Evaluating the microcirculation in early phase clinical trials: novel methodologies and interventions

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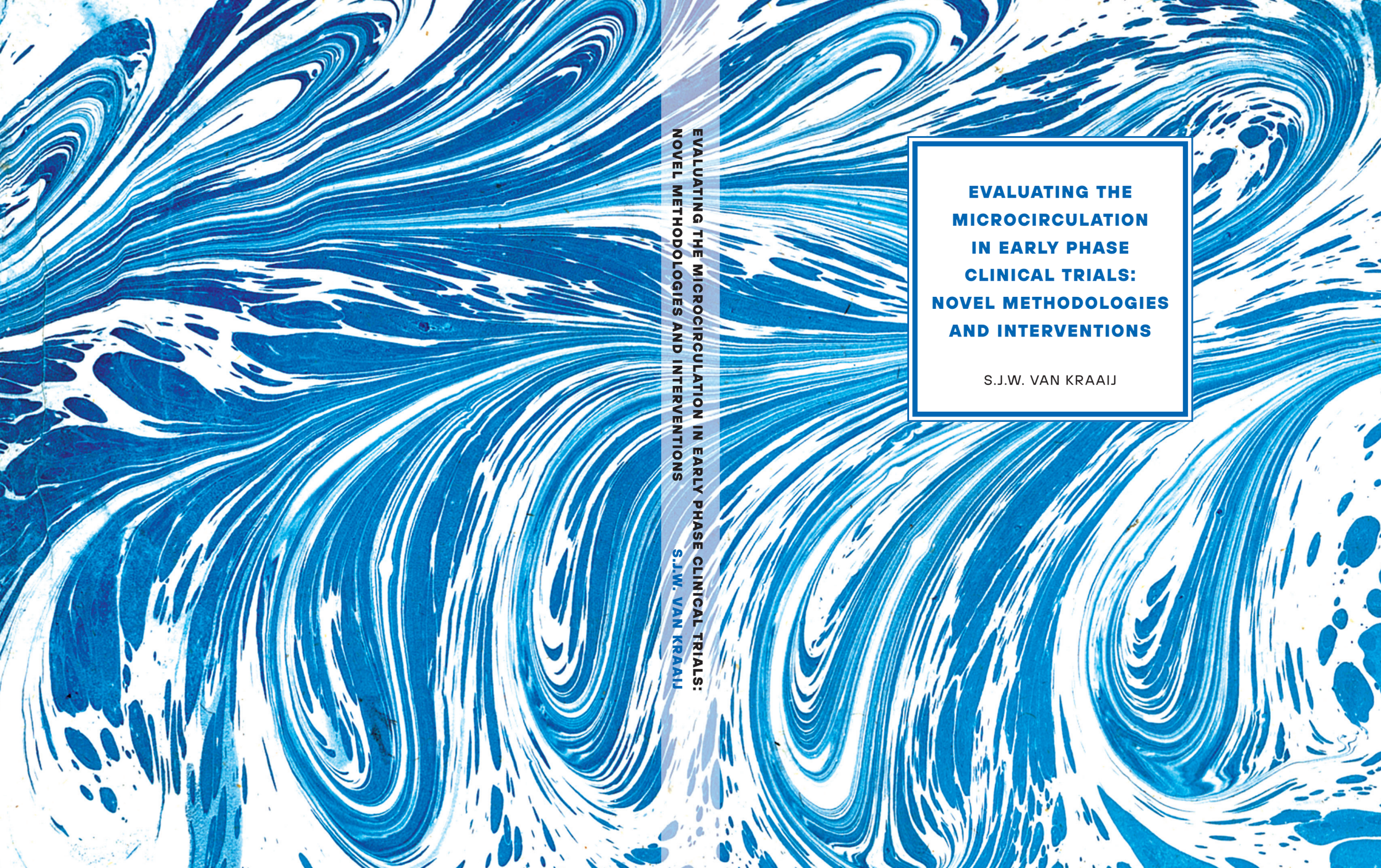

EVALUATING THE MICROCIRCULATION IN EARLY PHASE CLINICAL TRIALS: NOVEL METHODOLOGIES AND INTERVENTIONS

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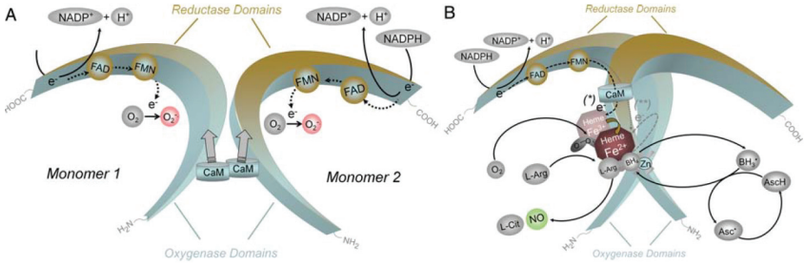
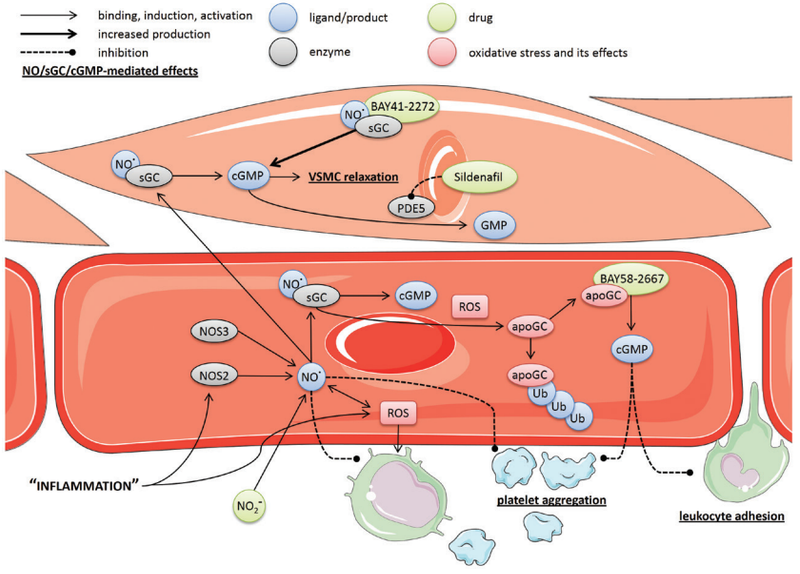
CH.1 / F.1 NOS form and function. A: two uncoupled NOS monomers. B: NOS in dimeric form.



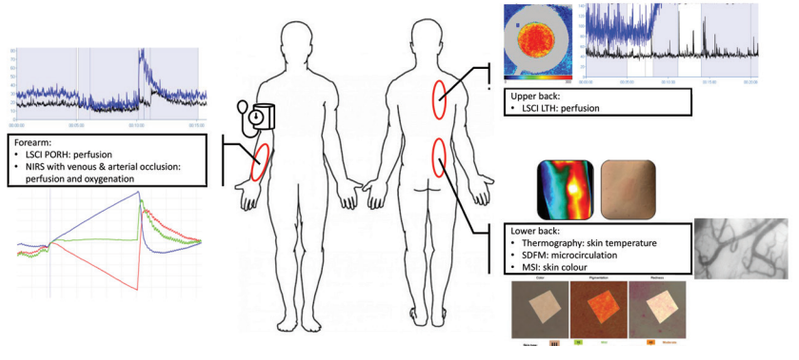
ASCH = ascorbic acid; BH4 = tetrahydrobiopterin; CAM = calmodulin; FAD = flavin adenine dinucleotide; FM = flavin mononucleotide; L-ARG = L-arginine; L-CIT = L-citrulline; NADP = nicotinamide adenine dinucleotide phosphate; NO = nitric oxide. (Adapted from Förstermann et al.[8])

CH.1 / F.2 The effects of NO, SGC and CGMP in endothelium and vascular smooth muscle.



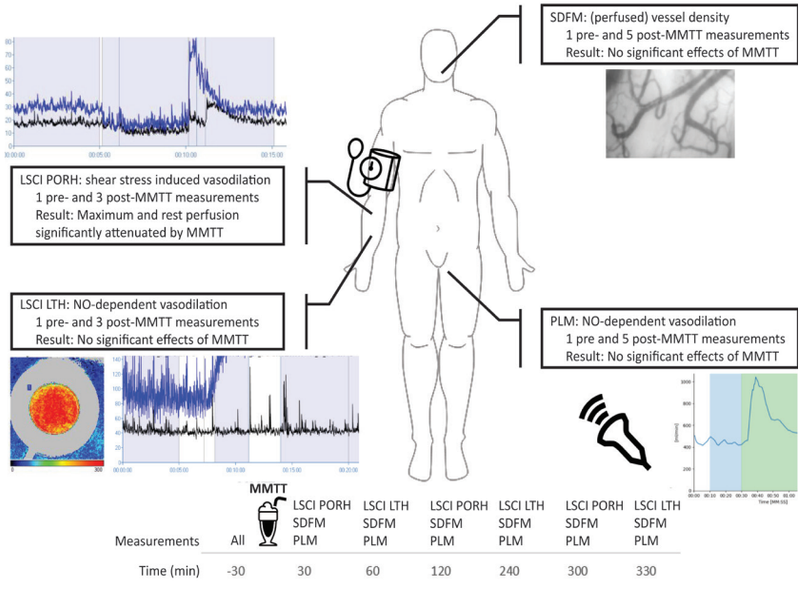
APOGC = heme-free guanylyl cyclase; CGMP = cyclic guanosine monophosphate; NO = nitric oxide; NO2 = nitrogen dioxide; NOS = nitric oxide synthase; PDE = phosphodiesterase; ROS = reactive oxygen species; SGC = soluble guanylyl cyclase; UB = ubiquitin; VSMC = vascular smooth muscle cell. (Adapted from Vandendriessche et al.[16])

CH.4 / F.1 Overview of measurements performed during study conduct and their locations.



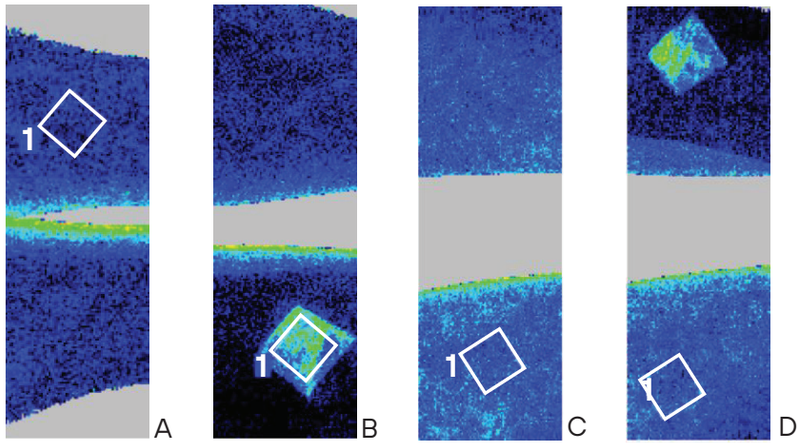
LSCI=laser speckle contrast imaging; LTH=local thermal hyperemia; MSI=multispectral imaging; NIRS=near infrared spectroscopy; PORH=post-occlusive reactive hyperemia; SDFM=side-stream dark field microscopy.

CH.2 / F.1 Overview of employed imaging techniques and timepoints of assessments pre- and post-MMTT administration.



LSCI=laser speckle contrast imaging; LTH=local thermal hyperaemia; min=minutes; MMTT=mixed meal tolerance test; NO=nitric oxide; PLM=passive leg movement; PORH=post occlusive reactive hyperaemia; SDFM=side-stream dark field microscopy.

CH.4 / F.4 Representative LSCI images of baseline flow before and after patch application for subject 4 (A, B) and 6 (C, D).



The window in the patch through which measurements were performed is shown in picture B and D (area marked with '1' in picture B). LSCI=laser speckle contrast imaging.