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

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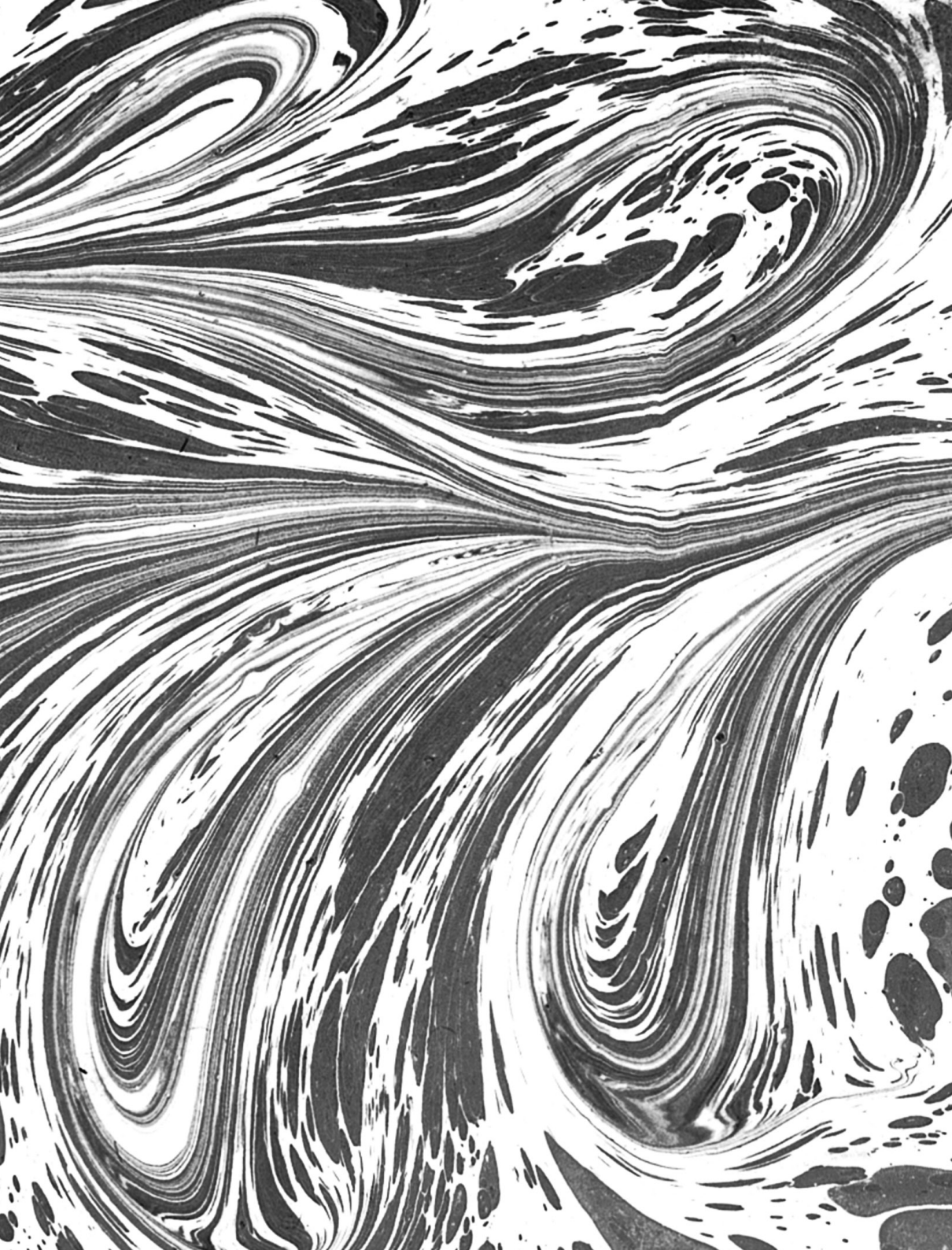

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CURRICULUM VITAE

Sebastiaan Jan Wilhelmus van Kraaij was born on the 12th of January 1994 in Nijmegen, The Netherlands. He graduated *cum laude* from secondary school "Sint-Maartenscollege" in Maastricht in 2011 and started studying medicine at Utrecht University. During his study, he joined the student association Unitas Studiosorum Rheno-Traiectina (U.S.R.), where he served several years as secretary of the debate society (A.D.C.) "Forsete Wara". After obtaining his bachelor's degree in 2015, he continued his education with the Master of Science in Medicine at Utrecht University, during which he performed research on renal Xenon-133 washout curves and their implications on the pathophysiology of hypertension, resulting in two poster presentations at international conferences. After graduating *cum laude* as a medical doctor in 2018, he started his professional career as a resident physician at the department of Internal Medicine in the Diakonessenhuis hospital in Utrecht. In 2019, he started working as a research physician at the Centre for Human Drug Research (CHDR). There he also started his PhD track investigating microcirculation under supervision of dr. P. Gal, dr. M. Moerland and prof. dr. J. Burggraaf. The studies contained in this thesis were performed at the CHDR, several in collaboration with different stakeholders in the pharmaceutical field. During his work at CHDR, he also contributed to numerous other clinical studies in the fields of immunology, neurology, and psychiatry. After completion of his PhD thesis, he continued his professional medical career and is currently employed as resident Internal Medicine in the Tergooi Hospital located in Hilversum.

LIST OF ABBREVIATIONS

1H-MRS	Proton magnetic resonance spectroscopy
AC	Adenyl cyclase
ADMA	Asymmetric dimethylarginine
AE_{last}	Amount excreted in urine until last sample, absolute
$AE_{last\%}$	Amount excreted in urine until last sample, percentage of plasma concentration
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APOGC	Haem-free guanylate cyclase
ASL	Arterial spin labelling
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AU	Arbitrary units
AUC	Area under the curve
AUC_{0-24}	Area under the curve from timepoint 0 to 24 hours
AUC_{0-tz}	Area under the curve from timepoint 0 to the last measurable timepoint
AUC_{τ}	Area under the curve during 1 dosing interval
AUC_{last}	Area under the curve until the last measurable concentration
AUC_{inf}	Area under the curve extrapolated to infinity
$AUEC_{0-tz}$	Area under the biomarker curve from time point 0 to the last quantifiable data point
BEBO	Stichting Beoordeling Ethiek Biomedisch Onderzoek
BH_4	Tetrahydrobiopterin
BLQ / BLOQ	Below limit of quantification
BMI	Body mass index
BOLD	Blood-oxygen-level-dependent
BP	Blood pressure
C_{max}	Maximum concentration
C_{trough}	Trough concentration
CAM	Calmodulin
CAMP	Cyclic adenosine monophosphate
CBF	Cerebral blood flow
CFB	Change from baseline
CI	Confidence interval
CIAS	cognitive impairment associated with schizophrenia
CGMP	Cyclic guanosine monophosphate
CL_R	Renal clearance
CL/F	Total clearance
CNS	Central nervous system
CO_2	Carbon dioxide
COVID-19	Coronavirus disease 2019
COX	Cyclooxygenase
CRP	C-reactive protein
CSE	Cystathionine-lyase
CSF	Cerebrospinal fluid
CTNI	Cardiac troponin I
CV	Coefficient of variation
CYP3A4	Cytochrome P450 3A4
CYP450	Cytochrome P450 epoxygenase
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
E_{max}	Maximum exposure-related concentration
EC	Endothelial cell
ECAR	Extracellular acidification rate
ECG	Electrocardiogram
ECLIA	Electrochemiluminescence immunoassay
EETS	Epoxyeicosatrienoic acids
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ERP	Event-related potential
EU	European Union
FAD	Flavin adenine dinucleotide
FCCP	Carbonyl cyanide-p-trifluoromethoxy-phenylhydrazone
FDA	Food and Drug Administration
FDR	False discovery rate
FI	Food-interaction
FIH	First-in-human
FIR	Far infrared radiation
FMD	Flow mediated dilation
FMN	Flavin mononucleotide
FMRI	Functional magnetic resonance imaging
FMSF	Flow mediated skin fluorescence
GDF-15	Growth/differentiation factor 15
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLP	Good laboratory practice
GPCR	G-protein coupled receptor
H_2O_2	Hydrogen peroxide
H_2S	Hydrogen sulfide
HB	Hemoglobin
HBA1C	Glycated hemoglobin
HED	Human equivalent dose
HETES	Hydroxyeicosatrienoic acids
HNOX	Heme-NO-oxygen binding domain
HV	Healthy volunteer
ICU	Intensive care unit
IL-6	Interleukin 6
JC1	Tetraethylbenzimidazolylcarbocyanine iodide
K2EDTA	Dipotassium ethylenediaminetetraacetic acid
K_{Ca}	Ca^2+-actived potassium channel
KATP	ATP-sensitive potassium channel
KIR	Inwardly rectifying potassium channel
L-ARG	L-arginine
L-CIT	L-citrulline
(HP)LC-MS/MS	(High performance) liquid chromatography with tandem mass spectrometry
LDH	Lactate dehydrogenase
L-NAME	L-nitro-arginine methyl ester
L-NMMA	NG-monomethyl-l-arginine
LOX	Lipoxygenase
LSCI	Laser speckle contrast imaging
LSM	Least squares mean
LTH	Local thermal hyperaemia
LTS	Leukotrienes
LXS	Lipoxines
MAD	Multiple ascending dose
MAX	Maximum
MEDDRA	Medical dictionary for regulatory activities
MEGJ	Myoendothelial gap junctions
MELAS	Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes
MIN	Minimum
MITOD	Mitochondrial disease
MMP	Mitochondrial membrane potential
MMT	Milner learning maze test
MMTT	Mixed meal tolerance test
MRI	Magnetic resonance imaging
N	Number
NAA	N-acetylaspartate
NAD+	Nicotinamide adenine dinucleotide
NADH	Reduced nicotinamide adenine dinucleotide
NADP	Nicotinamide adenine dinucleotide phosphate
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NF-L	Neurofilament light polypeptide
NIRS	Near infrared spectroscopy
NMDA	N-methyl-D-aspartate
NO	Nitric oxide
NO_2	Nitric dioxide
NOAEL	No observed adverse event level
NOS	Nitric oxide synthase
NOS1 / INOS	Inducible nitric oxide synthase
NOS2 / NNOS	Neuronal nitric oxide synthase
NOS3 / ENOS	Endothelial nitric oxide synthase
NT-PROBNP	N-terminal prohormone of brain natriuretic peptide
$O_2^{-\bullet}$	Superoxide
OCR	Oxygen consumption rate
OONO-	Peroxynitrite
OXPHOS	Oxidative phosphorylation
PAT	Peripheral arterial tonometry
PD	Pharmacodynamic
PDE	Phosphodiesterase
PEEG	Pharmaco-electroencephalography
PGS	Prostaglandins
PK	Pharmacokinetic
PKA	Protein kinase A
PKG	Protein kinase G
PLA_2	Phospholipase A2
PLM	Passive leg movement
PMBC	Peripheral blood mononuclear cell
PORH	Post occlusive reactive hyperaemia
PPV	Proportion perfused vessels
PTR	Peak-to-trough ratio
PTX3	Pentraxin 3
PU	Perfusion unit
QD	Once per day
QEEG	Quantitative electroencephalography
R_{csf}	Ratio of cerebrospinal fluid / plasma concentration
$R_{csf-free}$	Ratio of cerebrospinal fluid / free plasma concentration
R_{AUC}	Accumulation ratio calculated from AUC_{τ} at steady state and after a single dose
R_{max}	accumulation ratio calculated from C_{max} at steady state and after a single dose
R_{trough}	accumulation ratio calculated from C_{trough} at steady state and after a single dose
ROS	Reactive oxygen species
SAD	Single ascending dose
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SDFM	Sidestream dark field imaging
SDMA	Symmetric dimethylarginine
SEM	Standard error of the mean
SGC	Soluble guanylyl cyclase *(syn.: soluble guanylate cyclase)*
SMC	Smooth muscle cell
SOD	Superoxide dismutase
SST	Serum separator tube
$T_{½}$	Elimination half life
$T_{½,eff}$	Effective half life based on accumulation
T_{max}	Time to maximum concentration
TEAE	Treatment emergent adverse event
UB	Ubiquitin
ULN	Upper limit of normal
VAS	Visual analogue scale
VCAM-1	Vascular cell adhesion molecule 1
VSMC	Vascular smooth muscle cell
VVLT	Visual verbal learning test

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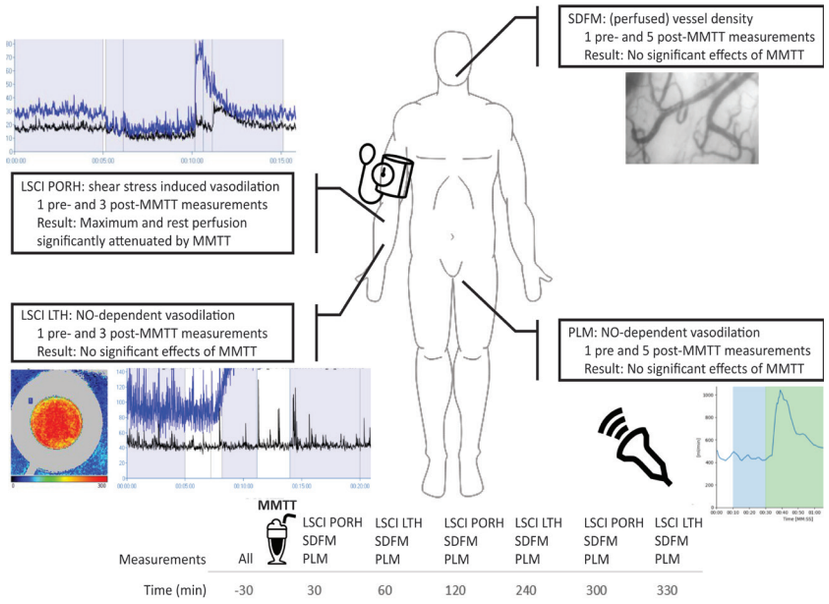
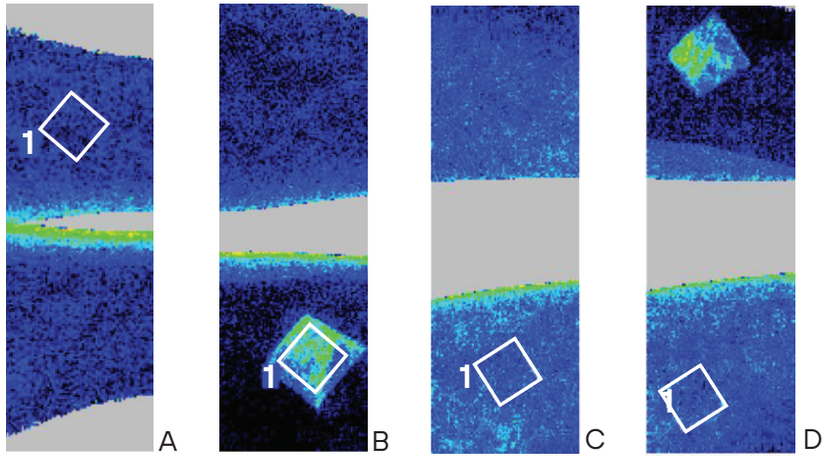
CH.2 / F.1 Overview of employed imaging techniques and timepoints of assessments pre- and post-MMTT administration.



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.