# IN-SILICO ENHANCED CHRONIC ANIMAL EXPERIMENT TO INVESTIGATE CARDIOVASCULAR IMPLANTABLE DEVICES

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## Introduction

High-risk medical devices are subject to rigorous regulation requiring thorough assessment of device safety and efficacy. Different methods for generating evidence of a novel device exist. However, ultimately in-vivo experiments, first in animals and finally human clinical trials, are still mandatory. These in-vivo experiments are coming at large economic, personnel, and ethical costs. In recent years, in-silico methods for assessing medical devices are becoming increasingly important as an alternative in generating evidence for the safety of medical devices and first regulatory frameworks for this approach have been established [1].

In general, in-silico methods are excellent at providing information on engineering metrics, such as stresses, strains, and velocities. However, translating these engineering metrics to the relevant metrics of clinical trials, such as relevant observable clinical endpoints as device thrombosis, is difficult. If in-silico methods are meant to replace real clinical trials, strategies for mapping calculated engineering metrics to these clinical endpoints must be elaborated.

In this study, we demonstrate a joint approach by accompanying a chronic animal experiment using simulation models to generate insights on engineering metrics of hemodynamics and thus aiming to facilitate mapping of these engineering metrics and device thrombosis.

## Methods

This study utilized data obtained during a chronic animal experiment performed to investigate a pulmonary artery pressure sensor (PAPS). For 10 pigs, each 2 PAPS device have been implanted via a catheter-based procedure into the left and right pulmonary artery. CT scans have been performed before, directly after, 1 and 3 months after sensor implantation. Three relevant clinical endpoints have been investigated, device migration, perforation of the arterial vessel wall, and lung embolism due to thrombus formation triggered by the device. This study focuses on the thrombosis-related endpoint, which was investigated via histopathological assessment after euthanasia.

For each animal, the patient-specific anatomy was reconstructed using the pre-interventional CT scans. Virtual device implantation was performed by placing 3D models of the PAPS devices at the exact locations indicated by the CT scans performed one month after PAPS implantation. Subsequently, the intravascular hemodynamics have been calculated using transient computational fluid dynamic simulations. Wall shear stresses (WSS) and oscillatory shear indices (OSI) have been calculated for the vessel and the device surfaces individually. Changes in WSS and OSI due to device implantation have been investigated as well as the pressure drop induced by the device.

## Results

To increase occurrence rates of adverse events, PAPS implantation was performed in optimal and non-optimal positions, such as skewed positions or landing sites out of the technical specification limits. Of the 20 implanted devices 8 were found to be in non-optimal positions. No significant differences could be observed for either WSS or OSI calculated at the sensor surface and the vessel wall when comparing values before and after implantation. Furthermore, the pressure drop caused by the device was below 1 mmHg in all cases and therefore neglectable. Even in cases where the device was non-optimally positioned, no relevant changes in any hemodynamic parameters could be observed. Finally, histopathological examination revealed no sign of lung embolism in any of the animals and no relevant thrombus formation at the device was observed.

## Discussion and Conclusion

The aim of this study, to map hemodynamic parameters calculated using in-silico models against observed clinical endpoints, could not be achieved as no clinical endpoint was observed. While reported thrombus-related events for existing PAPS are very low [1], not even strongly non-optimal device positioning resulted in any thrombosis-related event withing the 3 months of the trial duration. Nonetheless, the CFD simulations demonstrated that the effect of the device on the intravascular hemodynamics was indeed neglectable both for optimal and non-optimally positioned sensors thus confirming histological results.

## References

1. Chaudhry, Sarwat I et al. “Telemonitoring in patients with heart failure.” *The New England journal of medicine* vol. 363,24 (2010): 2301-9.

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