Risk factors and mechanisms for falls in the elderly
Findings from a falls clinic and head-up tilt tests

Marte Rognstad Mellingsæter

Faculty of Medicine, University of Oslo
and
Department of Geriatric Medicine
Oslo University Hospital, Ullevål,
Norway
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”Det mest beundringsverdige ved å leve, er ikke aldri å falle, men å reise oss hver gang vi faller”

Nelson Mandela
Anerkjennelse og takk

Jeg visste ikke at jeg var så interessert i fall før jeg begynte å jobbe med pasienter med hoftebrudd og møtte eldre i poliklinikken som var henvist med problemstillingen fall. Opplevelslen av å ha så lite å tilby i møtet med utryggheten disse pasientene opplever og de til dels dramatiske konsekvensene, fikk meg til å etterspørre en mer systematisk utredning - slik det ble gjort andre steder. Jeg var ung, kanskje lovende, og var så heldig å ha Torgeir Bruun Wyller som leder, han gav meg muligheten til og ansvaret for å etablere en fallpoliklinik ved Ullevål sykehus, etterhvert OUS. Jeg er stolt av det vi fikk til. Tverrfaglig samarbeid blir kanskje aldri det samme. Fysioterapeut Solveig Granum og sykepleier Elisabet Sigurjonsdottir har støttet, oppmuntret, moret, inspirert og gitt meg selvtilt i tillegg til alt vi har lært oss sammen. At Fallpoliklinikken lever videre etter at jeg begynte på Ahus betyr mye.

Studiene hadde ikke vært mulige uten velvillighet fra alle de friske kontrollene, inkludert Birkebeinerne, og pasientene ved Fallpoliklinikken og hukommelsesklínikken ved OUS. Det krever tålmodighet å stå opppreist i 40 minutter uten å få si noe særlig. Jeg skylder dem en stor takk alle sammen.


Gjennom hele prosjektet har jeg hatt en interessant og interessert veileder-troika rundt meg. De har alle tre bidratt på hvert sitt uvurderlige vis. Anette Hylen Ranhoff har vært min hovedveileder og er mitt kvinnelige geriatriske "ikon". Hun åpner dører, er verdensvant, imponerende bredt geriatrisk interessert, praktisk og klinikk orientert, elegant, og en tøff langrennsløper.

Uten Torgeir er det ikke sikkert jeg hadde vært geriater. Han gav meg passe ansvar, undervisningsoppgaver, rekrutterte meg til forskning og fikk meg til å starte Fallpoliklinikken. Alt mens livet mitt ellers var litt trøblete. Og da han skjønte det sa han: "Så flaks at du har en litt fleksibel jobb nå da". Tillit, trygghet og troverdighet - min geriaterhelt - det er Torgeir det!

I tillegg har han introduseret meg for Vegard, lillebror og biveileder. Vegard kan metoden og har bidratt med vesentlig kunnskap, klarhet og konstruktiv kritikk.
Takk også til mine øvrige medforfattere Kristofer L. Smebye, Torkel Steen og Nenad Bogdanovic.

Prosjektet har strukket seg over mange år og folk har kommet, disputert og gått på "Loftet" (vår forskningsseksjon ved OUS). Forvist til et annet bygg og kanskje mer ensom enn jeg ville innrømme, gav møtene på "Loftet" tiltrengt moro, inspirasjon, hjelp og kunnskap i tillegg til å være en kanal for alminnelig frustrasjonsutveksling. Takk til dere alle - jeg skulle besøkt dere mer!

Takk også til hele 'Husmorklubben', dere er viktige, for liv og gjerning. Ingebjørg for så mye - lenge. Tonje for å være en faglig bauta, som har tatt meg i mot først på Ullevål og siden kortvarig på Åhus. Siri og jeg fryder oss over geriatrien og Torgeir, og sannelig har ikke Maria utvidet interesseområdet til sykehjems-etikk - mer prat gjenstår med dere alle etter at jeg som den siste i klubben disputerer!


Frode kom til alt hell inn i livet mitt underveis i arbeidet med graden - og jeg har virkelig fått erfare at både det å være virkelig trist og virkelig forelsket setter arbeidskapasiteten tilbake. Men at det siste er langt å foretrekke! Du er interessert i det jeg gjør, søker klarhet, støttet, stiller krav og er stolt av meg. Men aller viktigst er viljen til å være den viktigste, jeg gleder meg til flere skiturer, mer padling og daglig ettermiddagskaffe med deg!

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Oslo, november 2015

Marte Rognstad Mellingsætær
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## Abbreviations

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<tbody>
<tr>
<td>AD</td>
<td>Alzheimer's dementia</td>
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<tr>
<td>ANS</td>
<td>Autonomic nervous system</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>BPV</td>
<td>Blood pressure variability</td>
</tr>
<tr>
<td>BRS</td>
<td>Baroreceptor reflex sensitivity</td>
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<tr>
<td>CDR</td>
<td>Clinical dementia rating</td>
</tr>
<tr>
<td>ChEls</td>
<td>Cholinesterase inhibitors</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CO/CI</td>
<td>Cardiac output / Cardiac index</td>
</tr>
<tr>
<td>CSH</td>
<td>Carotid sinus hypersensitivity</td>
</tr>
<tr>
<td>CSM</td>
<td>Carotid sinus massage</td>
</tr>
<tr>
<td>CSS</td>
<td>Carotid sinus syncope</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>EDV/EDVI</td>
<td>End diastolic volume / End diastolic vol. index</td>
</tr>
<tr>
<td>GP</td>
<td>General practitioner</td>
</tr>
<tr>
<td>HF</td>
<td>High frequency</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>HRV</td>
<td>Heart rate variability</td>
</tr>
<tr>
<td>HUT</td>
<td>Head-up tilt-test</td>
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<tr>
<td>LF</td>
<td>Low frequency</td>
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<tr>
<td>MAP</td>
<td>Mean arterial blood pressure</td>
</tr>
<tr>
<td>MCI</td>
<td>Mild cognitive impairment</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini mental status examination</td>
</tr>
<tr>
<td>OH</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>RRI</td>
<td>R-R interval</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
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<tr>
<td>SBPV</td>
<td>Systolic blood pressure variability</td>
</tr>
<tr>
<td>SV/SI</td>
<td>Stroke volume / Stroke index</td>
</tr>
<tr>
<td>T-LOC</td>
<td>Transient loss of consciousness</td>
</tr>
<tr>
<td>TPR/TPRI</td>
<td>Total peripheral resistance / Total peripheral resistance index</td>
</tr>
</tbody>
</table>
List of publications

Paper I
Kristofer Lislerud Smebye, Solveig Granum, Torgeir Bruun Wyller, Marte Rognstad Mellingsæter. Medical findings in an interdisciplinary geriatric outpatient clinic specialising in falls. Tidsskr Nor Legeforen 2014; 134: 705-9
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Paper II
Marte Rognstad Mellingsæter, Torgeir Bruun Wyller, Torkel Steen. An elderly woman with unexplained falls and ‘tingling sensations in the head’. Tidsskr Nor Legeforen 2014; 134: 717-20
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Paper III

Paper IV

Paper V
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Norsk sammendrag

Denne avhandlingen beskriver noe av kompleksiteten rundt utredning av fall og synkope slik det kan gjøres i en fallpoliklinikk. I tillegg er målsettingen å bidra med kunnskap om autonom (ikke viljestyrte) regulering av blodtrykk og hjertefrekvens hos eldre. Den siste delen er absolutt mest fysiologisk, om enn med klinisk relevans.

Fall er en av de "geriatriske gigantene". Det var Bernard Isaacs (1924-95), professor i eldremedisin i Storbritannia, som beskrev dem først. De begynner alle på "i": instabilitet, immobilitet, intellektuell svikt (eller kognitive svikter om man vil) og inkontinens. I artikkel I (og II) beskriver vi resultatene fra de første 111 pasientene vi hadde ved Fallpoliklinikken ved Oslo universitetssykehus, etter at den ble etablert i 2008. Det er en kohortstudie uten oppfølging som illustrerer hvordan fall hos eldre har mange og ulike årsaker, og at alvorlig underliggende patologi hos eldre kan manifestere seg som falltendens. Funnene viser betydningen av en tverrfaglig undersøkelse av eldre som faller. Resultatene passer med de få resultatene som er publisert fra lignende poliklinikker, men dette er den første studien i sitt slag i Norge.

Tidligere fall, polyfarmasi, lett kognitive svikter og multimorbiditet var vanlig hos pasientene. De fleste hadde redusert styrke og balanse. Ortostatisk hypotensjon, det vil si blodtrykkssfall i stående stilling, og synkope forekom ofte. Ortostatisk hypotensjon og autonom dysfunksjon er relatert til fall og er mer vanlig hos eldre, men det gjenstår mye forskning.

Eldre kvinner faller oftere enn menn, men årsakene er ikke klarlagt. Vi undersøkte regulering av blodtrykk og pulser hos 48 friske, eldre kvinner og menn, halvparten av hvert kjønn. Ingen av dem brukte medisiner fast. Vi utsatte dem for vippetest (HUT = head-up tilt test) der de skulle stå oppreist, lett tilbakelent mot en skråstilt benk, i 40 minutter. Blodtrykk, hjertefrekvens, slagvolum, total perifer motstand i blodårene, hjertefrekvensvariabilitet (HRV) og blodtrykksvariabilitet (BPV) ble målt og/eller beregnet. HRV og BPV er størrelser som sier noe om hvilke deler av det autonome nervesystemet som er involvert i reguleringen. Til forskjell fra det som er tilfelle hos yngre kvinner, tyder våre resultater i artikkel III, på at friske, eldre kvinner har bedre evne til å stå oppreist over tid enn jevngamle menn. Det ser ut som det har mer sammenheng med forskjeller i den autonome kontrollen av hvordan blodårene utvider og trekker seg sammen enn kontrollen av hjertets frekvens.
Artikkel IV føyer seg inn i rekken av et økende antall artikler som dreier seg om "vellykket aldring". Noen studier har vist at yngre, mannlige atleter har lavere ortostatisk toleranse enn de mindre spreke, som uttrykt i dette sitatet av Greenleaf: "Spreke menn kan løpe, men de kan ikke stå". Stillesitting bedrer absolutt ikke evnen til å opprettholde blodtrykket i stående stilling, men det er ikke klart hvor spreke man kan være før fordelene oppveies av ulempene. Om eldre atleter vet man enda mindre.

Vi undersøkte 30 birkebeinere (deltagere i Birkebeinerrennet på ski), over 65 år og sammenlignet dem med de 24 friske mennene fra artikkel III. Ortostatisk toleranse var ikke redusert hos birkebeinerne. Det var heller en tendens til bedre ortostatisk toleranse, som kan knyttes til sterkere parasympatisk kontroll av hjertet og økt blodvolum. Parasympatisk kontroll vil svært forenklet si det som styres av vagusnerven og er det systemet som er mest aktivt når kroppen er i rolig vedlikeholdstilstand og ikke er i alarmberedskap. Vi konkluderer med at bedre ortostatisk toleranse kan være en tilleggsgevinst ved trening i eldre år.

Pasienter med demens er svært utsatt for fall og i artikkel V beskriver vi forskjeller i sympatisk respons ved vippetest hos eldre med mild kognitiv svikt og mild Alzheimers demens sammenlignet med friske eldre. Forandringer i tidlige stadier av demens kan tyde på svekket sympatisk kontroll av hjerte og blodårer i forbindelse med oppreising og kan eventuelt reflektere tidlige forandringer i hjernen.
1. Summary

This dissertation provides some insight into the complexity of falls from a clinical view, and attempts to fill in some of the gaps in knowledge about ageing and autonomic cardiovascular regulation. The latter with a clear physiological approach.

Falls are one of the “giants” of geriatrics: instability, immobility, intellectual impairment, and incontinence, first described by Bernard Isaacs, former Professor of elderly medicine, UK (1924–95). In paper I (and II) we describe the results from the first 111 patients after the establishment of an outpatients falls clinic ("Fallpoliklinikken") at Oslo University Hospital. This cohort study without follow-up illustrates that falls among elderly people have varying and complex causes. Serious underlying pathology may manifest itself as a tendency to fall. This underlines the importance of a thorough interdisciplinary assessment of falls. Our results concur well with the few other studies abroad, and is the first study presented in Norway from an outpatient clinic specialising in falls.

Previous falls, polypharmacy, cognitive impairment (mostly mild) and multimorbidity characterised the patients. Impairments in strength and balance, orthostatic hypotension and syncope were among the most frequent medical findings. Orthostatic hypotension and autonomic dysfunction are related to falls and are more common in the elderly, but scarcely studied.

Women fall more often than men, but causes remain unclear. We assessed cardiovascular regulation in 48 healthy elderly who were free from medication (24 men and 24 women) by subjecting them to head-up tilt test for 40 minutes. Blood pressures, heart rate, stroke volume, total peripheral resistance, heart rate variability, and blood pressure variability were recorded or calculated. Together these measures express how the autonomic nervous system controls the cardiovascular system. Unlike the case in young women, our results in paper III indicate that elderly women have better orthostatic tolerance during long lasting postural stress than men of the same age. The underlying reason might be differences in vascular rather than cardiac autonomic control.

Paper IV complies with the increasing number of studies in the field of successful ageing. Some studies have shown decreased orthostatic tolerance among young male athletes, expressed by Greenleaf as: "Fit men can run but they cannot stand". A sedentary lifestyle does not improve orthostatic
tolerance, but the degree of fitness necessary to negate the benefits is unknown. Our knowledge about orthostatic tolerance in elderly athletes is scarce. We subjected 30 elderly male cross-country skiers to head-up tilt and compared them with healthy male controls. Orthostatic tolerance was not reduced among the endurance athletes. Rather, there was a trend towards better orthostatic tolerance, which might be attributed to stronger parasympathetic cardiovascular control and larger blood volume. We concluded that better orthostatic tolerance might be an additional benefit of physical activity in older age.

Patients with dementia are very likely to fall, and in paper V we describe differences in sympathetic response to head-up tilt in patients with mild cognitive impairment and mild Alzheimer's dementia as compared to healthy controls. The findings might indicate attenuation of sympathetic cardiovascular control that possibly reflects early neuropathological processes in the brain.
2. Introduction

"If you could give only a single lecture, talk about falls. Then you can get into almost everything that is important in geriatrics." I have taken this fatherly advice, from late Professor Exton-Smith, retold by the Swedish Professor Emeritus Bertil Steen (1), to my heart. Knowledge about falls is extremely useful in the everyday work at a hospital ward.

2.1 Falls in the elderly

Falls are undoubtedly related to ageing, with the life span curve obviously u-shaped. My concern is not the toddler's struggle and stamina to achieve balance, but the often harmful and alarming falls in the elderly. I often think of a quote from an old lady cited in an article about experiences after hip fracture: “I always thought I was stable...” The authors conclude that a hip fracture not only impacts physical function, but causes dramatic changes in life situation, including existential thoughts and reappraisal of remaining years (2). Thus, falls and their consequences are not only related to being old, but also feeling old, or even worse, to be perceived old (3). To recognise this is important for measures to prevent falls and increase motivation for training (4).

The link between frailty and falls seems obvious from a clinical point of view. In research, the interest of linking those two phenomena is also increasing. Nowak expresses it almost lyrically: "(...) falling can be viewed as a perceptible marker of failure of a complex system that was already in a dangerous state of vulnerability prior to the application of a stressor that pushed it over the edge"(5).

2.1.1 Definition of a fall

Although everyone knows what it means to fall, the field has long lacked one unifying definition. This is a challenge particularly for researchers (6), but should be of concern also for health care professionals communicating with elderly patients (7). While health care professionals highlight consequences of falls, the elderly themselves are more concerned about unsteadiness and external factors like slips and trips that eventually lead to falls (8).

The most widely used definition denotes a fall as "an unexpected event in which the participant comes to rest on the ground, floor, or lower level" (7). This definition, also used in the "WHO Global Report on Falls Prevention in Older Age" (9), is broad, including all causes except assaults and intentional self-harm; falls from animals, burning buildings and transport vehicles; and falls
into fire, water and machinery. The definition is consistent with the general understanding (10) and from a medical perspective, falls from all thinkable diagnoses and diseases are included.

There has been a discussion whether or not falls due to syncope should be included in the definition, and according to the above, they are. There is an overlap between falls and syncope, especially in the elderly (11). Up to 40 % of falls are unwitnessed and many patients have impaired cognition and thus reduced ability to present a reliable history. Also cognitively intact elderly, however, tend to have amnesia for falls and syncope (12). In about 40 % of patients given an attributable diagnosis of carotid sinus syncope, falls were the only symptom, and patients with hip fracture have more often carotid hypersensitivity than patients hospitalized for elective hip surgery (12).

### 2.1.2 Epidemiology of falls

Almost every article written about falls in the elderly is preceded by the fact that approximately one third of home-dwelling people over 65 years fall each year (13, 14), with about half of them experiencing more than one fall. The incidence rises steadily with age (13, 15). The figures are based on retrospective studies, and self-reporting might underestimate the incidence, due to lack of recall, and overestimate the proportion that reports more than one fall (6, 16). The incidence among institutionalised elderly is higher, with large variations between studies. Meta-analyses report incidence rates up to 40-50 % (13). People in institutions are both older and frailer and the routines for reporting falls might be better. Elderly women fall nearly twice as often as men (17) and are more often hospitalised due to falls and fractures (15, 18), albeit differences seem to disappear after the age of 90 (19) and in severe dementia (20).

WHO denotes fall prevention as a challenge from population ageing (9). 10-15 % of falls cause a serious injury such as fracture, serious soft tissue injury or traumatic brain injury (14, 19, 21). Hip fractures are almost always caused by a fall, and the great majority happen in persons older than 65 years (18). An estimate from 2013 suggests that the cost of the more than 9000 annual hip fractures in Norway amounts to 3 billion NOK (22) or about 3 % of the total health budget (23) (my calculation). The largest components of this cost are mortality, lost quality of life, long-stay care costs and hospital inpatient costs (24).

Even those who avoided a serious injury might have a decline in the ability to care for themselves and a reduction in self-confidence after a fall, thus
changing their habits, leading to isolation and passivity (25-27) and increased risk of falling again (28). A Norwegian study registered falls prospectively for one year and showed a relative risk of 1.6 for mortality during the nine-year follow-up in women who suffered from 2 falls or more. The figures were adjusted for age, number of diseases and self-reported health (29).

2.1.3 Reasons and risk factors for falls
Falling is classified as a geriatric syndrome. A geriatric syndrome is typically caused by the contribution of multiple factors: the interaction between chronic predisposing diseases and impairments and an acute precipitating event or illness (30). Because of this, fall mechanisms are many and often multifactorial (31). The strongest risk factors for falls are previous falls, cognitive impairment, gait and balance disturbances, reduced muscle strength, polypharmacy in general, and in particular the use of psychoactive drugs (14, 28).

Syncope is rarely listed as a cause of falls. Estimates are only 0.3 - 5 % in general (13) and higher in falls leading to hospitalisation (32). Syncope may, however, constitute a much more common fall mechanism according to the overlap between falls and syncope (12, 33). Up to one quarter of syncopal events will present as unexplained falls (34).

2.2 Hemodynamic regulation and autonomic nervous system (ANS)
Overall the main purpose of the autonomic nervous system (ANS) is maintenance of the relatively stable internal conditions in the body; homeostasis. In contrast to the somatic nervous system which is related to voluntary action and conscious perception, the control mechanisms of ANS are involuntary and unconscious (35). Organ functions are constantly monitored by the afferent part of the ANS and adjusted through the effects of the efferent part of the ANS on smooth muscles, heart muscle and glands.

2.2.1 Short overview of the most relevant parts of ANS
The central nervous system receives input from sensory receptors in the ANS, and of main interest for this thesis are those involved in short-term regulation of heart rate and blood pressure.

Several brain regions are involved in regulation of BP: Parasympathetic preganglionic neurons originating in the nuclei in the brain stem, the nucleus of the tractus solitarius, the reticular formation (including the rostral ventral lateral medulla (RVLM), the raphe nuclei and locus coerules (LC)), and
hypothalamus (36). Epinephrine synthesizing neurons in the C1 region of RVLM are reciprocally projected to hypothalamus and might be regarded a "tonic" vasomotor centre that controls blood pressure via the baroreceptor reflex (37). The same neurons also stimulate noradrenergic neurons in the locus coeruleus and have been termed the body's "emergency medical technicians" due to their role in maintaining homeostasis (38).

The nucleus of the tractus solitarius in the brain stem receives input from visceral afferent fibres through different cranial nerves. Most important for regulation of blood pressure is input from arterial and cardiopulmonary baroreceptors (39). These receptors are mechanical stretch receptors, the arterial ones are located in the aortic arch and the carotid sinuses and the cardiopulmonary ones are located in the atria, ventricles and pulmonary vessels. The nucleus of the solitary tract also receives other visceral sensory information and might be involved in reflexes related to situational syncope, such as the cough reflex and other respiratory reflexes, chemoreceptor reflexes, the gag reflex and gastrointestinal reflexes controlling motility and secretion (35).

The effector part of the ANS comprises two branches: The sympathetic branch and the parasympathetic branch (35). The preganglionic neurons of the parasympathetic system originate in the brain stem and sacral spinal cord, and as many of them follow the vagal nerve, parasympathetic and "vagal" are often, imprecisely, used synonymously. The sympathetic neurons originate in the thoracolumbar part of the spinal cord (35). Both branches consist of chains of two neurons that synapse in an autonomic ganglion. The main neurotransmitter of these autonomic ganglia is acetylcholine, acting on nicotinic receptor proteins in the cell membrane of the postganglionic neuron. The postganglionic neuron is different in the two branches: Acetylcholine is the transmitter in the postganglionic parasympathetic neuron, while norepinephrine is the transmitter in the postganglionic sympathetic neuron.

Efferent sympathetic nervous activity releases norepinephrine from the nerve endings of the postganglionic neuron and epinephrine from the cells of the adrenal medulla. Both norepinephrine and epinephrine act on membrane-bound adrenergic receptor proteins for which there are two main groups (α- and β) and several subgroups. Efferent parasympathetic nervous activity releases acetylcholine from the postganglionic parasympathetic neuron, which in turn acts on muscarinic receptors on the target cells. Five different types are known, m1-m5, for which m1 and m2 are the most widespread (35). Due to
slower release, slow second messenger systems in the cells and slow removal/re-uptake of norepinephrine in nerve endings, the effects of sympathetic neural activity evokes and decays slower than parasympathetic neural activity (39). Also, postganglionic fibres are often unmyelinated and thus slower conducting. Hence, the different response time in the two parts of the ANS might partly be explained from the fact that postganglionic sympathetic neurons generally have long axons, while the postganglionic parasympathetic neurons are located close to or in the wall of the target organ (35).

As a general, although simplified rule, we consider the parasympathetic nervous system responsible for conservative, vegetative, "housekeeping" processes whereas the sympathetic system provides "emergency responses", when internal homeostasis is threatened.

**Arterial baroreceptor reflex**

- **Effects on blood vessels, heart rate and contractility**

Efferent sympathetic nervous activity causes vasoconstriction mainly in arterioles, but also small arteries and capacitance veins. A decrease in blood pressure diminishes the tonic firing from the arterial baroreceptors (most importantly, the carotid receptors); this, in turn, decreases the inhibition of efferent sympathetic activity to blood vessels, leading to vasoconstriction (39, 40). In situations of severe, sudden hypotension, this mechanism maintains blood supply to the heart and brain, while reducing blood flow to skeletal muscle, skin and renal and splanchnic vascular beds.

Changes in blood pressure elicit inverse changes in heart rate, mediated via the arterial baroreceptors. As mentioned, parasympathetic efferents are rapid, producing an immediate heart rate response, whereas the response mediated through sympathetic activity is somewhat delayed. The parasympathetic branch is dominating at rest, and heart rate is about 60-70 beats/min, while heart rate averages about 100 beats/min when both branches of the ANS are blocked (39). Parasympathetic as well as sympathetic activity influence on cardiac contractility and atrioventricular (AV) nodal conduction. High parasympathetic activity may cause AV-conduction block.

**Cardiopulmonary baroreceptor reflex**

- **Effects on blood vessels, heart rate and blood volume**

The cardiopulmonary baroreceptors, often called low-pressure baroreceptors or volume receptors, are sensitive for changes in intra cardiac pressure. A sudden decrease in venous return, which for instance might be due to
haemorrhage or dehydration, lowers intracardial pressures and elicits a reflex-mediated decrease in cardiovascular parasympathetic nervous activity and an increase in cardiovascular sympathetic nervous activity. The result is a decrease in muscular, skin, renal and splanchnic blood flow. In addition, renal sympathetic outflow activates the renin-angiotensin-aldosterone system. Finally, there is a neurally mediated increase in vasopressin (antidiuretic hormone) secretion from the pituitary gland, and also increased secretion of cardiac natriuretic peptides (39, 41).

The cardiopulmonary baroreceptors are also involved in other reflex mechanisms that are less well understood. The 'Bainbridge-reflex' connotes a phenomenon where a slight increase in venous return increases heart rate due to withdrawal of vagal activity and enhancement of sympathetic activity to the sinoatrial (SA) node (42-44). Analogously, a moderate reduction in cardiac filling might reduce heart rate. The Bezold-Jarisch reflex, on the other hand, is characterised by bradycardia, hypotension and eventually vasodepressor syncope in cases of severe underfilling of the heart. The precipitating stimulus is assumed to be vigorous myocardial contraction in a nearly empty ventricle (43).

2.2.2 Normal hemodynamic regulation
The possibility to stand upright over time requires a complex cooperation of the different parts of the cardiovascular system; this coordination is mainly brought about by the autonomic nervous system.

Moving from supine to upright position causes an immediate caudal dislocation of about 10 % of the blood volume (45), which is 90 % complete in 2-3 minutes. Most of this blood comes from the thorax and are of both arterial and venous origin. After the first five minutes, there is a transcapillary diffusion of plasma into the interstitial tissues, which decreases spontaneously after about 30 minutes due to pressure equilibrium (45).

As a result, ventricular filling is reduced and transmural pressure in aorta and carotid arteries decreases. Cardiac acceleration begins in 1-2 seconds, initially mediated solely by withdrawal of vagal activity. Due to instantaneous decomposition of acetylcholine, only the parasympathetic nervous system is capable of very rapid changes of heart rate (35).

The sympathetic response is slower, but after five seconds sympathetic stimulation also plays a role. Heart rate increase starts immediately and
reaches a maximum within 15 beats. Vascular resistance due to vasoconstriction increases to a maximum within the first 2-3 minutes.

Also the vestibular system is involved in the very early phases of orthostasis, as inputs from otolith organs contribute to the control of blood pressure by increasing sympathetic activity and thereby contributing to cardiac acceleration and adjustments of blood distribution (46, 47). These effects potentially occur before detectable changes in blood pressure, persist for only a few seconds, and act in synergy with other reflexes that maintain stable blood pressure during movement and the earliest changes in posture.

The skeletal muscle pump plays an important role in maintaining BP. Walking, but also standing, generate reflex contractions and relaxations in calf muscle that prepulse blood centrally (45).

The constant activity of the two branches of ANS results in small variations in the time interval between consecutive heartbeats (the R-R interval, RRI). This variation provides information about the cardiac autonomic nervous activity. Heart rate variability (HRV) analyses might be undertaken in the time-domain or frequency-domain; both are discussed further in chapter 4.2.2.2. There is also a third approach, which is increasingly used: Deterministic or non-linear analysis. This approach is based on chaos theory and nonlinear system theory, and assumes that the mechanisms involved in cardiovascular regulation interact with each other in a non-linear way (48).

Cardiac output (CO) is the product of heart rate (HR) and stroke volume (SV), and a change in one of these variables will influence the other two. Lower HR allows better filling and filling influence on contractility through the Frank Starling mechanism (39).

### 2.2.3 Measurements of cardiovascular autonomic function

Simple direct testing of the autonomic nervous system is difficult due to its distribution and localisation. Thus, testing often entails measurements of end-organ response to physiological or pharmacological provocations. Several techniques are used (49). Clinical non-invasive tests include: The Ewing battery, which is a collection of 5 tests designed for early detection of subtle autonomic dysfunction (50), active standing, isometric exercise, cold pressor test, and head-up tilt-test (49). In research, other tests and methods are also used, invasive as well as non-invasive (49): Heart rate variability analyses and different tests of baroreceptor sensitivity, microneurography (invasive
recording of electrical bursts in muscle, vessels or skin) and neurochemical methods like pharmacological testing and catecholamine measures. The methods and measurements of the tests used in this thesis - heart rate variability, blood pressure variability and baroreceptor sensitivity - are described and explained in chapter 4.2.2.2.

2.2.4 Changes due to ageing

In geriatric research, normality is often difficult to define because the young male is so often considered "the typical human being". An additional problem is to separate changes due to ageing from the growing burden of coexisting pathological conditions.

Both immediate and delayed HR augment to postural change is lower in elderly people, whereas the total peripheral resistance (TPR) response is larger (genders seen together) (45, 51). An age related attenuation of cardio vagal baroreflex sensitivity, i.e. the ability to respond with heart acceleration to a reduction in blood pressure, is observed (52). Age related changes in the sympathetic outflow to skeletal muscle are, however, less pronounced (53). Thus, elderly people in general rely more on their TPR to maintain blood pressure during orthostasis, as compared to younger persons.

Studinger et al. showed that sympathetic activity in response to a drop in blood pressure is decreased, possibly due to stiffening of carotid arteries (54). This is in line with the findings of decreased baroreceptor reflex sensitivity (BRS) in hypertension (55). The findings suggest a link between orthostatic hypotension and vascular stiffness (54, 56).

There is some loss of thin myelinated nerve fibres in the ageing brain, probably contributory to attenuated cooperation between different parts of the cortex (35). However, more important and challenging are the age related attenuation of peripheral sense organs. Proprioception and skin sensibility, which are dependent on conduction in thick myelinated nerve fibres are especially vulnerable to age related demyelination, and might contribute to instability and falls (35).

Also the vestibulo-sympathetic responses mentioned above (2.2.2) are attenuated with age, and contributes to the increased susceptibility of orthostatic hypotension in old age (57).
An adequate orthostatic response also depends on circulating blood volume. Thirst is a result of both hypovolemia and increased osmolality (58). Elderly persons are especially vulnerable in hot environments and during diseases with enhanced fluid loss. First, they have a higher osmotic set point for thirst sensation. Second, fluid consumption in response to increased osmolality is lower, although reported thirst sensation is about the same (59). Third, older people appear to be less sensitive to volume changes when it comes to thirst sensation, than younger people, resulting in reduced fluid intake (58).

Heart rate variability (HRV) decreases with age (60-62); both HF-variability (high-frequency-variability, reflecting parasympathetic modulation) and LF-variability (low-frequency-variability, reflecting both sympathetic and parasympathetic modulation). See 4.2.2.2 for further details. The greatest decline takes place up to an age of 70-75 years, and thereafter levels off. Decrease in parasympathetic activity following standing up is one of the major regulatory mechanisms in maintaining orthostatic balance in the young and healthy (63). The age-related decrease in HRV and especially HF-variability (an expression of parasympathetic modulation) suggests that this regulatory mechanism may be limited in elderly people (51).

Some studies have shown a U-shaped curve in HRV, with higher values in centenarians (64, 65) and have related it to longevity. However this is controversial, others claim that the most likely explanation is that random variation in HR (i.e. a sinus arrhythmia that is not of respiratory origin) increases with age and masks the age-related decline (61, 66).

HRV is associated with cardiovascular risk. Decreased HRV is a predictor of death and non-fatal events both after a myocardial infarction (67) and in persons without symptoms (68). Erratic beats and non-sinus arrhythmia may, however, mask the predictive value of decreased HRV (66).

2.2.5 Men versus women
Young women are considered less tolerant of orthostatic stress than men (69-71), but the mechanisms are poorly understood. Women are shown to have a greater decline in cardiac output with the same level of lower body negative pressure, and although HR and total peripheral resistance (TPR) was the same at baseline and presyncope, women reach presyncope at a smaller lower-body-negative pressure or after shorter head-up-tilt (HUT) time. Among the proposed mechanisms are attenuated responsiveness in heart rate (HR) in response to carotid baroreceptor stimulation or maximal responsiveness being
reached at an earlier point (69). Other mechanisms have also been suggested: Parasympathetic predominance and lower venous compliance in women (the latter with the explanation that lower compliance results in less activation of compensatory mechanisms that could protect against orthostatic hypotension)(72), greater pelvic pooling of blood, and blunted splanchnic vasoconstriction. All these factors might reduce cardiac filling. Others point at smaller and stiffer hearts or hormonal factors in women as important mechanisms for the observed gender differences (69-73).

When considering elderly people, evidence for gender differences in orthostatic tolerance and their potential mechanisms are utterly scarce. As elsewhere in the geriatric field, there are problems separating changes due to disease and medication from ageing of the cardiovascular system.

Recently a study of orthostatic intolerance in elderly (mean age 73) did not show any difference in symptoms between genders, but men tended to have larger drops in blood pressure, and women had greater total peripheral resistance (74).

Some differences in resting HRV variables have been described. Women over the age of 65 years seem to have lower LF-variability and LF/HF ratio (often thought of as an expression of sympathovagal balance) than men at the same age, and also to have higher HF-variability (63, 75). The ageing pattern is also different, with men having a clear decline in total power and a more marked fall in LF/HF ratio (75). Gender does not seem to greatly influence autonomic response to head-up tilt (51). Baroreceptor sensitivity decreases with age, but so do also the differences between men and women (52).

2.2.6 Elderly athletes
Physical activity is beneficial and is associated with lower mortality (76, 77), extended life expectancy (78) and a net gain of disability-free years (79). Elderly athletes, e.g. the cross-country skiers ("Birkebeineren") have better self reported health than others of the same age (80). Resting heart rate is a marker of cardiovascular risk (81) and lower heart rate variability is associated with all known cardiovascular risk factors (75). Higher HRV is associated with aerobic fitness level and regular physical activity in the elderly (82, 83), which is in line with findings in younger age groups (60). Randomized control studies of training effects are diverging, showing both increased HRV (84) and unchanged HRV and BPV (85).
Orthostatic tolerance in athletes has been discussed for years. Most of the research has been done on young men and astronauts. Greenleaf stated in 1981 that “Fit men can run, but they cannot stand” (86) and some later studies support this (87-89). Hemodynamic changes, heart rate variability and orthostatic tolerance in elderly athletes have scarcely been studied. A few short intervention studies that increased cardiorespiratory fitness did not seem to change orthostatic tolerance negatively (90-93).

2.2.7 Patients with cognitive impairment and dementia

Dementia mainly affects older people and the prevalence increases with age (94). Dementia is characterized by an acquired cognitive decline, failure of emotional control, and inability to cope with activities of daily living (94). Projections suggest that the number of patients with dementia in Norway will double over the next 40 years, due to ageing of the population (95).

Alzheimer’s dementia (AD) accounts for about 60 % of cases of degenerative diseases leading to dementia (94). Life expectancy is decreased (96) and caregiver burden is high (97) in dementia. Comorbidities like depression (98), cardiovascular disease (99), autonomic dysfunction (100-102), orthostatic hypotension (100, 102, 103), and falls (104) are more common in Alzheimer’s disease and mild cognitive impairment (MCI), as well as in other forms of dementia (105).

Orthostatic hypotension is often worsened by medication or caused by hypovolemia. However, its physiological basis might be related to autonomic dysfunction, the mechanisms are still unclear. Both attenuated reflexes and/or decreased vascular responsiveness are involved. Arterial stiffness and decreased baroreceptor sensitivity are also associated (106).

There are some studies of HRV in dementia, most of them show decreased HRV in AD, mainly parasympathetic dysfunction (107, 108), or both parasympathetic and sympathetic dysfunction (102).

2.3 Multifactorial assessment and prevention of falls

2.3.1 Multifactorial assessment

The multifactorial etiology of falls constitutes the basis for the updated guidelines (2011) for prevention of falls from the American and British geriatrics societies (109). A multifactorial falls risk assessment is recommended for individuals who have had two or more falls or report difficulties with gait and balance. A single fall in an otherwise steady person is considered bad luck
or coincidence. According to the guidelines, a clinician with appropriate skills and experience should assess actual patients.

In order to comply with guidelines, and as a result of growing evidence for their significance, falls clinics have been established in many hospitals worldwide during the last years (31, 109, 110). Please see Figure 2.1 and paper I for a summary and review of a multifactorial assessment (111). Despite increased attention on falls and specialised falls clinics in many places (112, 113), many patients are still discharged and only scheduled for follow-up of their fall-related injury (114).

![Algorithm for assessment of fall risk in the elderly](image)

Figure 2.1 Algorithm for assessment of fall risk in the elderly (modified from the guidelines of the American Geriatrics Society and the British Geriatrics Society (109)). © Tidsskrift for Den norske legeforening. Reprinted from paper II, by permission.
2.3.2 Intervention in general...

The multifactorial assessment must be followed by direct intervention on all the identified risk factors (109). The following measures are effective in reducing risk of falls: strength- and balance training, vitamin D-supplementation, home intervention, medication reduction (psychoactive drugs in particular), managing orthostatic hypotension and cardiac pacing in case of carotid hypersensitivity syndrome or arrhythmia, and cataract surgery (28, 31, 109, 110).

2.3.3 ...and training in particular

Strong evidence has shown that strength- and balance training is the most successful measure for the prevention of falls among home-dwelling elderly (28, 110, 112, 113, 115), and recently a large review indicated reduction also in injurious falls and falls requiring medical care (116). A minimum of 50 hours of balance training is required to reduce risk of falls and should be progressive, focusing on moderate to high-intensity balance training (117). Despite this knowledge, many elderly fallers do not receive any training facilities or the training is neither adapted or sufficient (118). In 2014 the Norwegian Directorate of Health published new recommendations on diet, nutrition and physical activity (119). They emphasised prevention of falls and recommended strength- and balance training several times a week for elderly people with gait disturbances.

Attitude and motivation for participating in strength- and balance training does not differ between different European countries (4). Perceived benefits (joy, independence and improved health) and encouragement from health care personnel, friends or family are important motivators. Focusing on elements of coping more than the threats increases adherence (120), as do practical measures like offering transport or home-based programs if desirable (4).

2.3.4 Multicomponent intervention to specific groups of elderly

As our main interest has been home dwelling elderly and their falls and hemodynamic regulation, focus has been on multifactorial assessment and individual intervention in this group. Less is known about benefits from intervention and prevention in institutionalised and/or elderly with dementia (109). Traditionally, variants of multicomponent intervention have been used in hospitals and long-term care institutions. Such models imply a set of interventions to all the patients and can include staff education, training, evaluation of medication, use or removal of restraints, hip protectors etc. Results on risk of falls are diverging and even effects of training are
inconclusive (121). Some effect of vitamin D-supplementation and multifactorial intervention in hospitals has been reported (121).

2.4 Orthostatic intolerance and syncope - their significance for falls

2.4.1 Orthostatic hypotension in the elderly

Orthostatic hypotension (OH) is defined by consensus as a drop in systolic blood pressure of at least 20 mmHg and/or diastolic pressure of at least 10 mmHg within the first three minutes of standing or head-up tilt (122). The prevalence of orthostatic hypotension among home dwelling elderly is reported between 5 and 30 %, and increases with age (123-125). OH is associated with falls, syncope, frailty, polypharmacy, neurodegenerative disorders, and hospitalisations (123, 126-131). OH may be asymptomatic or cause symptoms of orthostatic intolerance, i.e. presyncopal symptoms such as dizziness, light-headedness, weakness, nausea, visual disturbances, and may lead to syncope (132, 133). OH is an attributable cause of syncope in up to 30 % of older patients (34).

Altered blood pressure regulatory mechanisms, vascular stiffness and reduced ventricular compliance are among the age related changes that might contribute to the high prevalence of orthostatic hypotension (106, 134).

Non-invasive continuous blood pressure measurement has made it possible to measure drop in blood pressure earlier, within the first seconds of standing. The technology also enables immediate registration of blood pressure recovery. Some researchers claim that the initial drop in systolic blood pressure and the recovery taking place during the first 30 seconds are more important determinants of orthostatic intolerance than the total drop in blood pressure (135). They argue for measurements of initial orthostatic hypotension (IOH), defined as a drop in systolic or diastolic blood pressure within 15 seconds of standing of more than 40 mmHg or 20 mmHg, respectively (136). A recent study showed an association between mortality and the magnitude of blood pressure recovery 40-60 seconds after standing up, even after adjustment for age, comorbidity, and other baseline characteristics (137).

Among healthy elderly there are diurnal variations in orthostatic blood pressure and poor intra individual consistency (138, 139). Orthostatic hypotension is more common in the morning and afternoon than during the evening. Measurements have to be repeated if a diagnosis of OH is likely (139).
Rarely mentioned, but of importance, is that transient hypotension or only moderate hemodynamic changes, insufficient to cause syncope, may result in falls in frail individuals with gait- and balance problems (33, 126, 140).

Since orthostatic hypotension is associated with many adverse events and can be remedied and prevented in many cases (141), screening is important in groups with high prevalence of this condition (142, 143).

2.4.2 Syncope in the elderly

Syncope is a transient loss of consciousness (T-LOC) due to transient global cerebral hypoperfusion, characterized by a rapid onset, short duration and with spontaneous complete recovery (33). This is a precise definition and enables a structured and targeted assessment as mentioned in the guidelines from European Society of Cardiology (33). Such a statement, however, assumes that you know that the patient really had syncope, which is not always the case in the elderly (144). As discussed above, one quarter of syncopes in the elderly present as an unexplained fall (34). An Italian study found that 30-40% of falls in patients admitted to an orthopaedic ward remained unexplained after excluding medical falls, accidents and falls related to dementia (145).

Syncope is often divided into three main groups due to the most involved mechanism: cardiac, orthostatic and reflex mediated syncope (33).

![Figure 2.2 Schematic showing classification of syncope subtypes, with basic details of mechanisms and causes, according to the ESC guidelines (33).](image)

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Syncope is reported about equally common among adult men and women, with a mean incidence rate of six per 1000 person years, the incidence increasing with age with a peak in those aged above 70 (146). Above 80 years of age the incidence is 17-19 per 1000 person years. However, Kenny et al. recently reported that lifetime cumulative incidence of syncope in women is almost twice that of men (147), a peak in teenage-girls may explain some of this difference. Only cardiac syncope is associated with increased mortality.
Reflex syncope dominates in all ages, but orthostatic and cardiac syncope represent larger proportions after 75 years (11, 149, 150). Additionally, which variant of reflex syncope that dominates vary, with a shift from classical vasovagal syncope to carotid sinus syncope and situational syncope among the elderly (151).

When a reflex mediated syncope happens in specific and identifiable situations like coughing, micturition, post-exercise, or a postprandial state, it is often referred to as a situational syncope. Also carotid sinus syncope (CSS) is reflex mediated, with an exaggerated bradycardia and/or hypotension in response to a pressure on the area of the carotid sinus at the bifurcation of the common carotid artery (152). When used diagnostically, this pressure is applied along the artery for 5-10 seconds, and is known as carotid sinus massage (CSM).

Carotid sinus syncope is rare before 40 years of age but might be an attributable cause in about 20 % of syncopes in the elderly (11). Paper II (153) illustrates the diagnostic procedure in an old lady with unexplained falls and symptoms suspect of syncope. During CSM, she experienced a ventricular pause and reproduction of symptoms and had a pacemaker implanted after one week. According to the guidelines from the European Society of Cardiology; pacemaker implantation is indicated in patients with dominant cardioinhibitory carotid sinus syndrome and recurrent unpredictable syncope (154).
3. Aims

Syncope, orthostatic hypotension and autonomic dysfunction are possible mechanisms and explanations for falls, but are often under diagnosed or overseen.

- We aimed to explore the multifactorial causes of falls, to register and to analyse the results from our falls clinic: "Fallpoliklinikken". (*Paper I and II*)

- We aimed to study gender differences in orthostatic tolerance and hemodynamic regulation in healthy elderly without medication and diseases. (*Paper III*)

- We wanted to study whether endurance training is associated with differences in orthostatic tolerance and hemodynamic regulation by comparing elderly male athletes with healthy men. (*Paper IV*)

- We wanted to explore differences in hemodynamic regulation in persons with mild cognitive impairment (MCI) and early stages of Alzheimer's dementia by comparing them with healthy controls. (*Paper V*)
4. Material and methods

<table>
<thead>
<tr>
<th>Paper</th>
<th>Population</th>
<th>Setting</th>
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<td>Multifactorial fall risk assessment, summarised in</td>
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<td></td>
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<td>to &quot;Fallpoliklinikken&quot;</td>
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<td>II</td>
<td>Single patient study</td>
<td>Clinical</td>
<td>Multifactorial fall risk assessment, included HUT and</td>
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<td>Age &gt;80 years</td>
<td>Case report</td>
<td>carotid sinus massage</td>
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<tr>
<td>III</td>
<td>48 healthy elderly</td>
<td>Experimental</td>
<td>Passive HUT, 40 minutes.</td>
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<tr>
<td></td>
<td>(24 women)</td>
<td></td>
<td>Hemodynamics, HRV, BPV, BRS and syncope-analyses</td>
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<tr>
<td></td>
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<td></td>
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<tr>
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<td>54 healthy men,</td>
<td>Experimental</td>
<td>Passive HUT, 40 minutes.</td>
</tr>
<tr>
<td></td>
<td>(30 endurance athletes and the 24 men from paper III)</td>
<td></td>
<td>Hemodynamics, HRV, BPV, BRS and syncope-analyses</td>
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<tr>
<td></td>
<td>Mean age 71 years</td>
<td></td>
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<tr>
<td>V</td>
<td>14 patients with AD/MCI (7 women) and the 48 individuals from paper III</td>
<td>Experimental</td>
<td>Passive HUT, 40 minutes, only 15 minutes for patients.</td>
</tr>
<tr>
<td></td>
<td>Mean age 74 and 72 respectively (p&gt;0.05)</td>
<td></td>
<td>Hemodynamics, HRV, BPV and BRS analyses</td>
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</table>

Table 4.1 briefly summarises the material and methods in the papers included in this thesis
Author’s figure, unpublished.

4.1 Material

4.1.1 Paper I (and II)

The establishment of an outpatient clinic for assessment of falls (hereafter "Fallpoliklinikken") in 2008 inspired and enabled us to create a patient register, approved by the Data Protection Officer at Oslo University Hospital. Every referred patient was considered suitable for inclusion and almost everyone (98%) accepted and gave a written consent. Patients with falls and/or problems with balance and walking were referred from general practitioners, emergency services and hospitals (mainly internal medicine, geriatric or orthopaedic wards).

Data registration was done as part of the ordinary clinical consultation, kept anonymous and separate from the patient journals. In close cooperation, Solveig Granum (physiotherapist) and the author (MD) founded
"Fallpoliklinikken" and have assessed almost every patient. In 2011, we had 111 patients in the register, and decided to analyse and present the material. The study is descriptive, without follow-up. Paper I is the result of a student mandatory assignment, with Mellingsæter as the guarantor and supervisor. Paper II is a case report about one of the patients included in the register, with an interesting medical story that illustrates the challenging overlap between falls and syncope.

4.1.2 Paper III - V
Healthy elderly men and women were recruited from senior centres, senior walking groups, and golf clubs, among participants in courses focusing on healthy ageing, and through acquaintances. None of them were daily smokers. Individuals having chronic diseases, especially cardiovascular disease, or were using any drugs regularly, were excluded.

Athletes were recruited from participants in the 54 kilometre long Birkebeiner cross-country ski race. For practical reasons, only participants living in or near Oslo were invited, by including a separate letter in the envelope of an on going study about training, atrial fibrillation and general health; “The Birkebeiner ageing study”(80). All participants were 65 years or older and had participated in the race at the year of inclusion in our study. Due to the low percentage of older female participants in the Birkebeiner cross-country ski race, we included only men in this study.

Athletes and healthy elderly respondents were asked about factors that could exclude them; daily smoking, medication, chronic diseases, and especially atrial fibrillation, which makes variability analyses impossible. Healthy users of solely acetylsalicylic acid, vitamins and cod-liver oil were accepted for inclusion.

Persons with mild cognitive impairment (MCI) and mild Alzheimer's dementia (AD) Patients with an established diagnosis of MCI or Alzheimer's dementia of mild severity were recruited from the Memory Clinic at Oslo University Hospital. They were already included in a register and had accepted to be contacted in case of new research projects.

Dementia is a chronic, often progressive syndrome, typically affecting higher cortical functions with significant influence of daily living. Diagnoses of dementia are in Norway based on the ICD-10 criteria, and require evidence of decline in memory and at least one additional cognitive task such as judgement, planning, thinking, organizing or abstraction. Alzheimer's disease is
the most frequent cause of dementia. A diagnosis of MCI indicates cognitive decline, but the symptoms does not influence on activities of daily living (94).

The participants were all considered competent to give consent. They had a score on the Mini-Mental State Examination (MMSE) (155, 156) above 20 and in addition they were scored according to the Clinical Dementia Rating (CDR) scale (157) by one of the specialists at the Memory Clinic. Median CDR was 1 (range 0.5-2). They were 65 years or older, without a history of cardiovascular disease and should not use any cardiovascular drugs.

The table below shows the four groups we included and combined for analyses in this thesis. The first column shows the different analyses, and the actual numbers of persons included in the different analyses are in the corresponding rows in the other columns.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Athletes, men (n=34)</th>
<th>Healthy men (n=25)</th>
<th>Healthy women (n=24)</th>
<th>MCI/ mild AD (n=15)</th>
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<td>Syncope analysis</td>
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<td>24</td>
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Table 4.2 Study populations for Papers III-V

We tested 34 healthy athletes and had to exclude 4 of them, one because of wrong test equipment, and three after inspection of the figures due to more than 10% ectopic beats. One of the male controls was excluded due to more than 10% ectopic beats. One of the patients with dementia was excluded after assessment, because it turned out that she still used antihypertensive medication. For the variability analyses we excluded persons if they happened to be extreme outliers in descriptive analyses, and ended up with slightly different numbers for the analyses (see the particular papers for details).

4.2 Methods

4.2.1 Paper I and II

4.2.1.1 Design
We conducted a descriptive observational study. The assessment performed by
"Fallpoliklinikken" is summarised in Table 4.3, and involves a doctor, a physiotherapist and a nurse. The medical component consists of a standard internal medicine assessment, plus examination of vision, cognitive function, peripheral nerves, proprioception, reflexes and cortical, extrapyramidal, and cerebellar function. Cognitive function was tested with the Mini-Mental State Examination (MMSE)(156) and the clock-drawing test (158), where the intention was to map deficits rather than diagnose dementia. Scores on the clock-drawing test can range from 0 – 5 points, with three points or less considered a fail (158).

The physiotherapist evaluated walking ability, strength, and various aspects of balance linked to the risk of falling. Timed Up and Go is a test of basic mobility (159), the Berg Balance Scale is used to identify elderly individuals at risk of falling (160), and the Dynamic Gait Index examines the ability of patients with balance problems to correct their gait upon encountering various obstacles (161). A functional strength test is used as an indirect measure of muscle strength and measures the time taken to get up from a chair without armrests and sit down again five times (162).

Examinations and findings were summarised at a brief meeting in which all three professions participated. The purpose of the meeting was to highlight all factors that could contribute to falls in a given patient and to agree on specific preventive measures and, if appropriate, further treatment and/or additional diagnostic workup. In the end of the consultation, our conclusions and thoughts were conveyed to the patient (and relatives), and they received a handwritten summary from this meeting before they left.
Table 4.3 Summary of the structure and assessments in "Fallpoliklinikken". © Tidsskrift for Den norske legeforening. Reprinted from paper I, by permission.

4.2.1.2 Data analyses
Data from the patient registrations were manually transferred to Microsoft Excel® for calculations and then exported to SPSS (SPSS Inc., Chicago, Illinois) for descriptive statistical analyses.

4.2.2 Paper III - V

4.2.2.1 Design/experimental protocol
The experiments were performed between 9.30 a.m. and noon. The athletes' and the healthy controls' health status was verified by a medical doctor (the principal investigator), and supplied with blood tests (haemoglobin, creatinine, pro-brain natriuretic peptide, thyroid stimulating hormone, non-fasting glucose, and alanine aminotransferase) to confirm absence of biochemically detectable illness in the main organs. Participants were asked not to drink beverages containing alcohol or caffeine from 8 pm on the day before the
assessment. The day of assessment they were told to eat a light breakfast, drinking at least one and maximum two glasses of milk, water or juice.

**Head-up tilt-test**

We used head-up tilt-test as an orthostatic challenge in healthy persons without known syncope. When used in assessments of syncope, a conventional head-up tilt-test with tilt angle 60 - 80° for 30 - 40 minutes is used (33, 163), often supplied with glyceryl trinitrat (GTN) after 20 minutes to shorten the time to tilt positivity, the so-called "Italian protocol" (164). The use of head-up tilt-test in assessment of syncope has declined during the last years, focusing more on educational purposes like identification of prodromal symptoms and giving instructions in manoeuvres to prevent syncope (33). Our protocol did not imply use of intravenous cannula or GTN, only passive standing, in order to imitate the challenge of ordinary standing and to reduce the risk of syncope (163, 165).

The assessments were performed in a quiet room maintained at a comfortable temperature. A 5-minute baseline recording was obtained before the subjects were head-up tilted to 30° for 10 minutes. Due to the relatively high proportion of participants with low orthostatic tolerance during ordinary tilt, we also used a low-grade challenge with 30° tilt angle, which is often used in experimental settings (44, 166). The test persons were tilted back to a horizontal position for 10 minutes before they were head-up tilted again, to 70° over approximately 18 seconds, and remained in that position for 40 minutes or until syncope or unbearable orthostatic intolerance (33) occurred. The chosen tilt angle of 70° and time in head-up tilt-position is in line with the Newcastle protocols 2008 (164). Subjects were asked not to speak except for comments about symptoms or to mention discomfort.

**Syncope/presyncope**

The participants included in *Paper III and IV*, were all subjected to an ordinary HUT. False positives are relatively common during HUT; even in the absence of provocative pharmacological agents, up to 20 % false positives are reported (163). Thus, time until syncope or presyncopal symptoms leading to termination before end of test (40 minutes) was registered.

Full loss of consciousness occurred only in some of the participants. Those observed to be pale and sweating and who reported nausea, malaise/discomfort and visual disturbances were perceived to be presyncopal. According to results from the Italian Group for the Study of Syncope in the Elderly, these symptoms are among the most prevalent in the presyncopal phase, also in this age group (167). We used classification of the presyncopal
phase in vasovagal syncope according to Brignole (168). All except one had a vasovagal presyncopal pattern, either dysautonomic (13 persons) or cardio-inhibitory (one person). One person had a constantly falling blood pressure and terminated the HUT because of discomfort after 6 minutes. We interpreted this as orthostatic hypotension, and the person was thus excluded from further analysis of syncope.

Registrations
Mean arterial blood pressure (MAP) depends on total peripheral resistance (TPR) and cardiac output (CO). Thus, information about how the body responds to orthostatic stress can be achieved from measures that fill the equation:

**TPR = MAP/CO**

Where MAP is a mathematical deliberate misrepresentation of the delta value between arterial and venous pressure. But central venous pressure is often considered zero, and thus the equation fits.

CO is the product of heart rate (HR) and stroke volume (SV).

The subjects lay supine on a tilt table with footboard support. They were attached to the Task Force® Monitor (Model 3040i, CNSystems Medizintechnik, Graz, Austria), a combined hardware and software device for non-invasive recording of cardiovascular variables (169, 170).

Heart rate and R-R interval (RRI) were obtained from ECG. Impedance cardiography is a non-invasive method for estimating stroke volume (SV) and cardiac output (CO). A small electrical potential is applied between three band electrodes on the neck and upper abdomen, to obtain a continuous recording of the temporal derivate of the transthoracic impedance (dZ/dt) (171). Continuous blood pressure using the vascular unloading technique (172) was recorded from the second or middle finger of the right hand, and calibrated every second minute against oscillometric measurement of arterial blood pressure in the left arm. Although the technology does not permit measurements of absolute blood pressures in individual patients, the measurements have proven satisfactory to track changes in blood pressure and is thus of great value in diagnosis of syncope and orthostatic hypotension (172). Also, the recordings can be used for analyses of blood pressure variability (BPV). Age does not affect the correlation between invasive and non-invasive beat-to-beat pressure significantly (172).
In accordance with the definition of orthostatic hypotension (122, 173), orthostatic blood pressure in Paper V was calculated as the difference (Δ) between the nadir in continuous blood pressure and blood pressure at rest before head up tilt. Nadir systolic (SBP) and diastolic blood pressure (DBP) was defined as the lowest pressure within the first three minutes after full head up tilt to 70°.

4.2.2.2 Data analyses

Conventional cardiovascular variables
All recorded signals were transferred online to the built-in recording computer of the Task Force® Monitor, running software for real-time data acquisition. Beat-to-beat stroke volume (SV) and end diastolic volume index (EDI) were calculated from the impedance signal (169). Cardiac output (CO) was calculated as SV x heart rate (HR). Total peripheral resistance (TPR) was calculated as mean arterial pressure (MAP) divided by CO. The variables based on volume measurements i.e. CO, SV and TPR were normalized according to body surface area (BSA), using the formula of Gehan and George (174), and termed CI, SI and TPRI, respectively.

Heart rate variability and blood pressure variability
As mentioned in chapter 2.2.2, spontaneous variability of cardiovascular variables is a result of interplay between the different branches of the autonomous nervous system. Heart rate variability (HRV) and blood pressure variability (BPV) are quantitative measures of such variability (175). The oscillations in the interval between consecutive heartbeats, the RR-interval, are called heart rate variability. There are two main methods of evaluation of HRV, namely time domain methods and frequency domain methods. For the time domain analyses, statistical methods are used to express the variability in recordings of a certain length (175-177).

Frequency domain analyses apply more sophisticated mathematical methods. By spectral analysis, signals are decomposed into a sum of sine waves of different amplitudes and frequencies (177, 178). The squared amplitudes (power, a measure of variance) of the sine waves are presented as a function of frequency in the power spectrum. The most common methods are classified as either non-parametric (e.g. Fast Fourier Transform) or parametric (e.g. Autoregressive modelling) (175, 179, 180). Spectral analyses of short-term recordings of 2 to 5 minutes result in three distinct peaks or bands in the power spectrum (175): very low frequency (VLF, <0.04 Hz), low frequency (LF, 0.04-0.15 Hz) and high frequency (HF, 0.15-0.4 Hz). However, peaks are often broad and may not always be confined to one of these bands.
The power in the HF-band is considered an index of parasympathetic modulation of the heart rhythm, and is closely related to respiratory sinus arrhythmia (179). Only the parasympathetic system has a potential for these most rapid changes. The power density in the LF-band is due to the combined effect of parasympathetic and sympathetic activity, and the HR oscillations are most likely a baroreflex response to sympathetically mediated oscillations of blood pressure (Mayer waves) (181). A blockade of both parasympathetic and sympathetic nervous system by use of a muscarinic blocking agent and beta blockade respectively, results in a metronome-like heartbeat without variability in short-time recordings (178, 182). The LF/HF-ratio is often considered an expression of sympathovagal balance (183). The physiological basis of VLF is still uncertain, but appears to be related to the renin-angiotensin system, thermo-regulation, and peripheral vasomotor tone (177).

Blood pressure variability (BPV) has not the same direct coupling to the autonomous nervous system; variability in the HF-band is mainly due to mechanical effects of respiration, and variability in the LF-band is predominantly caused by sympathetically mediated fluctuations in vasomotor tone and vascular resistance (179).

The Task Force® Monitor uses an autoregressive algorithm to compute spectral power densities from consecutive segments of the biosignals (175, 184). This technique enables dynamic variability analyses when changes occur as a result of an intervention (185). The default output is spectral power densities of RRI and blood pressures in the low-frequency (LF) band and the high-frequency (HF) band, both in absolute (LFabs/HFabs) and normalized units (LFnu/HFnu). The normalized units represent the relative value in proportion to the total power minus VLF power (175), thus minimizing the effects of changes in total power.

**Baroreceptor reflex sensitivity**
The functions of the baroreceptors are briefly described in 2.2.1 and 2.2.4. In short periods of time this reflex system prevents wide fluctuations of the arterial blood pressure (40). Monahan writes: "Neural regulation of blood pressure occurs via tonic and reflexive modulation of autonomic nervous system outflow (both parasympathetic and sympathetic nervous system)"(53). Baroreceptor reflex gain/sensitivity (BRS) is defined as change in RRI following a change in systolic blood pressure (ms/mmHg) (176).

Several techniques are used to measure BRS (40). Some are invasive, e.g. the
phenylephrine method where blood pressure and HR are measured continuously during infusion of the alpha-adrenoceptor agonist phenylephrine. Mechanical manipulation by use of neck chamber is another method where changes in RRI following an increase/decrease in pressure are measured.

More recently, non-invasive and simple computer-based techniques have come to use. Based on registrations of spontaneous variations in blood pressure and HR, two approaches have been proposed: the sequence method and spectral methods, the latter is based on frequency analyses (40).

We obtained an index of BRS from the Task Force® Monitor, using the 'sequence method' from Lag0 registrations, i.e. changes in heart rate lasting a minimum of three consecutive beats following a change in blood pressure (40, 176, 186). The sensitivity of the reflex is obtained by computing the slope of the regression line that relates changes in blood pressure to changes in RRI (40).

**Mathematical processing of beat-to-beat recordings**

Data was exported to Microsoft Excel® for further calculations. We selected epochs of four minutes' length from each test person in the resting state and in the tilted positions of 30° and 70°. Both the latter epochs started after an initial stabilisation period of 30 seconds from initiation of tilt. Delta tilt values were calculated (30° tilt – Rest and 70° tilt – Rest). Ectopic beats and their corresponding blood pressure values were manually removed and replaced with linear interpolation between values that were interpreted as valid. Recordings with more than 10% ectopic beats were excluded. The medians of the variables in all epochs were transported to SPSS (SPSS Inc., Chicago, Illinois) for statistical analysis.

**Statistical analyses**

Data plots were inspected to assess their empirical distribution. The conventional cardiovascular variables (HR, BP, SI, CI, TPRI) showed normal distributions, and the mean was taken as an estimate for the expectancy of the population under study. Standard deviation (SD) was calculated as expression of the variation. Group differences (women vs. men, athletes vs. controls and MCI/AD-patients vs. controls) were explored with use of parametric methods (t-test).

Plots of heart rate variability, blood pressure variability and baroreceptor sensitivity data deviated from normality, and median with quartiles were calculated. For the variability data, extreme outliers from descriptive analyses
were excluded. Group differences were explored by use of non-parametric methods (Mann-Whitney test). For all analyses a p-value < 0.05 was considered indicative of statistical significance.

COX-regression multivariable analysis was used to check for associations between syncope and potentially explanatory variables (*Paper III and IV*).

In *paper III* a Kaplan-Meier plot for survival analysis of syncopal/presyncopal events was constructed and a Log Rank test was used to explore gender differences.

### 4.3 Ethical considerations

This thesis is based on five publications, from two different studies, each with its own approval and ethical considerations. The Regional committee for ethics in medical research (REK) and The Data Protection Officer at Oslo University Hospital have approved both studies (REK numbers S-08232a and S-08065b).

For the observational study from Fallpoliklinikken (*Paper I*) every patient referred was asked to participate and all but two gave written consent to the recording of clinical information for research purposes. We emphasised their right to refuse or withdraw at any time without implications for further medical care at the hospital. No medical procedures or test were done, that would not have been done otherwise as part of the ordinary assessment at "Fallpoliklinikken". *Paper II* is a case report and the information is anonymised as far as possible. The patient has read the Norwegian version and agreed to the publication both in The Journal of the Norwegian Medical Association and in this thesis.

The other papers (*III-V*) are based on experiments and the participants were recruited solely for this purpose. All participants were thoroughly informed about the content of the experiments both orally and in written form. A written consent was obtained before inclusion, and the right to withdraw was emphasised. None of the participants received a fee.

None of the experiments were considered harmful, but the potential unpleasant dizziness and risk of syncope during head-up tilt-test were mentioned. They were asked to report symptoms of discomfort during the test, and were assured that we would terminate the test whenever they told us to. However, we considered the possibility of syncope to be toned somewhat
down, because the expectation or fear of syncope in itself could impact on the results.

A heart start first aid defibrillator was located just outside the assessment room. The participants were secured with safety belts around the chest and over the knees, to protect them from falling in case of syncope.

The athletes and healthy controls underwent the whole protocol with 40 minutes of standing with tilt angle 70°, and about 18 % terminated because of syncope or unbearable orthostatic intolerance or presyncopal symptoms. Our protocol is used in standard assessments of syncope (164), and we used foot support and not saddle support nor intravascular canalisation, which are both known to increase the likelihood of syncope (163, 165). One person had a cardio depressive vasovagal syncope during 70° HUT with a ventricular pause of 30 seconds, and his ECG was immediately presented to a cardiologist.

The patients with MCI and mild AD were assessed with a shorter protocol than the controls. They were all considered competent to give consent, but we assumed that their cognitive capacity could influence on their understanding of the project, their stamina or reporting of symptoms, and thus we did not find it proper to expose them to the entire protocol.

Both studies were conducted in accordance with the Declaration of Helsinki. The authors are all qualified according to the Vancouver guidelines and none of them possess any conflicts of interest.
5. Results

Paper I

Results We included 111 patients, average age was 82 years, and the patient group had a number of known risk factors for falls. The most frequently identified risk factors besides problems with gait and balance, included orthostatism (24 %), vitamin D deficiency (14 of 79 patients, 18 %) and carotid sinus hypersensitivity (6 of 55 patients examined, 11 %). Measures of vitamin D were included after Fallpoliklinikken had been run for some time; therefore we ended up with only 79 blood samples. Carotid sinus massage (CSM) was considered relevant only on indication (unexplained falls, suspected syncope), and was performed in about half of the cases. Rare, but significant findings included colon cancer, subdural haematoma (one case of each) and normal pressure hydrocephalus (two cases). The most frequent measures for preventing new falls included exercise/physiotherapy (nearly all patients), adjustment of medications (25 patients, 23 %) and implantation of a pacemaker (six patients, 5 %).

Interpretation Falls among elderly people have varying and complex causes and serious underlying pathology may manifest itself as a tendency to fall. This testifies to the importance of a thorough interdisciplinary study of falls.

Paper II

The paper is a case report about a woman in her 80's, who after many falls, finally was diagnosed with carotid sinus syncope in the falls clinic, and was implanted with a pacemaker. Syncope is often overlooked as a cause of falls in the elderly. The case report illustrates the importance of a thorough medical history together with a multifactorial assessment in order to make a diagnosis.

Paper III

Results Mean age was 72; women and men differed in body mass index; 22.2 versus 24.8, respectively (p<0.01). Mean blood pressures were lower among women than men, with 88 and 98 mmHg respectively (p<0.01) (rest) and 86 and 96 mmHg (p<0.01) (tilt 30°). Mean total peripheral resistance index was significantly higher among women during 30° tilt, 13.5 versus 10.8 (p<0.05), no gender differences in heart rate were seen. Women had lower LF/HF-ratio (an index of sympathovagal balance) at rest and during 70° tilt (both p<0.05), other heart rate variability measures and baroreceptor sensitivity did not differ. Two women, 9 %, and 8 men 33 %, terminated head-up tilt test due to vasovagal syncope or presyncopal symptoms. Gender difference was marginally
significant (p=0.05, log-rank test). Higher heart rate at rest (p<0.01) was the only variable significantly associated with risk of syncope.

**Interpretation** Our results indicate that healthy elderly men have poorer orthostatic tolerance during long lasting postural stress than women of the same age. The underlying reason might be differences in vascular rather than cardiac autonomic control.

**Paper IV**

**Results** Mean age 71 years (range 65-84); athletes had lower body mass index (23.4 versus 24.8, p<0.05) and lower resting heart rate (50 versus 61, p<0.01). Blood pressures and total peripheral resistance were equal. End diastolic volume index, baroreflex sensitivity, and heart rate variability were higher among athletes, both HF-RRI (high-frequency-variability, reflecting parasympathetic activity) and LF-RRI (low-frequency-variability, reflecting both sympathetic and parasympathetic activity). Syncope or presyncopal symptoms occurred in 11 persons, 4 athletes and 7 controls (p = 0.2). Cox Regression analysis showed that higher heart rate at rest was the only variable associated with syncope.

**Interpretation** Orthostatic tolerance was not reduced among elderly endurance athletes. Rather, there was a trend towards better orthostatic tolerance, which might be attributed to stronger parasympathetic cardiovascular control and larger blood volume. Better orthostatic tolerance might be an additional benefit of physical activity in older age.

**Paper V**

**Results** Fourteen patients with mild cognitive impairment (MCI) or mild Alzheimer's dementia and 48 healthy controls were included. Mean age (73.6 versus 72 years) and BMI (23.5 versus 23.5) did not differ. There were no differences between patients and controls in standard cardiovascular variables, neither at supine rest, at 30°, nor at 70° head-up tilt. Heart rate variability was equal at supine rest and 30° head-up tilt; at 70° head-up tilt, patients had significantly higher HFnu (high frequency variability, normalized units) and lower LFnu (low frequency variability, normalized units) and LF/HF-ratio as compared with healthy controls. Systolic blood pressure variability was equal at rest; at 30° tilt, patients had significantly lower SBPV in the low-frequency range (normalized units), and also a significant decrease in low-frequency variability from baseline (both normalized an absolute units) as compared with healthy controls.

**Interpretation** The results indicate poorer sympathetic response to orthostatic stress in MCI and mild AD.
6. General discussion

According to the differences in design, material and methods, I will present the methodological considerations in separate sections, but attempt to discuss the findings in an overall context.

6.1 Methodological considerations

6.1.1 Paper I and II

This was a descriptive, cross-sectional observational study, without follow up. The purpose was mainly educational, as the concept of an outpatient clinic (hereinafter called "Fallpoliklinikken") for assessments of falls was new in our department and relatively undescribed in Norway. The possibilities to compare our findings with others, and to inform colleagues about the relevant patient group, were among the perceived benefits. The articles were first written in Norwegian and submitted to the Journal of the Norwegian Medical Association, because we hoped our work could inspire geriatric departments or general practitioners to assess falls in this group more systematically.

When "Fallpoliklinikken" started up in 2008, literature about falls clinics was sparse. Some small studies from single clinics with highly specialised staff had promising results (187, 188). There were some publications from Australia, where the first falls clinics started up in 1988 (189, 190), pointing out the need for such services, but also the lack of standardisation and reporting (189), as well as the importance of cooperation with, and follow up in primary care (191). During the same period there was increasing evidence for the efficacy of exercise as fall prevention (192). One of the few studies published before 2007, showed that assessments in falls clinics provided access to evidence based strategies like strength- and balance training (190).

6.1.1.1 Patients and referral

The patients were referred from general practitioners, hospital wards or emergency services because of falls, syncope and/or unsteady walking. The same physician (the principal investigator) assessed all referrals to the clinic. During the years of inclusion, the clinic became better known, received more referrals and both the ability and need to select the right patients increased. We did not dismiss many, but patients with severe cognitive impairment and those who were supposed unable to participate in even light physical tests, were not awarded a consultation.
One can argue whether the decision to exclude the very frail and/or fallers with dementia, is right. These patients have the highest risk for new falls (14) and high mortality after hip fracture (193), and it was not without ethical qualms we rejected these referrals. However, as yet there is no evidence for recommending an extensive assessment in a specialised falls clinic for these patients (109, 194, 195). Studies of intervention and training among patients in nursing homes are inconsistent (195). Training may even have an adverse effect on falls risk among the frailest patients (196), probably because patients can overestimate their own ability (195). Local measures such as staff education, post-fall evaluation, environmental assessment and modification, gait training, and advice on assistive devices all seem beneficial (195). In these cases, we gave written advice to the general practitioner or referred the patients to the ordinary geriatric outpatient clinic or day hospital.

Our data suggests that "Fallpoliklinikken" has received referrals of appropriate patients according to guidelines (109). Negative results from fall prevention strategies are sometimes explained by incorrect selection, i.e. selection of low-risk patients (197, 198). Our patients were generally frail with reduced walking ability. Nearly three-quarters used walking aids and more than one-third needed personal assistance with mobility outdoors. Three of four had fallen more than once in the past six months and 12 % had sustained a fracture in their last fall.

6.1.1.2 Assessment and intervention
Parallel to the increasing number of falls clinics, consensus on the content of such clinics is also growing. Cochrane published an intervention review in 2012, showing evidence for reduced rate of falls after multifactorial intervention, but no reduction in risk of falling (110). Rate of falls are numbers of falls per person year, and risk of falling are numbers of fallers in the group. An intervention that only reduces rate of falls, does not affect the number of fallers, but the number of falls per person. If one suggests, like I do, that every fall is about equally dangerous, this distinction might be more of an academic exercise.

In 2010 the American Geriatrics Society and the British Geriatrics Society published an updated "Clinical Practice Guideline for Prevention of Falls in Older Persons" (109). The content is summarised in chapter 2.3. Briefly repeated; selection of high-risk patients, multifactorial assessment, individually tailored follow-up and adherence to programs that include balance-, gait-, and strength training are the most important recommendations for home-dwelling elderly.
Also, more recently published results from falls clinics show positive results or trends, albeit many studies are small (199, 200). But this year a large randomized, controlled study from two falls clinics in Finland was published (201). The control group and intervention group consisted of more than 600 persons each, and follow up was 12 months. The assessment and organisation seemed to be in accordance with guidelines, and falls were reported every third month. Both number of falls, fallers and injuries, except fractures, were reduced up to 30 %.

6.1.2 Paper III - V

The investigations were designed to conduct cross-sectional comparisons of standard hemodynamic and other indirectly measured, autonomic responses in different groups of elderly people during head-up tilt:

*Healthy men versus healthy women*
*Endurance athletes versus less active healthy controls*
*Patients with mild cognitive impairment or mild Alzheimer's dementia versus healthy controls*

6.1.2.1 Recruitment of participants

To be able to say anything about normal haemodynamic regulation in the elderly we wished to include healthy elderly without chronic diseases and medication, which meant that we had to find them outside the hospital. We recruited many women from walking groups, lectures for elderly, and social meetings. But our experience was, in line with previous findings, that elderly men rarely attend these settings (202). Thus, only a few healthy men were recruited this way, others were recruited through personal acquaintances and finally, from golf clubs.

All the athletes responded to an invitation and were benevolent to participate. It is a weakness of our study that we did not verify their athlete "status" beyond knowing that they were capable to participate in "Birkebeineren", the 54 km long cross country ski race, the year of inclusion. Maximal oxygen consumption (VO\textsubscript{2}max) is a measure of cardiorespiratory fitness that is also validated in the elderly (203). Alternatively, a less strenuous test, like the six-minute walk test could have been used as an index of fitness. This test shows a moderate association with VO\textsubscript{2}max, and inclusion of characteristics like BMI, resting heart rate and gender increases the predictive value (204). Having said that, due to the ceiling effect, we expect all participants would score high.

We knew, however, the participants' racing time and numbers of years of participation. Others have shown that VO\textsubscript{2}max and racing time are strongly and
positively related (205). Based on this we might assume that the athletes in our study are relatively fit, see figure 6.1.

Figure 6.1 Finishing time (TimeBB_min) is related to heart rate at rest (HR_rest) in the Birkebeiner cross-country ski race. Provided with the information that the maximum time* one can use in order to receive the coveted award "merket", in this age group was about 4 hours and 25 minutes (265 minutes); the plot also illustrates that these men were quite fit.
*Maximum time is calculated from the mean finishing time of the 5 best skiers in the age group adding 25 %, and is achieved by about 25-30 % of the participants each year. Author's figure, unpublished data.

Albeit the participants' achievements are really good, an objective measure of aerobic capacity would have enabled us to ensure that the controls and athletes were not equally fit. Also among the healthy controls there were individuals capable of long distance cross-country skiing, and finishing time varied among the athletes in the ski race. This heterogeneity in the material may have given type 2 statistical error; that means not finding a difference that was there. However, we found significant differences among the groups, and the possible overlap in fitness has most probably weakened the differences, not reinforced them.
It is our impression that healthy people are often interested in proving that they are (still) healthy. This project was attractive because of the opportunity to have a long-term registration of blood pressure and an ECG registration. The possibility of syncope during test was also mentioned to the participants. We cannot rule out that some of the participants have had symptoms that they did not tell us about, and wanted to go through the assessment as a health check. Eventually, this could have led to higher prevalence of syncope during HUT. A medical history and blood tests were undertaken to ensure as best as possible against such selection bias.

It is also possible that there are differences in the response to an invitation like ours according to gender or fitness, but it is unclear how such bias might affect the results.

It could also have influenced the results if the athletes differed from the controls in several areas other than fitness. An epidemiologic study of the same group of Birkebeiner cross country skiers (80), states that compared with a general population, these athletes valued their own health better. A higher proportion of the athletes reported college or university education and current full-time employment, and their BMI were lower than in the general population. However, our control group members were not fully representative of the general population either. They were similar to the athletes in many aspects related to autonomic function, as they were normotensive, without chronic diseases or medication, and did not smoke (75). Differences in BMI, as long as both groups were in the normal weight range, are not likely to impact on the results (206, 207).

6.1.2.2 Experimental protocol
Assessments of autonomic function

We used non-invasive methods to study autonomic response to orthostatic stress. The autonomic system is also available to direct testing/invasive methods like microneurography or measurements of neurotransmitters and their metabolites (49). Indirect measurements rely on measurable adjustments in end organs, an approximation with both advantages and disadvantages.

Invasive procedures introduce a source of error because they affect autonomic function in itself. Especially in a study like this, blood sampling or cannulation, may increase the risk of vasovagal syncope (163). Non-invasive tests are less painful and less harmful, which are advantageous in recruitment of participants. Also ethically, this methodology is considered less problematic.
Indirect measures are clearly associated with more uncertainty because they must be interpreted to give understandable information. See below in section 6.1.2.5 for (a short) discussion on disagreements about heart rate- and blood pressure variability indices.

Assessments of orthostatic tolerance
As orthostatic tolerance is related both to clinical findings from "Fallpoliklinikken" and the experimental studies, their results and methodological discussions are presented together in chapter 6.2.3.

Head-up tilt test with footboard support
This protocol reproduces, to some extent, the normal physical and physiological process of standing, but without the normal muscle involvement necessary to stand up. Use of footboard implies lower prevalence of syncope than HUT with saddle support (163, 208). Footboard support enables use and activity of leg muscles that might delay or prevent syncope.

Due to the expected amount of participants with low orthostatic tolerance during ordinary tilt, we also included low-grade tilt to 30° in the protocol. This set up is often used in experimental settings, challenging the cardiovascular system (45), but with less discomfort.

Syncope
Syncope was expected to occur in any of the assessments when 40 minutes ordinary HUT was used (study III and IV), due to the number of false positive associated with the test (163). However, the studies were not planned with enough power to detect differences in syncope between the groups.

Other limitations
We did not control or measure respiratory activity during tests. Respiratory activity influence on cardiovascular variability, mainly HF power (175), but respiratory rate does not increase from supine to standing position (209).

The principal investigator performed all assessments, which minimised the influence of random error. However, risk of systematic errors might have been increased. Participants were assessed in the order they were recruited. Although enrolment occurred in parallel throughout the period, there may have been some clustering in time. Clustering in time could eventually result in systematic errors in terms of technical or climatic influence on HR and autonomic measures (i.e. time since calibration or variations in temperature).
Mental stress might influence autonomic function tests (210, 211). We did not familiarise the participants with a primary visit, but were committed to giving appropriate information and creating a safe and calm test situation.

Meals were not standardised, participants were told to eat an ordinary breakfast (without tea/coffee) before they came. Variations in eating habits might affect digestion and thus autonomic function (212). Small differences in water consumption, and thus fluid balance and orthostatic tolerance, was also possible, as participants were asked to drink at least one, but not more than two glasses the same morning.

6.1.2.3 Quality of data
Conventional cardiovascular variables are dependent on indices calculated from the impedance signal and thus subject to uncertainty due to the technique used. The absolute values are not good enough for diagnostic use, e.g. estimation of stroke volume in a single patient in a clinical setting. But the method is useful and validated in research when the measurement of changes (e.g. in volumes as a result of orthostatic challenge) is of interest (170, 213). The limited absolute validity of stroke volume (SV) and end diastolic volume index (EDVI) also applies to the values derived from these, such as cardiac output (CO) and the total peripheral resistance index (TPRI). Absolute blood pressure values must be interpreted with caution, but can be considered valid for comparisons and to detect changes (172). The Task Force® Monitor is validated in healthy persons in supine, during tilt, and during infusion of vasoactive drugs, and in patients with autonomic failure (169, 170).

6.1.2.4 Use of statistical methods
We have studied many variables in the studies III-V, thus increasing the risk of obtaining statistically significant results just by chance. That is, making a type 1 statistical error. No mathematical correction was made for multiple comparisons. Results must therefore be interpreted with caution. However, many of the variables are related, for instance measures of blood pressure and the indices of HRV and BPV. When interpreting these data, one should primarily be aware of results that do not seem physiologically plausible, even if they look statistically significant.

Our studies are small, but we try to explore aspects of clinical physiology in an age group that is scarcely studied. Thus, we considered the potential benefits from detecting less known mechanisms and generating new hypothesis as most important.
Corrections could have been done with the Bonferroni method; dividing the value of the significance level (5 %) by the number of comparisons made, and using this new value as the significance level (214). But since this method is based on stochastically independent variables, and our variables in fact were related, Bonferroni correction would have been too conservative in this case.

We could also have overcome the problem of multiple comparisons by use of principle component analysis (PCA). This analysis provides an estimate of the "effective number of independent variables" which might be used as a less conservative divisor in a Bonferroni correction.

In paper III we used survival analysis and Cox regression to explore the somewhat unexpected high numbers of syncope among men and women. The methods were chosen because we used time-to-syncope, and not the occurrence of syncope as the endpoint. In order to reduce the methodological problem of test multiplicity, only significant relationships from t-tests were subjected to multivariable analyses.

6.1.2.5 Disagreements about interpretation and use of variability measures

In chapter 4.2.2.2 the methodology of HRV and BPV were discussed. It remains to mention the considerable controversies that exist in this field (215). Among the criticisms are that these indices invariably are taken as quantitative measures of autonomic interactions instead of measurements of the resulting phenomenon (216).

The results of spectral analysis are, as previously stated, expressed as three distinct peaks in the power spectrum; very low frequency (VLF, <0.04 Hz), low frequency (LF, 0.04-0.15 Hz) and high frequency (HF, 0.15-0.4 Hz). However, this is, as most models, simplified. The peaks are often broad and may originate from more than one cardiac control mechanism. One single control mechanism may, on the other side, contribute to more than one peak (179).

Most researchers agree that heart rate variability in the high frequency area (HF variability) is strongly associated with cardiovagal control and reflects respiratory sinus arrhythmia (212, 215). Whether LF variability represents an expression of combined sympathovagal control (most common opinion) or pure sympathetic activity, is an on-going discussion (183, 212, 217).
6.2 Discussion of the results

6.2.1 General findings from the falls clinic

Falls among elderly people have varying and complex causes. Findings of serious underlying pathology and indications for pacemaker implantation testify to the importance of a thorough interdisciplinary assessment of falls. Nevertheless, our results also illustrate that some highly relevant and possibly preventable causes are more frequent than others. Orthostatic hypotension and gait- and balance problems represent findings and causes of falls that advantageously could be detected and managed in primary care.

The study patients are not representative of all fallers. They belong to the 10-20 % of patients that seek medical attention after a fall, and in addition, they have had a second referral to a falls clinic from the medical doctor they consulted. Many elderly people never seek medical attention for falls that did not result in serious harm, and are thus not referred for further assessment or prevention.

A study from Denmark reports about 1000 falls requiring help or medical attention annually among a population of 15 000 elderly over 65 years. The need for post fall assessments was estimated to be 65 % of the patients. These figures clearly illustrates that the needs exceed the capacity (218), and that our patients constitute a selected group. This does, however, not necessarily mean that they are not representative for the group who need post fall assessments.

Referrals to "Fallpoliklinikken" also changed somewhat during the registration period; more patients came from the emergency department towards the end of the registration. The clinic has a special interest in syncope. The fact that we, as the only department at our hospital, routinely performed carotid sinus massage (CSM), might have led to some extra referrals with suspected syncope.

Our results would definitely have been more interesting if we could have followed patients over time, counted falls and compared them with a control group. Our referred patients, assessments and findings concur well with results from studies that have been published by similar institutions (112, 200, 201). However, we cannot say anything definite about the effects of our interventions at "Fallpoliklinikken".
Despite the personal experience of providing quality care, conscientious medication reviews, and innovative assessments of syncope, I fear we would have ended up with negative results if we had compared our patients with a control group. There are a couple of reasons for that. The greatest shortcoming was definitely that we could not offer the patients strength- and balance training. The physiotherapist made great efforts to find such training elsewhere, but not every district had suitable training facilities. Nor could we provide after-control for more than a few but had to leave the follow-up to the general practitioner. In order to overcome this shortcoming, we wrote a clear and informative note to the patients and caregivers on the outcome of the assessment.

6.2.2 Strength and balance; relation to other risk factors in "Fallpoliklinikken"

Most patients had impaired balance and reduced strength in their lower limbs. More than half had results on the Berg Balance Scale and/or the Timed Up and Go that are associated with a high risk of falling (159, 160, 219). More than one in three were unable to get up from a chair without using their arms – a simple indicator of reduced muscle strength in the lower limbs and an increased falls risk (220). The co-existence of other risk factors increases the risk of falls (14).

Age and cognitive impairment
Mean age was 82 years, and one third of the patients were cognitively impaired. In old age, the ‘strategy’ for maintaining balance after a slip shifts from the rapid correcting ‘hip strategy’ (fall avoidance through weight shifts at the hip) to the ‘step strategy’ (fall avoidance via a rapid step) to total loss of ability to correct in time to prevent a fall (31). In 2013, a study was published in the Lancet in which video recordings from more than 200 falls were analysed. Incorrect weight shift (41 %) and stumbling accounted for 62 % of the falls (221). Dementia increases the risk of falls, and findings from a recent study indicate that all aspects of balance control deteriorate with increasing severity of cognitive impairment. Executive function plays an important role in balance control (222).

OH and balance
Presence of initial orthostatic hypotension (IOH) is shown to be associated with reduced ability to maintain standing balance in semi-tandem stance with eyes closed (223). OH is associated with gait and balance disorders and falls (224). OH may be asymptomatic, but can also lead to syncope, with symptoms most often somewhere between these two extremes. Blurred vision, decreased
cognitive capacity, confusion, and loss of postural tonus are all results of cerebral hypoperfusion, and associated with falls (140, 225-227).

*Polypharmacy*

Three of four patients used four or more drugs daily. A review from 2013 showed that psychoactive drugs (antipsychotics, sedatives, antidepressants), and cardiovascular drugs (antihypertensive agents, vasodilators, diuretics) were associated with OH (224). Improved cardiovascular homeostasis is observed after cessation of such drugs (228). Recently, Tinetti et al. showed that antihypertensive medications were associated with increased risk of serious fall injuries (229).

6.2.3 Orthostatic hypotension and falls

Anyone who has experienced the little unsteadiness that might occur when getting up after sitting on their haunches, has felt the association between transient hypotension and balance. Such light-headedness or non-vestibular dizziness on postural change is often referred to as orthostatic dizziness (OD) (230). It seems intuitively correct that reduced balance and muscle strength make elderly especially vulnerable to falls due to orthostatism and transient hypotension (33, 126, 140).

6.2.3.1 Orthostatic hypotension in "Fallpoliklinikken"

In *paper I* (*and II*) we illustrate how the multifactorial causes of falls are identified through a broad, interdisciplinary assessment. One quarter of patients was diagnosed with orthostatic hypotension (OH) and still more experienced a significant drop in blood pressure upon standing (20 mmHg systolic or 10 mmHg diastolic), but without symptoms. Blood pressure was measured with sphygmomanometer according to the old consensus definition (173).

This definition is not helpful when symptoms occur without a significant fall in blood pressure. More recent comments to the guidelines emphasise the clinical relevance of symptoms (143). We asked about and noticed symptoms of orthostatic intolerance, and considered symptoms together with a significant fall in blood pressure as clinically relevant. This constitute a relatively conservative interpretation, accounting for our finding of 24 % OH while others have found percentages ranging from 10 to 30 % in asymptomatic individuals and up to 50 % in those who are frail (123, 124, 143).

Although theoretically plausible, the association between falls and orthostatic hypotension is poorly characterised, possibly due to variations in
measurements, with respect to devices as well as to types of assessment (231). Active stand results in a greater reduction in blood pressure and higher increase in heart rate during the first 30 seconds than passive tilt (232). It is suggested that the use of leg and abdominal muscles during active stand, causing compression of vessels and an initial translocation of blood to the thorax, results in systemic vasodilatation mediated by cardiopulmonary baroreceptors (231, 232).

New technology with continuous measurements of blood pressure has extended the possibility to register the earliest changes (172). Prevalence of OH in up to 60% of persons from sit to stand is reported with this technique, compared to 17% in the same material when they used sphygmomanometer (233). When active stand is used together with continuous measurements of BP, even higher numbers are reported. Romero-Ortuno et al. reported OH in 94% of elderly persons according to the consensus definition (136). The participants were a mix of patients referred to a falls clinic, but the majority were self-referrals for a "health-check".

The potential problem of over-diagnosing OH with these measures has been addressed (234). There is an ongoing discussion whether the lowest blood pressure from a single beat or from five (or more) seconds average should be used (231). Blood pressure from five seconds average shows the best association with falls (235).

To accommodate these challenges, new guidelines were requested (135, 235), and a new or extended definition was published in 2011 (122). Both initial orthostatic hypotension (IOH) (i.e. decrease in blood pressure of 40 mmHg systolic or 20 mmHg diastolic within 15 seconds of standing), and delayed orthostatic hypotension (i.e. decrease after 3 minutes) were included. Longer registrations of BP than three minutes might increase the diagnostic yield when OH is suspected (236). However, despite limited concordance between the tests, the guidelines neither recommend a specific method (HUT versus active stand) nor measurement (continuous versus intermittent)(231, 236).

We could possibly have improved the diagnostic yield with continuous BP measurements (223); Romero-Ortuno et al. (136) found that IOH was related to falls and frailty, while orthostatic hypotension (OH) according to the consensus definition (173) was not. However, one can speculate that this lack of association might be due to unawareness of symptoms during test and the high prevalence of OH also in unselected populations (237). A study from Finland
reported OH in 34 % of home dwelling elderly over 75 years (123).

6.2.3.2 Orthostatic blood pressure in the study with MCI/mild AD-patients
Mean decrease in both groups was larger than 20 mmHg in systolic and 10 mmHg in diastolic blood pressure, with no differences between the groups. We did not calculate the prevalence in each group. Orthostatic blood pressure was defined as the drop between blood pressure before tilt and the lowest blood pressure (nadir) from a single beat, within the first three minutes after full tilt.

In this study we used tilt-table and measured continuous blood pressure. Because we used nadir, the measures will include cases of initial orthostatic hypotension. Along with that, the lowest blood pressure might be representative for only one heartbeat, and overestimation of the drop is very likely (231, 235).

According to the consensus definition of orthostatic hypotension (122), active stand and tilt-test are equivalent, but tilt-test tends to reduce the occurrence of initial orthostatic hypotension (122). However, some researchers claim that a shift in position from to supine to stand should be rapid, about 2 seconds, to be comparable (45). Thus with 18 seconds from supine to erect position, as in our study, we cannot exclude the possibility that our registration method gives a less marked drop in blood pressure.

However, these results were used to compare two groups, which underwent the same tests, and it is not likely that these methodological issues affected the groups differently.

6.2.4 Head-up tilt test and syncope
In our study reported in paper III, 22 % of healthy elderly people without a medical history of syncope terminated the test because of presyncopal symptoms or syncope, with a tendency to male overrepresentation. An elevated resting heart rate was associated with syncope and lower orthostatic tolerance during the head-up tilt (HUT) in this group.

The high number of syncope/presyncope is consistent with the high rate of false positive results from HUT (163). Our findings of mainly neuromediared syncope/presyncope are not representative for clinically occurring syncopes. Both orthostatic and cardiac syncope are unlikely in this setting, since our test participants were free from medication and cardiac disease (33, 144, 149).
Resting heart rate was the only variable that predicted syncope/presyncope in our material. Parry et al found higher resting heart rate in a group of patients with known syncope compared to controls, but the findings were not associated with outcome of HUT (238). In a small study of healthy middle-aged men without prior syncope, heart rate and muscular sympathetic nerve activity at rest were significantly higher among those who became presyncope during orthostatic challenge (239). Possible explanations are that relative or functional hypovolemia or higher compliance in capacitance vessels stimulates volume receptors in the heart, leading to higher HR at rest (39). When persons with such characteristics are tilted, they will have reduced ventricular filling and be more prone to vasovagal reflexes and syncope.

High supine HR could also be an expression of reduced vagal tone, as can be seen in low-fit individuals or vagal dysfunction in some neurological diseases. However, this is not a likely explanation for the observed difference between those who experienced syncope and the others, due to the healthy status of all the participants. Also reduced parasympathetic activity or sympathetic hyperactivity, due to stress or anxiety could result in increased HR, and be a marker of underlying susceptibility to emotional syncope (35). The degree of perceived control in such circumstances has an influence on the degree of vasovagal symptoms (240). All participants were given the same information and time was spent to familiarise them with the investigator and equipment.

Also when we analysed syncope among athletes and healthy controls in paper IV, higher HR at rest was associated with syncope. This is not surprising due to overlap in the material, the males in the control group are the same as in paper III. High resting HR is related to low central volume (39). In a large study of factors contributing to orthostatic intolerance in the elderly, decreased left ventricular preload and alterations of left ventricular diastolic filling were among the factors involved (241). Also, diuretics are strongly associated with orthostatic hypotension (224). Thus, our results indirectly support the important impact of total blood volume on orthostatic tolerance among elderly.

6.2.5 Cardiovascular regulation and gender

We found better orthostatic tolerance in a group of healthy, elderly women (mean age 72) compared to healthy men of same age. Women had lower blood pressure in supine, but changes during tilt were similar. Total peripheral resistance index (TPRI) were similar at rest but significantly lower among males
both during 30° and 70° HUT, indicating differences in vascular autonomic control.

Very few studies have assessed gender differences in orthostatic tolerance in healthy elderly. Orthostatic hypotension is more common in women (233), at least until old age (123). Young women also tend to have lower orthostatic tolerance during HUT (69-71, 73). Interestingly, elderly men are more often hospitalised due to orthostatic hypotension (127), while women have more hospitalisations from falls in general. In one of the relatively few studies in this field looking for gender differences in older people, Romero-Ortuno et al. recently found a larger drop in blood pressure among men during 3 minutes of active stand. The orthostatic tolerance was, however, similar. In the same study, TPR was lower among men both at rest and during recovery (74). Frey showed augmented TPR with age in response to standing in men and women 21-59 years, and especially among the oldest women (242).

The heart rate variability (HRV) indices differed at rest and 30° HUT; HFnu was higher in women and LFnu and LF/HF higher in men. Gender differences in supine position and during HUT are consistent findings, but seem to disappear after 50-60 years of age (55, 63, 243-246). We found no gender differences in cardiac autonomic control (heart rate, heart rate variability, blood pressure variability, and baroreceptor sensitivity) in response to HUT; this is consistent with other studies (51, 245).

Gender differences persisted in our material, despite mean age above 70 years. As risk factors for cardiovascular disease (e.g. hypertension, hypercholesterolemia, smoking) tend to decrease HRV (55, 75), and physical activity tend to increase both LF- and HF-power (75), the participants' good health might explain why HRV-indices remained different between the genders.

While young persons rely more on vagal withdrawal (augmented heart rate) to maintain blood pressure in situations with orthostatic challenge, elderly people rely more on an increase in total peripheral resistance (51). The observed differences in total peripheral resistance (TPR) indicate that vascular response, not cardiac regulation, matters the most.

Lower TPR could contribute to orthostatic hypotension and syncope. The underlying mechanisms, in turn, might be altered vascular reflexes among men, a reduction in the performance of the skeletal muscle mass, differences in the
age related down-regulation of adrenergic receptor density or sensitivity in peripheral arterioles, or enhanced stiffness due to arteriosclerosis, as suggested by others (45, 247-250).

There are some findings in the literature indicating gender differences that might be related to the observed differences in our study. Men have attenuated venous resistance during ageing (251), whereas it seems to remain stable in women (250). Older women demonstrate larger increase in MAP during HUT, despite lower plasma norepinephrine; possibly indicating impaired norepinephrine action in men (51). Splanchnic vein compliance also contributes significantly to orthostatic reflexes, and is much more sensitive to adrenergic stimulation (252). Hypertensive elderly women are shown to have higher TPRI during tilt than men (253).

6.2.6 Cardiovascular regulation in athletes

Orthostatic tolerance was not reduced in elderly endurance athletes compared to less fit, but healthy controls. However, they rely on different compensatory strategies. There was a trend towards better orthostatic tolerance that might be attributed to stronger parasympathetic cardiovascular control and larger blood volume in the athletes.

Supine
Athletes in our study showed the normal physiological changes associated with endurance training compared to controls. Stroke volume was elevated (254, 255), partly due to increased blood volume (256). A larger stroke volume maintains cardiac output with lower heart rate; thus, parasympathetic (vagal) drive dominated over sympathetic drive of the sinus node, resulting in higher values in the indices of HRV in the high frequency area (39, 82, 84). Also, short-time arterial BRS was stronger among athletes, presumably due to parasympathetic predominance.

Is training associated with better or poorer orthostatic tolerance?
Based on historical reports in the literature, we hypothesised that orthostatic intolerance would be more common among the elderly endurance athletes (86-88). However, better orthostatic tolerance is also observed both in young (257) and elderly (93) athletes. Increased blood volume is a possible mechanism for improved tolerance also in elderly athletes (257). Shorter periods of training have shown diverging results; both unchanged (90, 92) and better orthostatic tolerance (255, 258) has been described.
In a review, Convertino claims that physiological changes observed in athletes, like lower HR and larger decreases in BP or SV in response to HUT, not necessarily mean lower orthostatic tolerance (257). He further claims that orthostatic tolerance must be tested with an orthostatic challenge like HUT or lower body negative pressure in order to make conclusions. Among the possible explanations for the diverging results is a lack of standardisation of tests, but also different levels of fitness. The "inverted U shape" is highlighted as a model to explain prevalence of orthostatic intolerance as a function of "fitness" (259). With this construct, orthostatic intolerance is most pronounced in the highest- and lowest-fit subjects, with moderate exercise training being associated with improved orthostatic tolerance.

An important objection to this study is that we have no objective measure of fitness. We cannot prove that the endurance athletes were fit "enough" to deserve the comparison with athletes with low orthostatic tolerance in other studies.

*Differences in response at 30° and 70° HUT*

Despite a more prominent fall in SBP and MAP among athletes during the first minutes of low-grade tilt, they increased less in HR than did controls. During 70° HUT, the two groups responded with comparable changes in BP, HR, SI and TPRI.

The Frank-Starling mechanism connotes the phenomenon in which stretching of cardiac fibres during diastole facilitates ventricular contraction and increases cardiac output (39). Reduction in central blood volume would affect cardiac filling and hence stroke volume, blood pressure, and HR. A larger blood volume in the athletes might result in a smaller blood volume displacement, and thus also smaller changes in heart rate. This mechanism alone cannot, however, explain the differences between the responses to 30° versus 70° HUT.

One possible explanation is that both arterial and cardiopulmonary baroreceptors are involved in blood pressure regulation, but to different extent according to the degree of orthostatic challenge. Mild orthostatic challenge, such as 30° HUT, primarily activates the cardiopulmonary baroreflex through reduction of central volume (44). Typically, this low level of activation leads to simultaneous increases in cardiac sympathetic and vagal activity that offset each other leading to only small changes in HR. The term “Bainbridge reflex” is used to describe these volume related HR changes (42). See also chapter 2.2.1.
The actual change in HR may reflect the sum of influences from the arterial baroreceptor reflex and the Bainbridge-reflex (39).

Thus, the Bainbridge reflex appears to be more pronounced in athletes, and suggests that short-term cardiovascular control is optimised at mild hypervolemia (44). The underlying reason might be higher central volume and therefore higher end diastolic volume index (EDVI) among athletes. This starting point may cause a stronger activation of the cardiopulmonary baroreceptors and thus prevail over the effects of the arterial baroreceptor reflex, leading to a smaller augment in HR and ultimately lower blood pressure during 30° tilt.

Our data does not allow conclusions to be made with regards to blood volume. EDVI is indirectly measured and can be seen as an indication of higher blood volume, but caution in the interpretation is necessary, as mentioned in chapter 6.1.2.3.

With the cross-sectional design, the only appropriate conclusion is one of association rather than cause-and-effect. Thus we do not know whether the findings are the results of training. Since there are many physiological functions that develop over a lifetime that could contribute to the orthostatic response of an individual, it might be misleading to attribute physical fitness as the only (or primary) contributing factor.

Another possibility is that of selection bias. The observed differences may be the results of different physiological constitution and not of training; i.e. that the athletes are born with innate characteristics that keep them healthy and fit.

### 6.2.7 Reduced sympathetic response to HUT in patients with MCI and mild AD

Our most important finding was divergent HRV and SBPV responses to orthostatic challenge among patients with mild cognitive impairment (MCI) or mild Alzheimer’s dementia (AD), indicating attenuation of sympathetic cardiovascular control and possibly reflecting early neuropathological processes in the brain. It seems that parasympathetic function remained unchanged, which was also supported by the preserved baroreceptor sensitivity (BRS).
HRV - supine
Very few studies have assessed patients with MCI/mild AD, thus most studies cited here comprise patients with AD. Most studies show decreased HRV in AD (260), mainly interpreted as parasympathetic dysfunction (107, 108) or as a combination of parasympathetic and sympathetic dysfunction (102). A study from 2005 (261) did not show any difference between patients with AD and controls, but the controls had more cardiovascular disease, more hypertension and were more often smokers, all factors known to decrease HRV.

The degree of dysfunction seems to increase with the severity of the dementia (108). This may explain why most studies of patients with MCI report no differences in HRV at rest (108, 262, 263). Nor did we find any differences in HRV (or SBPV) at rest. Collins et al., in a larger study, reported lower HF-variability among MCI-patients, but there were no differences in LF/HF-ratio or LF-variability (102).

HRV - response to standing
Differences in autonomic function (lower LF and LF/HF in AD and MCI), possibly early signs of reduced sympathetic response upon standing, became evident only during HUT. This observation is coherent with results recently published by Nicolini et al.(263). They found, like us, attenuated changes in HF, LF and LF/HF in patients with MCI, suggestive of reduced vagal withdrawal and reduced sympathetic response. Neither patients nor controls were, however, free from cardiovascular disease and medications in that study.

Some of our patients used cholinesterase inhibitors (ChEIs) or antidepressants (SSRIs) that could possibly influence the measures. Giubilei et al. tested the same group of patients before and during use of ChEIs, and found that medication made their response to HUT more similar to that in controls (262). Others have shown that ChEIs reduce HF-variability more than LF-variability, and thus increase the LF/HF-ratio (264, 265). Use of ChEIs in our sample would then diminish rather than exaggerate the differences. The use of citalopram (the most prevalent SSRI) is not shown to alter autonomic function in healthy controls (266). Effects in patients with dementia are not known, but enhanced side effects like orthostatic hypotension are likely to occur.

Our results are to some extent surprising, given that cholinergic deficiency is generally believed to be a central pathophysiological mechanism in dementia (108, 262, 267). LFnu-values are influenced by total variability as well as by HFnu-values. One might thus hypothesise that our finding of reduced LFnu in
AD and MCI patients might be a result of failure to switch off the parasym pathetic system. However, this hypothesis would imply a higher cholinergic activity in the patient group, not consistent with cholinergic deficiency. The observed changes in blood pressure variability (BPV) further support reduced sympathetic response as the most likely explanation of the results.

Elderly people rely more on an increase in total peripheral resistance, i.e. vascular sympathetic regulation, than on vagal withdrawal when orthostatically challenged. This can be seen as a smaller decrease in HF and thus a smaller increase in LF/HF-ratio when compared to younger persons (51). Ageing is also associated with a smaller increase in LF power of BPV during orthostatic challenge (51, 268). On this background, our findings might indicate that changes related to ageing appear earlier in AD.

Contrary to what we hypothesised, we did not find a greater reduction in orthostatic blood pressure in patients with MCI or mild AD compared to controls, nor did they differ in any of the other hemodynamic measures such as HR, TPRI, SI, and CI. This is in conflict with some studies (100, 102, 103, 105), but consistent with a study limited to MCI patients (263). There are several possible explanations for this finding.

As already mentioned, our HUT procedure might have been too gentle, with a relatively long time-span from supine to upright position (45). As orthostatic hypotension worsens with the degree of dementia (103), changes might not be detectable in the earliest stages, especially when the test is less challenging.

In addition, the low number of participants increases the risk of type 2 statistical error. The most striking weakness of our study may be that the healthy controls were not cognitively screened, which theoretically could imply that the controls comprised some patients with MCI or mild AD, thus making the groups too similar as to detect differences. However, this possibility seems unlikely, given the very good general health status of the control group.

Another possibility is that our results, and the fact that our patients and controls were free from cardiovascular disease and antihypertensive medication, illustrate confounding in other studies. In the much larger study by Collins et al., the MCI group had more cardiovascular disease and there were more men among them. This could, according to our results in paper III, possibly influence the results (269).
6.3 Conclusions

- Orthostatism and polypharmacy were among the most frequent findings in our clinical sample from "Fallpoliklinikken".

- Four of five patients in our material had at least two of eight major risk factors with potential for intervention and follow-up (orthostatism, pathological ECG/heart disease, carotid sinus syncope, low body mass index, vitamin D deficiency (270), reduced muscle strength and balance, polypharmacy, or cognitive decline). 17% had four or five of these risk factors, and only five patients had none.

- Male gender was associated with lower orthostatic tolerance during HUT in healthy elderly.

- Elderly male athletes showed a trend towards better orthostatic tolerance than their more sedentary peers, which might be attributed to stronger parasympathetic cardiovascular control and a larger blood volume.

- Our findings indicate poorer sympathetic response to orthostatic stress in the earliest stages of dementia as compared to healthy elderly.

6.4 Implications for clinical practice

Falls, assessments and prevention

Evidence for multifactorial assessment and intervention, especially strength- and balance training, is good. A study from Norway indicates that falls prevention saves money (271). Thus, in the next few years, effort should be made to bridge the "know-do gap" - the gap between what we know and what we do in practice.

Falls clinics are relatively rare and outpatient clinics do not have the capacity to handle all fallers (218). Our health care system is based on interested and competent general practitioners (GPs). Ideally they should be the first to notice falls and problems with gait and balance among their elderly patients. Some important elements from the multifactorial assessment in falls clinics could, as I see it, easily be implemented in GP: Measurements of orthostatic blood pressure, medication review, awareness of nutritional status and vitamin levels, and a simple evaluation of gait and balance (from the waiting area to the office). Easily available bilateral communication between home-based services and the GPs might provide consultations or referrals in time to initiate training or to make changes to medication.
Accident and emergency clinics, emergency departments and orthopaedic departments treat many patients with falls. Elderly patients who present to emergency departments with falls are often scheduled for follow-up for their fall related injury only. Many do not receive care that meets current guidelines for falls, and studies have shown that their falls-risk worsens (114, 272, 273). Knowledge, awareness and appropriate routines for referral and follow-up might improve care of this patient group.

The assessment was time consuming but feasible in an ordinary geriatric outpatient clinic. It is our experience that the clinical work benefited from the structural framework of a register. The implementation of CSM for assessment of syncope, was new in our department, and meant that "Fallpoliklinikken" in general provided a clinical service close to current guidelines (109), with the exception of occupational therapy.

**Head-up tilt test**
During CSM in "Fallpoliklinikken" and the assessments that form the basis of papers III-V, we have gained experience with head-up tilt test (HUT), both in healthy and more frail elderly persons. The test is time consuming, especially when used without nitro glycerine. A recent paper shows that the diagnostic yield of HUT was lower in patients with unexplained falls than unexplained syncope, 36 vs. 51 % respectively. In both groups 80-85 % of the positive tests show mixed or vasodepressive reflex mediated syncope (274).

Due to the high false positive rate among healthy elderly and the degree of exhaustion observed in fragile or cognitively impaired patients, we rarely use HUT in daily clinical work. The few possibilities for treatment of vasodepressive syncope; mainly avoidance of precipitating factors, increasing fluid intake and recognition of prodromal symptoms (152), are most of all based upon clinical history and witness' statements.

**6.5 Suggestions for further research**

*Falls, assessments and prevention*
Health budgets and hospital budgets in particular, are limited. Thus, translation of methods of falls assessments and intervention from a hospital setting to the elderly in the community is necessary. According to this, we should develop an algorithm for selection of elderly patients with falls to primary versus secondary care. Criteria must be set to refer the right patients from GP to outpatient clinics/falls clinics.
Since most elderly patients with falls or unsteadiness need strength and balance training, such groups and facilities must be implemented in the community. In my opinion, this is more dependent on political will than on research. Cooperation across levels in the health care system, and also across health care professions, is needed. Enthusiasm, ardent souls and increased attention in the society to the needs of elderly people, are vital for success. We should seek simplicity in assessment and quality in training!

Use of the active stand test
Many recent studies are focusing on the earliest changes in blood pressure during active stand, and also recovery of blood pressure during the first minute. Findings in the assessment of such indicators have also been associated with falls and frailty. Active stand is very time saving compared to HUT. It would be of interest to explore the diagnostic yield from use of active stand with continuous blood pressure measurements, in assessments of elderly with falls in a clinical setting. Conducting a follow up with focus on polypharmacy and the effects of discontinuing medication on falls and measurements during active stand is also clinically relevant.

Dementia and autonomic function
Dementia is associated with falls and autonomic dysfunction in late stages. Our findings indicate poorer sympathetic response to orthostatic stress in the earliest stages of dementia/MCI. The differences were not present in supine position and might be associated with early neuropathological changes. We do not know whether dysregulation comes before or as a result of dementia, and further studies are needed. Associations between white matter lesions in the brain, cerebrovascular damage, rate of cognitive decline and relations with autonomic dysfunction are not clear (275-277), but early detection of dysregulation of blood pressure might become important in order to prevent further cognitive decline.

Our study was limited in many respects. Number of participants was low; we did not include results from radiological imaging or results from cerebrospinal fluid analyses and did not measure catecholamine concentrations. These are measures that probably would have contributed to improved understanding, and might be subject of further research.
7. References

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