long-term endothelial cell cultivation during perfusion with defined flow conditions and includes controlled substrate stretching and a temperature management. This perfusion system makes a conventional cell incubator obsolete and maintains system sterility.

Benefits

- *Microscope inspection:*
  Cell growth and reactions are easily monitored during the colonization process with standard microscopes since no conventional CO_2 incubator is required.
- *Open platform that allows real-time monitoring:*
  Beyond the microscopic inspection the system has an open design and allows integration of sensors and probes for process control, like pH, pCO_2, impedance.
- *Co-culture:*
  Cultivation of endothelial cells is feasible together with other cells (e.g. epithelial) on the same substrate. Counteractions of different cell types under perfusion stress can be examined.
- *Large active cell culture surface:*
  Flexible configuration with surface areas of up to 10 cm^2 suited for experimental setups which require a larger number of cells for the downstream detection of low abundant analytes.
- *Long time sterility due to a closed loop tubing system:*
  All components with contact to cells or media are sterilizable disposables.
- *Blood vessel model system by imitation of realistic vascular environment:*
  A unique cell cultivation system has been developed to stimulate cells by mechanical strains. The system controls shear-stress, inner pressure, and perfusion in combination with circumferential stretch, simulating the conditions within a real vascular vessel.

Applications

- *Arteriosclerosis and hypertension research:*
  Arteriosclerotic formation and vascular diseases can be examined by imitation of realistic vascular environment and monitoring of cell responses.
- *Active drug response and tolerability tests:*
  Substance screening regarding absorption within the human body (e.g. studies on the background of REACH regulations). The endothelial vascular layer is involved in nearly all active substance transfer processes.
- *Replacement of animal experiments:*
  Cardio-vascular active drugs and their response in endothelial cells can be evaluated with the system.
- *Intravascular implants:*
  Stents, new materials and shapes can easily be pretested and characterized.

2 *3D cell cultivation module*
3 *Vascular model within cultivation chamber*