Chapter 1

Introduction

Introduction

An ageing Europe, an ageing Italy

Europe's population is rapidly ageing[1,2]. Adults aged 75 years and over now account for 8.3% of the European population, a proportion which is expected to increase up to 10.7% by 2030[2]. In parallel, the birth rate is decreasing[2]. As a result, the population age structure will dramatically change. The proportion of older adults in non-working age will increase compared to that of adults in working age[2]. In the future, older adults may lack social support from younger generations. Therefore, it will be crucial to preserve functional independence in old age.

This demographic transition is already evident in Italy. The population proportion over 75 years is now 10.7% of the total (6.6 million out of 62 million inhabitants)[2]. Italy's life expectancy at birth is now 79.5 years for men and 84.9 years for women, among the highest in the world[3]. Such structural changes in the population represents a big challenge for both society and medicine[4]. With ageing, the burden of age-related diseases, disability and functional dependency increases[5]. Among age-related diseases, cardiovascular diseases and dementia are prominent[5-7]. Their prevalence dramatically increases with advancing age[5-9]. Both cardiovascular diseases and dementia are leading causes of disability and mortality[5].

It can be postulated that age-related diseases lead to a loss of function of different physiological systems and therefore to a state of frailty, an increased vulnerability to stressors, which eventually results in functional decline or death[10-13]. Conversely, mechanisms that preserve the homeostasis of different physiological systems may favor resilience to stressors, and eventually delay functional decline or death.

The homeostasis of the cardiovascular system is crucial for preserving cognitive and functional status[14-17].

However, the mechanisms behind homeostasis may change with ageing. With ageing, changes in different physiological parameters may occur. The optimal values of these parameters as well as the threshold of disease may shift with age. Blood pressure and thyroid status may be among these parameters. Older adults may benefit from different set-point of homeostasis,

compared to younger adults. A deeper insight in the homeostasis of older adults is necessary to tailor interventions aimed at delaying functional decline and mortality in old age.

The aim of this thesis is to explore the homeostasis of older adults, with emphasis on the cardiovascular system. This thesis will examine the associations of cardiovascular parameters (blood pressure and its variability, heart rate, heart rate variability) and thyroid status with clinically relevant outcomes (functional and cognitive status, mortality).

Blood pressure: shifting the cut-off values

With ageing, systolic blood pressure increases, while diastolic blood pressure increases until the age of 60 years and then gradually decreases[18]. Optimal blood pressure targets in old age are still controversial, as reflected by divergent recommendations in different international guidelines[19-23]. In middle-age, higher blood pressure is strongly and consistently associated with adverse health outcomes, including increased risk for dementia and mortality[24]. However, these associations attenuate or even reverse with ageing[24]. Findings from population-based studies have suggested that these associations may be modified by chronological and biological age[25-30]. Indeed, lower blood pressure may be associated with increased mortality risk in the oldest and in the frailest adults[25-30]. In contrast, findings from trials indicate that antihypertensive treatment effect may not vary according to frailty[31]. For instance, the Hypertension in the Very Elderly Trial (HYVET) showed no difference in antihypertensive treatment benefit between the frailer and the fitter participants[31]. However, HYVET excluded older adults with dementia, thus potentially limiting the generalizability of its findings[31].

Thyroid status: shifting the cut-off values

Thyrotropin (TSH), free thyroxine (fT4) and free triiodotironine (fT3) have profound effects on the ageing process, which may vary according to sex and age[32-34]. Optimal thyroid status in old age is an area of controversy[33,34]. The distribution of TSH progressively shifts towards higher values with ageing[35,36]. This shift may arise from a higher prevalence of occult thyroid disease or from selective survival of individuals with a constitutively lower thyroid status[37,38].

Therefore, it is debated whether the upper reference limit for TSH should be age- and sex-specific[33,34].

Heart rate, heart rate variability

Heart rate variability is the physiological variation in the beat-to-beat time interval[39]. By modulating heart rate and heart rate variability, the autonomic nervous system keeps blood pressure constant within a certain range, so to maintain adequate perfusion to vital organs. In particular, higher heart rate variability is a homeostatic mechanism to buffer detrimental variations in blood pressure in response to stressors[40,41].

Blood pressure variability

Visit-to-visit blood pressure variability is the intra-individual variation in blood pressure measures over different clinic visits[42]. Higher blood pressure variability, independent of mean blood pressure, has been associated with clinical and subclinical vascular organ damage[42]. Higher blood pressure variability may reflect impaired homeostasis, in particular impaired baroreflex function, in the context of central autonomic dysregulation[43]. Furthermore, it may cause oscillations in perfusion of vital organs, including the brain, the heart and the kidney, thus leading to damage of these organs.

The Milan Geriatrics 75+ Cohort Study

Current evidence for the treatment of older adults comes from population-based cohort studies and randomized clinical trials. However, this evidence may not be easily extrapolated to patient populations, whom clinicians encounter in everyday clinical practice (Figure 1). Clinical trials tend to selectively recruit fit older adults with few comorbidities. The HYVET trial aimed at solving the controversies on antihypertensive treatment in the very old individuals, by specifically enrolling adults aged 80 years or over[44]. However, a recent population based study showed that only one out of ten older adults would have been eligible for inclusion in HYVET[45]. Despite HYVET's focussed aim and large sample, the benefits and harms of

antihypertensive treatment in frailer old adults remain a controversial topic. Population-based studies may enrol older adults with a broader spectrum of impairment and co-morbidities. However, also population-based studies may be affected by a response bias, as particularly frail older adults tend to refuse participation in these studies[46]. The generalizability of data from trials and population-based studies to patients' populations is debatable. Clinicians are confronted with lack of data in patients' populations, in which comorbidities, functional and cognitive impairment may be more prevalent and severe, and their interplay within homeostasis more complex.

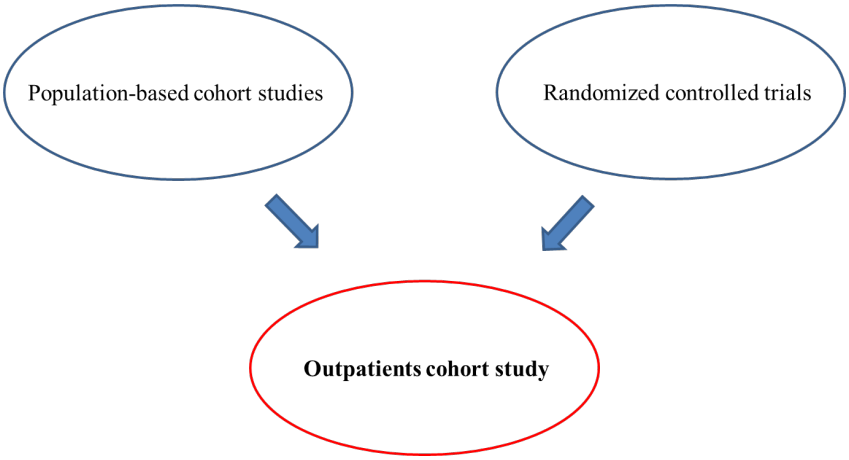

Figure 1. Bridging the gap. Current evidence is derived from population-based cohort studies and randomized controlled trials. Both types of studies may be biased by failing to include frail individuals, due to either lower response rate in the frailer or exclusion criteria. Data are lacking on older outpatients, a potentially diverse population, thus the need for an outpatients cohort study.

To bridge the gap between current evidence and clinical practice needs, we designed the Milan Geriatrics 75+ Cohort Study, a prospective hospital-based outpatient cohort study (Figure 1). This study included 1861 men and women aged 75 years and older who were consecutively referred for a first comprehensive geriatric visit to the Geriatric Unit of the IRCCS Ca' Granda, Milan, Italy, in the period between January 3, 2000 and March 25, 2004. These participants routinely underwent an extensive standardized structured medical examination and comprehensive geriatric assessment. As the Italian health care system guarantees universal

coverage, the Milan Geriatrics 75+ Cohort Study represents the population seeking geriatric care with no restriction based on socio-economic status[47].

The Milan Geriatrics 75+ Cohort Study enrolled mainly women (about two thirds of participants). This may have resulted from higher life expectancy, higher prevalence of comorbidities such as dementia, and higher health care utilization in women compared to men[48,49]. This significant proportion of women allowed us to explore sex-differences in the association between thyroid status and mortality.

The PROSPER Study

The PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) was a randomised, double blind, placebo controlled trial designed to investigate the effect of pravastatin in the prevention of vascular events[50,51]. The PROSPER cohort included older adults aged 70-82 years with pre-existing, or risk factors for, cardiovascular disease, from three collaborating centres in Ireland, Scotland, and the Netherlands. Approximately half of the participants had a diagnosis of cardiovascular disease, defined as myocardial infarction or stable angina, intermittent claudication, stroke or transient ischaemic attack, or previous vascular surgery. The rest of the participants had one or more major cardiovascular risk factors, defined as hypertension, cigarette smoking, or diabetes mellitus. The PROSPER participants had high functional and cognitive status at baseline. Therefore, the PROSPER cohort allowed us to explore the associations between cardiovascular risk factors (heart rate, heart rate variability and blood pressure variability) and functional decline in a cohort with high baseline functional status and at high risk for cardiovascular disease.

Outline of this thesis

Chapter 2, 3 and 4 report findings from the Milan Geriatrics 75+ Cohort Study.

Chapter 2 explores the association between blood pressure and cognition, and whether it varies according to age and functional status.

Chapter 3 examines the relationship between blood pressure and mortality risk, and whether it varies according to functional and cognitive status.

Chapter 4 investigates the association between thyroid status and mortality risk in euthyroid older adults, and whether it differs by sex and age.

Chapter 5 and 6 report findings from the PROSPER cohort.

Chapter 5 presents new evidence on the association of heart rate and heart rate variability with functional decline in older adults at high risk of cardiovascular disease.

Chapter 6 analyses the relationship between blood pressure variability and functional decline in older adults at high risk of cardiovascular disease.

Chapter 7 summarises and discusses the main findings of this thesis.

References

1. United Nations, Department of Economic and Social Affairs, Population Division (2013). World Population Ageing 2013. ST/ESA/SER.A/348.
2. United States Census Bureau. International Programs. International Data Base. Available at: http://www.census.gov/population/international. Accessed October 27, 2015.
3. Vaupel JW. The remarkable improvements in survival at older ages. Philos Trans R Soc Lond B Biol Sci 1997;352:1799–804.
4. Christensen K, Doblhammer G, Rau R, et al. Ageing populations: the challenges ahead. Lancet 2009;374:1196–208.

5. World Health Organization. The global burden of disease: 2004 update. Available at http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/index.html. Accessed October 30, 2015.
6. Global Atlas on Cardiovascular Disease Prevention and Control. Mendis S, Puska P, Norrving B editors. World Health Organization, Geneva 2011.
7. World Health Organization and Alzheimer's Disease International. Dementia: A Public Health Priority, 2012. Available at http://www.who.int/mental_health/publications/dementia_report_2012/en. Accessed October 27, 2015.
8. Berr C, Wancata J, Ritchie K. Prevalence of dementia in the elderly in Europe. Eur Neuropsychopharmacol 2005;15:463-71.
9. Mozaffarian D, Benjamin EJ, Go AS, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation 2015;131:e29-322.
10. Fried LP, Tangen CM, Walston J, et al; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146-56.
11. Li Q, Wang S, Milot E, et al. Homeostatic dysregulation proceeds in parallel in multiple physiological systems. Aging Cell 2015 Sep 29. doi: 10.1111/acel.12402. [Epub ahead of print]
12. Mitnitski AB, Mogilner AJ, MacKnight C, et al. The mortality rate as a function of accumulated deficits in a frailty index. Mech Ageing Dev 2002;123:1457-60.
13. McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. Arch Intern Med 1993;153:2093-101.
14. Eggermont LH, de Boer K, Muller M, et al. Cardiac disease and cognitive impairment: a systematic review. Heart 2012;98:1334-40.
15. Qiu C, Winblad B, Marengoni A, et al. Heart failure and risk of dementia and Alzheimer disease: a population-based cohort study. Arch Intern Med 2006;166:1003-8.
16. Jefferson AL, Beiser AS, Himali JJ, et al. Low cardiac index is associated with incident dementia and Alzheimer disease: the Framingham Heart Study. Circulation 2015;131:1333-9.
17. Jefferson AL, Himali JJ, Beiser AS, et al. Cardiac index is associated with brain aging: the Framingham Heart Study. Circulation 2010;122:690-7.

18. Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988-1991. Hypertension 1995;25:305-13.
19. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507-20.
20. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013;34:2159-2219.
21. National Institute for Health and Clinical Excellence. Hypertension (CG127). http://www.nice.org.uk/guidance/cg127 . Accessed October 08, 2015.
22. Canadian Hypertension Education Program. 2015. https://www.hypertension.ca/images/CHEP_2015/CHEP2015_Full_EN.pdf . Accessed October 08, 2015.
23. American Diabetes Association. Standards of medical care in diabetes—2015. Diabetes Care 2015;38(Suppl. 1):S49–S57
24. Lewington S, Clarke R, Qizilbash N, et al; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903-13.
25. Satish S, Freeman DH Jr, Ray L, et al. The relationship between blood pressure and mortality in the oldest old. J Am Geriatr Soc 2001;49:367–374.
26. Boshuizen HC, Izaks GJ, van Buuren S, et al. Blood pressure and mortality in elderly people aged 85 and older: community based study. BMJ 1998;316:1780-4.
27. van Bemmel T, Gussekloo J, Westendorp RG, et al. In a population based prospective study, no association between high blood pressure and mortality after age 85 years. J Hypertens 2006;24:287–292.
28. Odden MC, Peralta CA, Haan MN, et al. Rethinking the association of high blood pressure with mortality in elderly adults: the impact of frailty. Arch Intern Med 2012;172:1162-8.
29. Peralta CA, Katz R, Newman AB, et al. Systolic and diastolic blood pressure, incident cardiovascular events, and death in elderly persons: the role of functional limitation in the Cardiovascular Health Study. Hypertension 2014;64:472-80.

30. Post Hospers G, Smulders YM, Maier AB, et al. Relation between blood pressure and mortality risk in an older population: role of chronological and biological age. J Intern Med 2015;277:488-97.
31. Warwick J, Falaschetti E, Rockwood K, et al. No evidence that frailty modifies the positive impact of antihypertensive treatment in very elderly people: an investigation of the impact of frailty upon treatment effect in the HYpertension in the Very Elderly Trial (HYVET) study, a double-blind, placebo-controlled study of antihypertensives in people with hypertension aged 80 and over. BMC Med 2015;13:78.
32. Taylor PN, Razvi S, Pearce SH, et al. Clinical review: A review of the clinical consequences of variation in thyroid function within the reference range. J Clin Endocrinol Metab 2013;98:3562-71.
33. Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. Thyroid 2014;24:1670-751.
34. Pearce SH, Brabant G, Duntas LH, et al. 2013 ETA Guideline: Management of Subclinical Hypothyroidism. Eur Thyroid J 2013;2:215-28.
35. Hollowell JG, Staehling NW, Flanders WD, et al: Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002; 87: 489–499.
36. Surks MI, Hollowell JG. Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. J Clin Endocrinol Metab 2007;92:4575-82.
37. Asvold BO, Vatten LJ, Midthjell K, et al. Serum TSH within the reference range as a predictor of future hypothyroidism and hyperthyroidism: 11-year follow-up of the HUNT Study in Norway. J Clin Endocrinol Metab 2012;97:93-99.
38. Atzmon G, Barzilai N, Surks MI, et al. Genetic predisposition to elevated serum thyrotropin is associated with exceptional longevity. J Clin Endocrinol Metab 2009;94:4768-75.
39. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J 1996;17:354-81.
40. Sloan RP, Demeersman RE, Shapiro PA, et al. Cardiac autonomic control is inversely related to blood pressure variability responses to psychological challenge. Am J Physiol 1997; 272:H2227-32.

41. Sloan RP, DeMeersman RE, Shapiro PA, et al. Blood pressure variability responses to tilt are buffered by cardiac autonomic control. Am J Physiol 1997;273:H1427-31.
42. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. Lancet 2010; 375: 938-48.
43. Meel-van den Abeelen AS, Lagro J, Gommer ED, et al. Baroreflex function is reduced in Alzheimer's disease: a candidate biomarker? Neurobiol Aging 2013; 34: 1170-6.
44. Beckett NS, Peters R, Fletcher AE, et al; HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008;358:1887-98.
45. Jacobs JM, Stessman J, Ein-Mor E, et al. Hypertension and 5-year mortality among 85-year-olds: the Jerusalem Longitudinal Study. J Am Med Dir Assoc 2012;13:759.e1-6.
46. der Wiel AB, van Exel E, de Craen AJ, et al. A high response is not essential to prevent selection bias: results from the Leiden 85-plus study. J Clin Epidemiol 2002;55(11):1119-25.
47. Lo Scalzo A, Donatini A, Orzella L, et al. Italy: Health system review. Health Systems in Transition, 2009; 11(6)1-216.
48. Gao S, Hendrie HC, Hall KS, et al. The relationships between age, sex, and the incidence of dementia and Alzheimer disease: a meta-analysis. Arch Gen Psychiatry 1998;55:809-15.
49. Hubbard RE, Rockwood K. Frailty in older women. Maturitas 2011;69:203-7.
50. Shepherd J, Blauw GJ, Murphy MB, et al. The design of a prospective study of Pravastatin in the Elderly at Risk (PROSPER). PROSPER Study Group. PROspective Study of Pravastatin in the Elderly at Risk. Am J Cardiol 1999;84:1192-1197.
51. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360:1623-1630.