UvA-DARE (Digital Academic Repository)

Physical manoeuvres to prevent vasovagal syncope and initial orthostatic hypotension

Krediet, C.T.P.

Publication date

2007

Document Version

Final published version

[Link to publication](#)

Citation for published version (APA):

Krediet, C. T. P. (2007). *Physical manoeuvres to prevent vasovagal syncope and initial orthostatic hypotension*. [Thesis, fully internal, Universiteit van Amsterdam]. Vossiuspers - Amsterdam University Press.

General rights

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

Physical Manoeuvres to Prevent Vasovagal Syncope and Initial Orthostatic Hypotension

C.T.P. Krediet

UNIVERSITEIT VAN AMSTERDAM

Physical Manoeuvres to Prevent Vasovagal Syncope and Initial Orthostatic Hypotension

The studies described in this thesis were supported by a grant from the Netherlands Heart Foundation (NHF-2004T007).

Financial support by the Netherlands Heart Foundation and the Amsterdam Pathophysiology of the Circulation Research Foundation for the publication of this thesis is gratefully acknowledged.

Cover: artist's impression of the effects of leg crossing with muscle tensing on blood volume distribution: (front), and blood volume distribution during prolonged orthostatic stress without intervention (back), by I. E. M. Kos-Oosterling, Department of Medical Illustrations, Academic Medical Center at the University of Amsterdam

Ontwerp omslag: René Staelenberg, Amsterdam

Lay out: V3-Services, Baarn

ISBN 978 90 5629 493 9

NUR 870

© Vossiuspers UvA – Amsterdam University Press, 2007

All rights reserved. Without limiting the rights under copyright reserved above, no part of this book may be reproduced, stored in or introduced into a retrieval system, or transmitted, in any form or by any means (electronic, mechanical, photocopying, recording or otherwise) without the written permission of both the copyright owner and the author of the book.

Physical Manoeuvres to Prevent Vasovagal Syncope and Initial Orthostatic Hypotension

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. D.C. van den Boom
ten overstaan van een door het College voor Promoties
ingestelde commissie, in het openbaar te verdedigen
in de Aula der Universiteit
op donderdag 4 oktober 2007, te 14.00 uur

door

Constantijn Thomas Paul Krediet

geboren te Zeist

Promotiecommissie:

Promotores: Prof. dr. M. M. Levi
Prof. dr. M. J. Joyner
Co-promotores: Dr. W. Wieling
Dr. J. J. van Lieshout
Leden: Dr. N. Charkoudian
Prof. dr. E. Fliers
Dr. D. L. Jardine
Dr. J. M. Karemaker
Prof. dr. A. F. M. Moorman
Prof. dr. M. de Visser
Prof. dr. A. A. M. Wilde

Faculteit der Geneeskunde

Contents

Acknowledgements 7

Co-authors and their Current Affiliations 9

1 Introduction 11

2 Management of Vasovagal Syncope: Controlling or Aborting Faints
by Leg Crossing and Muscle Tensing 27

3 Leg Crossing, Muscle Tensing, Squatting and the “Crash-position”
Are Effective Against Vasovagal Reactions Through Increases in
Cardiac Output 39

4 Leg Crossing Improves Orthostatic Tolerance in Healthy Subjects:
a Placebo Controlled Cross-over Study 51

5 Lower Body Muscle Tensing Diminishes the Blood Pressure Decrease
upon Standing from Squatting in the Post-vasovagal State 61

6 Management of Initial Orthostatic Hypotension: Lower Body Muscle
Tensing Attenuates the Transient Arterial Blood Pressure Decrease
upon Standing From Squatting 73

7 Conclusions 83

Samenvatting (Dutch Summary) 87

References 91

Abbreviations 109

Acknowledgments

On the completion of this thesis, I am deeply grateful to the many people who have contributed to its realization.

Foremost I wish to express my gratitude to Dr. Wouter Wieling, who, from the moment he offered me employment as a technician at the tilt table while I was still a medical student, mentored me and guided me in performing clinical physiological research, both inside and outside the laboratory.

Dr. Han van Lieshout also went to great lengths to support my work. I thank him for teaching a meticulous approach, both in doing experiments and reporting them.

I am indebted to Professors Marcel Levi and Michael Joyner as promotores. I thank Marcel Levi for his support and advice, which started before this project took shape. I am looking forward to working under his clinical leadership in the near future. I thank Michael Joyner for his welcoming and motivating attitude during my recent stay at his laboratory at Mayo Clinic (Minnesota, USA). I hope we will have an ongoing collaboration.

Dr. David Jardine from Christchurch (New Zealand) welcomed me to his department in 2001 for six months. It is a delight that one of the tangible results of that stay, the published description of vasovagal sleep syncope syndrome (107) did not go unnoticed and was acknowledged by an international panel on syncope (20). It is an honour that David Jardine accepted the promotores' invitation to join the doctoral committee. I feel equally honoured that Dr. Nisha Charkoudian (Mayo Clinic), Professor Eric Fliers, Dr. John Karemaker, and Professors Antoon Moorman, Marianne de Visser and Arthur Wilde also agreed to join the doctoral committee.

The studies presented here are foremost a collaborative effort and it is a pleasure to share the credit with Sander Bogert, Ivar de Bruin, Dr. Nynke van Dijk, Karin Ganzeboom, Ingeborg Go-Schön, Rogier Immink and Yu-Sok Kim. Special

thanks go to Professor Mark Linzer, whose thorough but careful adjustments to the manuscript drafts set an inspiring example, and considerably improved the quality of the published work.

These studies would not have been possible without the emphatic support of the Netherlands Heart Foundation and its contributors. I sincerely thank the Foundation for its continuing trust and support.

I would also like to thank the Fulbright Program for granting me a scholarship at Mayo Clinic. In addition, over the period from the first observations reported in this thesis to its completion, I am grateful for financial support from the Dutch VSB Foundation, the Van Walree Foundation (Royal Netherlands Academy of Arts and Sciences), the Clinical Autonomic Research Society (UK), the Amsterdam Society for Physics, Medicine and Surgery, the Ruitinga Van Zwieten Foundation (Amsterdam), the Spinoza Fund (Amsterdam University Association), and the Amsterdam Pathophysiology of the Circulation Research Foundation.

Finally, I thank the volunteers who participated in the studies and hope that the work described in this thesis may be to the benefit of syncope patients.

P.K.

Utrecht, 25 June 2007

Co-authors and their Current Affiliations

L. W. J. Bogert, Department of Internal Medicine, Academic Medical Center at the University of Amsterdam

I. G. J. M. de Bruin, Department of Surgery, Medical Center Alkmaar

Dr. N. van Dijk, Departments of Clinical Epidemiology and Bio-Statistics and of General Practice, Academic Medical Center at the University of Amsterdam

K. S. Ganzeboom, GGD Amsterdam

R. V. Immink, Department of Anaesthesiology, Academic Medical Center at the University of Amsterdam

Y. S. Kim, Department of Internal Medicine, Academic Medical Center at the University of Amsterdam

Dr. J. J. van Lieshout, Department of Internal Medicine, Academic Medical Center at the University of Amsterdam

Prof. M. Linzer, Department of Medicine, University of Wisconsin

I. K. Go – Schön, Department of Internal Medicine, Academic Medical Center at the University of Amsterdam

Dr. W. Wieling, Department of Internal Medicine, Academic Medical Center at the University of Amsterdam

I. Introduction^I

Transient loss of consciousness (TLOC) is a common medical problem, constituting ~1% of emergency department visits (29, 187). Vasovagal reactions are by far the most frequent cause; estimates in the emergency department setting range from 40 (93) to 60% (22). In the general population the life-time cumulative incidence of TLOC up to the age of 60 years is ~35% and >90% of these episodes are considered to be of vasovagal origin (62). Patients with vasovagal syncope may suffer from recurrent loss of consciousness, varying from once a year to weekly (and in rare cases daily) episodes. The majority of the patients with vasovagal syncope also experience frequent pre-syncope, which can be just as incapacitating as syncope itself (202).

Vasovagal syncope is not a dangerous condition as episodes are self-limiting. However, the quality of life of patients with recurrences can be seriously affected (118, 119, 201, 202). The costs from the diagnostic work-up of vasovagal syncope are high and the yield of extensive diagnostic testing is limited (6, 27, 29). Therapy of vasovagal syncope is therefore an important issue; however, the therapeutic options are limited and their efficacy suboptimal.

Terminology

Syncope is a subclass of TLOC. The term syncope is derived from the Greek word *συν-κόπτω* (“syg-kopto”), meaning “to cut short”, and Hippocrates himself provided the first (known) description of the disorder (82). In the modern medical jargon syncope refers to an episode of TLOC with loss of postural tone that spontaneously resolves and that can be provoked by any condition that jeopardizes cerebral perfusion (20, 209).

^I In part adapted from (110), © 2007 Oxford University Press and from (225), © 2007 Biochemical Society

The terminology of syncope and its related disorders is diverse and if used unpunctually may easily become misleading (192, 194). TLOC covers all syncopal, epileptic, metabolic and psychogenic forms of loss of consciousness that spontaneously resolve. “Syncope” refers to TLOC caused by transient cerebral hypoxia by transient disturbances in blood pressure control either from cardiac arrhythmias (“cardiac syncope”) or neurally mediated mechanisms. The majority of neurally mediated syncopes are “vasovagal syncopes” (another example is the carotid sinus syndrome). Sir Thomas Lewis introduced the term “vasovagal syncope” in its current meaning in 1932, stressing that both the blood vessels – vaso – and the heart – vagal – are involved (116). “Faint” is a lay term for TLOC, whereas “the common faint” refers specifically to vasovagal syncope. For the latter “vasovagal fainting” may be a useful synonym.

Epidemiology

Self reported episodes of TLOC in the general population are very common (62). However, only about a third (62) to half (179) of all episodes of TLOC in the general population reaches medical attention .

Patients with presumed vasovagal syncope present themselves to general practitioners according to a bimodal age distribution, with a first peak at the age of ~15 years, and a second peak in adults >60 years of age (35).

Figure 1.1 Frequency of “fainting” as a reason to consult a general practitioner in The Netherlands (based on 93, 297 patient years). White dots represent males, black dots females. Reproduced from (222) with permission from the publisher, ©2003 Bohn Stafleu van Loghum

Studies in teenagers, adolescents and young adults show a strikingly high incidence of TLOC of presumed syncopal origin. Two recent surveys of the frequency of syncope in medical students demonstrated that 20 – 25% of males and 40 – 50% of females report to have experienced at least one such episode (61, 166). The majority of the syncope triggers identified in these students involved stresses or conditions that affect orthostatic blood pressure control. Vasovagal syncope was therefore a likely cause of the symptoms in these young subjects. The incidence peak of presumed neurally mediated syncope around the age of 15 years and the much higher incidence in young females is a consistent finding (35, 61, 62, 166, 173). A family history of presumed vasovagal syncope in the first degree relatives is often present in young subjects who fainted (128, 166). Compared to the 30% prevalence of presumed vasovagal syncope in young medical students, the prevalence of epileptic seizures in a similar young age group is much lower (<1%) (211) and syncope from cardiac arrhythmias or structural heart disease, i.e. cardiac syncope is even less common (35).

A first neurally mediated syncopal episode is rare in adults aged 30 – 50 years (62, 173). About 80% of the syncope patients in this age group have experienced presumed neurally mediated episodes as teenagers and adolescents, which may be of help in establishing a diagnosis (62, 166). Often vasovagal syncope presents in clusters (56) The recurrence risk for treated (see below) vasovagal syncope after tilt-table testing is 49% in the three years after the test (172).

In general, vasovagal syncope is less common in senior persons (173). It is not unusual that episodes of vasovagal syncope in a senior patient are far less typical (i.e. not accompanied by a typical prodromal pattern) than vasovagal syncope at younger age (45). Thus, vasovagal syncope may be considered a chronic life long condition, with different clinical presentation and triggers among episodes (35, 112, 173).

Impact on quality of life from transient loss of consciousness

Several studies have documented the impact of recurrent TLOC on the quality of patients' lives (118, 119, 148, 201, 202). Theoretically the physical functioning of TLOC patients in between episodes should be normal (202). However, the quality of life is seriously affected especially in patients with pre-syncopal episodes and a recent onset of clinical symptoms. Both physical and mental functioning are impaired by TLOC to a degree similar to that reported in chronic diseases such as severe rheumatoid arthritis (119, 202) and recurrent moderate depressive disorder (202). Not surprisingly, the impact on quality

of life is positively correlated to the number of episodes of TLOC (148, 202), possibly related to the patients' fear of a recurrence especially during dangerous activities (e.g. driving a car), and legal restrictions that may limit participating in daily physical activities (202). For frequent pre-syncope episodes the continuous confrontation with upcoming episodes can have an additional impact on quality of life (202).

Vasovagal syncope

Triggers

Recognised triggers for vasovagal syncope are prolonged orthostatic stress, blood drawing, instrumentation and psychological stressors (116, 184, 208).

Psychological stressors include stirring emotional news or witnessing a distressing accident (55, 116) and both anticipated and unexpected pain or threat (70, 116, 168). Unpleasant smells may trigger vasovagal syncope (54, 61). During blood drawing, vaccination (18) or instrumentation, the pain associated with the procedure may contribute to the occurrence of vasovagal syncope. Sharp pain is reported to be an important factor during arterial blood sampling (154). However, in a patient with blood phobia just thinking or talking about blood drawing may elicit a common faint (203), so there may not always be an external triggering factor. Interestingly blood phobia is the only phobia that can induce vasovagal syncope (even in the supine position (70)). Other phobias usually cause arousal with tachycardia and an increased systemic blood pressure (125).

There are several situational factors that, by themselves do not trigger syncope, but can act as predisposing factors, such as a high ambient temperatures (69, 230). Other environmental factors include confined spaces or crowding that force the patient to stand still ('church syncope' and 'rock concert syncope') (69, 115, 116, 135, 169), stopping of strenuous exercise ('post exercise vasovagal syncope') (111), staying at high altitude (51, 217), presence of fever (101) or migraine (193), recent "illness" (40, 116, 214), sleep deprivation (61), menstruation (69), rapid weight loss (65), after prolonged bed rest or weightlessness (space travel) (25, 65), nausea (169) and motion sickness (16), presence of fatigue (69), period of fasting and starvation (10, 69) and the use of alcohol (138) and drugs.

Witnessing a faint may trigger vasovagal fainting in the witness himself, mass vasovagal fainting can be the result (115, 135). All the factors mentioned here typically affect young, rather than older subjects (>50 years of age).

Figure 1.2 Example of blood pressure (BP) and heart rate (HR) records during a vasovagal reaction provoked by a tilt test. Time represents duration of head-up tilting. Left arrow indicates occurrence of first prodromal symptoms, right arrow the tilt back to the horizontal position. Reproduced from (104) with permission from the publisher, ©2003 Bohn Stafleu van Loghum

Pathophysiology of vasovagal syncope

Vasovagal syncope has a complex pathophysiology (208). As described above various environmental, somatic and non-somatic factors may contribute to its occurrence. However, since the vast majority of vasovagal syncopes occur when exposed to orthostatic gravitational stress this is generally regarded as the predominant triggering factor. In discussing the pathophysiology of vasovagal syncope we will focus on the orthostatic type.

Fluid shifts during orthostatic stress

When changing to the erect posture from supine, within 10 s an estimated 500 – 800 ml of blood shifts from above to below the diaphragm (3, 175). Most of this volume pools in the large deep veins of the upper legs and buttocks (49, 120). Additionally, there is some pooling in the abdominal and pelvic regions (76, 151). This blood is not stagnant; rather its circulatory transit time through the dependent region is increased by the increase of the venous volume below the diaphragm (146). Following this initial rapid fluid shift after standing up, with prolonged orthostatic stress the increased capillary trans-mural pressure in the dependent parts of the body facilitates filtration of fluid into the extra-vascular space. Estimates range to a further 700 ml decrease of plasma volume within 10 minutes (123).

Reflex adjustments to orthostatic fluid shifts

As a result of these volume shifts venous return to the heart is reduced and right atrial pressure decreases from 5 – 6 mmHg in the supine position to little more than 0 mmHg while upright (95, 130), with a decreased cardiac filling and left ventricular stroke volume. The subsequent drop in arterial pressure is sensed by stretch sensitive mechanoreceptors in the aortic arch and carotid sinus and counteracted by an increase in heart rate and sympathetic vasoconstrictor activity (26). This feedback mechanism is known as the arterial baroreflex. In addition the reduction of venous return is sensed by low pressure receptors in the right atrium and ventricle and the pulmonary circulation, which also affect efferent arterial baroreflex behaviour (73). The cardiovascular adaptation after attaining the upright posture takes less than one minute, at which time a quasi steady state is reached (224). Typically at this point cardiac output is ~80% of its supine value (57, 183, 204, 213) and sympathetic vasoconstrictor tone is increased a 2 – 3 fold (26, 57). During prolonged orthostatic stress cardiac output may further decrease to ~65% after 40 minutes (57, 77). Due to normal arterial baroreflex function, in consequence there is a sustained increase in sympathetic vasoconstrictor tone (26, 57, 92, 160).

Mechanical factors promoting venous return

In addition to the baroreflex mechanisms described above, an important mechanism that contributes to maintaining blood pressure during (prolonged) orthostatic stress is the “skeletal muscle pump”. This pump facilitates venous return to the heart (8, 78, 87, 121). It refers to the mechanism in which skeletal muscles surrounding the venous capacitance vessels in the lower limbs, promote flow in those veins during contractions either during exercise or during slight unconscious body and leg movements during standing. The leg veins have a valve system that facilitates this mechanism. Voluntary contraction of calf and thigh muscles at maximum voluntary force may expel 30 – 40% of the pooled volume (120, 185).

When in the upright position, the most important defence against a critical reduction in central blood volume and thus cardiac preload is that of muscle activity and in everyday life, activation of the skeletal muscle pump limits extensive pooling. Also in the upright moving position, maintenance of sufficient venous return is assisted by the circulatory effects of contracting muscles (8). If the muscle pump is not activated, this may result in the syncope that even healthy humans can experience.

In the absence of dynamic muscle contractions, the static skeletal muscle tone associated with “active” standing limits the blood pooling capacity of the lower limbs. Application of low levels of isometric leg muscle tension (5 – 10% of maximal voluntary capacity) causes a significant increase of orthostatic tolerance when assessed by a supine lower-body negative pressure (LBNP) challenge (178). There is also (albeit unconfirmed) evidence that a reduced leg intra-muscular pressure is associated with lower orthostatic tolerance (131). Interestingly, orthostatic tolerance is not associated with leg muscle mass (113), pointing out that an adequately functioning muscle pump may rely more on tensing levels than anatomical factors. Along the same lines, it was recently shown that the postural sway (with tensing of large skeletal muscle groups in the lower body) of healthy subjects with poor orthostatic tolerance (as assessed using tilt-LBNP, see below) during free standing, is greater as compared to that of subjects with a normal orthostatic tolerance (32). In contrast to healthy subjects with a low orthostatic tolerance, patients with recurrent vasovagal syncope (i.e. with a low orthostatic tolerance too) showed lower levels of postural sway. This suggests that patients with recurrent vasovagal syncope fail to compensate orthostatic stress by enhanced postural sway, which may contribute to their predisposition to syncope (33).

There is yet another mechanical mechanism supporting venous return to the heart: the “respiratory muscle pump”. During inspiration, the intra-thoracic pressure is lowered. This low pressure is transmitted across the walls of the right atrium thus promoting right atrial filling (133). During predominantly diaphragmatic breathing, the subsequent increase in intra-abdominal pressure may compromise venous return. However on a breath-to-breath time resolution both diaphragmatic and ribcage breathing equally promote femoral venous blood flow (133). The application of a device that lowers inspiratory impedance can augment the circulatory effects of the respiratory muscle pump (38, 132). By selectively lowering the intra-thoracic pressure during inspiration, this device increases venous return and thereby cardiac output during orthostatic stress (38, 132).

Triggering of a vasovagal reaction

The triggering pathway of vasovagal reactions is incompletely understood. Hainsworth stresses that vasovagal syncope does not depend on abnormal physiological control (74). He continues, “...the responses [to orthostatic stress] seen in healthy subjects with a high orthostatic tolerance are similar to those in frequent fainters. The difference is the amount of stress that is required to induce the same reaction” (74). The vasovagal response during orthostatic stress becomes manifest when the mechanisms, that are normal-

ly capable of maintaining blood pressure can no longer compensate for the gravitational burden to the circulation. This may be the case when circulating volume is inadequate, the muscle pump is deactivated (e.g. during standing still) or vasodilator substances blunt the effects of the sympathetic system (e.g. use of alcoholic beverages). When healthy subjects are subjected to a 1 hour orthostatic challenge by means of a tilt-table with a saddle (i.e. deactivation of the muscle pump) 87% of subjects experience vasovagal reactions (124). Using a double strop around thorax and knee bends prevents this (Fig. 1.3).

Figure 1.3 Sustained non-syncope probability (Kaplan-Meier) curves for 79 subjects during 1 hour of 50 degrees head-up tilt on a table with a bicycle saddle (figures on next page), and for 9 subjects during double strop suspension with elevated legs, that secures venous return. Sustained non-syncope probabilities differ ($p < 0.02$). Reproduced from (124) with permission from the publisher, ©1998 Aerospace Medical Association

Formerly, much attention has been given to the mechanism that during venous pooling, the low level of cardiac filling and the increased heart rate would activate left ventricular receptors which would then trigger a vasovagal reaction ("Von Bezold-Jarisch hypothesis" (89)). This hypothesis has lost much of its attraction since vasovagal reactions have been documented in heart transplant recipients (i.e. denervated hearts) (64, 134, 153, 159, 205). However recently Diehl introduced a new theory that may revive part of the Von Bezold-Jarisch hypothesis (50). He suggests that vasovagal reactions are an evolutionary remnant that supports haemostasis (50), and which can be triggered by (experimental) stimuli of various nature, that commonly are phylogenetically associated with blood loss. Support for this theory is found in the similarity between the vasovagal reaction and the response to hemorrhagic hypovolemia (158, 164) and the observation that vasovagal reactions are associated with increases of pro-coagulatory factors (30). (Phase II of hypovolemic shock is characterized by systemic vasodilatation by sympathetic withdrawal and a vagally mediated bradycardia. This response is triggered when venous return is ~65% of its supine baseline values which is also the level at which vasovagal reactions are commonly triggered (158).) This hypothesis is particularly attractive since it unifies part of the pathophysiological bases of orthostatic vasovagal syncope (due to decreased central blood volume) and the emotional faints in response to (minor) injuries.

In contrast to the ongoing discussion about the afferent (triggering) pathway for vasovagal reactions, the efferent pattern is currently little disputed. The

vasovagal reaction consists of two sub-acute brain stem mediated mechanisms that are thought to originate in the nucleus tractus solitarius (9). The first is a decrease of sympathetic vasoconstrictor tone (88, 212). The second is an increase of parasympathetic (vagal) activity, which slows the sino-atrial nodal pacing rhythm and AV-node conduction and possibly decreases cardiac contractility (88). This may result in sinus arrest or complete AV-block. Asystolic pauses as long as 50 s have been reported (203). In addition vasovagal pre-syncope is associated with a sharp rise of epinephrine (157, 190), which contributes to β_2 -receptor mediated skeletal muscle vasodilatation as well as α -receptor mediated vasoconstriction in skin and localised sweat gland activation (60).

It should be noted that the extent to which both vascular and cardiac elements of the vasovagal reaction are present may vary among patients and among episodes in the same patients (23). For instance vasovagal syncope in a heart transplant recipient is dependent on vasodilatation only. Moreover, the vascular and cardiac elements may change with age; in general the rapidity of the blood pressure change (in mmHg $\cdot$ s⁻¹) during vasovagal reactions decreases with age (210).

Within seconds to minutes, this “reflex pattern” results in a fall in systemic blood pressure that produces cerebral hypoperfusion and eventually syncope. After adjusting to the supine position, and restoration of adequate cardiac filling the vasovagal reaction ceases. When cardiac filling is not timely restored (lethal) cerebral damage may be done, and at least one such fatality has been reported (124).

Tilt-table testing

The tilt-table has been used as a means of assessing orthostatic adaptation since the 1890's (80, 81). Only since the 1980's the test has been regularly used in clinical practice to induce vasovagal syncope in patients with unexplained TLOC (20, 98).

The tilt-table test is a provocation test that aims at triggering a vasovagal reaction. A currently widely used protocol (“Italian protocol” (7)) consists of 5 – 15 minutes of supine rest followed by a 20 minutes, 60 – 70 degrees head-up tilting on a table with a foot board. If after 20 minutes of tilting no vasovagal reaction has occurred a pharmacological stimulus is added by means of sublingual administering of (400 μ g) nitro-glycerine (20). During the test blood pressure is continuously measured, preferentially non-invasively (e.g. by FinapresTM). A positive test is defined as the occurrence of a relentless fall in blood pressure

to below 90 mmHg systolic and prodromal symptoms of impending syncope (20). Once this happens, the test ends and the patient is tilted to the horizontal position.

The diagnostic value of the tilt-table test is disputed. The “Italian protocol” (i.e. head-up tilt testing potentiated by sublingual nitro-glycerin) is reported to provoke a positive response in 60 – 70% of patients with TLOC of unknown origin (7, 46, 47). There is no gold standard for the diagnosis of vasovagal syncope and as discussed above, the vasovagal reaction is thought to be part of normal physiology (2, 74). Those fundamental factors have complicated quantifying the sensitivity and the specificity of the test. The reproducibility of an initial negative response is 85 – 94% (12, 24, 72). The reproducibility of an initially positive test is considerably lower: 31 – 92% (12, 24, 72).

Apart from its diagnostic use, tilt-table testing has potential as an educational tool for physicians to explain to patients the mechanisms underlying vasovagal syncope. In addition, there is evidence that undergoing a tilt test is the equivalent of a therapeutic intervention. Sheldon *et al.* reported a decrease of median syncope frequency from 0.3 per month to 0.03 after testing (172).

In an attempt to improve the test characteristics of the tilt test and to produce a more reproducible measure of orthostatic tolerance, Hainsworth and co-workers have added a “lower body negative pressure” (LBNP) challenge to the tilt test (52). In this approach an air-tight cover is sealed to the tilt-table and to the subject at the level of the iliac crest (231). In the protocol, after head-up tilting for 20 minutes a sub-atmospheric pressure is applied to the cover so that venous pooling in the lower body is augmented and eventually a vasovagal response is triggered. Orthostatic tolerance can then be expressed as the time needed to produce (pre-)syncope. The reproducibility of this test is high (114). A further advantage of the tilt-LBNP technique over regular tilt tests is that it allows quantification of orthostatic tolerance in subjects with high orthostatic tolerances.

Treatment of vasovagal syncope

Although numerous therapeutic options are available for the prevention of vasovagal syncope, the choice of therapy is usually empirical and the efficacy suboptimal. Reasons for this are the sporadic and episodic nature of the disorder, the heterogeneous patient population and the lack of sufficient properly designed randomized controlled clinical trials (20, 56).

The cornerstone of the non-pharmacological management of patients with vasovagal reflex syncope is education and counselling regarding the benign nature of the condition (20, 218). In this perspective, the tilt-table test provides a safe setting for teaching patients to recognize early premonitory symptoms (20). The frequency of syncopal events decreases substantially after tilt-table testing (172). It is possible that the clinical encounter, education and counselling that accompany this diagnostic test serve as a positive therapeutic intervention (170, 172).

Patients, family members and other care providers often benefit from clear and simple descriptions of the physiological mechanisms that underlie the hypotensive and bradycardic response, and its effect on cerebral perfusion (218). Such explanations help clarify the rationale for the self-protective measures that include the assumption of the supine position and other measures to increase cerebral blood flow if syncope becomes imminent. Some patients may consider resumption of the supine position socially embarrassing and this may limit compliance to this advice. Elevation of the legs may be performed in order to increase venous return to the heart (80, 142). Initial advice should also include early recognition of warning symptoms and “common sense” avoidance of triggering events such as prolonged standing possibly in hot, confining environments. Patients can be informed that there is minimal risk of sudden death in the absence of structural heart disease (20, 56, 172, 179). Vasodilating and diuretic medications should be modified if medically appropriate.

Further non-pharmacological treatment focuses on body fluid expansion. This can be achieved by increasing dietary salt and fluid intake (31, 53, 136), sleeping 30 degrees head-up tilted (228) or by moderate exercise training (137, 221). A low salt diet should be avoided (221). Such therapies may however be contraindicated in hypertensive patients. In highly motivated patients, tilt training may be an option. This therapy constitutes a regimen of daily increasing orthostatic exposures, either with the use of a tilt-table or while standing against a wall (1, 48, 100).

Pacemaker therapy as well as various drugs (e.g. β -blockers, clonidine, serotonin re-uptake inhibitors) have been used in the treatment of vasovagal syncope. In general, while the results have been promising in uncontrolled trials or short term, controlled trials, long term placebo controlled trials are either not available or have been unable to show a benefit of the intervention over placebo (20, 96, 186).

Initial orthostatic hypotension

In young people, initial orthostatic hypotension (IOH) is thought to be the second most common cause of TLOC (next to vasovagal syncope) (61).

The earliest (known) clinical report dates back to 1864 (117), when Liebermeister described three subjects (a 50 year old man, a 40 year old woman and a male medical student) with syncopal episodes shortly after rising from prolonged recumbence. In 1932 Sir Thomas Lewis also referred to IOH in his classical lecture on vasovagal syncope, writing "(...) there is another and frequent form of giddiness occasionally leading up to syncope, which is due to a distinct mechanism; it is characteristic of this giddiness that it is usually related to the act of rising to the erect position" (116).

Figure 1.4 A 37-year old female, an enthusiastic horse rider had experienced transient loss of consciousness (TLOC) after she had squatted to bandage the legs of her horse and then stood up. Before the TLOC she saw "black spots" and felt light-headed. The TLOC lasted <1 minute and afterwards, the patient was well oriented. During her medical examination, the patient mimicked the procedure of bandaging the four legs of her horse. She squatted (white bar) for ~30 s and stood up quickly (black bar). This was repeated three times. After the fourth time, the patient remained standing. Each time she stood up, she complained of seeing "black spots" and being light headed. Based on this reproducible blood pressure (BP) change after standing up and the patient's recognition of symptoms similar to those she had experienced spontaneously, initial orthostatic hypotension was identified as the cause for TLOC. HR: heart rate. Reproduced from (103) with permission from the publisher, ©2002 Steinkopff Springer Verlag

IOH is defined as symptoms of cerebral and retinal hypoperfusion such as light-headedness, visual disturbances and / or syncope within 15 s after standing up from supine or squatting caused by an abnormally large transient blood pressure decrease (224). IOH is a clinical diagnosis, which in some patients can be confirmed by an active standing test which has however probably a limited sensitivity (225).

Epidemiology of initial orthostatic hypotension

Many people are familiar with the occasional experience of a brief feeling of light-headedness, and sometimes seeing black spots almost immediately following standing up.

In teenagers and adolescents fainting upon standing appears to be fairly common in the general population (149). De Marées reported that 22% of Hannover students ($n = 466$) “often or always had complaints of seeing black spots immediately after rising” (44) and our group found that 8% of medical students who had experienced one or more episodes of TLOC, related it to standing up (61). Since there is no readily apparent alternative diagnosis, it may be reasonable to assume that in the majority of these patients an exaggerated blood pressure fall upon standing was the underlying cause.

The incidence of IOH as a cause of syncope in the general population is unknown. In the recent Fainting Assessment Study, IOH as a primary diagnosis had an incidence of 3.6% (197).

Pathophysiology of initial orthostatic hypotension

Complaints of light-headedness and even syncope upon active standing are related to a marked transient fall in arterial blood pressure, that also occurs in healthy subjects upon active standing (14, 15, 182). Comparable events are observed on arising from sitting (84, 85, 150, 180, 223) or squatting (103, 150) and at the onset of whole-body exercise without a change in posture such as the bicycle exercise (180, 223). This initial blood pressure response to the upright position is exclusively associated with active rising. Any fall in pressure provoked by passive tilting, is much smaller and in most cases absent (14, 180-182, 226, 227, 227). Thus, a prerequisite for the observed hypotension appears to be large skeletal muscle contractions.

Arterial blood pressure reflects a balance between the rate of blood volume entering and leaving the arterial vasculature (cardiac output and peripheral

resistance effects respectively). Thus, initial hypotension upon standing indicates that the rate at which blood volume is entering the arterial circulation is temporarily less than the rate it is leaving (i.e. cardiac output is not matching peripheral resistance effects on arterial outflow). Since it has been established that this mismatch is due to a reduction in peripheral resistance (182, 216, 223) and not cardiac output, and since the observed hypotension requires skeletal muscle contraction, three potential mechanisms have been proposed: 1) the muscle pump, 2) rapid locally mediated vasodilatation effects (both two factors in the active muscles involved in the effort of standing up), and 3) cardio-pulmonary receptor-mediated systemic sympathetic withdrawal in response to sudden increases in right atrial pressure.

Initial hemodynamic response to active standing

There is an immediate increase in heart rate upon standing, which peaks after ~3 s. This results from abrupt inhibition of cardiac vagal activity (it is absent after parasympathetic blockade) (15, 219, 220, 227). This vagal inhibition has been attributed to a general exercise reflex activated by two mechanisms. One is "central command", related to the motor signals from higher brain centres that stimulate the brainstem cardiovascular centres (41, 68), and the other is a feedback reflex from the contracting muscles due to activation of their mechanoreceptors (muscle-heart reflex) (83). At the same time, stroke volume remains stable. This is likely because of an elevation in right atrial pressure, which compensates for reduced diastolic filling time as heart rate is increased.

The combination of the instantaneous and substantial heart rate increase and stable stroke volume results in a pronounced increase in cardiac output, with a maximum ~7 s after the onset of standing up (182, 189). Nevertheless, a simultaneous fall of ~25 mmHg in mean arterial pressure is found (181, 182, 189). This can be explained by a pronounced drop in systemic vascular resistance, which some studies have shown to be ~40% (182, 189, 216). In fact, there appears to be a strong relationship between the decrease in systemic vascular resistance and the depth of the blood pressure trough (189).

Treatment of initial orthostatic hypotension

Because IOH has only recently been recognised as a pathophysiologically and clinically separate entity from "classic" orthostatic hypotension, specific treatment has not been given much attention so far (225).

Treatment of IOH is symptomatic (225). The goal is to diminish the drop in blood pressure after standing up. A clear explanation of the underlying mecha-

nism and avoidance of the main triggers (i.e. a rapid rise) are the mainstay of the management. In addition volume-expansion can be applied by raising water- and salt-intake (174, 221). Another option is the use of an inspiratory impedance device that augments the action of the respiratory muscle pump (38). The feasibility of this therapy in daily life has however, not yet been documented.

Physical counter-manoevres

In patients with “autonomic failure”, the autonomic nervous system chronically fails (for various reasons) to compensate for the fluid shifts resulting from orthostatic stress by the reflex mechanisms as discussed above. As a result the circulation of those patients is foremost volume dependent (176) and patients suffer from chronic orthostatic hypotension.

Currently physical counter-manoevres are an integrated part of the treatment of autonomic failure. In 1928, Ghrist and Brown presented a patient with idiopathic orthostatic hypotension, who could relieve his pre-syncopal symptoms by crossing his legs in a “scissors fashion” (63). This was one of the cues for investigations in our and other departments in the 1990’s to study the potential of physical counter-manoevres as a symptomatic therapy in orthostatic hypotension due to autonomic failure. These studies revealed that leg crossing, squatting, isometric leg muscle contractions and “tiptoeing” increase cardiac output and thereby standing blood pressure and cerebral blood flow and oxygenation in patients with autonomic failure (17, 191, 206, 229). Leg crossing can increase blood pressure by $\sim 20 / 10$ mmHg (systolic / diastolic), which can be augmented to $\sim 30 / 15$ mmHg when leg and buttock skeletal muscles are contracted (17, 177, 191, 206). Squatting can produce an increase in systolic and diastolic blood pressure of $\sim 60 / 35$ mmHg (17, 177, 229, 229). Interestingly, the effect of physical manoeuvres on blood pressure of healthy subjects is absent, thanks to normal arterial baroreflex function (191, 204).

This thesis

Vasovagal syncope and (pre-)syncope from initial orthostatic hypotension are by the number of affected patients and the size of their impact on quality of life vast medical problems. The treatment options are often unsatisfactory. The studies in this thesis were set out to investigate the potential benefits of physical counter-manoevres in the acute management of vasovagal syncope and initial orthostatic hypotension, and after shown effective, elucidate their mechanisms of action.

2. Management of Vasovagal Syncope: Controlling or Aborting Faints by Leg Crossing and Muscle Tensing¹

C. T. P. Krediet, N. van Dijk, M. Linzer, J. J. van Lieshout and W. Wieling

Introduction

Vasovagal reflex syncope is the most frequent cause of transient loss of consciousness (56). The vasovagal reaction consists of vasodilatation and a heart rate (HR) decrease. During prolonged standing, this reaction is triggered by a reduction of the central blood volume because of pooling in the lower body veins, sometimes combined with other provocative factors (56, 97, 147, 208). Patients with reflex syncope may suffer from recurrent loss of consciousness, varying from once a year to weekly or even daily episodes. Most of these patients also experience frequent pre-syncope, which can be just as incapacitating as syncope itself. Vasovagal syncope is usually not a dangerous condition, because episodes are self-limiting. However, the quality of life of patients with recurrences can be seriously affected (118). The rapid loss of consciousness and the possibility of trauma tax the patient's sense of physical control and self-esteem.

The present management of vasovagal syncope consists of providing the patient with an explanation of the pathophysiology involved and advising him or her to avoid provocative situations and to increase salt intake. Various drugs have been proposed in the treatment of vasovagal syncope. In general, although the results have been satisfactory in uncontrolled or short-term controlled trials, several long-term prospective trials have been unable to show consistent benefit of the active drug over placebo (20). There is strong consensus of opinion that the role for pacing in the treatment of patients with vasovagal syncope is minor (20). Therefore, a simple and effective interventional approach rel-

¹ Originally published in "Circulation" (108), reproduced with permission from the publisher, © 2002 Lippicott Williams & Wilkins

evant to most patients suffering from vasovagal syncope and without side effects would be an important addition to present management and helpful for combating pre-syncope. In patients with orthostatic hypotension attributable to autonomic failure, crossing legs increases orthostatic tolerance by decreasing blood pooling in the lower body veins (17, 129, 177, 191, 204, 229). Muscle tensing enhances this effect (177). Inflation of an antigravity suit that promotes the return of pooled blood from the lower body and increases cardiac after-load can abort an impending vasovagal faint (Fig. 2.1) (102, 215). Against this background, we addressed the hypothesis that leg crossing combined with tensing of leg, abdominal and buttock muscles can be applied as a means of improving venous return such that the vasovagal syncope is aborted or at least temporarily controlled. We report results in 21 consecutive patients with vasovagal syncope that support this hypothesis.

Figure 2.1 Original record by Weissler *et al.* during antigravity suit inflation (at arrow) during a vasovagal reaction. Note the instantaneous increase of central venous pressure (CVP) and the subsequent rise in arterial blood pressure after the start of inflation. "Resp." indicates thoracic respiratory excursions. Reproduced from (215) with permission from the publisher, ©1957 Lippincott Williams & Wilkins

Methods

We included consecutive patients who were referred to the Syncope Unit of the Academic Medical Center at the University of Amsterdam for routine tilt-table testing who developed a vasovagal reaction during the test. From March to September 2001, 58 patients underwent a tilt-table test at our laboratory for suspected vasovagal syncope. Twenty-seven developed a vasovagal reaction dur-

ing the test. Six were excluded because of inability to perform the counter-manoevre. The remaining 21 patients (11 males; median age: 41 (range 17 – 74); median number of life-time faints: 3 (range 1 – ~200); number of patients with ≥ 1 pre-syncope per month: 13) constitute our study population. Electro- and echocardiography, performed in all patients, revealed no structural heart disease of clinical relevance. At inclusion, patients had no co-morbidities of clinical relevance.

Before the test, subjects received oral instruction on how to perform the manoeuvre (Fig. 2.2) and practiced it once. We used a manually controlled tilt-table with a footboard. Subjects were not strapped to the tilt-table, to provide the freedom of movement to perform the manoeuvre. Risk of falling and potential for injury were minimized by close observation of the patient by two investigators and continuous blood pressure (BP) monitoring.

Figure 2.2 Leg crossing and muscle tensing during tilt-table testing. The manoeuvre consists of crossing the legs in standing position with tensing of leg, abdominal, and buttock muscles. The legs are firmly squeezed together. (Photograph by the Department of Medical Illustrations at the Academic Medical Center at the University of Amsterdam)

One of the investigators was ready to tilt the patient back to horizontal position immediately, in case of imminent syncope. The manually controlled tilt-table allowed a tilt back in ~1 s. Beat-to-beat systolic and diastolic BPs and HR were measured continuously and non-invasively using finger volume-clamp photoplethysmography (Finapres model 5, TNO-BMI, The Netherlands) (86, 90). The tilt-table test started with 5 minutes of supine rest. The subjects were then 60 degrees head-up tilted for 20 minutes. If no vasovagal faint developed, nitro-glycerine was administrated sublingually (0.4 mg) before an additional 15 minutes tilt (20).

At the moment of a relentless fall in BP accompanied by prodromal symptoms indicating an impending faint, subjects were instructed on verbal command to start the physical counter-manoevre. They were asked to uncross their legs after at least 30 s following the disappearance of prodromal symptoms. If symptoms returned, subjects resumed the counter-manoevre until symptoms disappeared. In case syncope appeared imminent in spite of the manoeuvre, subjects were tilted back in ~ 1 s.

Figure 2.3 Original tracing in a male subject aged 34 years, during a vasovagal episode while tilted head-up. A: onset of prodromal symptoms; B: start of physical counter-manoevre; C: blood pressure nadir; D: latency between start of physical counter-manoevre and disappearance of prodromal symptoms; E: stabilization of blood pressure

An example of the BP and HR tracings during the manoeuvre is given in Figure 2.3. Averaged systolic and diastolic BP and HR were determined between 4.5 and 5 minutes of supine rest, between 2.5 and 3 minutes of head-up tilt, between 2 and 1.5 minutes before the first episode of leg crossing, and during the 30 s immediately after BP was stabilized by the physical counter-manoeuve. The lowest BP and HR values of the impending faint were determined (Fig. 2.3). The following latencies were determined: 1) between the start of the counter-manoeuve and the increase of BP and 2) between the BP nadir and a stabilized BP.

Data fitted a normal distribution (according to Kolmogorov-Smirnov). The differences in BP and HR at nadir and during the manoeuvre were examined by paired t-test. A telephone follow-up was performed after a median of 10 months (range 7 – 14) after the tilt-table test. Patients were asked if they had experienced any syncopal or pre-syncopal events in the period after the test and whether they had used the counter-manoeuve and, if so, benefited from it.

We performed an additional experiment to assess the contribution of a central nervous drive (“central command”) to the cardiovascular events induced by the physical counter-manoeuve. We compared the effects of leg crossing and lower body muscle tensing with those of hand gripping. Three consecutive tilt-positive patients performed isometric handgrip exercise at maximal voluntary at the moment of an impending faint.

The Medical Ethical Committee of the Academic Medical Center at the University of Amsterdam approved the study.

Results

Values of supine and orthostatic BP and HR are given in Table 2.1. Four subjects developed a vasovagal reaction without and 17 of 21 after the addition of nitro-glycerine. During the first vasovagal episode, systolic BP decreased to 65 ± 3 mmHg (mean $\pm$ SE) and diastolic BP to 43 ± 2 mmHg. A total of 14 of 21 subjects had a systolic BP <75 mmHg and 7 of 21 <60 mmHg. In 10 of 21 subjects, HR decreased >10 beats $\cdot$ min $^{-1}$ in the 30 s before the manoeuvre. Prodromal symptoms were present in all patients. Based on these observations, we concluded that at the moment they started the manoeuvre, all patients were experiencing a vasovagal reaction with development of syncope if no counter-measures were instituted.

Table 2.1 Blood pressure (BP) and heart rate (HR) at various stages during the tilt test in 20 subjects who performed the physical counter-manoeuvre (mean $\pm$ SD)

	Systolic BP (mmHg)	Diastolic BP (mmHg)	HR * (beats $\cdot$ min ⁻¹)
After 5 minutes supine rest	120 $\pm$ 16	62 $\pm$ 9	72 $\pm$ 14
After 3 minutes head-up tilt	117 $\pm$ 11	69 $\pm$ 7	84 $\pm$ 15
90 s before BP nadir	105 $\pm$ 13	68 $\pm$ 8	91 $\pm$ 18
At BP nadir	65 $\pm$ 13 (SE 3)	43 $\pm$ 9 (SE 2)	73 $\pm$ 22 (SE 5)
During manoeuvre	106 $\pm$ 16 (SE 4)	65 $\pm$ 10 (SE 3)	82 $\pm$ 15 (SE 4)

* n = 19, subject with postural tachycardia (130 beats $\cdot$ min⁻¹) excluded

Figure 2.4 Original blood pressure tracings in 20 patients during performance of leg crossing with lower body muscle tensing. Black bars indicate manoeuvre. The arrows indicate tilt to supine position at moment of impending syncope. The patients in panels A – E averted syncope; in F – T, patients postponed syncope. In panels F – J, tilt back occurred minutes after the traced period, because the manoeuvre was successful in prolonging the time to syncope

One subject developed a pronounced tachycardia (HR supine: 62 beats $\cdot$ min⁻¹; just before start of the manoeuvre: 130 beats $\cdot$ min⁻¹). The other subjects exhibited a stable or slightly increased HR. One subject was near to unconsciousness before performing the physical counter-manoeuvre and was tilted back. The

remaining 20 subjects performed the physical counter-manoeuve one to four times. Performing the manoeuvre stabilized BP (Fig. 2.4) and HR in all subjects. Prodromal symptoms vanished during the performance of the manoeuvre in all subjects shortly after stabilization of BP. None of the subjects lost consciousness while performing the manoeuvre.

In 5 of 20 subjects, the vasovagal reaction was averted by the manoeuvre (Figs. 2.4A – 2.4E). The remaining 15 subjects could not avert the faint or requested to be tilted back after having performed the manoeuvre but did postpone the faint by on average 2.5 minutes (range 0.5 – 11) (Figs. 2.4F – 2.4T).

During the first episode of leg crossing, systolic BP rose from 65 ± 3 (mean $\pm$ SE) to 106 ± 4 mmHg ($p < 0.001$) and diastolic BP rose from 43 ± 2 to 65 ± 3 mmHg ($p < 0.001$). HR increased from 73 ± 5 to 82 ± 4 beats $\cdot$ min $^{-1}$ ($p < 0.01$). In the subject with postural tachycardia the HR decreased during the physical counter-manoeuve from 130 to 108 beats $\cdot$ min $^{-1}$, whereas BP rose from 54 / 41 to 100 / 71 mmHg. The latency between the start of the physical counter-manoeuve and the start of the increase of BP ranged from 3 to 6 s. In some subjects, an almost instantaneous increase in BP was observed, whereas in others BP rose slowly (Fig. 2.4).

Patients who could completely abort the faint started the manoeuvre at a significantly higher BP level than patients who could not (mean 79 / 51 vs. 61 / 41 mmHg, $p < 0.01$). The latencies between the BP nadir and stabilization of BP were on average 9 s (range 3 – 18 s). For the follow-up interview, 19 of 20 subjects who had performed the manoeuvre on the tilt-table were contacted. Their number of recurrences is given in Table 2.2. In one subject, Addison's disease was diagnosed during follow-up. Three subjects had experienced no syncopal complaints since the test. Two subjects who still suffered from syncope did not use the manoeuvre; one of them reported a too short prodromal period to apply. The remaining 13 patients used the counter-manoeuve in daily life for preventing or controlling syncope in provocative situations, and two of them had experienced syncope since the test. Ten patients, who, apart from syncope, had suffered from pre-syncope as well, indicated that they also benefited from the manoeuvre to alleviate pre-syncopal complaints.

The results of isometric handgrip exercise at the moment of an impending syncope are given in Figure 2.5. With hand gripping there was some stabilizing effect on BP but far less pronounced than during leg crossing with muscle tensing. Hand gripping could not abort the faint, and all three patients had to be tilted back to horizontal within 1 minute.

Table 2.2 Follow-up

Patient ID *	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
n syncope in last year	3	2	1	3	10	20	30	2	1	2	1	1	1	o	5	o	24	6	1	13
n syncope in life-time	10	3	2	6	20	50	100	2	1	11	2	1	10	3	6	3	30	22	1	13
Time follow-up (months)	9	11	9	10	†	12	7	9	11	10	11	12	13	11	10	10	13	13	9	8
Manoeuvre during follow-up (Yes / No)	Y	Y	N	Y	†	N‡	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y
n syncope during follow-up	0	0	0	0	†	20	0	0	1	1§	0	3	0	0	2	0	0	0	0	0

* Patient IDs correspond to Figure 2.4

† Lost to follow-up

‡ Patient reports: to short prodromal period to apply manoeuvre

§ During follow-up diagnosis Addison's disease

|| Last year: severe pre- syncopal complaints

Figure 2.5 Additional experiment in additional three patients (α : female, aged 36 years; β : male, aged 29 years; $\gamma 1$ and $\gamma 2$: female, aged 52 years) during tilt-table test provoked vasovagal faint. Black bars indicate leg crossing and muscle tensing. Striped bars indicate hand gripping. Arrows indicate tilt back. Stabilizing effect of hand gripping on blood pressure (BP) is trivial compared to during leg crossing and muscle tensing, and patients are tilted back because of impending faint

Discussion

The main finding of this study is that crossing legs combined with lower body muscle tensing can abort or delay impending syncope in subjects prone to vasovagal reactions. Previous case reports have indicated a beneficial effect of skeletal muscle pumping and tensing on BP and HR in patients with vasovagal syncope (52, 139, 163, 178, 199). This is the first report that documents the efficacy of aborting a vasovagal faint by leg crossing and muscle tensing in a series of consecutive patients and the effectiveness of the manoeuvre in daily life. The manoeuvre also seems to be effective in combatting pre-syncopal complaints.

The posture-related vasovagal reaction is thought to be elicited in response to a postural reduction of the central blood volume (56, 97, 147, 208). The effects of leg crossing are explained by breaking the vicious cycle that maintains the ongoing vasovagal response. Weissler *et al.* demonstrated that an impending vasovagal faint could be aborted by inflation of antigravity suit (Fig. 2.1) (215). They observed rapid increases in central venous pressure and cardiac output, indicating re-infusion of pooled blood. Previous studies have shown an increase in central venous pressure (204) and cardiac output (191, 204) during muscle tensing. Changes in peripheral resistance should also be considered as a contribution to the stabilization of BP.

Sustained tensing of skeletal muscles is associated with activation of a central nervous drive (central command) (41, 195) and of the muscle chemo-reflex (152). These mechanisms induce an increase in sympathetic outflow and thereby in peripheral resistance with stabilization of BP. In addition to these neurogenic effects, mechanical effects of muscle tensing on peripheral conductance could be involved. The muscle chemo-reflex is not likely to play an important role in the instantaneous BP raising effect of the physical counter-manoeuve, because muscle chemo-afferents are activated only after ~1 minute of sustained muscle contractions (152). The trivial effect of hand gripping on the vasovagal response (Fig. 2.4) suggests that central command plays a minor role only. Therefore, the mechanical effects of the combination of leg crossing and muscle tensing alone seem to explain almost all of the BP raising effect. In contrast, the instantaneous increase in HR observed at the onset of the physical counter-manoeuve (Fig. 2.2) is likely to be of neurogenic origin. It may be attributed to withdrawal of vagal outflow to the heart related to the muscle-heart reflex (67) or central command (41, 42, 195). The latency between the start of the physical counter-manoeuve and the subsequent stabilization of BP can be explained by various

factors. One variable is the time needed by the pre-syncopal subject to perform the manoeuvre effectively. Other factors include unintentional straining during the onset of the manoeuvre and transit delay of the venous return through the pulmonary circulation (223).

For patients who could not abort the vasovagal episode by the leg crossing and muscle tensing, the manoeuvre was useful in postponing the syncope. Maintaining the muscles tensed after uncrossing may counteract the subsequent fall in BP. The patients can then sit or lay down controlled, keeping their BP stabilized by tensing.

Sheldon *et al.* followed up a large group of patients with vasovagal syncope induced by head-up tilt-table testing for up to 3 years and developed a predictive model for recurrence of syncope after a positive tilt-table test (170, 172). They found that the frequency of syncopal events decreased substantially after head-up tilt-table testing. It has been suggested that the diagnostic procedure of head-up tilt-table testing and the associated clinical encounter, including counselling on avoidance of situational provocation, has the effect of a positive therapeutic intervention (56). This would be associated with a reduction in the number of events in follow-up, and therefore the absence of a control group is a potential limitation of our study. Based on Sheldon *et al.*'s predictive model, we estimated the recurrence risk in the follow-up cohort without intervention at 0.30. The observed recurrence rate of 0.15 after 10 months of follow-up supports that, apart from the effect of tilt-table testing itself, application of the physical counter-manoeuve has contributed to the reduced frequency of events.

Laboratory studies show that pacing during the onset of a vasovagal faint has a modest stabilizing effect on BP by increased HR supporting cardiac output (188). However, it does not counteract the vasodilatation. Therefore, cardiac pacing has in general been proven to be successful in prolonging the premonitory warning phase of vasovagal syncope (20). The combination of leg crossing and muscle tensing at the onset of a vasovagal faint seems to have a greater BP raising effect than cardiac pacing and overall at least the same beneficial effect. We therefore propose that the physical counter-manoeuve should be considered in patients with vasovagal syncope before cardiac pacing treatment because it offers a safe, inexpensive, and effective alternative. This easy-to-perform manoeuvre has a significant clinical effect, is without any side effects or additional patient burden, and may be equally effective in combating pre-syncope and syncope.

The only limitations to the use of the manoeuvre are motor handicaps and absence of warning time. The observation that the patients who aborted the faints

started the manoeuvre at a significant higher BP than the patients who could not emphasizes the importance of an early commencement of the manoeuvre. Because early patient recognition of prodromal symptoms is the key to adequately performing the physical counter-manoeuve, the tilt-table test provides patients with a safe setting to become familiar with their prodromal symptoms so they can use them as a cue to apply the physical counter-manoeuve.

Conclusion

Leg crossing combined with muscle tensing applied as a simple physiological measure at the onset of prodromal symptoms can prolong the time to or prevent vasovagal syncope. By aborting or delaying syncope, this manoeuvre can increase patients' sense of control over their symptoms and thereby improve their quality of life.

3. Leg Crossing, Muscle Tensing, Squatting and the “Crash-position” are Effective Against Vasovagal Reactions Through Increases in Cardiac Output¹

C. T. P. Krediet, I. G. J. M. de Bruin, K. S. Ganzeboom, M. Linzer, J. J. van Lieshout and W. Wieling

Introduction

Background

Recurrent vasovagal syncope is a common medical problem, significantly affecting the quality of life (118). Therapeutic options are limited (20), but recently several physical counter-manoevres have been introduced that are effective in counteracting vasovagal faints. Leg crossing with tensing of leg, abdominal and buttock muscles was proven to be an effective manoeuvre to stabilize blood pressure (BP) during an impending vasovagal faint (108). Two other studies documented that isometric arm exercise was an effective counter-manoevre (21, 43). Leg and buttock muscle tensing alone was documented in an elderly patient to prevent posture induced syncope (155). Another case report showed such beneficial effects of isometric leg extensions in a young subject (163). Earlier, whole body tensing proved effective in controlling impending vasovagal syncope related to blood phobia (141). In patients with autonomic failure, squatting counteracts hypotension presumably through its action on pre-load (191). Traditionally sitting with the head lowered between the knees (“crash position”) is a manoeuvre against impending faints (208).

The presumed mechanism underlying the beneficial effect of physical counter-manoevres on systemic blood pressure is that skeletal muscle tensing of the lower body reinfuses pooled venous blood back to the chest thereby increasing cardiac filling pressure, stroke volume (SV) and cardiac output (CO) (191). This mechanism has, however, never been documented during vasovagal reactions. In

¹ Previously published in the “Journal of Applied Physiology” (105), reproduced with permission from the publisher, ©2005 the American Physiological Society

addition, the possibility that physical counter-manoevres increase peripheral vascular resistance should also be considered (21). Skeletal muscle contractions are accompanied by an increase in central command, which is known to increase the sympathetic outflow (152, 162). Finally, isometric contractions up from 10% of maximal power can compress arteries in skeletal muscle (156, 165) and such mechanical increases in total peripheral resistance (TPR) have also been suggested to play a role in the efficacy of physical counter-manoevres (140, 167).

Table 3.1 **Manoeuvres**

Abbreviation	Manoeuvre	Reference
LBMT	Lower body muscle tensing: tensing of muscles in legs, buttock and abdomen at maximal voluntary power	(155)
LCMT	Leg crossing with muscle tensing, i.e. tensing of muscles in legs, buttock and abdomen at maximal voluntary power	(108, 191, 229)
WBT	Whole body tensing: tensing of all skeletal muscles at maximal voluntary power, except those in the instrumented left hand	(141)
Squat	Squatting	(140, 167, 191)
HBK	Sitting on a bed side (height 60 cm) with the head bent between the knees (“crash position”)	(208)

Hypotheses

The aims of this study were threefold: 1) to investigate the functional mechanisms underlying the effectiveness of the above mentioned physical counter-manoevres (Table 3.1), 2) to search for clinically relevant differences in BP changes between lower body muscle tensing with (LCMT, Table 3.1) and without leg crossing (LBMT), respectively whole body tensing (WBT), and 3) to document the efficacy of squatting and that of sitting with the head bent between the knees (HBK) as applied in vasovagal reactions.

We hypothesized that the external pressure to the lower extremities in leg crossing with lower body muscle tensing would cause an additional increase in venous-return and thereby in more pronounced effects on CO. We expected that leg crossing with lower body muscle tensing would be more effective in raising blood pressure than lower body muscle tensing alone. Secondly, we hypothesized that, if central command elicits a reflex increase in peripheral resistance, more extensive skeletal muscle contractions would be accompanied by a more pronounced effect (162). Consequently, we expected that the increase in TPR would be higher in total body tensing compared to lower body muscle tensing. The third part of the study had a descriptive purpose, aiming to document the

effects of squatting and sitting down with the head lowered between the knees on all the above-mentioned parameters during vasovagal syncope.

Methods

At the Syncope Unit of the Academic Medical Center at the University of Amsterdam, patients with vasovagal syncope are instructed how and when to apply physical counter-manoevres during vasovagal reactions provoked by head-up tilting. Usually a symptomatic vasovagal reaction returns after termination of the manoeuvre. This gives the opportunity to have patients use more than one manoeuvre to combat a vasovagal reaction and to compare the effects. Table 3.1 summarizes the manoeuvres.

Inclusion

From a consecutive series of 66 patients who developed a vasovagal reaction during tilt-table testing, 26 patients were selected who successfully had applied either of the next two combinations of manoeuvres: LBMT and LCMT (series A, $n = 9$) or WBT and LCMT (series B, $n = 12$). Patients who had squatted or applied HBK constituted series C ($n = 14$) and series D ($n = 9$) respectively. Consequently, there was some overlap between the patients series.

Medical history in all patients consisted of at least one episode of loss of consciousness, with prodromal symptoms such as diaphoresis, pallor, visual disturbances ("seeing black spots") in the presence of either of the following triggers: (prolonged) orthostatic stress, pain or the experience of an unusually strong emotional circumstance. Exclusion criteria for tilt testing were pregnancy or the presence of structural or (possibly) arrhythmogenic heart disease that could lead to syncope.

Tilt protocol and manoeuvres

Investigations took place in the morning, at least 1 hour after breakfast, in a room with a temperature of $\sim 23^{\circ}\text{C}$. Patients were strapped by a single torso belt to a manually controlled tilt-table with a foot-board. After 5 minutes of supine rest, patients were 60 degrees tilted head-up for 20 minutes. If no vasovagal reaction developed, 0.4 mg nitro-glycerine was administered sublingually prior to an additional 15 minute tilt (20). Beat-to-beat systolic and diastolic blood pressures were measured continuously non-invasively using finger volume-clamp photo-plethysmography (Finapres model 5, TNO-BMI, The Netherlands). The finger cuff was applied to the mid-phalanx of the left middle finger. To avoid hydrostatic level differences, the patients held the cuffed finger at right-atrial level in the mid-axillary line. Finapres™ recordings accurately reflect BP changes

during orthostatic stress (86). One of the investigators operated a marker pulse to identify the onset and termination of each manoeuvre. For off-line analysis all signals were digitally stored in a personal computer at a sampling rate of 100 Hz, as well as real-time printed by a thermo-paper writer (Thermal Arraycorder WR 7700, Graphtec, Germany) for direct inspection and annotation.

Prior to the test patients had practiced the manoeuvres that they performed during the vasovagal reaction. Patients were instructed to avoid straining during performance of the manoeuvres.

All manoeuvres started at the moment of a rapid fall in BP in association with symptoms of impending syncope (Fig. 3.1). Each manoeuvre was sustained for 40 – 60 s. Half of patients in series A started with LBMT and applied LCMT at faint recurrence; the another half performed these in reverse order. In series B manoeuvre order was split similarly.

In series C and D patients were tilted back, or had applied one of the muscle tensing manoeuvres when a faint was imminent. After a subsequent head-up tilt or a release of the manoeuvre they stepped off the tilt-table. Standing next to the table the patients waited until faint recurrence and then squatted in series C and in series D performed HBK. For safety reasons (i.e. risk of collapse when stepping off the table and consequences) patients aged >55 years are not instructed about HBK or squatting when a vasovagal reaction is present.

During all testing two experienced investigators closely monitored the patients. In case of syncope during or following a manoeuvre, the tilt-table was tilted down immediately or if the patient was standing, they were laid down on the bed.

Stroke volume and total peripheral resistance computation

From the continuous BP measurement, the arterial pulse wave was analyzed by a pulse wave analysis method that computes changes in left ventricular SV from the pulsatile systolic area. We used the improved method of Wesseling as described in detail previously, using the Modelflow™ program (model-based measurement method based on a non-linear, 3-element model of the input impedance of the aorta) (91). This methodology tracks rapid changes in SV accurately (compared to gas-rebreathing) during leg crossing with and without muscle tensing (198). During conditions with a low systemic blood pressure the technique provides accurate values for SV and CO (77, 91).

Mean arterial pressure (MAP) was obtained as the time integral of pressure over one beat. CO was computed as $SV \cdot HR$ and TPR was calculated as $MAP \cdot CO^{-1}$.

Analysis

As baselines, BP, HR, SV, CO and TPR were averaged over the intervals 4.5 to 5 minutes supine rest and 2.5 to 3 minutes head-up tilt respectively. The same parameters were then determined 1) right before the start of the manoeuvre over an interval of 3 beats and 2) over an interval after onset of each manoeuvre of 30 s when a stable BP was reached (Fig. 3.1). SV, CO and TPR were expressed as percentage of head-up tilted baseline values (%bl.).

For each manoeuvre we compared all parameters prior to and during the manoeuvre, using Student's paired t-tests. In series A and B, we compared the parameters during each of the two manoeuvres in each series, also using paired t-tests. P-values <0.05 were considered statistically significant.

Figure 3.1 The top panel shows excerpts from the original continuous blood pressure (BP) recording in a subject (female, aged 21 years) from series A, at indicated intervals during the protocol. Lower four panels show derived heart rate (HR), stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR). SV, CO and TPR are represented as percentage of baseline (% bl., i.e. mean over the interval 2.5 to 3 minutes after head-up tilt (HUT)). The vertical grey bars indicate the intervals at which hemodynamic parameters were determined for comparison as described in the method section

Results

Patient characteristics and hemodynamic base line values are given in Table 3.2.

Table 3.2 Patient characteristics and baseline values per series

	Series A LBMT vs. LCMT n = 12	Series B WBT vs. LCMT n = 9	Series C Squat n = 14	Series D HBK n = 9
Patient characteristics				
Age (years, median, range)	46 (18 – 80)	37 (16 – 71)	27 (16 – 52)	28 (16 – 38)
Sex	7 F / 5 M	4 F / 5 M	9 F / 5 M	7 F / 2 M
Body height (cm)	175 ± 12	176 ± 9	174 ± 11	173 ± 6
Body weight (kg)	72 ± 12	72 ± 13	68 ± 9	67 ± 8
n syncopal episodes – 1 year (median, range)	2 (1 – 10)	2 (1 – 20)	3 (1 – 30)	5 (1 – 30)
n syncopal episodes life-time (median, range)	6 (1 – 40)	3 (1 – 30)	10 (1 – 40)	10 (1 – 35)
5 minutes supine rest				
SBP (mmHg)	116 ± 16	105 ± 12	120 ± 17	123 ± 14
DBP (mmHg)	63 ± 9	56 ± 8	63 ± 10	66 ± 8
MAP (mmHg)	81 ± 9	72 ± 8	81 ± 11	84 ± 10
HR (beats · min ⁻¹)	73 ± 10	73 ± 11	71 ± 11	73 ± 14
3 minutes head-up tilt				
SBP (mmHg)	118 ± 15	113 ± 18	123 ± 18	124 ± 15
DBP (mmHg)	73 ± 11	67 ± 14	75 ± 11	74 ± 12
MAP (mmHg)	88 ± 11	80 ± 14	89 ± 12	89 ± 12
HR (beats · min ⁻¹)	88 ± 19	91 ± 21	89 ± 12	89 ± 15

LBMT, LCMT, WBT, Squat, HBK: see Table 3.1 Unless indicated otherwise, variables are given as mean ± SD.

Based on the nadir values and the presence of prodromal symptoms, at the start of each manoeuvre all patients had a vasovagal reaction with imminent syncope if no measures were taken. BP, HR and derived parameters prior to start of each manoeuvre are given in Tables 3.3 and 3.4.

Table 3.3 Effects of manoeuvres in series A and B

		LBMT vs. LCMT				WBT vs. LCMT			
		LBMT		LCMT		WBT		LCMT	
		Start	10 – 40 s after start	Start	10 – 40 s after start	Start	10 – 40 s after start	Start	10 – 40 s after start
SBP (mmHg)	77 ± 8	104 ± 18	75 ± 14	120 * ± 13	73 ± 6	115 ± 23	70 ± 10	123 * ± 19	
DBP (mmHg)	54 ± 8	69 ± 12	53 ± 11	76 * ± 11	51 ± 8	73 ± 16	50 ± 10	76 * ± 14	
MAP (mmHg)	61 ± 7	79 ± 13	60 ± 12	89 * ± 11	56 ± 7	83 ± 16	55 ± 10	88 * ± 14	
HR (beats · min ⁻¹)	96 ± 28	103 ± 20	93 ± 23	97 ± 16	94 ± 27	110 ± 21	99 ± 23	107 ± 22	
SV	66 ± 19	83 ± 25	64 ± 24	100 * ± 24	53 ± 16	80 ± 23	55 ± 19	90 ± 28	
CO	69 ± 12	95 ± 21	65 ± 17	110 * ± 22	54 ± 12	94 ± 21	59 ± 16	104 ± 23	
TPR	104 ± 22	99 ± 20	62 ± 30	96 ± 21	137 ± 38	115 ± 26	132 ± 47	112 ± 34	

LBMT, LCMT, WBT: see Table 3.1; Values are means ± SD. Stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) are given as percentage baseline, i.e. over the interval 2.5 – 3 minutes after head-up tilt. *: significant difference between compared manoeuvres ($p < 0.05$), data given as mean ± SD

Table 3.4 Effects of manoeuvres in series C and D

		Squat		HBK	
		Start manoeuvre	10 – 40 s after start	Start	10 – 40 s after start
SBP (mmHg)	76 ± 13		122 * ± 15	69 ± 8	115 * ± 16
DBP (mmHg)	50 ± 10		74 * ± 10	48 ± 7	70 * ± 16
MAP (mmHg)	57 ± 12		88 * ± 11	53 ± 8	82 * ± 15
HR (beats · min ⁻¹)	90 ± 21		80 ± 8	99 ± 14	78 * ± 12
SV	65 ± 19		115 * ± 15	50 ± 12	98 * ± 30
CO	66 ± 23		104 * ± 15	57 ± 16	84 * ± 15
TPR	107 ± 33		99 ± 16	127 ± 51	117 ± 38

Squat, HBK: see Table 3.1; values are means ± SD. stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) are given as percentage baseline, i.e. after 2.5 – 3 minutes head-up tilt. *: < 0.05

All manoeuvres caused an increase in BP (Tables 3.3 and 3.4, Figure 3.2) varying from a rise in SBP from 77 ± 8 mmHg to 104 ± 18 mmHg ($p < 0.05$) in series A during LBMT to a rise from 70 ± 10 mmHg to 123 ± 9 mmHg ($p < 0.05$) in series B during LCMT. With the onset of each manoeuvre BP started to increase after ~ 3 s and in all patients stabilizing BP took less than 15 s. HR increased in LBMT, LCMT and WBT ($p < 0.05$). In HBK HR decreased from 99 ± 14 to 78 ± 12 beats $\cdot$ min $^{-1}$ ($p < 0.05$). All manoeuvres elicited an increase in CO ($54 \pm 12\%$ of baseline values to 94 ± 21 in WBT to a rise from 65 ± 17 to 110 ± 22 in LCMT in series A) without significant changes in TPR. The hemodynamic effects of manoeuvre per group are given in Tables 3.3 and 3.4 and Figure 3.2.

Figure 3.2 The effects of the five manoeuvres on mean arterial pressure (MAP), heart rate (HR), stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR). SV, CO and TPR are represented as percentage of baseline (% bl., i.e. mean over the interval 2.5 to 3 minutes after head-up tilt). Each grey plots represent the indices at the start of and during the manoeuvre. The black plots represent the group means. The graphs on LCMT combine all subjects in series A and B. *: significant change ($p < 0.05$); n. s.: non-significant. For abbreviations, see Table 3.1

In series A, SBP rose to 104 ± 18 mmHg in LBMT, whereas in LCMT SBP stabilized at 120 ± 13 mmHg ($p < 0.05$). In series B WBT showed slightly less effective on BP than LCMT: SBP was 123 ± 19 mmHg vs. 115 ± 23 mmHg ($p < 0.05$). CO was lower during LBMT than during LCMT ($95 \pm 21\%bl.$ vs. $110 \pm 22\%bl.$, $p < 0.05$). All other values (including HR) within both series did not differ. In Figure 3.3 MAP, HR, SV, CO and TPR during the two compared manoeuvres in series A and B are plotted.

Figure 3.3 Mean arterial pressure (MAP), heart rate (HR), stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) in series A (left panels) and series B (right panels). SV, CO and TPR are represented as percentage from baseline (%bl, i.e. mean over the interval 2.5 to 3 minutes after head-up tilt). Each line represents the effects in one individual. The black plots represent the group means. *: significant difference ($p < 0.05$); n. s.: non-significant. For abbreviations, see Table 3.1

Discussion

This study shows that the circulatory effect of various physical counter-manoeuvres during vasovagal reactions is exclusively due to an increase in CO rather than any consistent effect on TPR. The small differences in the BP effects of LCMT and LBMT respectively WBT do not seem clinically relevant. The study also documents the efficacy of squatting and the “crash position” as counter-manoeuvres to increase BP immediately during vasovagal reactions.

The effects of physical counter-manoeuvres on cardiac output and peripheral resistance

There are remarkable resemblances between the effects of the physical counter-manoeuvres in the present study on CO and those when inflating an antigravity suit at the onset of an impending vasovagal faint (215). CO rises by a factor of 1.3 – 1.7 in our manoeuvres (Tables 3.3 and 3.4) and a factor 1.4 during suit inflation. In both experiments CO increased to ~100% of baseline upright values (Tables 3.3 and 3.4). In another study in two healthy individuals squatting caused a factor 1.6 increase in CO measured by dye-dilution (140).

In the classical study by Weissler *et al.* inflation of an antigravity suit during an impending vasovagal faint induced an instantaneous increase in central venous pressure (Fig. 2.1). More recently it was shown that leg muscle tensing during upright free standing also increased central venous pressure instantaneously (204). These observations document the rapid effect of these interventions on right ventricular filling pressure. However, an effect on systemic blood pressure was observed with a latency of ~3 s (108, 215). The explanation for this latency is straightforward and was likely due to the time it took to translocate the venous blood from the right ventricle through the pulmonary circulation to the left ventricle and the systemic circulation (223).

In the above mentioned antigravity suit experiment the effects of the intervention were solely explained by an increase in CO (determined by the dye-dilution method) (215). No effects were observed on TPR and the vasovagal faints reoccurred after deflation of the antigravity suit. Accordingly, none of the physical counter-manoeuvres in the present study had any significant effect on TPR and vasovagal reactions reoccurred after release of muscle tensing. The lack of an effect of physical counter-manoeuvres on TPR may be surprising, but it is not when the time course of the effects of skeletal muscle tensing on sympathetic outflow and TPR under similar circumstances is considered. During preparation and initiation (first minute) of upright leg-cycling exercise in healthy volunteers muscle sympathetic nerve activity is decreased suggesting

facilitation of increased muscle blood flow (28). During the first minute of sitting static leg exercise (at 30% of maximal voluntary power) in an experiment by Ray *et al.* muscle sympathetic nerve traffic was also found to decrease. One of the explanations given by the authors is loading of the cardiopulmonary baroreceptors due to the rapidly increased thoracic blood volume (143). In their study muscle sympathetic activity only started to increase after one minute of exercise (143). This increase in sympathetic nerve activity is mediated by the muscle chemo-reflex, which is activated after 1 – 2 minutes of static muscle exercise (152).

In our study skeletal muscle tensing was only sustained for 40 – 60 s. Thus, an increase in muscle sympathetic outflow and TPR is not to be expected. Previous observations that show that lower body muscle tensing during orthostatic stress increases orthostatic tolerance but does not increase TPR (178) and that isolated hand gripping has only a trivial effect on orthostatic tolerance (108) are in excellent agreement with this explanation of the event.

The observation that isometric handgrip does not increase orthostatic tolerance (108) seems in conflict with the observation by Brignole *et al.* who showed that forceful isometric arm counter-manoevres during free standing are effective to combat vasovagal reactions (21). We attribute this difference to leg and abdominal contractions that are inevitable during maximal isometric arm exercise in the upright position in order to stabilize the body.

So far, we have attributed the rise in BP during muscle tensing manoeuvres to mechanical effects on CO and not to reflex effects. The HR response, however, documents that reflex effects are involved as well. The instantaneous increase in HR at the onset of muscle tensing (Fig. 3.1, (108)) is a reflex effect by a combination of central command and the muscle-heart reflex (13, 152). Reflex sympathetic stimulation of cardiac contractility at the onset of exercise may have contributed to the increased CO. In contrast to the muscle tensing manoeuvres, the crash position (where no skeletal muscle tensing is involved but only passive abdominal compression) subsequently does not increase HR.

In squatting where compression of arteries would be expected most prominently, TPR also did not change significantly, indicating that mechanical effects on arterial conductance play a minor role in the efficacy of the manoeuvres. This corresponds to an earlier study that was unable to show an effect of squatting on TPR (140).

Limitations

A potential limitation of our study is that we did not objectify levels of skeletal muscle tension. Although we took care that the different manoeuvres were performed with comparable effort in all subjects at all times, the lack of its measurement makes muscle tension an uncontrolled variable in the study. We also did not measure possible changes in intra-abdominal and intra-thoracic pressure. Especially in whole body tensing, unintentionally increasing intra-thoracic pressure (closing the glottis when commencing whole body tensing) may have impaired venous return, thereby not fully effecting the manoeuvre's potential.

A potential limitation of generalizability lays in our protocol in which we used nitro-glycerine to induce a vasovagal reaction. Although this method is widely used, and considered by many as a satisfactory model for vasovagal episodes outside the laboratory (20), there are indications that this provocation leads to predominantly CO (i.e. decreased cardiac filling) mediated vasovagal reactions (66). Among vasovagal episodes outside the laboratory, the bradycardiac and peripheral vasodilatory effects may be more prevalent. This study may thus overestimate the effects of physical counter-manoevres on CO, compared to vasovagal reactions without nitro-glycerine provocation.

Clinical use of physical counter-manoevres

Although there are differences in the BP effects of the investigated manoeuvres, they are small and, since all manoeuvres prevented syncope, they do not seem clinically relevant. Thus when advising patients, the daily applicability of each manoeuvre should be taken into account, and the advice can be customized to the individual patient's ability to perform the manoeuvre.

Leg crossing (without muscle tensing) could be used in provocative situations as a preventive measure and either lower or whole body muscle tensing seems a reasonable next step when symptoms develop. If symptoms persist, patients could squat which may be less embarrassing socially than the formerly advocated laying down. The "crash position" is especially appropriate when syncope occurs while sitting or for patients who have motor disabilities that would prevent squatting or make them more vulnerable in case of collapse. Recognition of prodromal signs is pivotal in the timely institution of any of the manoeuvres, and thus the manoeuvres do not apply to the (relatively small) subset of patients who experience syncope without warning. The range of manoeuvres in this study could however offer physicians and the mainstay of their patients a means of tailoring therapy to the individual patient's needs. By having a short-list of readily accomplishable manoeuvres, patients could increase control over their symptoms and potentially improve the quality of their lives.

4. Leg Crossing Improves Orthostatic Tolerance in Healthy Subjects: a Placebo Controlled Cross-over Study¹

C. T. P. Krediet, J. J. van Lieshout, L. W. J. Bogert, R. V. Immink, Y. S. Kim and W. Wieling

Introduction

About 40% of the general population experiences at least one episode during life-time of transient loss of consciousness (35) of which vasovagal fainting is the most common cause. Vasovagal reactions include reflex mediated vasodilatation and / or bradycardia that can occur in most otherwise healthy subjects when exposed to a sufficiently severe orthostatic stress (56). Recurrences are common and may have a profound impact on the quality of patients' lives (119). The therapeutic options for recurrent vasovagal syncope are limited. Management focuses on patient education and volume loading if feasible (31, 71). Usually, the episodic nature of the disorder does not justify permanent medications (e.g. midodrine)(71) and pacemaker therapy is controversial (71).

Physical counter-manoevres such as leg crossing combined with leg, buttock and abdominal muscle tensing (99, 108) and isometric arm exercise (21, 99) have been introduced as effective measures in aborting an impending vasovagal faint. Although these manoeuvres are helpful in managing vasovagal reactions, they are only a means of tertiary prevention: containing an evoked vasovagal reaction thus preventing loss of consciousness. As a drawback such manoeuvres are only feasible for patients who recognize (if any) prodromal symptoms and vasovagal reactions often return after terminating the manoeuvre (21, 105, 108).

Aiming for leg crossing as secondary prevention for orthostatically induced vasovagal reactions, this study investigated the hypothesis that leg crossing

¹ Previously published in the "American Journal of Physiology" (109), reproduced with permission from the publisher, ©2006 the American Physiological Society

(i.e. without additional muscle tensing) would improve orthostatic tolerance. We choose a human model for vasovagal syncope in a randomized cross-over, placebo controlled study design and applied progressive central blood volume depletion by combining head-up tilting (HUT) with incremental lower body negative pressure (LBNP) to induce pre-syncope in healthy subjects (52, 114).

Methods

After approval of the Medical Ethical Committee of the Academic Medical Center at the University of Amsterdam, nine subjects (6 females, median age 25 years (range 20 – 41), mean height 176 cm (SD 12), mean body weight 72 kg (SD 12), mean body mass index $23 \text{ kg} \cdot \text{m}^{-2}$ (SD 2)) responded to an advertisement in a national newspaper. Except for four subjects on oral contraceptives, they used no medications. All subjects had a normal exercise tolerance. Six had fainted previously, none of them had sought medical attention for it and none had fainted in the previous year. Standard physical examination and electrocardiogram revealed no abnormalities. All subjects received a detailed demonstration of the protocol before giving written consent.

Protocol

In a cross-over design orthostatic tolerance was challenged at the same time of the day (± 15 minutes) on three consecutive days. The tests were carried out a) without intervention, b) with leg crossing and c) with oral placebo tablet (Albochin, FNA, Dutch generic) in randomized order. One hour (± 5 minutes) before start of the test subjects took the placebo with ~ 50 ml of tap water. The investigators had informed the subjects that one of the study's aim was to "compare the effects of leg crossing to those of this approved medication", that they "expected the drug to stabilize the blood pressure", and that the subjects would thus "sustain a more profound orthostatic stress than without". After the study, the investigators informed the subjects about the nature of the placebo.

Subjects abstained from alcohol, tobacco and caffeine from 24 hours before the first test until after the third test. From 2 hours prior to each test, they also abstained from any other food or liquid intake (apart from the tap water with the placebo). Before the test, the subjects practiced leg crossing supervised by one of the investigators. During the manoeuvre, the subjects positioned both feet flat on the footboard of the tilt-table, bearing weight on both without any specific leg tensing. The manner in which they crossed the legs (right over left or vice versa) was left to the subjects' preferences and recorded.

Tests took place in a climate-controlled room at ambient air temperature of -23°C . Finger blood pressure (BP, Finometer, Finapres Medical Systems, The Netherlands) and a lead-II electrocardiogram (ECG, Hewlett Packard 7834I, USA) were measured continuously. The cuff was applied to the mid-phalanx of the left hand, and held in the mid-axillary line at heart level. Thoracic impedance (TI) was monitored each 15 s (C-Guard, Danmeter, Denmark) as an index of thoracic blood volume. Two pairs of electrodes were positioned with an internal distance of 5 cm behind the right sternocleidomastoid muscle, and another pair in the left midaxillary line at the level of the xiphoid process.

After fitting a LBNP-box closely on a manually operated tilt-table (after a design by R. Hainsworth, Leeds, UK; modifications by the Department for Medical Technological Development of the Academic Medical Center at the University of Amsterdam, The Netherlands) at the level of the subjects' iliac crests, further instrumentation and a subsequent 5 minutes supine baseline period, they were 60 degrees head-up tilted. When testing leg crossing, this manoeuvre commenced 3 minutes after onset of tilt. Through a window in the LBNP-box the investigators verified the manoeuvre was performed correctly. After 20 minutes of HUT, increasing LBNP (-20 , -40 and -60 mmHg) was stepwise applied for 10 minutes at each level. The protocol ended when systolic blood pressure (SBP) fell to ≤ 85 mmHg, or if HR (HR) was ≥ 140 beats $\cdot$ min $^{-1}$ and subjects were tilted horizontally.

Data acquisition and analysis

Signals of BP and ECG were converted analog-to-digital at 100 Hz (Beatscope 1.1, TNO-BMI, The Netherlands) for off-line analysis. SV was calculated using Modelflow[™] (Beatscope 1.1, TNO-BMI, The Netherlands). This methodology tracks rapid changes in SV accurately during postural stress and leg crossing compared to SV determined by inert gas rebreathing and (198) Doppler ultrasound (207). Mean arterial pressure (MAP) was the integral over one heart beat and HR was the inverse of the pulse interval. CO was SV $\cdot$ HR. Total peripheral resistance (TPR) was MAP $\cdot$ CO $^{-1}$ and pulse pressure (PP) was systolic minus diastolic pressure. SV, CO, and TPR are expressed relative to supine rest.

Off-line data were printed for visual inspection of beat-to-beat results. Beat-to-beat data were digitally transformed to re-sampled data at 1 Hz for analysis (Beatscope 1.1, Finapres Medical Systems, The Netherlands).

Outcomes

The primary outcome was orthostatic tolerance, defined as time (minutes) of tilting to pre-syncope with development of symptoms such as light headedness, profuse perspiration and abdominal discomfort, and SBP ≤ 85 mmHg, or HR ≥ 140 beats $\cdot$ min⁻¹. Secondary outcomes were MAP, HR, SV, CO, PP, TPR and TI at relevant stages during the test.

Statistics

The original study design ($n = 21$) had a power of 70% to demonstrate an effect on the primary outcome of 4 minutes ($\alpha: 0.05$). After interim analysis for the primary end point after five subjects had been studied the number of subjects in the study was adjusted to nine. For the primary outcome a value of $p < 0.01$ was then considered significant. For all other variables it remained $p < 0.05$.

Unless otherwise indicated, data that are considered to fit a normal distribution in the general population (i.e. hemodynamic variables and orthostatic tolerance) are expressed as mean $\pm$ SE. Intra-individual differences in orthostatic tolerance in the three tested conditions were compared by paired t-tests. To control for the potential accumulated Type I Error the p-value for significance was adjusted to < 0.005 . Differences in secondary outcomes were only tested between control and leg crossing.

Results

Leg crossing and orthostatic tolerance

Six subjects crossed the right over the left leg, the remaining vice versa. At the start of tilt back all subjects met the predefined criteria for pre-syncope. Figure 4.1 compares the hemodynamic variables in the control and leg crossing test during the first 27 minutes of the protocol. This time frame was chosen because shortly after the 27th minute several subjects were tilted back and from this instant on the scatter of the results of the remaining subjects became too large to provide for a realistic plot lacking statistical power. Accounting for the differences in tolerated tilt time per individual and per intervention, the responses for MAP, PP and HR in the late stages are given in Figure 4.2, grouped per intervention in all subjects relative to the time of start of tilt back (i.e. from 5 minutes before to 2 minutes after tilt back).

Figure 4.1 Hemodynamic variables during the first 27 minutes of the protocols (n = 9; from 13 minutes n = 8 when subject # 5 was tilted back during control study). Data are averaged over 30 s. Control (black dots) vs. leg crossing (white dots, mean ± SE). *: p <0.05, **: p <0.01

Figure 4.2 Hemodynamic variables from 5 before until 2 minutes after tilt back (n = 9). MAP: Mean arterial pressure; PP: Pulse pressure; HR: Heart rate. Data are averaged over 30 s intervals. Control (black dots) vs. leg crossing (white dots) vs. placebo (grey dots, mean $\pm$ SE). At this stage of the protocols there are no significant differences between the three tested conditions

Table 4.1 gives the prevailing values for BP and HR at which subjects were tilted back. Within subjects the tolerated tilt time differed with condition (no intervention vs. placebo vs. leg crossing) but BP and HR responses prior to tilt back were similar for each subject on three days (Fig. 4.2). With leg crossing all subjects sustained a greater orthostatic challenge than during control or with placebo (34 ± 2 vs. 26 ± 2 vs. 23 ± 3 minutes, $p < 0.001$). There was no significant difference in orthostatic tolerance between control and placebo (Fig. 4.3).

Table 4.1 Blood pressure and heart rate at pre-syncope (3 beats averages prior to start of tilt back)

		Control				Leg crossing				Placebo			
#	Sex	Tilt time (min)	SBP (mmHg)	DBP (mmHg)	HR (beats · min ⁻¹)	Tilt time (min)	SBP (mmHg)	DBP (mmHg)	HR (beats · min ⁻¹)	Tilt time (min)	SBP (mmHg)	DBP (mmHg)	HR (beats · min ⁻¹)
1	M	30	37	29	105	42	75	64	110	40	75	63	133
2	F	22	80	58	128	29	73	49	129	6	79	58	114
3	M	25	40	26	51	43	75	50	91	26	57	34	68
4	M	32	84	57	86	37	85	56	98	27	89	63	98
5	F	12	71	42	77	24	75	51	87	14	66	40	77
6	F	25	100	64	143	28	108	68	140	9	70	38	75
7	F	29	84	59	140	35	77	55	140	32	67	46	115
8	F	31	85	59	125	36	84	54	119	29	76	49	88
9	F	24	69	42	105	32	76	52	128	22	71	50	121
Mean		26	72	48	107	34	81	55	116	23	72	49	99
SE		2	7	5	10	2	4	2	7	4	3	4	8

abbreviations: SBP: systolic blood pressure, DBP: diastolic blood pressure; HR: heart rate

Figure 4.3 The individual orthostatic tolerances expressed as time to tilt back under the three tested conditions (mean ± SE). n.s.: non-significant

Hemodynamic effects of leg crossing

From 5 to 20 minutes of HUT with leg crossing MAP was not different from control (81 vs. 81 mmHg, Fig. 4.3), but the increase in HR compared to the supine position remained lower (+ 13 vs. 18 beats $\cdot$ min⁻¹, $p < 0.05$) and was accompanied by a larger SV (79 vs. 74% supine, $p < 0.05$) with CO and TPR unchanged (CO: 95 vs. 94% supine, TPR: 122 vs. 122% supine). There was a trend toward lower TI from the onset of leg crossing (Fig. 4.1).

Discussion

This study shows that leg crossing (without additional leg tensing) enhances orthostatic tolerance in healthy subjects. The documented increase in orthostatic tolerance likely represents a factual improvement because BP and HR at which the test was terminated did not differ with and without intervention. The average improvement in tolerance of 8 minutes (and to placebo 11 minutes) may seem minor, but compares well with studies that apply the same orthostatic stress to explore therapeutics such as water ingestion (5 minutes, (161)) and salt loading (9 (75) and 12 minutes (31)).

The strengths of this study are in its randomized placebo controlled design and the repeated measurements within 50 hours in an accepted model. We used naive subjects and controlled for learning effects and circadian variation in cardiovascular regulation. We did not control for menstrual cycle or phase of oral contraception since all measurements were performed within 50 hours and are, therefore, not likely to have importantly influenced our results.

To maintain orthostatic tolerance humans need to use the muscles in the legs to prevent accumulation of blood and fluid in dependent parts of the body (124, 131), but it is unresolved how much skeletal muscle activity is needed. Therefore, it may seem unfortunate that in this study there is no evaluation of how much activity leg crossing without additional active muscle tensing induced. However this study was not set out to make such estimation where the studied intervention comprised of leg crossing alone. We consider any changes in leg muscle tension to originate from direct mechanical compression (i.e. impact on and from the crossing leg) and probably also from active skeletal muscle contraction in order to keep balance, as stance width (which is decreased during leg crossing) is a known determinant of leg muscle activity (79).

We used Modelflow™ to document relative changes in SV (90) and for this purpose the method has been validated during active and passive postural stress

(against thermodilution (77) and Doppler ultrasound (207)) and leg crossing (against gas rebreathing (198)).

From previous work it is known that at the onset of skeletal muscle contractions in the lower body central venous pressure rises and right atrial pressure increases (223). This causes instant reflex sympathetic withdrawal, more pronounced in the upright than in the supine position (144), with a decrease in TPR and a subsequent transient arterial baroreflex mediated HR increase. After some 3 heart beats the translocated blood has passed through the pulmonary circulation to contribute to left ventricular SV (223). The resulting surge in CO and decrease in TPR subside and within 1 – 2 minutes BP, CO and TPR return to baseline values. In addition to previous work that focused on the response during one (191) or two minutes (198) of leg crossing this study documents the sustained increase in SV with reflex inhibition of HR. The trend towards a lower TI conforms to an elevated cardiac pre-load as a result of reduced leg venous pooling capacity. Salt loading studies show that increases in circulating volume of only 4 – 5% can increase orthostatic tolerance to 5 – 6 minutes in the same head-up tilt- LBNP protocol as used in the present study (136).

In an earlier supine study using LBNP, Smith *et al.* (178) found a stabilising effect on orthostatic tolerance from leg contractions at 5 – 10% of maximum voluntary contraction force. In addition hereto our study shows that very low increases in skeletal muscle tone such as from leg crossing (with no extra voluntary force involved) has a similar effect and with Smith *et al.* we emphasize the importance of insuring a relaxed state during interventions such as LBNP if valid observations are to be made.

Apart from the hemodynamic mechanism of the gained orthostatic tolerance other factors should be taken into account. Standing with the legs crossed is likely to affect the motor programmes for keeping balance by decreasing stance width (79). Via central command mechanisms this may influence baroreflex sensitivity (59) and subsequently orthostatic tolerance.

In 1928 Ghrist and Brown described the stabilising hemodynamic effects of leg crossing in a patient with autonomic failure (63) and after systematic investigations in the 1980 – 90's, leg crossing became an integrated part in the treatment of chronic orthostatic hypotension. In a recent multi-center trial leg crossing as tertiary prevention for vasovagal syncope showed its clinically significant effect on syncope burden (200). The present study shows the efficacy of leg crossing as a secondary prevention measure. Apart from those with motor disabilities, this essentially costless therapy is feasible in all subjects, also those without prodromal symptoms.

5. Lower Body Muscle Tensing Diminishes the Blood Pressure Decrease Upon Standing From Squatting in the Post-vasovagal State^I

C. T. P. Krediet, I. K. Go – Schön, J. J. van Lieshout and W. Wieling

Introduction

Transient loss of consciousness (TLOC) is a common medical problem, constituting ~1% of emergency department visits (22, 187). An estimated 40 (93) to 60% (22) of those are caused by vasovagal reactions. In the general population younger than 60 years, the life-time incidence of TLOC is ~35% and >90% of these episodes are considered to be of vasovagal origin (62). About 50% of patients who present with vasovagal syncope will face at least one recurrence in the following three years (172). The direct and indirect costs of recurrent syncope are high (27). In addition, the majority of patients with vasovagal syncope also experience pre-syncope, which can be as incapacitating as syncope itself (202). The quality of life of patients with recurrences and / or pre-syncope is seriously affected and comparable to that of patient with chronic diseases like rheumatoid arthritis or recurrent moderate depressive disorder (119, 202).

By the number of affected patients, the costs from the disorder and its impact on the quality of life, even marginally optimizing the existing management strategies for vasovagal syncope may result in significant benefits at population level. In recent years physical counter-manoevres that raise blood pressure by augmenting venous return to the heart and increasing cardiac output (CO) at the onset of an impending vasovagal faint, have been on the advent as a therapy (e.g. leg crossing with muscle tensing (108), lower body muscle tensing (105), squatting (99, 105), isometric arm exercise (21)). An international randomized controlled clinical trial showed that adding physical counter-manoevres to the traditional therapy resulted in a relative risk reduction for syncope recurrence of 39% (200).

One of the most potent physical counter-manoevres is squatting (99, 105). It is an easy, natural manoeuvre at the onset of pre-syncopal complaints. As an advantage over other physical counter-manoevres, squatting is a passive manoeuvre, i.e. once the patient is squatting there is no need for additional muscle tensing. In the confusion of an impending faint, this may be an important advantage. However a major drawback is that standing up from the squatted position is a large hemodynamic stressor that may cause new (pre-)syncopal symptoms (105, 225). As a result, patients report that they often choose not to use squatting as a counter-manoeuve at all. Finding ways to overcome this limitation to the use squatting as a counter-manoeuve is an obvious and potentially rewarding challenge.

Recently we showed that lower body muscle tensing (LBMT) attenuates the transient blood pressure decrease upon standing in healthy subjects and patients with initial orthostatic hypotension (i.e. with an abnormally large blood pressure decrease upon standing from supine or squatting) (106). LBMT could possibly also attenuate the blood pressure decrease after standing up from squatting when used to combat a vasovagal reaction. However, considering the autonomic and hemodynamic differences between the initial phase after standing up and shortly after aborting a vasovagal reaction (e.g. lowered sympathetic tone from vasovagal reaction may persist) the potentially beneficial effects of LBMT after squatting during a vasovagal reaction are not self-evident.

With this information as a background, we set out to test the hypothesis that lower body skeletal muscle tensing attenuates the decrease of arterial blood pressure upon standing from squatting when used as a manoeuvre to prevent vasovagal syncope. In addition, this study gives some important insight in the hemodynamic differences between the circulation during squatting before and after a vasovagal reaction. We studied patients with vasovagal syncope, in resting conditions and during tilt test (with additional nitro-glycerine) provoked pre-syncopal episodes, measuring blood pressure continuously and deriving continuous indexes of cardiac output and peripheral resistance using pulse wave analysis.

Methods

Inclusion

Eighteen consecutive patients (10 females; median age 37.5 years (range 18 – 65); median body weight 75.5 kg (range 60 – 103); median body height 175.5 cm (range 161 – 190)) who were able to squat participated in the study. Five

patients used an oral contraceptive, two used anti-hypertensive drugs and two a selective serotonin reuptake inhibitor. At our institution, patients with vasovagal syncope are instructed how and when to apply physical counter-manoevres during vasovagal reactions provoked by head-up tilting with additional nitro-glycerine.

Medical history in all patients consisted of at least one episode of loss of consciousness, with prodromal symptoms such as diaphoresis, pallor, visual disturbances (e.g. “seeing black spots”) in the presence of either of the following triggers: prolonged orthostatic stress, pain or an unusually strong emotional circumstance and electrocardiography did not reveal arrhythmogenic heart disease possibly related to syncope. All patients therefore confirmed to the clinical diagnosis “vasovagal syncope” (20).

Protocol

Investigations took place between 8:00 AM and 1:00 PM, in a temperature-controlled room ($\sim 23^{\circ}\text{C}$). First patients rested supine on a bed for >5 minutes. After a subsequent ~ 5 minutes standing they squatted for 30 – 50 s and then rose within 1 s (“pre-tilt squat 1”) and stood for another ~ 1 minute.

Patients were then positioned on a manually controlled tilt table with a foot-board. After 5 minutes of supine rest, patients were 60 degrees head-up tilted for 20 minutes. If no vasovagal reaction developed, 0.4 mg nitro-glycerine was administered sublingually prior to an additional 15 minutes tilt. Once there was a relentless fall in blood pressure in the presence of pre-syncopal symptoms, the patients were tilted to the horizontal position. After 1 – 5 minutes they were again head-up tilted and stepped off the tilt table. Standing next to tilt table, they performed two squat manoeuvres (“post-tilt squat 1” and “post-tilt squat 2”). Squatting was performed for 60 s. Immediately after post-tilt squat 2 they performed lower body muscle tensing (LBMT) for 30 – 40 s. LBMT consisted of tensing of all skeletal muscles in the abdomen, buttocks and legs at maximal voluntary capacity. The patients received instruction to breathe normally and to avoid straining. After each standing up manoeuvre the investigators asked the patients for pre-syncopal symptoms and they documented their answers.

After completing the protocol, 12 of the 18 patients repeated the post-tilt squat protocol twice. (This was done to give them further explanation and instruction.) These subsequent squats are referred to as “post-tilt squat 3 – 6” (e.g. “post-tilt squat 3” without, “post-tilt squat 4” with LBMT etcetera). The first of the three trials was taken into the primary analysis.

Blood pressure was measured continuously non-invasively using finger volume-clamp photo-plethysmography (Finometer, Finapres Medical Systems, The Netherlands). The finger cuff was applied to the mid-phalanx of the left middle finger. To avoid hydrostatic column artifacts, the patients held the cuffed finger at right-atrial level in the mid-axillary line. One of the investigators operated a marker pulse to identify the timing of each manoeuvre. For off-line analysis, all signals were digitally stored at a sampling rate of 200 Hz, as well as real-time printed by a thermo-paper writer (Thermal Arraycorder WR 7700, Graphtec, Germany) for direct inspection and annotation.

Analysis

Off-line, beat-to-beat systolic (SBP) and diastolic (DBP) arterial blood pressure and heart rate (HR) were derived from the arterial pulse wave. Corrupted data-points (i.e. artefacts on the arterial pulse waveform) were identified by an expert system and omitted (<2%). Using Modelflow™ (Finapres Medical Systems, The Netherlands (90)) relative changes in left ventricular stroke volume (SV) were calculated. This method has been validated during active and passive postural stress against thermo-dilution (77) and Doppler's ultrasound (207), and during physical counter-manoevres against gas re-breathing (198). CO was $HR \cdot SV$. Mean arterial pressure (MAP) was the time-integral over the beat-to-beat pressure recording. Beat-to-beat TPR was $MAP \cdot CO^{-1}$. All beat-to-beat data were subsequently re-sampled at 1 Hz.

Baseline values were taken from the interval 20 – 5 s before standing up from supine. CO and TPR values are expressed as percentage of this baseline. MAP nadir (MAP_{min}) was determined after pre-tilt squat 1 and post-tilt squats 1 and 2. Of each MAP_{min} the synchronous SBP, DBP, CO and TPR were determined. All hemodynamic variables fitted a normal distribution (according to Kolmogorov-Smirnov) and are given as mean $\pm$ SE unless indicated otherwise.

In the primary analysis MAP_{min} of post-tilt squats 1 and 2 were compared by Student's paired t-test. The same test run was used to identify potential differences in underlying CO and TPR respectively. A p-value <0.05 was considered statistically significant. We also compared MAP, CO and TPR during pre-tilt squat 1 to those during post-tilt squat 1.

Results

Figure 5.1 shows the hemodynamic changes after standing up from pre-tilt squat 1 and post-tilt squats 1 and 2 in a representative patient.

Figure 5.1 Original continuous blood pressure (BP) and heart rate (HR) records of a representative patient during the three standing up manoeuvres from squatting. Black bars indicate standing up. White bar indicates LBMT. Lower panels show derived stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR)

Standing up from pre-tilt squat 1 caused MAP to decrease to 79 ± 3 mmHg (SBP 110 ± 5 mmHg, DBP 62 ± 3 mmHg). This was accompanied by a transient increase of CO to $107 \pm 7\%$ and TPR to decrease transiently to $80 \pm 4\%$ of supine levels. (Fig. 5.2).

Figure 5.2 Mean arterial pressure (MAP), cardiac output (CO) and total peripheral resistance (TPR) during standing up from squatting. CO and TPR are expressed as percentage of the supine (baseline) values. Time 0 refers to start of standing up

The head-up tilt test was terminated at the occurrence of pre-syncope symptoms after a median of 25 minutes (range 22 – 35). SBP at the start of tilt back was 63 ± 2 mmHg, DBP 45 ± 2 mmHg (MAP 50 ± 2 mmHg) and HR 88 ± 5 beats $\cdot$ min⁻¹. CO at this moment was $42 \pm 4\%$ and TPR $148 \pm 11\%$ of supine baseline.

During post-tilt squat 1, HR was slightly higher (80 ± 5 vs. 75 ± 4 beats $\cdot$ min⁻¹, $p = 0.02$) and CO was lower than during pre-tilt squat 1. (70 ± 4 vs. $93 \pm 2\%$ of

supine values, $p < 0.001$) (Fig. 5.2). TPR did not differ significantly. This resulted in a significantly reduced MAP during post-tilt squat 1 (108 vs. 118 mmHg, $p = 0.012$).

After post-tilt squat 1, MAP decreased to a nadir of 64 ± 4 mmHg (SBP 84 ± 5 mmHg, DBP 55 ± 3 mmHg), CO at this moment was $73 \pm 5\%$ and TPR $99 \pm 5\%$ of supine values (Fig. 5.2). Thirteen patients reported pre-syncope symptoms. When standing up from squatting was repeated (post tilt squat 2) with application of LBMT MAP nadir was 76 ± 3 mmHg ($p < 0.001$ compared to post-tilt squat 1; simultaneous SBP 103 ± 3 mmHg, DBP 65 ± 3 mmHg) (Figs. 5.2 and 5.3). Whereas without LBMT 13 (from 18) patients reported pre-syncope symptoms after standing up from squatting, with LBMT 11 from those 13 patients reported significantly less or no symptoms. LBMT was accompanied by a higher CO ($85 \pm 6\%$, $p < 0.009$); TPR did not differ ($101 \pm 7\%$).

Figure 5.3 Mean arterial pressure (MAP), cardiac output (CO) and total peripheral resistance (TPR) at MAPmin during post-tilt squat 1 (control) and post-tilt squat 2 (with LBMT) respectively. Error bars indicate mean $\pm$ SE. n.s.: non-significant

In those patients who repeated the squat protocol ($n = 12$) LBMT resulted in a similar attenuation of the blood pressure response during successive trials (Fig. 5.4). Figure 5.5 gives a representative example.

Figure 5.4 Mean arterial pressure (MAP) during consecutive standing up from squatting after the tilt test; between brackets the numbers of patients included (see method section). Time 0 refers to start of standing up

Figure 5.5 Continuous blood pressure (BP) record in a representative patient during six consecutive squat and standing up manoeuvres. White bars indicate squatting, grey bars indicate standing without LBMT and black bars indicate standing with LBMT

Discussion

The results of this study can be summarized as follows: 1) LBMT is effective in blunting the blood pressure decrease after standing up from squatting in the post-vasovagal state. LBMT leads to a significant reduction of (pre-) syncopal symptoms by limiting the reduction in CO and thereby stabilizing blood pressure. 2) Squatting in the post-vasovagal state is associated with a lower CO and MAP (compared to squatting before the vasovagal reaction).

The effectiveness of LBMT in preventing the decrease in blood pressure when used as a “follow-up manoeuvre” to squatting, makes squatting a more attractive therapeutic option for patients with recurrent vasovagal reactions. In the patients who repeated the squat protocol LBMT had a similar effect during successive trials, indicating that the order of intervention and control does not affect the intervention’s effectiveness and that the manoeuvre can be applied repeatedly.

Recently it was demonstrated that the blood pressure trough after standing up may also be blunted by the use of a device that increases the inspiratory impedance and thereby facilitates venous return by augmentation of the respiratory pump (38, 132). LBMT has as an additional advantage that it is a device-less intervention. Because of the number of affected patients, the costs from the disorder and its impact on the quality of life, this simple adjustment to the existing therapies for vasovagal syncope has the potential to reduce the total burden from the disorder at population level.

This study is the first to document beat-to-beat the acute hemodynamic response to standing up from squatting, which is characterized by a transient decrease of TPR and a transient increase of CO (Fig. 5.2, pre-tilt squat 1). This acute fall in TPR (38) is attributed to the following factors (34, 150). 1) The acute decompression of arterial vessels in the legs may cause an instantaneous mechanical decrease in vascular resistance. 2) There is probably an increase in the arterio-venous pressure gradient, due to decompression of the venous vessels. 3) The relative ischemia in the leg muscles during squatting may augment the fall in arterial resistance by local factors (“the post-tourniquet effect” (39)). 4) The muscle activity during the standing up manoeuvre may promote venous return which can trigger right cardiopulmonary volume receptors and lead to a transient decrease of sympathetic vasoconstrictor outflow (223). The vastly decreased TPR is not completely offset by the concomitant increase in CO (as such the initial cardiovascular response is similar to that after standing up from supine (182)). The present study is the first to directly and continuously

measure this CO increase (and TPR decrease) after standing up from squatting, and document its timing (Fig. 5.2).

A progressive reduction in TPR is widely considered to be the main underlying mechanism of vasovagal syncope (hence the term “vasodepressor syncope”) (56). However, the present study indicates that at the start of the tilt to horizontal TPR is still far above its supine baseline (148%) whereas CO has been reduced to about half its supine baseline. This is in agreement with previous studies that showed that a decrease in CO related to the reduction in central blood volume is the predominant mechanism of blood pressure decrease during tilt induced vasovagal reactions (58, 66, 88), although in the final stage of the vasovagal reaction sympathetic withdrawal may be dominant (88, 212). We consider that in the present study by design the patients were tilted back to horizontal upon the first occurrence of syncopal complaints preventing the full manifestation of the effects of sympathetic withdrawal on TPR.

Little is known about the hemodynamic status during the recovery from a vasovagal reaction. This study documents that during squatting after a vasovagal reaction CO is only $70 \pm 4\%$ of supine baseline values (vs. $93 \pm 2\%$ during squatting prior to the vasovagal reaction). This is in agreement with a recent study that documented a sustained decreased of CO in 10 – 15 minutes supine recovery after a tilt induced vasovagal reaction (at $\sim 90\%$ of its pre-tilt supine value (58)). The reason for this attenuation of CO is likely to be a sustained decrease of total circulating volume due to hydrostatic extra-vasation during the prolonged orthostatic stress as well as ongoing venous pooling by nitroglycerine (see below). With TPR and HR unaffected (Fig. 5.2, lower panel) a reduction in cardiac contractility is unlikely to play a major role.

By its design, this clinical study has some inherent limitations. The use of nitro-glycerine as an additional provocation for vasovagal reactions may complicate data interpretation. Sublingual nitro-glycerine decreases cardiac preload by increasing venular capacitance (126). The tilt-nitro-glycerine provoked vasovagal faint may therefore be more CO mediated than faints in daily life (66). In addition, nitro-glycerine reaches its maximum effect ~ 7 minutes after administering and has a half life ~ 4 minutes. Therefore there is a potential interference with at least part of the hemodynamic response during and after standing up from squatting, limiting the generalisability of our findings. However in defence of our findings, interventions that were first shown effective in the lab using the same methodology (i.e. leg crossing with muscle tensing (105, 108) and arm tensing (21)) showed later also effective in (randomized controlled) outpatient trials (43, 200).

In conclusion, LBMT is an effective follow-up manoeuvre to squatting when applied to counteract a vasovagal reaction and syncope patients should be advised about the use of this combination of manoeuvres.

6. Management Of Initial Orthostatic Hypotension: Lower Body Muscle Tensing Attenuates The Transient Arterial Blood Pressure Decrease Upon Standing From Squatting¹

C. T. P. Krediet, I. K. Go – Schön, Y. S. Kim, M. Linzer, J. J. van Lieshout and W. Wieling

Introduction

Transient loss of consciousness (TLOC) is a common medical problem, usually caused by intermittent disturbances in neural blood pressure (BP) control (94). One of its causes is initial orthostatic hypotension (IOH). IOH is defined as symptoms of cerebral and retinal hypoperfusion (e.g. light-headedness, visual disturbances and / or syncope) within 15 s after standing up from a supine, sitting or squatting position caused by an abnormally large transient BP decrease (e.g. >40 mmHg systolic) (225). Especially standing up from squatting has been recognised as an acute hemodynamic stressor (5, 140) which can provoke these complaints.

As with vasovagal syncope, for which according to current guidelines history taking rather than tilt testing is of diagnostic importance (20, 36, 171), the diagnosis of IOH also depends on a typical history. The active standing test as a diagnostic provocation for IOH has probably an even lower “sensitivity” than the tilt test for vasovagal syncope; the latter is estimated to amount to only 50% in patients with a classical history (36, 171, 225).

In a hospital setting IOH is the underlying cause of TLOC in 3 – 4% of syncope cases (225). Syncope and pre-syncope, regardless of their aetiology may markedly decrease quality of life (118, 202). Therapeutic management of IOH is thus an important issue. However the current therapeutic options are limited to general volume measures (e.g. salt loading (174)) that may have hypertensive side effects. The advice to rise slowly (225) may not always be feasible, especially when rising from squatting.

¹ In press at “Clinical Science”

Tensing of leg, buttock and abdominal skeletal muscles, i.e. “lower body muscle tensing” (LBMT), is effective in increasing BP both in patients with postural hypotension due to autonomic failure (229) and during vasovagal reactions (99, 105, 108). LBMT acutely minimises blood pooling in the veins of the lower body and thereby reinfuses blood into the thoracic circulation, enhancing cardiac output (CO) during hypotensive episodes (105, 198). IOH is thought to be caused by active large skeletal muscle contractions (225). Therefore, although LBMT has been shown effective in other forms of (episodic) hypotension, it is unclear whether this intervention would have any beneficial effects on IOH.

With this information as background, we set out to test the hypothesis that LBMT blunts the BP response to standing up from squatting. In addition, we hypothesised that the beneficial effects of LBMT when applied to attenuate IOH would be caused by an increase in CO. We studied healthy subjects and IOH patients during standing up manoeuvres from squatting and used a combination of non-invasive continuous BP recording and pulse wave analysis to assess hemodynamic changes.

Methods

We studied 13 patients who were referred to our syncope unit for the evaluation of TLOC (9 males, median height 180 cm (range 152 – 204), median body weight 77 kg (range 55 – 97), median age 27 years (range 15 – 59), with a median of 4.5 episodes of syncope in their life-times (range 0 – 100)).

All patients had a clinical diagnosis of IOH based on a consistent history of (pre-)syncope occurring 5 – 15 s after rising from a supine or squatting position. There was no classic orthostatic hypotension (i.e. Δ SBP >20 mmHg and / or Δ DBP >10 mmHg, 3 minutes after standing up) (127). The median duration of (pre-)syncopal symptoms was 2 years (range 4 months – 10 years). Two patients had experienced frequent pre-syncope after standing up (i.e. daily to weekly) but this had never resulted in loss of consciousness. Of the patients with syncope 4 also had daily pre-syncopal complaints after standing up; 6 experienced such complaints on a weekly basis and one patient had occasional complaints.

Protocol

BP was measured continuously by finger volume-clamp photo-plethysmography (Finometer, Finapres Medical Systems, The Netherlands). After ~5 minutes free standing the patients squatted for ~1 minute, rose within 1 s and stood for ~1 minute. On repeat squat-stand after another ~1 minute of squatting, they

performed LBMT for 30 – 60 s immediately after rising. If patients reported light-headedness or other pre-syncope symptoms these were documented. LBMT consisted of tensing of all skeletal muscles in the abdomen, buttocks and legs at maximal voluntary capacity for 40 s.

The experiments were performed during the evaluation of the patients for IOH. Patients were positioned in front of the monitor and could observe their BP responses. The duration of squatting varied slightly among patients and was of shorter duration compared to the healthy subjects because of the patient evaluation setting. Repeated squatting for long periods is experienced as uncomfortable by some patients.

After completing the protocol, a subset of 5 patients repeated the squatting protocol twice. (This was done to give them further explanation and instruction.) The first of the three “trials” was used for the comparison described below.

To reduce the potential confounding influence of the fixed order of control and intervention in the patient series, we additionally studied 7 healthy volunteers (5 males, median age 27 years (range 25 – 59), height 179 cm (range 164 – 202), body weight 74 kg (range 52 – 85)) who had not experienced significant IOH symptoms over the last year. In a cross-over study design we assessed the effects of LBMT after standing up from squatting. First, all subjects squatted for 2 minutes, rose within 1 s and stood for 2 minutes. Standing up from the squatting position was repeated twice. Four randomly assigned subjects performed LBMT after rising from the second squatting, while the remaining 3 subjects performed LBMT after rising from the third squatting.

These experiments were performed in accordance to the standards set in the Declaration of Helsinki after approval by the Medical Ethics Committee of the Academic Medical Center at the University of Amsterdam and obtaining written informed consent.

Analysis

Off-line, beat-to-beat systolic (SBP) and diastolic (DBP) arterial blood pressure and heart rate (HR) were derived from the arterial pulse wave. Mean arterial pressure (MAP) was the time-integral over the beat-to-beat pressure recording. Corrupted data-points (e.g. artefacts in the continuous BP recording) were identified by visual inspection and omitted (<2%). Relative changes in left ventricular stroke volume (SV) were obtained using pulse wave analysis (Modelflow, Finapres Medical Systems, The Netherlands (90)). This method has been validated during active and passive postural stress against thermo-dilution (77),

during rapid changes in posture against Doppler ultrasound (207), and during physical counter-manoevres against gas re-breathing (198). $\text{CO} = \text{HR} \cdot \text{SV}$. Beat-to-beat TPR was $\text{MAP} \cdot \text{CO}^{-1}$. After pulse wave analysis, all beat-to-beat data were re-sampled at 1 Hz.

Baseline values were taken from the interval 40 – 10 s before each standing up manoeuvre. MAP nadir ($\text{MAP}_{\min}$) induced by each manoeuvre was identified and the synchronous CO and TPR were calculated. All variables are given as median and range. Using Wilcoxon's signed rank test we compared $\text{MAP}_{\min}$, CO and TPR respectively, in the patients after standing from squatting without and with LBMT. In the healthy subjects Friedman's repeated measures ANOVA on ranks identified differences between the two squats without and the single squat with LBMT. For all tests a p-value <0.05 was considered significant.

Follow up

Using a questionnaire, the perceived effectiveness of LBMT in the patients' daily lives was evaluated addressing the use of the LBMT (daily, weekly / monthly, or never), the frequency of (pre-) syncopal spells after learning LBMT as compared to before (less, same, disappeared), and the perceived benefit from the manoeuvre (some benefit, much benefit, no benefit).

Results

After rising from the first squat, the patients' MAP decreased from 110 mmHg (range 88 – 144) to 69 mmHg (range 53 – 91); SBP from 145 mmHg (range 121 – 201) to 90 mmHg (range 70 – 123); DBP from 88 mmHg (range 69 – 105) to 58 mmHg (range 40 – 76); Fig. 6.1). ΔSBP was >40 mmHg in 12 patients and all experienced pre-syncopal symptoms.

At baseline there were no differences between the first and the second squat in MAP (110 vs. 109 mmHg), CO (6.5 vs. 6.4 arbitrary units) and TPR (1.0 vs. 1.0 arbitrary units). When the stand up was repeated with LBMT, $\text{MAP}_{\min}$ was 19 mmHg higher than without LBMT (88 vs. 69 mmHg, $p < 0.05$). SBP at $\text{MAP}_{\min}$ was 111 mmHg (range 67 – 163); DBP 69 mmHg (range 43 – 87)) (Fig. 6.1). ΔSBP was >40 mmHg in 5 patients.

Figure 6.1 Hemodynamic changes from baseline, at mean arterial pressure nadir (MAPmin) in individual IOH patients (n=13) in two squat-stand manoeuvres; first without, second with LBMT. Black dots represent median, error bars are 25th and 75th percentile. n.s.: statistically non-significant differences between interventions

Figure 6.2 shows the continuous blood pressure recording in a representative patient during consecutive stand up manoeuvres from squatting with and without LBMT.

Figure 6.2 Continuous blood pressure (BP) record in a 17 years old male IOH patient during consecutive standing up manoeuvres from squatting. Standing up manoeuvres B, D and F are combined with LBMT. Black bars indicate standing up

At group level ($n = 13$) CO and TPR at MAP_{min} did not differ between control and LBMT. In 4 patients the MAP_{min} with LBMT was accompanied by a >10% higher TPR as compared to without LBMT; and in 8 subjects CO was >10% higher. Also in a sub-analysis of patients with a difference of $MAP_{min} > 10$ mmHg between control and LBMT ($n = 5$) there was no single pattern in TPR and / or CO.

Repeated squat-stand manoeuvres in a subset of 5 subjects revealed a trend for a larger ΔMAP after successive squats (Fig. 6.3). However the effect of LBMT seemed to increase over the course of 3 successive trials, suggesting a learning effect (Fig. 6.3).

Figure 6.3 Continuous systolic and diastolic blood pressures (BP) in 5 IOH patients who performed a standing up from squatting 6 times, alternating no intervention (grey) with the LBMT (black). In patient A only during the third trial LBMT seems effective, suggesting a learning effect

In the healthy subjects there was also no difference in MAP during the three squats (95 vs. 97 vs. 98 mmHg), CO (5.5 vs. 5.2 vs. 5.2 arbitrary units) or TPR (1.0 vs. 1.1 vs. 1.1 arbitrary units) at baseline. When the subjects used LBMT after standing up, MAP_{min} was higher than after either of the two squat-to stand manoeuvres without intervention (76 mmHg vs. 63 mmHg and 57 mmHg, $p < 0.05$, Fig. 6.4). This was associated with a higher TPR at MAP_{min} (50% vs. 45% and 38% of baseline, $p < 0.05$); CO at this point did not differ among interventions (Fig. 6.4). Over the interval 20 – 30 s after standing up CO was higher during LBMT than without (144% vs. 100% of squatted baseline, $p < 0.05$), TPR did not differ.

Figure 6.4 Hemodynamic changes from baselines, at mean arterial pressure nadir (MAPmin) in individual healthy subjects (n = 7) in three squatting conditions: two controls (Squat 1, Squat 2), one with LBMT. Black dots represent median, error bars indicate 25th and 75th percentile. * $p < 0.05$, n.s.: statistically non-significant differences

In clinical follow-up 12 of 13 patients were contacted after 2 months (range 1 – 26). Two patients had experienced no IOH symptoms since consulting with us and had not used LBMT. The remaining 10 patients reported using LBMT on a daily to weekly basis both after rising from squatting and from supine. In 8 of them the frequency of their complaints had decreased. Nine patients perceived some or much benefit from the manoeuvre in daily life. General comments included that patients sometimes would rise a first time not using LBMT, forcing them to sit or lay down again; on repeat standing up they would use LBMT and experience no symptoms.

Discussion

The main new finding of this study is that LBMT attenuated the BP decrease after standing from squatting in both IOH patients and healthy subjects. In the patients, CO and TPR at MAP_{min} did not differ consistently for LBMT and control. In healthy subjects the underlying mechanism was a blunting of the transient reduction of TPR related to assumption of the upright position. In clinical follow-up patients perceived beneficial effects of LBMT on IOH complaints in daily life. Rising from squatting is an every day orthostatic stress that may result in IOH complaints in otherwise healthy persons (103) and our results are directly applicable to them. We speculate that LBMT will be similarly effective in combating IOH after standing up from supine.

Testing the initial hemodynamic adaptation standing up from squatting has been used by various groups (11, 38, 39, 150). The manoeuvre's reproducibility has however never been systematically documented. Our findings in both patients (Fig. 6.3) and healthy controls (Fig. 6.4) suggest that the blood pressure decrease after successive standing up manoeuvres from squatting is augmented.

Rossberg and Peñáz documented a ΔMAP_{max} when standing up after 6 minutes of squatting of ~ 45 mmHg, (150). Rickard and Newmann found a ΔDBP of 25 ± 2 mmHg, 10 s after standing up from 4 minutes of squatting (ΔMAP 24 ± 2 mmHg), but did not document the exact timing of the ΔBP (145). During the squat-stand manoeuvre in healthy subjects in our study the maximum ΔMAP (-31 mmHg) was somewhat smaller compared to Rossberg and Peñáz's data which may be related to the shorter squatting period. The nadir of the ΔMAP in Rickard and Newmann's study may have been passed before the measurement. We conclude that based on the heterogeneity of the squat-stand protocols available in the literature, that vary in duration of squatting and standing times (4, 38, 39,

150), there is a need for studies that relate the duration of squatting to its initial (seconds) and prolonged (minutes) hemodynamic effects after standing up.

As also discussed in chapter 5, several factors may play a role in the immediate decrease in blood pressure when standing up from squatting (39, 150, 225). Most important is the acute fall in TPR (39), which is caused by a combination of the following factors (37, 150, 225). 1) The acute decompression of arterial vessels in the legs causes an instantaneous mechanical decrease in vascular resistance. 2) There is an increase of the arterio-venous pressure gradient, due to decompression of the venous vessels. 3) The relative ischemia in the leg muscles during squatting augments the fall in arterial resistance by local factors ("the post-tourniquet effect" (39)). 4) The muscle activity during the standing up manoeuvre may promote venous return which can trigger cardiopulmonary pressure receptors and lead to a transient decrease of sympathetic vasoconstrictor outflow (223). The vastly decreased TPR is not completely offset by the concomitant increase in CO (39, 150, 225).

How LBMT affects the hemodynamic transient in IOH patients after standing up from squatting is not fully explained by the data from this study, in terms of consistent differences in CO and / or TPR between control and intervention. The findings from the healthy subjects however suggest that, unlike our hypothesis that predicted primarily an effect on CO, an increased TPR at MAP_{min} may also play a role. In general the mechanical effects of tensing of large muscle groups on TPR (e.g. by "kinking" of arteries) are insignificant because they are off-set by fast (reflex) adaptations of the arteriolar conductance (196). We suggest that LBMT augments TPR after standing up from squatting because arteriolar conductance is very high at MAP_{min} (see above) and unable to further offset the mechanical effects of LBMT.

After the initial phase, LBMT causes a sustained elevated CO in both patients and healthy subjects. As CO during orthostatic stress is a function of cardiac filling rather than HR (151) this increase of CO is most likely facilitated by an augmented venous return. This finding is also in agreement with previous studies (198, 204) and supports the notion that LBMT acts as a natural antigravity suit that optimizes venous return to the heart and thereby optimizes CO. Previous work showed that central command as a determinant of arterial blood pressure (41), does not play a significant role in the effectiveness of physical counter-manoevres (108).

A limitation to the study design is that we did not use a validated measure to quantify the effect of LBMT on symptoms while measuring BP. However in

the IOH patients we found a difference in MAP_{min} with LBMT (as compared to control) of 19 mmHg which would generally be accepted as of clinical relevance (74).

Another concern may be that the order in which control and LBMT were performed in the patients was not alternated or randomised. However, the results from the series of healthy subjects show that the effect of the LBMT is consistent irrespective of order of control and intervention experiment.

Additional support for the efficacy of LBMT is found in results from the 5 patients who alternated LBMT and control during successive stand up manoeuvres (Fig. 6.3). The results of the follow up (albeit limited) indicate that LBMT may also be effective in daily life.

In conclusion, this study shows that the transient blood pressure decrease after standing up from the squatting position can be attenuated by LBMT. This manoeuvre is an essentially costless, easy to perform intervention without side effects. Future studies may compare LBMT with traditional therapeutic advice for IOH after rising (e.g. rising slowly) and test its efficacy in daily life. Based on this laboratory study and its limited follow-up data, LBMT seems a worthwhile addition to existing management options.

7. Conclusions

Physical counter-manoevres in the treatment of vasovagal syncope

Chapters 2 and 3 document the effectiveness of leg crossing with lower body muscle tensing, lower body muscle tensing alone, whole body tensing, squatting and sitting with the head bent between the knees respectively to prevent impending vasovagal syncope. Chapter 4 documents the attenuation of the risk of triggering a vasovagal reaction during orthostatic stress by standing with the legs crossed. Chapter 5 explores lower body tensing as a follow-up manoeuvre to squatting, and shows that this manoeuvre blunts the blood pressure decrease after standing up from squatting.

The underlying mechanism of all manoeuvres is minimization of the venous pooling in the lower limbs (and abdomen) and thereby facilitating adequate venous return to the heart and optimizing cardiac output as shown in these studies. As such, these results incorporate the mechanisms underlying the beneficial effects of anti-gravity suits and double strop suspension in an accessible therapeutic intervention. The studies in chapter 3 show that the manoeuvres' effects on total peripheral resistance are negligible.

By having a range of manoeuvres available, patients can tailor the use of physical counter-manoevres to their needs and capabilities. The studies that are presented here were mainly laboratory based. Meanwhile an international randomized controlled trial showed that adding physical counter-manoevres to the traditional therapy resulted in a relative risk reduction for syncope recurrence of 39% (200).

Physical counter-manoevres in the treatment of initial orthostatic hypotension

Chapter 6 shows the effectiveness of lower body muscle tensing in preventing a critical reduction of blood pressure after standing up from squatting in patients with a clinical diagnosis of initial orthostatic hypotension. The mechanisms for this effect are more heterogeneous than in vasovagal syncope and are mediated both by an increased cardiac output and total peripheral resistance. As discussed before, in future work this intervention should be compared to other interventions, such as rising slowly that are thought to prevent initial orthostatic hypotension.

Perspective

Although these studies had primarily a therapeutic goal, their findings also illuminate certain pathophysiological aspects of vasovagal reactions. In addition to the strong notions about decreased heart rate and sympathetic vasoconstrictor activity that constitute the vasovagal reaction, the circulatory effects of leg muscle tensing (and other manoeuvres) underscore a decreased central blood volume as a major determinant in the pathogenesis of vasovagal reactions.

The question is whether the wide inter-individual (and intra-individual) variability in orthostatic tolerance can be explained by variations in fluid shift dynamics. However, the knowledge about orthostatic fluid shifts is very limited. The amount of fluid shifted is estimated at 500 – 800 ml, with an additional loss of 700 ml during prolonged orthostatic stress, but these numbers (and their time course) are only based a limited number of studies (3, 121, 175). Inter-individual variation in the amount of fluid shifted, its time course and the effect of (potentially modifiable) physical factors have received little attention (122). With growing attention for the inter-individual differences in (orthostatic) blood pressure control, the differentiation of such fluid shifts may hold potentially rewarding applied physiological research challenges that may explain part of the inter-individual variability of orthostatic tolerance.

Conclusion

We introduced physical counter-manoevres in the treatment of vasovagal syncope at a time when the efficacy and proportionality of pacemaker and pharmacological treatment options were being questioned (19). As such, the manoeuvres provided a ready answer to a pressing question. However, the studies in

this thesis comprise only a small contribution to a long continuum that started with the description of the “scissor-posture” in a patient with autonomic failure in the 1920’s. Via the systematic introduction of manoeuvres in the treatment of autonomic failure and the studies in this thesis, this continuum recently resulted in an international randomized controlled trial that showed the effectiveness of physical counter-manoevres in the prevention of vasovagal syncope in daily life. At completion of this thesis, physical counter-manoevres are an integrated part of international guidelines on the treatment of syncope.

Samenvatting (Dutch Summary)

Manoeuvres ter voorkoming van vasovagale syncope en initiële orthostatische hypotensie

- Wegrakingen zijn een veel voorkomend medisch problem. Ongeveer 40% van de algemene populatie maakt tenminste één wegraking door voor het 60^e levensjaar. Meer dan 90% van deze wegrakingen wordt veroorzaakt door vasovagale reacties. Vasovagale reacties zijn het resultaat van activatie van op zich fysiologische hart-vaat reflexen waardoor binnen enkele minuten de arteriële bloeddruk afneemt ten gevolge van een systemische vasodilatatie en een hartfrequentie daling.
- Bij 3 – 4% van alle wegrakingen die onder medische aandacht worden gebracht is sprake van initiële orthostatische hypotensie. Hierbij is de normale kortdurende afname van de bloeddruk na opstaan uit liggende of gehurkte houding abnormaal versterkt.
- Vasovagale reacties en initiële orthostatische hypotensie leiden tot wegrakingen of bijna wegrakingen als de arteriële bloeddruk niet langer volstaat om een adequate breinperfusie te behouden.
- Omdat wegrakingen door deze bloeddrukverstoringen veel voorkomen en de kwaliteit van leven ernstig kunnen aantasten is de behandeling ervan een belangrijk onderwerp. Dit proefschrift behandelt de fysieke manoeuvres die voornoemde bloeddrukverlaging tegen gaan.
- **Hoofdstuk 2** (Chapter 2) beschrijft een onderzoek waarin in een groep van 21 patiënten met vasovagale reacties het effect van de manoeuvre benenkruisen met spierspannen werd onderzocht, tijdens onder laboratorium omstandigheden opgewekte vasovagale reacties. In deze studie bleek de manoeuvre effectief in 20 van de 21 patiënten. In vijf patiënten werd flauwvallen voorkomen, terwijl 15 patiënten het flauwvallen gemiddeld tweeënhalve minuut konden uitstellen.
- In **Hoofdstuk 3** (Chapter 3) wordt het effect van verschillende manoeuvres (benenkruisen met spierspannen, been-buik-bil spierspannen alleen en

aanspannen van alle spieren tegelijk) die vasovagale reacties moeten tegengaan met elkaar vergeleken in patiënten met vasovagale reacties, tijdens een kanteltafeltest. Daarnaast wordt de effectiviteit van hurken en zitten met het hoofd tussen de benen (beide traditionele manoeuvres) onderzocht. De studie toont dat al deze manoeuvres vergelijkbaar effectief zijn en dat het hun effectiviteit kan worden verklaard door toename van het hartminuutvolume doordat bij het aanspannen van de spieren bloed naar het hart wordt gepompt.

- **Hoofdstuk 4** (Chapter 4) behandelt de vraag of het met benen gekruist staan de gevoeligheid voor het optreden van een vasovagale reactie doet afnemen. In gezonde vrijwilligers werd drie maal de flauwvalgevoeligheid gemeten. Eenmaal zonder interventie, eenmaal met benenkruisen en eenmaal met een orale placebo. Benenkruisen veroorzaakte een belangrijke afname in flauwvalgevoeligheid, de placebo had geen effect.
- In **Hoofdstuk 5** (Chapter 5) wordt de effectiviteit van het aanspannen van buik, been en bilspieren ook aangetoond in het tegengaan van de bloeddruk daling na opstaan uit hurkzit bij patiënten die gehurkt zijn om een vasovagale reactie te couperen. Deze studie werd verricht met 18 patiënten tijdens vasogale reacties die waren geprovoceerd tijdens een kanteltafeltest. Deze effectiviteit kan volledig worden toegeschreven aan een toename van het hartminuutvolume.
- **Hoofdstuk 6** (Chapter 6) toont in patiënten met initiële orthostatische hypotensie de effectiviteit van dezelfde manoeuvre om ook de bloeddruk daling in aansluiting op opstaan uit hurkzit in deze groep te voorkomen. Dit onderzoek toont dat er tussen patiënten variatie is in het effect van de manoeuvre op hartminuutvolume en perifere weerstand.

Conclusie

De studies in dit proefschrift tonen de effectiviteit van fysieke manoeuvres ter voorkoming van (bijna-)wegrakingen ten gevolge van vasovagale reacties en initiële orthostatische hypotensie. Deze effectiviteit berust op het acuut verkleinen van de vasculaire ruimte beschikbaar voor ophopen van bloed. De manoeuvres brengen daarmee een toename van veneuze terugvloed met vergroting van het hart-minuutvolume tot stand. De effectiviteit van deze manoeuvres in het tegengaan van initiële orthostatische hypotensie berust op een combinatie van toegenomen hartminuutvolume en perifere weerstand.

Wij introduceerden fysieke manoeuvres in de behandeling van vasovagale syncope op een moment dat nut en noodzaak van pacemakers en farmacologische interventies aan de kaak werden gesteld. Manoeuvres vormden een aantrekkelijk alternatief. De studies in dit proefschrift vormen echter een bescheiden onderdeel van een lang continuüm dat begon met de eerste beschrijving van het gebruik van benenkransen in de jaren 1920. Na systematische studie en introductie van fysieke manoeuvres in de behandeling van orthostatische hypotensie bij autonoom falen, vormde het hier gepresenteerde werk de opmaat tot de eerste internationale gerandomiseerd gecontroleerde klinische trial. Op basis van de positieve resultaten van die trial zijn fysieke manoeuvres nu een vast onderdeel van de behandeling van vasovagale syncope.

References

1. Abe, H., Kondo, S., Kohshi, K. and Nakashima, Y. (2002) Usefulness of orthostatic self-training for the prevention of neurocardiogenic syncope. *Pacing and Clinical Electrophysiology* 25: 1454-1458
2. Alboni, P., Brignole, M. and Degli Uberti, E. C. (2007) Is vasovagal syncope a disease? *Europace* 9: 83-87
3. Asmussen, E. (1943) The distribution of the blood between the lower extremities and the rest of the body. *Acta Physiologica Scandinavica* 5: 31-38
4. Barbey, K. and Barbey, P. (1966) [Blood shift to the lower extremities in acute orthostatic burdening of the circulation]. 33: 1693-1698
5. Barbey, K., Kutscha, W. and Brecht, K. (1966) [Changes of the temporal arterial pulse and the phonocardiogram in acute orthostatic stress]. *Medizinische Welt* 35: 1824-1834
6. Baron-Esquivias, G., Moreno, S. G., Martinez, A., Pedrote, A., Vazquez, F., Granados, C., Bollain, E., Lage, E., de la Llera, L. D., Rodriguez, M. J., Errazquin, F. and Burgos, J. (2006) Cost of diagnosis and treatment of syncope in patients admitted to a cardiology unit. *Europace* 8: 122-127
7. Bartoletti, A., Alboni, P., Ammirati, F., Brignole, M., Del Rosso, A., Foglia, M. G., Menozzi, C., Raviele, A. and Sutton, R. (2000) 'The Italian Protocol': a simplified head-up tilt testing potentiated with oral nitroglycerin to assess patients with unexplained syncope. *Europace* 2: 339-342
8. Beecher, H. K., Field, M. E. and Krogh, A. (1935) The effects of walking on the venous pressure at the ankle. *Scandinavian Archives of Physiology* 73: 133-141
9. Benarroch, E. E. (1993) The central autonomic network: functional organization, dysfunction, and perspective. *Mayo Clinic Proceedings* 68: 988-1001
10. Bennett, T., Macdonald, I. A. and Sainsbury, R. (1984) The influence of acute starvation on the cardiovascular responses to lower body subatmospheric pressure or to standing in man. *Clinical Science* 66: 141-146
11. Berry, N. M., Rickards, C. A. and Newman, D. G. (2006) Squat-stand

- test response following 10 consecutive episodes of head-up tilt. *Aviation Space and Environmental Medicine* 77: 1125-1130
12. Blanc, J. J., Mansourati, J., Maheu, B., Boughaleb, D. and Genet, L. (1993) Reproducibility of a positive passive upright tilt test at a seven-day interval in patients with syncope. *American Journal of Cardiology* 72: 469-471
 13. Borst, C. and Karemaker, J. M. (1983) Time delays in the human baroreceptor reflex. *Journal of the Autonomic Nervous System* 9: 399-409
 14. Borst, C., van Brederode, J. F., Wieling, W., Van Montfrans, G. A. and Dunning, A. J. (1984) Mechanisms of initial blood pressure response to postural change. *Clinical Science* 67: 321-327
 15. Borst, C., Wieling, W., van Brederode, J. F., Hond, A., de Rijk, L. G. and Dunning, A. J. (1982) Mechanisms of initial heart rate response to postural change. *American Journal of Physiology* 243: H676-H681
 16. Bosser, G., Cailliet, G., Gauchard, G., Marcon, F. and Perrin, P. (2006) Relation between motion sickness susceptibility and vasovagal syncope susceptibility. *Brain Research Bulletin* 68: 217-226
 17. Bouvette, C. M., McPhee, B. R., Opfer-Gehrking, T. L. and Low, P. A. (1996) Role of physical countermeasures in the management of orthostatic hypotension: efficacy and biofeedback augmentation. *Mayo Clinic Proceedings* 71: 847-853
 18. Braun, M. M., Patriarca, P. A. and Ellenberg, S. S. (1997) Syncope after immunization. *Archives of Pediatrics and Adolescent Medicine* 151: 255-259
 19. Brignole, M., Alboni, P., Benditt, D., Bergfeldt, L., Blanc, J. J., Bloch Thomsen, P. E., Van Dijk, J. G., Fitzpatrick, A., Hohnloser, S., Janousek, J., Kapoor, W., Kenny, R. A., Kulakowski, P., Moya, A., Raviele, A., Sutton, R., Theodorakis, G. and Wieling, W. (2001) Guidelines on management (diagnosis and treatment) of syncope. *European Heart Journal* 22: 1256-1306
 20. Brignole, M., Alboni, P., Benditt, D. G., Bergfeldt, L., Blanc, J. J., Bloch Thomsen, P. E., Van Dijk, J. G., Fitzpatrick, A., Hohnloser, S., Janousek, J., Kapoor, W., Kenny, R. A., Kulakowski, P., Masotti, G., Moya, A., Raviele, A., Sutton, R., Theodorakis, G., Ungar, A. and Wieling, W. (2004) Guidelines on management (diagnosis and treatment) of syncope-update 2004. *Europace* 6: 467-537
 21. Brignole, M., Croci, F., Menozzi, C., Solano, A., Donateo, P., Oddone, D., Puggioni, E. and Lolli, G. (2002) Isometric arm counter-pressure maneuvers to abort impending vasovagal syncope. *Journal of the American College of Cardiology* 40: 2053-2059
 22. Brignole, M., Menozzi, C., Bartoletti, A., Giada, F., Lagi, A., Ungar, A.,

- Ponassi, I., Mussi, C., Maggi, R., Re, G., Furlan, R., Rovelli, G., Ponzi, P. and Scivales, A. (2006) A new management of syncope: prospective systematic guideline-based evaluation of patients referred urgently to general hospitals. *European Heart Journal* 27: 76-82
23. Brignole, M., Sutton, R., Menozzi, C., Garcia-Civera, R., Moya, A., Wieling, W., Andresen, D., Benditt, D. G., Grovale, N., De, S. T. and Vardas, P. (2006) Lack of correlation between the responses to tilt testing and adenosine triphosphate test and the mechanism of spontaneous neurally mediated syncope. *European Heart Journal* 27: 2232-2239
24. Brooks, R., Ruskin, J. N., Powell, A. C., Newell, J., Garan, H. and McGovern, B. A. (1993) Prospective evaluation of day-to-day reproducibility of upright tilt-table testing in unexplained syncope. *American Journal of Cardiology* 71: 1289-1292
25. Buckey, J. C., Jr., Lane, L. D., Levine, B. D., Watenpugh, D. E., Wright, S. J., Moore, W. E., Gaffney, F. A. and Blomqvist, C. G. (1996) Orthostatic intolerance after spaceflight. *Journal of Applied Physiology* 81: 7-18
26. Burke, D., Sundlöf, G. and Wallin, G. (1977) Postural effects on muscle nerve sympathetic activity in man. *Journal of Physiology* 272: 399-414
27. Calkins, H., Byrne, M., el-Atassi, R., Kalbfleisch, S., Langberg, J. J. and Morady, F. (1993) The economic burden of unrecognized vasodepressor syncope. *American Journal of Medicine* 95: 473-479
28. Callister, R., Ng, A. V. and Seals, D. R. (1994) Arm muscle sympathetic nerve activity during preparation for and initiation of leg-cycling exercise in humans. *Journal of Applied Physiology* 77: 1403-1410
29. Casini-Raggi, V., Bandinelli, G. and Lagi, A. (2002) Vasovagal syncope in emergency room patients: analysis of a metropolitan area registry. 21: 287-291
30. Casonato, A., Pontara, E., Bertomoro, A., Cattini, M. G., Soldara, C. and Girolami, A. (2003) Fainting induces an acute increase in the concentration of plasma factor VIII and von Willebrand factor. *Haematologica* 88: 688-693
31. Claydon, V. E. and Hainsworth, R. (2004) Salt supplementation improves orthostatic cerebral and peripheral vascular control in patients with syncope. *Hypertension* 43: 809-813
32. Claydon, V. E. and Hainsworth, R. (2005) Increased postural sway in control subjects with poor orthostatic tolerance. *Journal of the American College of Cardiology* 46: 1309-1313
33. Claydon, V. E. and Hainsworth, R. (2006) Postural sway in patients with syncope and poor orthostatic tolerance. *Heart* 92: 1688-1689
34. Clifford, P. S. and Hellsten, Y. (2004) Vasodilatory mechanisms in con-

- tracting skeletal muscle. *Journal of Applied Physiology* 97: 393-403
35. Colman, N., Nahm, K., Ganzeboom, K. S., Shen, W. K., Reitsma, J., Linzer, M., Wieling, W. and Kaufmann, H. (2004) Epidemiology of reflex syncope. *Clinical Autonomic Research* 14 Suppl 1: 9-17
 36. Colman, N., Nahm, K., Van Dijk, J. G., Reitsma, J. B., Wieling, W. and Kaufmann, H. (2004) Diagnostic value of history taking in reflex syncope. *Clinical Autonomic Research* 14 Suppl 1: 37-44
 37. Convertino, V. A., Brock, P. J., Keil, L. C., Bernauer, E. M. and Greenleaf, J. E. (1980) Exercise training-induced hypervolemia: role of plasma albumin, renin, and vasopressin. *Journal of Applied Physiology* 48: 665-669
 38. Convertino, V. A., Ratliff, D. A., Crissey, J., Doerr, D. F., Idris, A. H. and Lurie, K. G. (2005) Effects of inspiratory impedance on hemodynamic responses to a squat-stand test in human volunteers: implications for treatment of orthostatic hypotension. *European Journal of Applied Physiology and Occupational Physiology* 94: 392-399
 39. Convertino, V. A., Tripp, L. D., Ludwig, D. A., Duff, J. and Chelette, T. L. (1998) Female exposure to high G: chronic adaptations of cardiovascular functions. *Aviation Space and Environmental Medicine* 69: 875-882
 40. Cotton, Th. F. and Lewis, Th. (1918) Observations upon fainting attacks due to inhibitory cardiac impulses. *Heart* 7: 23-34
 41. Critchley, H. D., Corfield, D. R., Chandler, M. P., Mathias, C. J. and Dolan, R. J. (2000) Cerebral correlates of autonomic cardiovascular arousal: a functional neuroimaging investigation in humans. *Journal of Physiology* 523 Pt 1: 259-270
 42. Critchley, H. D., Melmed, R. N., Featherstone, E., Mathias, C. J. and Dolan, R. J. (2001) Brain activity during biofeedback relaxation: a functional neuroimaging investigation. *Brain* 124: 1003-1012
 43. Croci, F., Brignole, M., Menozzi, C., Solano, A., Donato, P., Oddone, D., Puggioni, E. and Lolli, G. (2004) Efficacy and feasibility of isometric arm counter-pressure manoeuvres to abort impending vasovagal syncope during real life. *Europace* 6: 287-291
 44. De Marées, H. (1976) [Orthostatic immediate regulation]. *Cardiology* 61 suppl 1: 78-90
 45. Del Rosso, A., Alboni, P., Brignole, M., Menozzi, C. and Raviele, A. (2005) Relation of clinical presentation of syncope to the age of patients. *American Journal of Cardiology* 96: 1431-1435
 46. Del Rosso, A., Bartoletti, A., Bartoli, P., Ungar, A., Bonechi, F., Maioli, M. and Ieri, A. (2000) Methodology of head-up tilt testing potentiated with sublingual nitroglycerin in unexplained syncope. *American Journal of Cardiology* 85: 1007-1011

47. Del Rosso, A., Bartoli, P., Bartoletti, A., Brandinelli-Geri, A., Bonechi, F., Maioli, M., Mazza, F., Michelucci, A., Russo, L., Salvetti, E., Sansoni, M., Zipoli, A., Fierro, A. and Ieri, A. (1998) Shortened head-up tilt testing potentiated with sublingual nitroglycerin in patients with unexplained syncope. *American Heart Journal* 135: 564-570
48. Di Girolamo, E., Di Iorio, C., Leonzio, L., Sabatini, P. and Barsotti, A. (1999) Usefulness of a tilt training program for the prevention of refractory neurocardiogenic syncope in adolescents: A controlled study. *Circulation* 100: 1798-1801
49. Diedrich, A. and Biaggioni, I. (2004) Segmental orthostatic fluid shifts. *Clinical Autonomic Research* 14: 146-147
50. Diehl, R. R. (2005) Vasovagal syncope and Darwinian fitness. *Clinical Autonomic Research* 15: 126-129
51. Douglas, C. G., Haldane, J. S., Henderson, Y. and Schneider, E. C. (1913) Physiological observations made on Pike's Peak Colorado, with special reference to adaptation to low barometric pressures. *Philosophical Transactions of the Royal Society of London Series B: Biological Sciences* B203: 185-381
52. El Bedawi, K. M. and Hainsworth, R. (1994) Combined head-up tilt and lower body suction: a test of orthostatic tolerance. *Clinical Autonomic Research* 4: 41-47
53. El Sayed, H. and Hainsworth, R. (1996) Salt supplement increases plasma volume and orthostatic tolerance in patients with unexplained syncope. *Heart* 75: 134-140
54. Engel, G. L. and Romano, J. (1947) Studies of Syncope: IV. Biologic interpretation of vasodepressor syncope. *Psychosomatic Medicine* 9: 288-294
55. Engel, G. L., Romano, J. and McLin, T. R. (1944) Vasodepressor and carotid sinus syncope – clinical, eletroencephalographic and electrocardiographic observations. *Archives of Internal Medicine* 74: 100-119
56. Fenton, A. M., Hammill, S. C., Rea, R. F., Low, P. A. and Shen, W. K. (2000) Vasovagal syncope. *Annals of Internal Medicine* 133: 714-725
57. Fu, Q., Shook, R. P., Okazaki, K., Hastings, J. L., Shibata, S., Conner, C. L., Palmer, M. D. and Levine, B. D. (2006) Vasomotor sympathetic neural control is maintained during sustained upright posture in humans. *Journal of Physiology* 577: 679-687
58. Fucà, G., Dinelli, M., Suzzani, P., Scarfò, S., Tassinari, F. and Alboni, P. (2006) The venous system is the main determinant of hypotension in patients with vasovagal syncope. *Europace* 8: 839-845
59. Gallagher, K. M., Fadel, P. J., Smith, S. A., Strømstad, M., Ide, K., Secher, N. H. and Raven, P. B. (2006) The interaction of central command

- and the exercise pressor reflex in mediating baroreflex resetting during exercise in humans. *Experimental Physiology* 91: 79-87
60. Ganong WF (2001) Review of medical physiology. Lange Medical Books / McGraw-Hill
 61. Ganzeboom, K. S., Colman, N., Reitsma, J. B., Shen, W. K. and Wieling, W. (2003) Prevalence and triggers of syncope in medical students. *American Journal of Cardiology* 91: 1006-1008
 62. Ganzeboom, K. S., Mairuhu, G., Reitsma, J. B., Linzer, M., Wieling, W. and Van Dijk, N. (2006) Lifetime cumulative incidence of syncope in the general population: a study of 549 Dutch subjects aged 35-60 years. *Journal of Cardiovascular Electrophysiology* 17: 1172-1176
 63. Ghrist, D. G. and Brown, G. E. (1928) Postural hypotension with syncope: its successful treatment with ephedrine. *American Journal of the Medical Sciences* 175: 336-349
 64. Giannattasio, C., Grassi, G. and Mancia, G. (1993) Vasovagal syncope with bradycardia during lower body negative pressure in a heart transplant recipient. *Blood Pressure* 2: 309-311
 65. Gisolf, J., Immink, R. V., Van Lieshout, J. J., Stok, W. J. and Karemaker, J. M. (2005) Orthostatic blood pressure control before and after space-flight, determined by time-domain baroreflex method. *Journal of Applied Physiology* 98: 1682-1690
 66. Gisolf, J., Westerhof, B. E., Van Dijk, N., Wesseling, K. H., Wieling, W. and Karemaker, J. M. (2004) Sublingual nitroglycerin used in routine tilt testing provokes a cardiac output-mediated vasovagal response. *Journal of the American College of Cardiology* 44: 588-593
 67. Gladwell, V. F. and Coote, J. H. (2002) Heart rate at the onset of muscle contraction and during passive muscle stretch in humans: a role for mechanoreceptors. *Journal of Physiology* 540: 1095-1102
 68. Goodwin, G. M., McCloskey, D. I. and Mitchell, J. H. (1972) Cardiovascular and respiratory responses to changes in central command during isometric exercise at constant muscle tension. *Journal of Physiology* 226: 173-190
 69. Graham, L. A. and Kenny, R. A. (2001) Clinical characteristics of patients with vasovagal reactions presenting as unexplained syncope. *Europace* 3: 141-146
 70. Greenfield, A. D. (1951) An emotional faint. *Lancet* 1: 1302-1303
 71. Grubb, B. P. (2005) Neurocardiogenic syncope and related disorders of orthostatic intolerance. *Circulation* 111: 2997-3006
 72. Grubb, B. P., Wolfe, D., Temesy-Armos, P., Hahn, H. and Elliott, L. (1992) Reproducibility of head upright tilt table test results in patients with syncope. *Pacing and Clinical Electrophysiology* 15: 1477-1481

73. Hainsworth, R. (1991) Reflexes from the heart. *Physiological Reviews* 71: 617-658
74. Hainsworth, R. (2004) Pathophysiology of syncope. *Clinical Autonomic Research* 14 Suppl 1: 18-24
75. Hainsworth, R. and El Bedawi, K. M. (1994) Orthostatic tolerance in patients with unexplained syncope. *Clinical Autonomic Research* 4: 239-244
76. Halliwill, J. R., Lawler, L. A., Eickhoff, T. J., Joyner, M. J. and Mulvagh, S. L. (1998) Reflex responses to regional venous pooling during lower body negative pressure in humans. *Journal of Applied Physiology* 84: 454-458
77. Harms, M. P., Wesseling, K. H., Pott, F., Jenstrup, M., Van Goudoever, J., Secher, N. H. and Van Lieshout, J. J. (1999) Continuous stroke volume monitoring by modelling flow from non-invasive measurement of arterial pressure in humans under orthostatic stress. *Clinical Science* 97: 291-301
78. Henderson, Y., Oughterson, A. W., Greenberg, L. A. and Searle, C. P. (1935) Muscle tonus, intramuscular pressure and the venopressor mechanism. *American Journal of Physiology* 114: 261-268
79. Henry, S. M., Fung, J. and Horak, F. B. (2001) Effect of stance width on multidirectional postural responses. *Journal of Neurophysiology* 85: 559-570
80. Hill, L. (1895) The influence of the force of gravity on the circulation of the blood. *Journal of Physiology* 18: 15-53
81. Hill, L. and Barnard, H. (1897) The influence of the force of gravity on the circulation part II. *Journal of Physiology* 20: 323-352
82. Hippocrates. (400) Case histories. In: Clendening L. (ed) *Source book of medical history* (1960). Dover Publications Inc. / Henry Schuman, New York, pp 21-25
83. Hollander, A. P. and Bouman, L. N. (1975) Cardiac acceleration in man elicited by a muscle-heart reflex. *Journal of Applied Physiology* 38: 272-278
84. Holmgren, A. (1956) Circulatory changes during muscular work in man; with special reference to arterial and central venous pressures in the systemic circulation. *Scandinavian Journal of Clinical and Laboratory Investigation* 8: 1-97
85. Imholz, B. P., Settels, J. J., van der Meiracker, A. H., Wesseling, K. H. and Wieling, W. (1990) Non-invasive continuous finger blood pressure measurement during orthostatic stress compared to intra-arterial pressure. *Cardiovascular Research* 24: 214-221
86. Imholz, B. P., Wieling, W., Van Montfrans, G. A. and Wesseling, K. H. (1998) Fifteen years experience with finger arterial pressure monitoring: assessment of the technology. *Cardiovascular Research* 38: 605-616

87. Inamura, K., Mano, T., Iwase, S., Amagishi, Y. and Inamura, S. (1996) One-minute wave in body fluid volume change enhanced by postural sway during upright standing. *Journal of Applied Physiology* 81: 459-469
88. Jardine, D. L., Melton, I. C., Crozier, I. G., English, S., Bennett, S. I., Frampton, C. M. and Ikram, H. (2002) Decrease in cardiac output and muscle sympathetic activity during vasovagal syncope. 282: H1804-H1809
89. Jarisch, A. (1941) Vagovasale Synkope. *Zeitschrift für Kreislaufforschung* 23: 267-279
90. Jellema, W. T., Imholz, B. P., Van Goudoever, J., Wesseling, K. H. and Van Lieshout, J. J. (1996) Finger arterial versus intrabrachial pressure and continuous cardiac output during head-up tilt testing in healthy subjects. *Clinical Science* 91: 193-200
91. Jellema, W. T., Wesseling, K. H., Groeneveld, A. B., Stoutenbeek, C. P., Thijs, L. G. and Van Lieshout, J. J. (1999) Continuous cardiac output in septic shock by simulating a model of the aortic input impedance: a comparison with bolus injection thermodilution. *Anesthesiology* 90: 1317-1328
92. Joyner, M. J., Shepherd, J. T. and Seals, D. R. (1990) Sustained increases in sympathetic outflow during prolonged lower body negative pressure in humans. *Journal of Applied Physiology* 68: 1004-1009
93. Kapoor, W. N. (1990) Evaluation and outcome of patients with syncope. 69: 160-175
94. Kapoor, W. N. (2000) Syncope. *New England Journal of Medicine* 343: 1856-1862
95. Katkov, V. E. and Chestukhin, V. V. (1980) Blood pressure and oxygenation in different cardiovascular compartments of a normal man during postural exposures. *Aviation Space and Environmental Medicine* 51: 1234-1242
96. Kaufmann, H. and Freeman, R. (2004) Pharmacological treatment of reflex syncope. *Clinical Autonomic Research* 14 Suppl 1: 71-75
97. Kaufmann, H. and Hainsworth, R. (2001) Why do we faint? *Muscle and Nerve* 24: 981-983
98. Kenny, R. A., Ingram, A., Bayliss, J. and Sutton, R. (1986) Head-up tilt: a useful test for investigating unexplained syncope. *Lancet* 1: 1352-1355
99. Kim, K. H., Cho, J. G., Lee, K. O., Seo, T. J., Shon, C. Y., Lim, S. Y., Yun, K. H., Sohn, I. S., Hong, Y. J., Park, H. W., Kim, J. H., Kim, W., Ahn, Y. K., Jeong, M. H., Park, J. C. and Kang, J. C. (2005) Usefulness of physical maneuvers for prevention of vasovagal syncope. *Circulation Journal* 69: 1084-1088

100. Kinay, O., Yazici, M., Nazli, C., Acar, G., Gedikli, O., Altinbas, A., Kahraman, H., Dogan, A., Ozaydin, M., Tuzun, N. and Ergene, O. (2004) Tilt training for recurrent neurocardiogenic syncope: effectiveness, patient compliance, and scheduling the frequency of training sessions. *Japanese Heart Journal* 45: 833-843
101. Kopp, J. (1937) Effect of fever on postural changes in blood pressure and pulse rate. *American Heart Journal* 13: 114-120
102. Kravik, S. E., Keil, L. C., Geelen, G., Wade, C. E., Barnes, P. R., Spaul, W. A., Elder, C. A. and Greenleaf, J. E. (1986) Effect of antigravity suit inflation on cardiovascular, PRA, and PVP responses in humans. *Journal of Applied Physiology* 61: 766-774
103. Krediet, C. T. (2002) Initial orthostatic hypotension in a 37-year old horse rider. *Clinical Autonomic Research* 12: 404
104. Krediet, C. T. (2003) Flauwvallen: vasovagale syncope. *Nederlands Tijdschrift voor Geneeskunde Studenteneditie* 6: 10-13
105. Krediet, C. T., De Bruin, I. G., Ganzeboom, K. S., Linzer, M., Van Lieshout, J. J. and Wieling, W. (2005) Leg crossing, muscle tensing, squatting, and the crash position are effective against vasovagal reactions solely through increases in cardiac output. *Journal of Applied Physiology* 99: 1697-1703
106. Krediet, C. T., Go-Schön, I. K., Kim, Y. S., Linzer, M., Van Lieshout, J. J. and Wieling, W. (2007) Management of initial orthostatic hypotension: lower body muscle tensing attenuates the transient arterial blood pressure decrease upon standing from squatting. *Clinical Science* (in press, available on-line)
107. Krediet, C. T., Jardine, D. L., Cortelli, P., Visman, A. G. and Wieling, W. (2004) Vasovagal syncope interrupting sleep? *Heart* 90: e25
108. Krediet, C. T., Van Dijk, N., Linzer, M., Van Lieshout, J. J. and Wieling, W. (2002) Management of vasovagal syncope: controlling or aborting faints by leg crossing and muscle tensing. *Circulation* 106: 1684-1689
109. Krediet, C. T., Van Lieshout, J. J., Bogert, L. W., Immink, R. V., Kim, Y. S. and Wieling, W. (2006) Leg crossing improves orthostatic tolerance in healthy subjects: a placebo-controlled crossover study. *American Journal of Physiology* 291: H1768-H1772
110. Krediet C.T. and Wieling W. (2007) Situational syncope. In: Mathias C.J. and Bannister R. (eds) *Autonomic failure a textbook of clinical disorders of the autonomic nervous system*. Oxford university press, Oxford (in press)
111. Krediet, C. T., Wilde, A. A., Wieling, W. and Halliwill, J. R. (2004) Exercise related syncope, when it's not the heart. *Clinical Autonomic Research* 14 Suppl 1: 25-36

112. Kurbaan, A. S., Bowker, T. J., Wijesekera, N., Franzen, A. C., Heaven, D., Itty, S. and Sutton, R. (2003) Age and hemodynamic responses to tilt testing in those with syncope of unknown origin. *Journal of the American College of Cardiology* 19: 1004-1007
113. Lawler, L. A., Halliwill, J. R., Summer, J. M., Joyner, M. J. and Mulvagh, S. L. (1998) Leg mass and lower body negative pressure tolerance in men and women. *Journal of Applied Physiology* 85: 1471-1475
114. LeLorier, P., Klein, G. J., Krahn, A., Yee, R., Skanes, A. and Shoemaker, J. K. (2003) Combined head-up tilt and lower body negative pressure as an experimental model of orthostatic syncope. *Journal of Cardiovascular Electrophysiology* 14: 920-924
115. Lempert, T. and Bauer, M. (1995) Mass fainting at rock concerts. *New England Journal of Medicine* 332: 1721
116. Lewis, Th. (1932) A lecture on vasovagal syncope and the carotid sinus mechanism with comments on Gowers' and Nothnagel's syndrome. *British Medical Journal* 1: 873-876
117. Liebermeister, C. (1864) Ueber eine besondere Ursache der Ohnmacht und über die Regulirung der Blutvertheilung nach der Körperstellung. *Prager Vierteljahrschrift für die praktische Heilkunde* 21: 31-47
118. Linzer, M., Gold, D. T., Pontinen, M., Divine, G. W., Felder, A. and Brooks, W. B. (1994) Recurrent syncope as a chronic disease: preliminary validation of a disease-specific measure of functional impairment. *Journal of General Internal Medicine* 9: 181-186
119. Linzer, M., Pontinen, M., Gold, D. T., Divine, G. W., Felder, A. and Brooks, W. B. (1991) Impairment of physical and psychosocial function in recurrent syncope. *Journal of Clinical Epidemiology* 44: 1037-1043
120. Ludbrook, J. (1966) The musculo-venous pumps of the human lower limb. *American Heart Journal* 71: 635-641
121. Ludbrook, J. and Loughlin, J. (1964) Regulation of volume in the postarteriolar vessels in the lower limb. *American Heart Journal* 67: 493-507
122. Ludwig, D. A. and Convertino, V. A. (1994) Predicting orthostatic intolerance: physics or physiology? *Aviation Space and Environmental Medicine* 65: 404-411
123. Lundvall, J. and Bjerkhoel, P. (1994) Failure of hemoconcentration during standing to reveal plasma volume decline induced in the erect posture. *Journal of Applied Physiology* 77: 2155-2162
124. Madsen, P., Svendsen, L. B., Jorgensen, L. G., Matzen, S., Jansen, E. and Secher, N. H. (1998) Tolerance to head-up tilt and suspension with elevated legs. *Aviation Space and Environmental Medicine* 69: 781-784
125. Marks, I. (1988) Blood-injury phobia: a review. *American Journal of Psychiatry* 145: 1207-1213

126. Mason, D. T. and Braunwald, E. (1965) The effects of nitroglycerin and amyl nitrite on arteriolar and venous tone in the human forearm. *Circulation* 32: 755-766
127. Mathias, C. J. (2002) To stand on one's own legs. 2: 237-245
128. Mathias, C. J., Deguchi, K., Bleasdale-Barr, K. and Kimber, J. R. (1998) Frequency of family history in vasovagal syncope. *Lancet* 352: 33-34
129. Mathias, C. J. and Kimber, J. R. (1998) Treatment of postural hypotension. *Journal of Neurology, Neurosurgery and Psychiatry* 65: 285-289
130. Matzen, S., Perko, G., Groth, S., Friedman, D. B. and Secher, N. H. (1991) Blood volume distribution during head-up tilt induced central hypovolaemia in man. *Clinical Physiology* 11: 411-422
131. Mayerson, H. S. and Burch, G. E. (1940) Relationships of tissue (subcutaneous and intramuscular) and venous pressures to syncope induced in man by gravity. *American Journal of Physiology* 128: 258-269
132. Melby, D. P., Lu, F., Sakaguchi, S., Zook, M. and Benditt, D. G. (2007) Increased impedance to inspiration ameliorates hemodynamic changes associated with movement to upright posture in orthostatic hypotension: a randomized blinded pilot study. *Heart Rhythm* 4: 128-135
133. Miller, J. D., Pegelow, D. F., Jacques, A. J. and Dempsey, J. A. (2005) Skeletal muscle pump versus respiratory muscle pump: modulation of venous return from the locomotor limb in humans. *Journal of Physiology* 563: 925-943
134. Morgan-Hughes, N. J., Dark, J. H., McComb, J. M. and Kenny, R. A. (1993) Vasovagal reactions after heart transplantation. *Journal of the American College of Cardiology* 22: 2059
135. Moss, P. D. and McEvedy, C. P. (1966) An epidemic of overbreathing among schoolgirls. *British Medical Journal* 2: 1295-1300
136. Mtinangi, B. L. and Hainsworth, R. (1998) Early effects of oral salt on plasma volume, orthostatic tolerance, and baroreceptor sensitivity in patients with syncope. *Clinical Autonomic Research* 8: 231-235
137. Mtinangi, B. L. and Hainsworth, R. (1998) Increased orthostatic tolerance following moderate exercise training in patients with unexplained syncope. *Heart* 80: 596-600
138. Narkiewicz, K., Cooley, R. L. and Somers, V. K. (2000) Alcohol potentiates orthostatic hypotension : implications for alcohol-related syncope. *Circulation* 101: 398-402
139. Newberry, P. D., Hatch, A. W. and MacDonald, J. M. (1970) Cardio-respiratory events preceding syncope induced by a combination of lower body negative pressure and head-up tilt. *Aerospace Medicine* 41: 373-378
140. O'Donnell, T. V. and McIlroy, M. B. (1962) The circulatory effects of squatting. *American Heart Journal* 64: 347-356

141. Öst, L. G. and Sterner, U. (1987) Applied tension. A specific behavioral method for treatment of blood phobia. *Behaviour Research and Therapy* 25: 25-29
142. Piorry, P. A. (1826) Recherches sur l'influence de la pesanteur sur la cours du sang; diagnostic de la syncope et de l'apoplexie; cause et traitement de la syncope. *Archives Général de Médecin* 12: 527-544
143. Ray, C. A., Rea, R. F., Clary, M. P. and Mark, A. L. (1992) Muscle sympathetic nerve responses to static leg exercise. *Journal of Applied Physiology* 73: 1523-1529
144. Ray, C. A., Rea, R. F., Clary, M. P. and Mark, A. L. (1993) Muscle sympathetic nerve responses to dynamic one-legged exercise: effect of body posture. *American Journal of Physiology* 264: H1-H7
145. Rickards, C. A. and Newman, D. G. (2003) A comparative assessment of two techniques for investigating initial cardiovascular reflexes under acute orthostatic stress. *European Journal of Applied Physiology and Occupational Physiology* 90: 449-457
146. Rieckert, H. (1976) [Physiology of orthostatic regulation]. *Cardiology* 61 suppl 1:69-77.: 69-77
147. Robertson, R. M., Medina, E., Shah, N., Furlan, R. and Mosqueda-Garcia, R. (1999) Neurally mediated syncope: pathophysiology and implications for treatment. *American Journal of the Medical Sciences* 317: 102-109
148. Rose, M. S., Koshman, M. L., Spreng, S. and Sheldon, R. (2000) The relationship between health-related quality of life and frequency of spells in patients with syncope. *Journal of Clinical Epidemiology* 53: 1209-1216
149. Ross RT (1988) Syncope. W.B. Saunders Company, London
150. Rossberg, F. and Penáz, J. (1988) Initial cardiovascular response on change of posture from squatting to standing. *European Journal of Applied Physiology and Occupational Physiology* 57: 93-97
151. Rowell LB (1993) Human cardiovascular control. Oxford University Press, New York
152. Rowell, L. B. and O'Leary, D. S. (1990) Reflex control of the circulation during exercise: chemoreflexes and mechanoreflexes. *Journal of Applied Physiology* 69: 407-418
153. Rudas, L., Pflugfelder, P. W. and Kostuk, W. J. (1992) Vasodepressor syncope in a cardiac transplant recipient: a case of vagal re-innervation? *Canadian Journal of Cardiology* 8: 403-405
154. Rushmer, R. F. (1944) Circulatory collapse following mechanical stimulation of arteries. *American Journal of Physiology* 141: 722-729
155. Sabin, N. (2001) The use of applied tension and cognitive therapy to manage syncope (common faint) in an older adult. *Aging and Mental Health* 5: 92-94

156. Saltin, B., Sjogaard, G., Gaffney, F. A. and Rowell, L. B. (1981) Potassium, lactate, and water fluxes in human quadriceps muscle during static contractions. *Circulation Research* 48: I18-I24
157. Sander-Jensen, K., Secher, N. H., Astrup, A., Christensen, N. J., Giese, J., Schwartz, T. W., Warberg, J. and Bie, P. (1986) Hypotension induced by passive head-up tilt: endocrine and circulatory mechanisms. *American Journal of Physiology* 251: R742-R748
158. Schadt, J. C. and Ludbrook, J. (1991) Hemodynamic and neurohumoral responses to acute hypovolemia in conscious mammals. *American Journal of Physiology* 260: H305-H318
159. Scherrer, U., Vissing, S., Morgan, B. J., Hanson, P. and Victor, R. G. (1990) Vasovagal syncope after infusion of a vasodilator in a heart-transplant recipient. *New England Journal of Medicine* 322: 602-604
160. Schobel, H. P., Oren, R. M., Mark, A. L. and Ferguson, D. W. (1995) Influence of resting sympathetic activity on reflex sympathetic responses in normal man. *Clinical Autonomic Research* 5: 71-80
161. Schroeder, C., Bush, V. E., Norcliffe, L. J., Luft, F. C., Tank, J., Jordan, J. and Hainsworth, R. (2002) Water drinking acutely improves orthostatic tolerance in healthy subjects. *Circulation* 106: 2806-2811
162. Seals, D. R. and Enoka, R. M. (1989) Sympathetic activation is associated with increases in EMG during fatiguing exercise. *Journal of Applied Physiology* 66: 88-95
163. Secher, N. H., Perko, G. and Olesen, H. L. (1992) Effect of exercise on vasovagal (pre-) syncope. *Scandinavian Journal of Medicine and Science in Sports* 2: 160-161
164. Secher, N. H. and Van Lieshout, J. J. (2005) Normovolaemia defined by central blood volume and venous oxygen saturation. *Clinical and Experimental Pharmacology and Physiology* 32: 901-910
165. Sejersted, O. M., Hargens, A. R., Kardel, K. R., Blom, P., Jensen, O. and Hermansen, L. (1984) Intramuscular fluid pressure during isometric contraction of human skeletal muscle. *Journal of Applied Physiology* 56: 287-295
166. Serletis, A., Rose, S., Sheldon, A. G. and Sheldon, R. S. (2006) Vasovagal syncope in medical students and their first-degree relatives. *European Heart Journal* 27: 1965-1970
167. Sharpey-Schafer, E. P. (1956) Effects of squatting on the normal and failing circulation. *British Medical Journal* 1072-1074
168. Sharpey-Schafer, E. P. (1956) Syncope. *British Medical Journal* 1: 506-509
169. Sharpey-Schafer, E. P., Hayter, C. J. and Barlow, E. D. (1958) Mechanism of acute hypotension from fear or nausea. *British Medical Journal* 2: 878-880

170. Sheldon, R. and Rose, S. (2001) Components of clinical trials for vasovagal syncope. *Europace* 3: 233-240
171. Sheldon, R., Rose, S., Connolly, S., Ritchie, D., Koshman, M. L. and Frenneaux, M. (2005) Diagnostic criteria for vasovagal syncope based on a quantitative history. *European Heart Journal* 27: 344-350
172. Sheldon, R., Rose, S., Flanagan, P., Koshman, M. L. and Killam, S. (1996) Risk factors for syncope recurrence after a positive tilt-table test in patients with syncope. *Circulation* 93: 973-981
173. Sheldon, R. S., Sheldon, A. G., Connolly, S. J., Morillo, C. A., Klingenhoben, T., Krahn, A. D., Koshman, M. L. and Ritchie, D. (2006) Age of first faint in patients with vasovagal syncope. *Journal of Cardiovascular Electrophysiology* 17: 49-54
174. Shichiri, M., Tanaka, H., Takaya, R. and Tamai, H. (2002) Efficacy of high sodium intake in a boy with instantaneous orthostatic hypotension. *Clinical Autonomic Research* 12: 47-50
175. Sjöstrand, T. (1952) The regulation of the blood distribution in man. 26: 312-327
176. Smit, A. A., Halliwill, J. R., Low, P. A. and Wieling, W. (1999) Pathophysiological basis of orthostatic hypotension in autonomic failure. *Journal of Physiology* 519: 1-10
177. Smit, A. A., Hardjowijono, M. A. and Wieling, W. (1997) Are portable folding chairs useful to combat orthostatic hypotension? *Annals of Neurology* 42: 975-978
178. Smith, M. L., Hudson, D. L. and Raven, P. B. (1987) Effect of muscle tension on the cardiovascular responses to lower body negative pressure in man. *Medicine and Science in Sports and Exercise* 19: 436-442
179. Soteriades, E. S., Evans, J. C., Larson, M. G., Chen, M. H., Chen, L., Benjamin, E. J. and Levy, D. (2002) Incidence and prognosis of syncope. *New England Journal of Medicine* 347: 878-885
180. Sprangers, R. L., Van Lieshout, J. J., Karemaker, J. M., Wesseling, K. H. and Wieling, W. (1991) Circulatory responses to stand up: discrimination between the effects of respiration, orthostasis and exercise. *Clinical Physiology* 11: 221-230
181. Sprangers, R. L., Veerman, D. P., Karemaker, J. M. and Wieling, W. (1991) Initial circulatory responses to changes in posture: influence of the angle and speed of tilt. *Clinical Physiology* 11: 211-220
182. Sprangers, R. L., Wesseling, K. H., Imholz, A. L., Imholz, B. P. and Wieling, W. (1991) Initial blood pressure fall on stand up and exercise explained by changes in total peripheral resistance. *Journal of Applied Physiology* 70: 523-530
183. Stead, E. A., Warren, J. V., Merrill, A. J. and Brannon, E. S. (1945) Cardiac output in male subjects as measured by technique of heart catheteriza-

- tion. Normal values with observations on the effect of anxiety and tilting. *Journal of Clinical Investigation* 24: 326-331
184. Stevens, P. M. (1966) Cardiovascular dynamics during orthostasis and the influence of intravascular instrumentation. *American Journal of Cardiology* 17: 211-218
185. Stewart, J. M., Medow, M. S., Montgomery, L. D. and McLeod, K. (2004) Decreased skeletal muscle pump activity in patients with postural tachycardia syndrome and low peripheral blood flow. 286: H1216-H1222
186. Sud, S., Massel, D., Klein, G. J., Leong-Sit, P., Yee, R., Skanes, A. C., Gula, L. J. and Krahn, A. D. (2007) The expectation effect and cardiac pacing for refractory vasovagal syncope. *American Journal of Medicine* 120: 54-62
187. Sun, B. C., Emond, J. A. and Camargo, C. A., Jr. (2004) Characteristics and admission patterns of patients presenting with syncope to U.S. emergency departments, 1992-2000. *Academic Emergency Medicine* 11: 1029-1034
188. Sutton, R. (2002) How and when to pace in vasovagal syncope. *Journal of Cardiovascular Electrophysiology* 13: S14-S16
189. Tanaka, H., Sjöberg, B. J. and Thulesius, O. (1996) Cardiac output and blood pressure during active and passive standing. *Clinical Physiology* 16: 157-170
190. Tatar, P., Bulas, J., Kvetnansky, R. and Strec, V. (1986) Venous plasma adrenaline response to orthostatic syncope during tilting in healthy men. *Clinical Physiology* 6: 303-309
191. Ten Harkel, A. D., Van Lieshout, J. J. and Wieling, W. (1994) Effects of leg muscle pumping and tensing on orthostatic arterial pressure: a study in normal subjects and patients with autonomic failure. *Clinical Science* 87: 553-558
192. Thijs, R. D., Benditt, D. G., Mathias, C. J., Schondorf, R., Sutton, R., Wieling, W. and Van Dijk, J. G. (2005) Unconscious confusion--a literature search for definitions of syncope and related disorders. *Clinical Autonomic Research* 15: 35-39
193. Thijs, R. D., Kruit, M. C., van Buchem, M. A., Ferrari, M. D., Launer, L. J. and Van Dijk, J. G. (2006) Syncope in migraine: the population-based CAMERA study. *Neurology* 66: 1034-1037
194. Thijs, R. D., Wieling, W., Kaufmann, H. and Van Dijk, G. (2004) Defining and classifying syncope. *Clinical Autonomic Research* 14 Suppl 1: 4-8
195. Thornton, J. M., Guz, A., Murphy, K., Griffith, A. R., Pedersen, D. L., Kardos, A., Leff, A., Adams, L., Casadei, B. and Paterson, D. J. (2001) Identification of higher brain centres that may encode the cardiorespiratory response to exercise in humans. *Journal of Physiology* 533: 823-836

196. Tschakovsky, M. E. and Sheriff, D. D. (2004) Immediate exercise hyperemia: contributions of the muscle pump vs. rapid vasodilation. *Journal of Applied Physiology* 97: 739-747
197. Van Dijk, N., Boer, K. R., Colman, N., Linzer, M., Reitsma, J. B. and Wieling, W. (2006) Diagnostic yield and accuracy of history in patients with syncope. *Europace* 8 Suppl 1: 45
198. Van Dijk, N., De Bruin, I. G., Gisolf, J., Bruin-Bon, H. A., Linzer, M., Van Lieshout, J. J. and Wieling, W. (2005) Hemodynamic effects of leg crossing and skeletal muscle tensing during free standing in patients with vasovagal syncope. *Journal of Applied Physiology* 98: 584-590
199. Van Dijk, N., Harms, M. P., Linzer, M. and Wieling, W. (2000) Treatment of vasovagal syncope: pacemaker or crossing legs? *Clinical Autonomic Research* 10: 347-349
200. Van Dijk, N., Quartieri, F., Blanc, J. J., Garcia-Civera, R., Brignole, M., Moya, A. and Wieling, W. (2006) Effectiveness of physical counterpressure maneuvers in preventing vasovagal syncope: the Physical Counterpressure Manoeuvres Trial (PC-Trial). *Journal of the American College of Cardiology* 48: 1652-1657
201. Van Dijk, N., Sprangers, M. A., Boer, K. R., Colman, N., Wieling, W. and Linzer, M. (2007) Quality of life within one year following presentation after transient loss of consciousness. *American Journal of Cardiology* (in press, available online):
202. Van Dijk, N., Sprangers, M. A., Colman, N., Boer, K. R., Wieling, W. and Linzer, M. (2006) Clinical factors associated with quality of life in patients with transient loss of consciousness. *Journal of Cardiovascular Electrophysiology* 17: 998-1003
203. Van Dijk, N., Velzeboer, S. C., Destree-Vonk, A., Linzer, M. and Wieling, W. (2001) Psychological treatment of malignant vasovagal syncope due to bloodphobia. *Pacing and Clinical Electrophysiology* 24: 122-124
204. Van Lieshout, J. J., Pott, F., Madsen, P. L., Van Goudoever, J. and Secher, N. H. (2001) Muscle tensing during standing: effects on cerebral tissue oxygenation and cerebral artery blood velocity. *Stroke* 32: 1546-1551
205. Van Lieshout, J. J. and Secher, N. H. (2003) Reflex control of sympathetic vasoconstrictor activity in vasovagal syncope. *Clinical Autonomic Research* 13: 175-177
206. Van Lieshout, J. J., Ten Harkel, A. D. and Wieling, W. (1992) Physical manoeuvres for combating orthostatic dizziness in autonomic failure. *Lancet* 339: 897-898
207. Van Lieshout, J. J., Toska, K., Van Lieshout, E. J., Eriksen, M., Walloe, L. and Wesseling, K. H. (2003) Beat-to-beat noninvasive stroke volume

- from arterial pressure and Doppler ultrasound. *European Journal of Applied Physiology and Occupational Physiology* 90: 131-137
208. Van Lieshout, J. J., Wieling, W., Karemaker, J. M. and Eckberg, D. L. (1991) The vasovagal response. *Clinical Science* 81: 575-586
 209. Van Lieshout, J. J., Wieling, W., Karemaker, J. M. and Secher, N. H. (2003) Syncope, cerebral perfusion, and oxygenation. *Journal of Applied Physiology* 94: 833-848
 210. Verheyden, B., Gisolf, J., Beckers, F., Karemaker, J. M., Wesseling, K. H., Aubert, A. E. and Wieling, W. (2007) Impact of age on the vasovagal response provoked by sublingual nitroglycerine in routine tilt testing. *Clinical Science* (in press, available on-line):
 211. Wallace, H., Shorvon, S. and Tallis, R. (1998) Age-specific incidence and prevalence rates of treated epilepsy in an unselected population of 2,052,922 and age-specific fertility rates of women with epilepsy. *Lancet* 352: 1970-1973
 212. Wallin, B. G. and Sundlöf, G. (1982) Sympathetic outflow to muscles during vasovagal syncope. *Journal of the Autonomic Nervous System* 6: 287-291
 213. Wang, Y., Marshall, R. J. and Shepherd, J. T. (1960) The effect of changes in posture and of graded exercise on stroke volume in man. 39: 1051-1061
 214. Wayne, H. H. (1961) Syncope. Physiological considerations and an analysis of the clinical characteristics in 510 patients. *American Journal of Medicine* 30: 418-438
 215. Weissler, A. M., Warren, J. V., Estes, E. H. J., McIntosh, H. D. and Leonard, J. J. (1957) Vasodepressor syncope; factors influencing cardiac output. *Circulation* 15: 875-882
 216. Wesseling K.H., Sprangers R.L. and Wieling W. (1992) Peripheral resistance changes upon stand-up compared to those upon tilt-up and the onset to cycling: implications of the cardiopulmonary reflex. In: Schmidt, Engel and Blümchen (eds) *Temporal variations in the cardiovascular system*. Springer-Verlag, Berlin Heidelberg, pp 222-239
 217. Westendorp, R. G., Blauw, G. J., Frolich, M. and Simons, R. (1997) Hypoxic syncope. *Aviation Space and Environmental Medicine* 68: 410-414
 218. White, W. D., Sheldon, R. S. and Ritchie, D. A. (2003) Learning needs of patients with vasovagal syncope. *Canadian Journal of Cardiovascular Nursing* 13: 26-30
 219. Wieling, W., Borst, C., van Brederode, J. F., van Dongen Torman, M. A., Van Montfrans, G. A. and Dunning, A. J. (1983) Testing for autonomic neuropathy: heart rate changes after orthostatic manoeuvres and static muscle contractions. *Clinical Science* 64: 581-586
 220. Wieling, W., Borst, C., Van Lieshout, J. J., Sprangers, R. L., Karemaker, J. M., van Brederode, J. F., Van Montfrans, G. A. and Dunning, A. J. (1985)

- Assessment of methods to estimate impairment of vagal and sympathetic innervation of the heart in diabetic autonomic neuropathy. *Netherlands Journal of Medicine* 28: 383-392
221. Wieling, W., Colman, N., Krediet, C. T. and Freeman, R. (2004) Non-pharmacological treatment of reflex syncope. *Clinical Autonomic Research* 14 Suppl 1: 62-70
 222. Wieling, W., Ganzeboom, K. S., Krediet, C. T., Grundmeijer, H. G., Wilde, A. A. and Van Dijk, J. G. (2003) [Initial diagnostic strategy in the case of transient losses of consciousness: the importance of the medical history]. *Nederlands Tijdschrift voor Geneeskunde* 147: 849-854
 223. Wieling, W., Harms, M. P., Ten Harkel, A. D., Van Lieshout, J. J. and Sprangers, R. L. (1996) Circulatory response evoked by a 3 s bout of dynamic leg exercise in humans. *Journal of Physiology* 494: 601-611
 224. Wieling W. and Karemaker J.M. (2001) Measurement of heart rate and blood pressure to evaluate disturbances in neurocardiovascular control. In: Mathias C.J. and Bannister R. (eds) *Autonomic failure a textbook of clinical disorders of the autonomic nervous system*. Oxford university press, Oxford, pp 196-210
 225. Wieling, W., Krediet, C. T., Van Dijk, N., Linzer, M. and Tschakovsky, M. E. (2007) Initial orthostatic hypotension: review on a forgotten condition. *Clinical Science* 112: 157-165
 226. Wieling, W. and Shepherd, J. T. (1992) Initial and delayed circulatory responses to orthostatic stress in normal humans and in subjects with orthostatic intolerance. *International Angiology* 11: 69-82
 227. Wieling, W., Ten Harkel, A. D. and Van Lieshout, J. J. (1991) Spectrum of orthostatic disorders: classification based on an analysis of the short-term circulatory response upon standing. *Clinical Science* 81: 241-248
 228. Wieling, W., Van Lieshout, J. J. and Hainsworth, R. (2002) Extracellular fluid volume expansion in patients with posturally related syncope. *Clinical Autonomic Research* 12: 242-249
 229. Wieling, W., Van Lieshout, J. J. and Van Leeuwen, A. M. (1993) Physical manoeuvres that reduce postural hypotension in autonomic failure. *Clinical Autonomic Research* 3: 57-65
 230. Wilson, T. E., Cui, J., Zhang, R. and Crandall, C. G. (2006) Heat stress reduces cerebral blood velocity and markedly impairs orthostatic tolerance in humans. *American Journal of Physiology* 291: R1443-1448
 231. Wolthuis, R. A., Bergman, S. A. and Nicogossian, A. E. (1974) Physiological effects of locally applied reduced pressure in man. *Physiological Reviews* 54: 566-595

Abbreviations

BP	Blood pressure
CO	Cardiac output
DBP	Diastolic blood pressure
HBK	Head bent between knees (“crash position”)
HR	Heart rate
HUT	Head-up tilting
LBMT	Lower body muscle tensing
LCMT	Leg crossing with muscle tensing
MAP	Mean arterial pressure
PP	Pulse pressure
SD	Standard deviation
SE	Standard error
SBP	Systolic blood pressure
SV	Stroke volume
TI	Thoracic impedance
TLOC	Transient loss of consciousness
TPR	Total peripheral resistance
WBT	Whole body tensing