Withstanding the flow

Human cardiovascular control during postural challenges

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Publication date
2018

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SECTION VII

APPENDICES

Summary

This thesis evaluates aspects of the physiology and pathophysiology of the cardiovascular response to posture change. It provides some insight in the postural redistribution of central and peripheral blood volume, sympathetic modulation of the baroreflex and finally the orthostatic influence on cerebral perfusion.

The first two chapters consider methods for the non-invasive and continuous monitoring of the cardiovascular system. In C***hapter 2*** methods for continuous and non-invasive hemodynamic monitoring are reviewed with an emphasis on finger photo-plethysmography. This latter method can be applied for continuous monitoring of blood pressure and heart rate derived from a finger in nearly every patient. Furthermore, the continuous blood pressure signal can be used for real-time stroke volume and cardiac output estimation. In this thesis finger photo-plethysmography is applied to evaluate the cardiovascular response to postural changes. The continuous nature of the photo-plethysmographic signal allows for the study of the interaction between variations in blood pressure at one hand and heart rate or cerebral blood flow at the other hand, quantifying baroreflex sensitivity and cerebral autoregulation, respectively. In the following chapters these parameters are applied to study the regulation of the cardiovascular system and the effects of gravitational challenges in health and disease.

Methods for non-invasive and continuous determination of cardiac output are generally validated against discontinuous estimates of cardiac output, while fluctuations in finger arterial physiology may affect cardiac output determinations by pulse contour methods obtained from the finger arterial pressure wave. In ***Chapter 3*** we demonstrated that variability in hemodynamics and peripheral vasculature physiology impact on the comparison between thermodilution and pulse contour determined cardiac output. In addition, we propose a classification to define hemodynamic stability that can be used when reporting validation studies of non-invasive, continuous cardiac output methods when compared against thermodilution determination of cardiac output.

Identification of the hypovolemic patient requires a definition of normal volume status. In ***Chapter 4*** we propose such a definition according to the Frank-Starling mechanism of the heart, which describes the relation between central blood volume (i.e. cardiac preload) and cardiac stroke volume. With this approach we defined normal volume status in humans as the point where the heart operates on the plateau of the Frank–Starling curve. Posture is an everyday moderator of central blood volume with blood volume migrating from the thoracic and splanchnic compartments to the lower parts of the body when the upright position is assumed. This leads to a reduction in venous return to the heart, resulting in a decrease in cardiac stroke volume. In healthy subjects the plateau of the Frank-Starling curve is established in the supine position.

The postural accumulation volume in the lower extremities has traditionally been studied using strain gauge plethysmography. Is has been assumed that the fall in central blood volume is induced by a rapid increase of leg blood volume, while the progressive decline in central blood volume in the upright position is considered to be driven by capillary fluid filtration due to the increased hydrostatic pressure. However, strain gauge plethysmography does not differentiate between the intra- and extra-vascular contributions of the postural

increase in leg volume. In ***Chapter 5*** we applied near-infrared spectroscopy (NIRS) to monitor the orthostatic induced increase in intravascular blood volume in the lower leg. We observed that the prolonged orthostatic increase in leg volume is not solely the result of transcapillary fluid filtration but at least in part by a sustained accumulation of blood volume.

With progressively decreasing cardiac preload the baroreflex is activated to compensate for the subsequent decrease in cardiac stroke volume and resulting lower blood pressure. Baroreflex sensitivity is a reflection of sympathico-vagal balance and offers a method to study autonomic cardiovascular regulation under several circumstances and has shown to be of clinical and prognostic importance. In ***Chapter 6*** we studied the effect of acute psychological stress induced by the gravitational challenge of bungee jumping on baroreflex sensitivity. Partial blockade of the sympathetic autonomic nervous system by the β-blocker propranolol appeared to improve baroreflex sensitivity during psychological stress. This may describe a mechanism behind the anti-arrhythmic effect of β-blockers during acute psychological stress, in particular in patients with heart disease.

The clinical effect of β-blockade in heart failure patients is influenced by the pharmacological selectivity to the β_1-and β_2-receptor. Still, a single type of β-blocker may have various responses among patients. This may partially be explained by genetic variations in the β_2-receptor associated with agonist-mediated desensitization of this receptor. In ***Chapter 7*** we studied the combined effect of β-blocker selectivity and two genetic polymorphisms of the β_2-receptor on baroreflex sensitivity in chronic heart failure patients. The data indicate that in particular patients relatively resistant to β_2-receptor desensitization could benefit from nonselective β-blockade.

Systemic cardiovascular reflexes alone cannot sufficiently secure blood flow to the brain in the upright position. Cerebral autoregulation supports adequate blood flow to the brain despite fluctuation in perfusion pressure, but does nevertheless not prevent a decrease in cerebral blood flow from supine to the upright position. The cerebral vasoconstriction induced by a decrease in arterial carbon dioxide partial pressure in the upright position has been suggested to account for this observation. In ***Chapter 8*** we demonstrated that the postural reduction in arterial carbon dioxide only explains the initial, but not the prolonged, reduction in cerebral blood flow after standing.

Local obstruction of cerebral blood flow may lead to ischemic stroke posing a serious threat to health and even to life. Horizontal head-of-bed position has been suggested as an intervention to optimize cerebral blood perfusion, while considerable heterogeneity of the cerebrovascular response to head-of-bed manipulation among patients exists. Under healthy conditions cerebral perfusion is more or less maintained during fluctuations in perfusion pressure by cerebral autoregulation. Ischemic stroke may affect cerebral autoregulation into various degrees. In ***Chapter 9*** we found that the cerebrovascular response to head-of-bed lowering relates to the efficacy of cerebral autoregulation after acute ischemic stroke. This questions the feasibility of generalized recommendations and could guide individualized positioning and mobilization of patients in the acute phase of ischemic stroke.

Samenvatting

In dit proefschrift worden aspecten van de fysiologie en pathofysiologie van de cardiovasculaire respons op houdingsverandering geëvalueerd. Inzicht wordt verkregen in de houdingsafhankelijke herverdeling van het centrale en perifere bloedvolume, de sympathische modulatie van de baroreflex en uiteindelijk de orthostatische invloed op de cerebrale perfusie.

De eerste twee hoofdstukken beschouwen methoden om het cardiovasculaire systeem niet-invasief en continu te monitoren. In **hoofdstuk 2** worden methoden voor continue en niet-invasieve hemodynamische monitoring beschreven, waarbij de nadruk ligt op foto-plethysmografie van de vinger. Deze methode kan worden toegepast voor de voortdurende controle van de bloeddruk en de hartfrequentie vanuit de vinger van vrijwel iedere patiënt. Bovendien kan het continue bloeddruksignaal worden gebruikt voor real-time cardiaal slagvolume en hartminuutvolume schatting. In dit proefschrift wordt vinger foto-plethysmografie toegepast om de cardiovasculaire respons op houdingsveranderingen te evalueren. Vanwege het continue karakter van het foto-plethysmografische signaal is de techniek geschikt om de interactie tussen variaties in bloeddruk, aan de ene kant, en hartslag of cerebrale bloedstroom, aan de andere kant, respectievelijk baroreflex gevoeligheid en cerebrale autoregulatie, te bestuderen. In de daaropvolgende hoofdstukken worden deze parameters toegepast om de regulatie van het cardiovasculaire systeem te onderzoeken en de effecten van zwaartekracht bij gezondheid en ziekte.

Methoden voor niet-invasieve en continue bepaling van het hartminuutvolume worden in het algemeen gevalideerd tegen intermitterende schattingen van het hartminuutvolume. Daarnaast kunnen schommelingen in de arteriële fysiologie bepalingen van het hartminuutvolume uit de arteriële drukgolf in de vinger doormiddel van pulse-contour methoden beïnvloeden. In **hoofdstuk 3** tonen we aan dat de variabiliteit in hemodynamiek en perifere vaatfysiologie invloed heeft op de vergelijking tussen het thermodilutie en pulse-contour bepaalde hartminuutvolume. We stellen een classificatie voor om hemodynamische stabiliteit te definiëren die gebruikt kan worden bij het rapporteren van validatiestudies tussen niet-invasieve, continue hartminuutvolume methoden tegen bepaling van het hartminuutvolume doormiddel van thermodilutie.

Identificatie van de hypovolemische patiënt vereist een definitie van het normale bloedvolume. In **hoofdstuk 4** stellen wij een definitie van normale bloedvolume voor volgens het Frank-Starling-mechanisme van het hart, dat de relatie tussen het centrale bloedvolume (cardiale ‘preload’) en het slagvolume van het hart beschrijft. Met deze benadering kan het normale bloedvolume in de mens worden gedefinieerd als het punt waar het hart op het plateau van de Frank-Starling-curve functioneert. Lichaamshouding is een alledaagse manipulator van het centrale bloedvolume waarbij het bloedvolume migreert vanuit de thoracale en splanchnische compartimenten naar de onderste delen van het lichaam wanneer de staande positie wordt aangenomen. Dit leidt tot een vermindering van de veneuze terugstroom van bloed naar het hart, wat resulteert in een afname van het cardiale slagvolume. Bij gezonde personen wordt het plateau van de Frank-Starling-curve in de liggende positie bereikt. Gezien houdingsverandering een fysiologische reactie induceert is deze manoeuvre regelmatig in dit proefschrift gebruikt om de cardiovasculaire autonome regulatie te bestuderen.

De houdingsafhankelijke accumulatie van bloedvolume in de onderste ledematen wordt traditioneel onderzocht met behulp van 'strain-gauge-plethysmography'. Aangenomen werd dat de afname in het centrale bloedvolume wordt geïnduceerd door een snelle vulling van de bloedvaten in de benen, terwijl de aanhoudende afname van het centrale bloedvolume in de staande positie wordt verklaard door capillaire vloeistoffiltratie als gevolg van de verhoogde hydrostatische druk. Met behulp van 'strain-gauge-plethysmography' kan echter geen onderscheid worden gemaakt tussen de intra- en extra-vasculaire bijdragen van de houdings-induceerde toename van het been volume. In **hoofdstuk 5** hebben we 'near-infrared spectroscopie' (NIRS) toegepast om de orthostatisch geïnduceerde toename in intravasculaire bloedvolume in het onderbeen waar te nemen. We constateerden dat de aanhoudende orthostatische toename van het beenvolume niet alleen het resultaat is van transcapillaire vloeistoffiltratie, maar dat er sprake is van een voortdurende accumulatie van het bloedvolume.

Met een toenemende daling van de cardiale 'preload' wordt de baroreflex geactiveerd om te compenseren voor de daaropvolgende afname van het cardiale slagvolume en de bloeddruk. Baroreflex gevoeligheid is een weerspiegeling van de sympathisch-vagale balans en biedt een methode om autonome cardiovasculaire regulatie onder verschillende omstandigheden te bestuderen en lijkt van klinisch en prognostisch belang te zijn. In **hoofdstuk 6** bestudeerden we het effect van acute psychologische stress veroorzaakt door de invloed van zwaartekracht, in de vorm van bungeejumpen, op de baroreflex gevoeligheid. Gedeeltelijke blokkade van het sympathische autonome zenuwstelsel door de β-blokker propranolol bleek de gevoeligheid van de baroreflex te verbeteren tijdens de psychologische stress. Dit beschrijft mogelijk een mechanisme achter het anti-aritmische effect van β-blokkers bij acute psychologische stress, in het bijzonder bij patiënten met hart- en vaatziekten.

Het klinische effect van β-blokkade bij patiënten met hartfalen wordt beïnvloed door de farmacologische selectiviteit voor de β_1- en β_2-receptor. Toch kan een enkel type β-blokker verschillende effecten veroorzaken tussen patiënten. Dit kan gedeeltelijk worden verklaard door genetische variaties in de β_2-receptor geassocieerd met agonist-gemedieerde desensibilisatie van deze receptor. In **hoofdstuk 7** bestudeerden we het gecombineerde effect van β-blokkerselectiviteit en twee genetische polymorfismen van de β_2-receptor op de baroreflex gevoeligheid bij patiënten met chronisch hartfalen. Deze bevindingen wijzen er op dat vooral patiënten die relatief bestand zijn tegen β_2-receptor-desensibilisering kunnen profiteren van niet-selectieve β-blokkade.

Systemische cardiovasculaire reflexen alleen zijn onvoldoende in staat om een adequate bloedstroom naar de hersenen in de staande positie te waarborgen. Cerebrale autoregulatie ondersteunt een adequate bloedstroom naar de hersenen ondanks schommelingen in de perfusiedruk, maar kan desalniettemin niet voorkomen dat een afname van de cerebrale bloedstroom optreedt als de staande positie wordt aangenomen. Cerebrale vasoconstrictie geïnduceerd door een afname in arteriële kooldioxide druk tijdens staan wordt gesuggereerd als verklaring voor deze waarneming. In **hoofdstuk 8** tonen we aan dat de posturale reductie van arterieel kooldioxide alleen de initiële, maar niet de aanhoudende vermindering van de cerebrale bloedstroom na staan verklaart.

Lokale obstructie van de cerebrale bloedstroom kan leiden tot een herseninfarct welke een ernstige bedreiging voor het functioneren en zelfs voor het leven vormt. De horizontale positie van het hoofdeinde van het bed is gesuggereerd als een interventie om de cerebrale

bloeddoorstroming te optimaliseren, echter bestaat er tussen patiënten aanzienlijke heterogeniteit in de cerebrovasculaire respons op de manipulatie van het hoofdeinde. Onder gezonde omstandigheden wordt de cerebrale perfusie min of meer gehandhaafd tijdens fluctuaties in perfusiedruk door de cerebrale autoregulatie. Na een herseninfarct kan de cerebrale autoregulatie echter in wisselende mate zijn aangedaan. In **hoofdstuk 9** vonden we dat de cerebrovasculaire respons op het verlagen van het hoofdeinde gerelateerd is aan de effectiviteit van de cerebrale autoregulatie na een herseninfarct. Dit trekt de bruikbaarheid van gegeneraliseerde aanbevelingen in twijfel en kan geïndividualiseerde adviezen t.a.v. lichaamshouding en mobilisatie van patiënten in de acute fase van een herseninfarct ondersteunen.

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Dankwoord

Om te beginnen wil ik alle proefpersonen die hun medewerking hebben verleend aan de door ons verrichtte onderzoeken hartelijk danken. De totstandkoming van dit proefschrift is daarbij van ondergeschikt belang aan de bijdrage die proefpersonen aan de wetenschap verlenen. Zonder hen zou de vooruitgang in de wetenschap, en in het bijzonder in de geneeskunde, een stuk minder voorspoedig zijn.

Beste *Han*, jou wil ik natuurlijk als een van de eersten veel dank tonen voor je onmiskenbare bijdrage aan de totstandkoming van dit proefschrift. Je staat aan het begin van mijn wetenschappelijke loopbaan en ik heb ontzettend veel van je geleerd. Vooral je ontembare enthousiasme en positivisme hebben mij het inzicht verschaft dat er altijd weer een oplossing is om de vele drempels te passeren voor resultaten wereldkundig worden gemaakt. Maar ook het gezamenlijk afstruinen van je muziekdatabase hebben een niet onbelangrijke bijdrage geleverd aan de plezierige samenwerking. Hierbij wisselden we onze toch enigszins verschillende muziekvoorkeuren uit, wat in ieder geval mijn muzikale horizon maar ik vermoed ook die van jou, verder verbreed heeft. Ik hoop en verwacht dat deze momenten niet uitsluitend tot het verleden zullen behoren.

Beste *Prof. Moorman*, beste Antoon, het is een grote eer om als één van de laatste (zo niet dé laatste?!) promovendi de doctorstitel te mogen ontvangen van een wetenschapper met zo een indrukwekkende staat van dienst. Veel dank voor uw tijd en de bijdrage aan de afronding van mijn promotie!

De leden van de promotiecommissie; *Prof. van Bavel, Prof. Roos, Prof. Stroes, Dr. Pott* en *Prof. Wang*. Thank you very much for your willingness to participate in the Doctorate Committee and for the time taken to read and evaluate the scientific quality of this thesis.

Yu-Sok, dank voor de mooie tijd die we samen hebben doorgebracht op M01 in het AMC. Hoewel we daar in de 'kelder' van het AMC zaten weggestopt, zou menig promovendus jaloers zijn op onze ruime kamer, met voor het AMC zeldzame daglichtinval en uitzicht op een prachtig gazonnetje. Je bent een fijne collega waarmee ik naast wetenschappelijk te kunnen sparren, ook veel gezellige momenten heb beleefd. Zowel het gezamenlijk uitvoeren van thermodiluties op de operatiekamer als onze verkenning van Seoul (voor jou iets minder onbekend dan voor mij) zijn dierbare herinneringen die mij nog lang bij zullen blijven. Uiteraard ben ik je ook dankbaar dat je bereid bent mijn paranimf te zijn.

Peter, we go way back! Dat is een uitspraak die op onze vriendschap zeker van toepassing is. Al onze herinneringen zouden een apart boek kunnen vullen, maar voorlopig heb ik even genoeg geschreven. Het betekent veel voor mij dat jij me tijdens de verdediging van dit proefschrift wilt bijstaan als paranimf!

Berend, naast je inhoudelijk grote bijdrage aan verschillende hoofstukken van dit proefschrift ben ik je ook dankbaar voor de fijne samenwerking en je (soms ietwat droge) humor en relativerende houding. Velen die mij goed kennen zullen beamen dat ik deze eigenschappen wel kan waarderen.

Wim, vrijwel geen enkele studie komt goed van de grond voordat jij er je technische en analytische blik op hebt geworpen. Mijn dank voor je onmisbare bijdrage is groot. Ik hoop dat het AMC, en in het bijzonder het Laboratorium voor Klinische Cardiovasculaire Fysiologie, nog lang van je talenten kunnen profiteren.

John, dank voor je kritische blik en feedback waar ik als startende wetenschapper veel van heb geleerd.

Shyrin, je hebt een belangrijke bijdrage geleverd aan de vele studies die we samen hebben uitgevoerd. Maar ook je prettige gezelschap is een onuitwisbare herinnering. Dank voor je inzet en de talloze momenten dat we hebben gelachen. Ik wens je een hele mooie toekomst!

Nina (Yanru), no matter that we grew up on opposite sides of the planet, we appreciated each other's humor and I enjoyed your company. I wish you a lot of happiness and good luck!

Stagiaires *Dagmar, Lotte, Renee, Saskia* en *Milène*. Dank voor jullie nieuwe inzichten en bijdragen aan de onderzoeken die we samen verricht hebben. Het was prettig met jullie samen te mogen werken en ik wens jullie een mooie carrière en veel geluk toe!

Collegae (ex-)promovendi *Erfan, Olav, Saskia, Bas* en *Barbara*. Jullie zijn mij inmiddels al vooruitgestreefd en hebben jullie promotie afgerond. Ik heb nu nog groter respect voor de prestatie die jullie hebben neergezet. Veel dank voor de fijne samenwerking en voor de mooie resultaten die we samen bereikt hebben.

I want to thank *all co-authors* for their contribution to the publications in this thesis. Teamwork is the only way to good science!

Jeroen van Goudoever en *Willy Colier*, zonder jullie technische bijdragen en ondersteuning zouden veel studies niet afgerond, of zelf niet van de grond, zijn gekomen. Veel dank daarvoor!

Collega's van de Interne geneeskunde en Vasculaire geneeskunde AMC, in het bijzonder *Bert-Jan van den Born* en *Jan Prins* die met enige regelmaat informeerden naar de afronding van dit proefschrift en daarmee de nodige stok achter de deur wisten te verstevigen.

Mijn *ouders en broers*, een belangrijk deel van de kansen die ik heb gekregen om dit proefschrift te schrijven zijn door jullie gecreëerd. Ik ben trots op mijn familie en ben dankbaar dat ik hierin heb mogen opgroeien. Ik hoop nog heel lang van jullie liefde, gezelschap en steun te mogen genieten.

Lieve *Lieke*, veel dank voor het bieden van een thuis waar ik liefde en rust vind. Niet alleen noodzakelijk om de energie te vergaren om, tijdens mijn opleiding tot internist, dit proefschrift af te ronden, maar vooral om gelukkig te zijn. Ik dank je voor je begrip dat ik vaak geen tijd had om samen activiteiten te ondernemen. Gelukkig hebben we nog een hele lange tijd voor ons, waarbij de komst van *Veerle* mij nog eens extra duidelijk heeft gemaakt wat echt belangrijk is in het leven.

Portfolio

1. PhD training		
	Year	**ECTS**
General courses		
- Practical Biostatistics	2008	1.1
Specific courses		
- Integrative Human cardiovascular control, Copenhagen	2009	3.0
Seminars, workshops and master classes		
- Masterclass by Prof. Stehouwer	2010	0.2
Conferences and Presentations		
- Jonge Fysiologen dag, Papendal (oral presentation)	2007	0.5
- Wetenschapsdag Nederlandse Hartstichting, Amsterdam (poster presentation)	2008	0.5
- 7th World Stroke Congress, Seoul (poster presentation)	2010	1.5
- 2nd Rembrandt Symposium, Amsterdam (poster presentation)	2011	0.5

2. Teaching		
	Year	**ECTS**
Tutoring, Mentoring		
- Master Technische Geneeskunde Universiteit Twente (3 students)	2011	4.0

Publications

Truijen J, Westerhof B, Kim YS, Stok W, de Mol BAJM, Preckel B, Hollmann M, van Lieshout JJ. The effect of hemodynamic and peripheral vascular variability on cardiac output monitoring: thermodilution and pulse contour cardiac output during cardiothoracic surgery. *Anaesthesia.* In press 2018.

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Curriculum Vitae

Jasper Truijen werd geboren op 27 juni 1980 in Tilburg. Na in 1997 zijn HAVO-diploma behaald te hebben op het Cobbenhagen College te Tilburg, behaalde hij op dezelfde school in 1999 zijn VWO-diploma. De eerste loting in het kader van de numerus fixus voor de studie Geneeskunde was niet succesvol en Jasper begon daarom met volle overtuiging en enthousiasme aan de studie Medische Biologie aan de Universiteit van Amsterdam. Eén jaar later pakte een herhaalde poging om ingeloot te worden voor de studie Geneeskunde alsnog succesvol uit. De studie Medische Biologie werd beëindigd met het behalen van de propedeuse in het jaar 2000 en Jasper startte in dat jaar met de studie Geneeskunde aan dezelfde universiteit. In 2007 behaalde hij zijn artsexamen en ging werken als arts-onderzoeker onder leiding van Prof. dr. J.J. van Lieshout in het laboratorium voor Klinische Cardiovasculaire Fysiologie binnen het AMC te Amsterdam. In 2012 begon Jasper aan zijn klinische werkzaamheden tijdens de specialisatie tot internist in het AMC. Gedurende deze opleiding is hij, naast het AMC, werkzaam geweest in het Rode Kruis Ziekenhuis te Beverwijk, het Onze Lieve Vrouwe Gasthuis te Amsterdam en het Westfriesgasthuis te Hoorn. Binnen de opleiding interne geneeskunde begon hij in 2016 aan de differentiatie tot vasculair geneeskundige in het AMC. In 2018 is deze opleiding afgerond en ging hij werken als internist-vasculair geneeskundige in het Waterlandziekenhuis te Purmerend. Jasper woont samen met zijn vriendin Lieke en dochter Veerle in Amsterdam.