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STUDY DESIGN

The transition from hypertension to hypertensive heart disease and heart failure: the PREFERS Hypertension study

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Abstract

Aims Despite evidence-based therapeutic approaches, target blood pressure is obtained by less than half of patients with hypertension. Hypertension is associated with a significant risk for heart failure, in particular heart failure with preserved left ventricular (LV) ejection fraction (HFpEF). Although treatment is suggested to be given early after hypertension diagnosis, there is still no evidence-based medical treatment for HFpEF. We aim to study the underlying mechanisms behind the transition from uncomplicated hypertension to hypertensive heart disease (HHD) and HFpEF. To this end, we will combine cardiac imaging techniques and measurements of circulating fibrosis markers to longitudinally monitor fibrosis development in patients with hypertension.

Methods and results In a prospective cohort study, 250 patients with primary hypertension and 60 healthy controls will be characterized at inclusion and after 1 and 6 years. Doppler echocardiography, cardiac magnetic resonance imaging, and electrocardiogram will be used for measures of cardiac structure and function over time. Blood biomarkers reflecting myocardial fibrosis, inflammation, and endothelial dysfunction will be analysed. As a proxy for HFpEF development, the primary endpoint is to measure echocardiographic changes in LV function and structure (E/e' and LAVI) and to relate these measures of LV filling to blood pressure, biomarkers, electrocardiogram, and cardiac magnetic resonance.

Conclusions We aim to study the timeline and transition from uncomplicated hypertension to HHD and HFpEF. In order to identify subjects prone to develop HHD and HFpEF, we want to find biomarkers and cardiac imaging variables to explain disease progression. Ultimately, we aim at finding new pathways to prevent HFpEF.

Keywords Hypertension; Hypertensive heart disease; Heart failure; Biomarkers; Diastolic function

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Introduction

Hypertension is common with a prevalence of approximately one third of the adult Swedish population[1], and similar figures are reported worldwide.[2] It is associated to cardiac structural (e.g. myocardial fibrosis, atrial and ventricular remodelling, and hypertrophy) and functional changes (e.g. impaired systolic and diastolic functions and arrhythmias) as well as vascular dysfunction, which all can be delayed or reversed by appropriate antihypertensive treatment.[3] Although blood pressure (BP) control is improving, target BP is still reached by less than half of the treated patients.[4]

Hypertension is the single risk factor with the greatest attributable risk for incident heart failure (HF)[5] and is considerably more common in HF with preserved left ventricular (LV) ejection fraction (HFpEF) than in HF with reduced ejection fraction (HFrEF).[6] In patients with established HFpEF, hypertension ranges between 50% and 70%.[7] However, the exact

mechanisms for the transition from hypertension to hypertensive heart disease (HHD) and HFpEF are less well understood. In contrast, pathophysiology and progression of HFrEF are better elucidated and may successfully be reversed by seven to eight evidence-based treatments.[8]

The evolution of myocardial fibrosis may be one early important mechanism in the transition from hypertension to HHD and subsequent HF. This can be studied through the recent development of cardiac imaging with advanced Doppler echocardiography,[9] cardiac magnetic resonance (CMR) imaging,[10] and assessment of circulating biomarkers reflecting myocardial fibrosis turnover, inflammation, and endothelial dysfunction.[11,12] Indeed, echocardiographic left chamber longitudinal strain and extracellular volume measured by CMR have recently been demonstrated to be useful to discriminate between healthy controls, patients with hypertension, and patients with HFpEF.[13] Also, circulating plasma biomarkers reflecting altered myocardial tissue turnover can differentiate patients with left ventricular hypertrophy (LVH) from patients with LVH and HFpEF.[14] In addition, biomarkers may identify phenotypes of high collagen cross-linking, which has been suggested to have impact on the response to medical treatment in HFpEF.[15]

An increased understanding of these mechanisms allows the development of specific treatments, guided by cardiac imaging and/or biomarker assessments, to delay or prevent the transition from hypertension to HF.[6] This may have considerable clinical implications in reducing cardiovascular complications to hypertension. Thus, the aim of the present study is to characterize and study the timeline and the transition from uncomplicated hypertension to HHD and HFpEF in subjects with primary hypertension using advanced cardiac imaging techniques and bioinformatics (*Table 1*). Furthermore, we aim to compare changes of HFpEF variables and biomarkers in this study with patients with new onset symptomatic HFpEF in the Stockholm PREFERS Heart failure study.[16]

Study design

The study PREFERS Hypertension is the last part of the PREFERS (*Preserved and Reduced Ejection Fraction Epidemiological Regional Study in Stockholm*, Clinical trial NCT03671122), a clinical trial first aiming at describing underlying pathophysiological mechanisms in new onset HF, either HFpEF or HFrEF with approximately 600 patients.[16] PREFERS Hypertension study is a single-centre, prospective clinical cohort study performed in collaboration between the Department of Cardiology at Danderyd Hospital and the Primary Health Care Services in Stockholm, Sweden. The study will recruit patients with a diagnosis of primary hypertension with an ongoing antihypertensive drug treatment as well as healthy control subjects, for comparison as previously described.[17] For inclusion and exclusion criteria, see *Table 2*. All subjects will be assessed at the Cardiovascular Research Laboratory, which is part of the Clinical Research Centre at Danderyd University Hospital (*Figure 1A* and *1B*).

Primary hypertension is defined as a diagnosis documented in primary care at some time point within the last 24 months and ongoing antihypertensive drug treatment (maximum up to two to three drugs). The currently recommended definition of hypertension as a systolic office BP $>$140 mmHg and/or diastolic BP $>$90 mmHg[18] is widely adapted in primary health care. Exclusion of secondary hypertension is at the discretion of the primary health care physician or may be excluded at the inclusion visit. Controlled hypertension is defined as $<$140/90 mmHg.

Table 1 Hypotheses and aims

Hypotheses of the present study:
1. Hypertension with normal left atrial/ventricular function deteriorates over time, starting with increasing filling pressure, left atrial enlargement followed by reduced global longitudinal strain with LVEF $>$50% and heart failure symptoms (HFpEF)
2. Circulating biomarkers reflecting myocardial fibrosis, inflammation and endothelial dysfunction reflects the transition from hypertension to hypertensive heart disease and HFpEF
As a proxy for HFpEF development, our overall aim is to investigate:
if change in diastolic cardiac function E/e' or LAVI after 1 year is associated to blood pressure at baseline.
Specific aims:
a. to study if change in diastolic cardiac function measured with E/e' or LAVI after 1 year is associated to change in blood pressure from baseline to 1 year
b. to assess if blood pressure control at baseline (according to guidelines and age adjusted) is associated to diastolic cardiac function measured with E/e' or LAVI after 1 year
c. to investigate if blood pressure control after 1 year (according to the guidelines and age adjusted) is associated to diastolic cardiac function measured with E/e' or LAVI after 1 year
d. to study the temporal evolution (baseline, 1 year, six years) of the diastolic function measured with E/e' or LAVI
e. to investigate gender aspects on the temporal evolution (baseline, 1 year, and 6 years) of the diastolic function measured with E/e' or LAVI
f. to study the temporal evolution (baseline, 1 year, and 6 years) of the diastolic function measured with echocardiography and CMR
g. to assess if temporal changes (baseline, 1 year, and 6 years) in circulating levels of biomarkers reflecting myocardial fibrosis, inflammation, and endothelial dysfunction are associated with changes in blood pressure
h. to assess if temporal changes (baseline, 1 year, and 6 years) in circulating levels of biomarkers reflecting myocardial fibrosis, inflammation, and endothelial dysfunction are associated with changes in diastolic function

CMR, cardiac magnetic resonance imaging; HFpEF, heart failure with preserved ejection fraction; LAVI, left atrial volume index.

Table 2 Inclusion and exclusion criteria in the PREFERS Hypertension study

Inclusion criteria
• Primary hypertension
• Age ≥ 18 years
• Preserved cognitive function and expected longevity 1 year
• Written informed consent
Exclusion criteria
• Heart failure and/or reduced LVEF
• Valvular heart disease of haemodynamic importance
• Resistant hypertension
• Pregnancy
• Renal failure, GFR <30 mL/min/1.73 m^2

GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction.

Recruitment of study participants and timeline

Hypertension in Sweden is usually managed at primary health care centres. Through a collaboration between hospital and primary care, the patients will be recruited from health care centres in various socio-economic areas in Stockholm (approximately 10 care centres, total catchment area of 100 000 inhabitants). To include 250 patients and with an expected response rate of 25–30%, each health care centre will identify and randomly select and invite 100 patients, gender 1:1 using the software MedRave4 (Medrave Software AB, Stockholm, Sweden; *Figure 1A*). Patients will be characterized at baseline and after 1 and 6 years per standardized protocol (*Figure 1B*), and they will have their medication optimized at baseline and follow-ups, according to the guidelines.[18] Parallel with patient recruitment, *healthy control subjects*, matched in age and gender, will be recruited by advertisement in local newspapers. Inclusion will be performed following a telephone interview, confirming they are apparently healthy and have no daily medication. Control subjects will follow the same study protocol as the patients but planned to be examined at inclusion only. The study protocol has been approved by the regional Ethics Committee and the Stockholm Health Care services, and all study participants will give their written informed consent.

Measurements

All study data will be collected into electronic case report forms using the Research Electronic Data Capture.

Blood pressure measurements and pulse wave velocity

Seated BP measurements will be made in accordance to the current guidelines.[18] Three consecutive BP measurements are recorded, 1–2 min apart, using an oscillometry device (Omron M3 Comfort, OMROM Healthcare Co., Ltd. Kyoto, Japan). BP will also be measured 1 and 3 min after standing from a seated position to assess orthostatic hypotension. To screen for lower extremity artery disease, an ankle-brachial index will be recorded, using continuous wave Doppler.

Ambulatory blood pressure monitoring during 24 h will be assessed by a Spacelabs ABP monitoring 90217A device (Spacelabs Healthcare, Snoqualmie, WA, USA), programmed to record BP at 20 min intervals to provide an average BP value for daytime, night-time, and 24 h. A diary of the patients' activities and sleep-time will be recorded. A minimum of 70% useable BP recordings are required for a valid ambulatory blood pressure monitoring session. The diagnostic threshold for hypertension is according to the ESC guidelines.[18] The carotid-femoral pulse wave velocity (PWV) is assessed by the SphygmoCor XCEL device (AtCor Medical, Sydney, Australia), which allows for non-invasive assessment of the central arterial pressure waveform and measures of aortic stiffness.[19]

Electrocardiogram

Twelve lead ECG data will be stored digitally (EC store version 4.1; Cardiolex Medical AB, Stockholm, Sweden). In harmony with the PREFERS HF study,[16] LVH will be assessed according to the Sokolov Lyon index. In addition, beside a conventional 12-lead ECG, we will analyse a resting 12-lead ECG that combines advanced and conventional ECG parameters within computerized ECG scores that have been demonstrated to increase the detection accuracy of concentric LVH and in screening for LV systolic dysfunction.[20]

Echocardiographic and cardiac magnetic resonance measurements

We will follow current recommendations for echocardiography[21] to record two-dimensional echocardiographic and Doppler variables and perform Doppler tissue imaging similar to those measured in the PREFERS HF study[16] (*Table 3*). All measurements will be presented as mean values of three cardiac cycles. A Vivid E9® (GE, Waukesha, Wisconsin, USA) Ultrasound System will be used. To reduce interobserver variability, only two sonographers will perform the investigations, which will be stored on a digital server and will be analysed offline.

For CMR, a Siemens Aera system (Siemens Healthcare, Erlangen, Germany) will be used to deliver standard measurements of chamber dimensions and function and signs of tissue scars of ischaemic and non-ischaemic origin. Myocardial extracellular matrix and signs of fibrosis will be examined by T1 mapping.[22] Fully automated quantitative perfusion mapping during rest and adenosine stress[23] will give a quantitative measurement for perfusion in mL/min/g, which will be used to search for perfusion defects; both focal defects

Figure 1 (A) Flow chart demonstrating recruitment, inclusion, and study protocol. (B) Flow chart demonstrating study protocol and follow-up plan. ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CMR cardiac magnetic resonance imaging; GP, general practitioner.

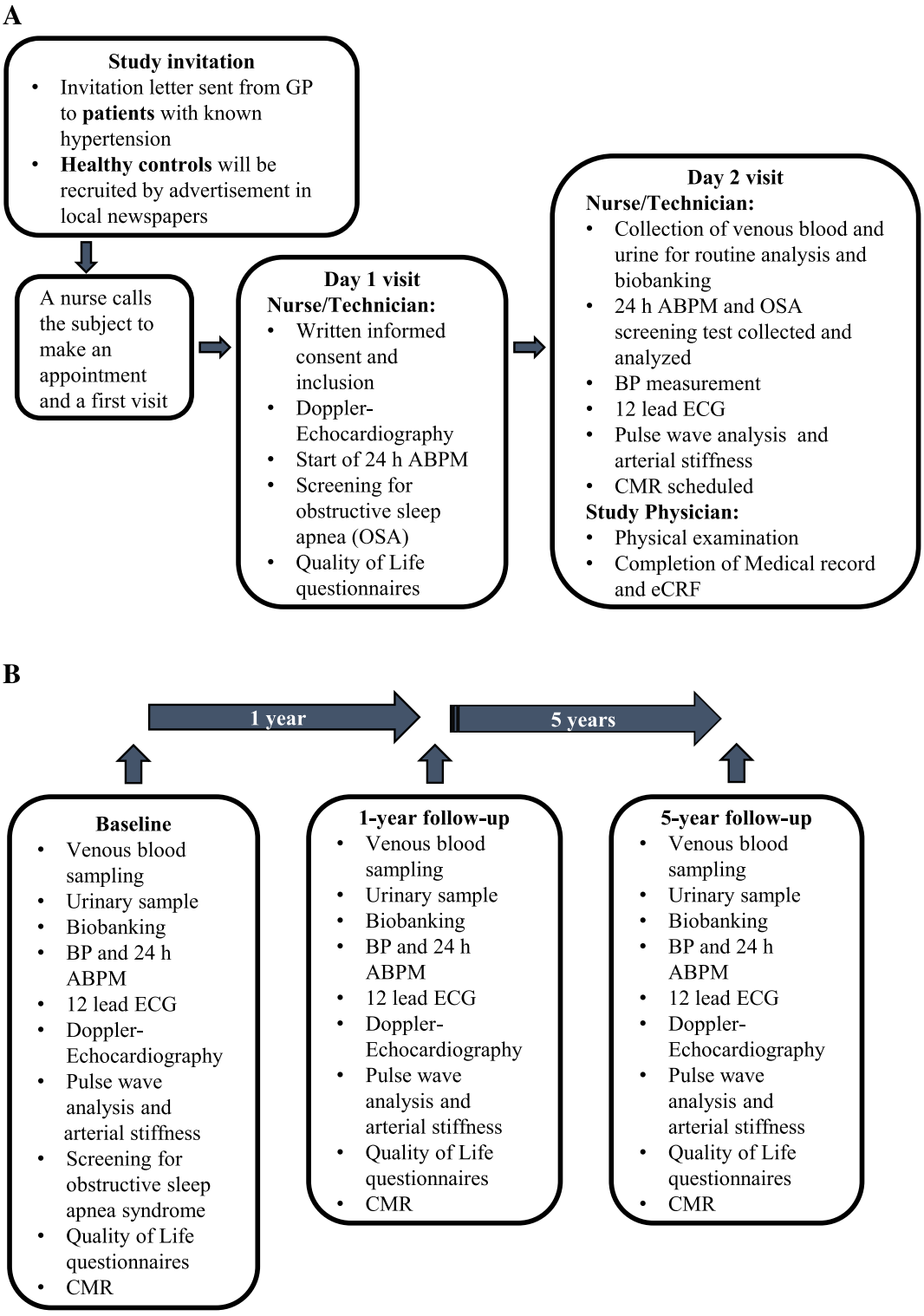

Table 3 Doppler echocardiography protocol

Dimensions and volumes	Systolic/diastolic function	Valves
Left ventricle • LVEED (mm) • LVESD (mm) • Septal thickness (mm) • Posterior wall thickness (mm) • LVEDV bi-plane (mL) • LVESV bi-plan (mL) • LVESVI (mL/m^2) Right ventricle • RVOT (mm) • RVEDD 4CH (m) Left atrium • LAVI bi-plan (A-L) (mL/m^2) • LA area 4CH (cm^2) Right atrium • RA area 4CH (cm^2)	Left ventricular function • Regional wall abnormalities (Y/N) • LVEF bi-plane (%) • Global longitudinal strain 2D (%) • Right ventricular systolic function • Tricuspid annular displacement (mm) Left ventricular diastolic function • E wave deceleration time (ms) • E wave velocity (m/s) • A wave velocity (m/s) • A wave duration (ms) • E/A ratio • E-wave velocity after Valsalva • A-wave velocity after Valsalva • E/A ratio after Valsalva Left atrial diastolic function • Global longitudinal strain 2D (%) Doppler tissue imaging • Septal e′ (m/s) • Lateral e′ (m/s) • E/e′ mean ratio • PVs velocity (m/s) • PVd velocity (m/s) • PV s/d ratio PV reversal velocity (m/s) • Signs of increased filling pressures (Y/N)	Aortic valve velocity (m/s) LVOT velocity (m/s) Aortic/mitral/pulmonary/tricuspid stenosis • non/mild/moderate/severe Aortic/mitral/pulmonary/tricuspid regurgitation • non/mild/moderate/severe Right ventricular systolic pressure • Tricuspid regurgitation velocity (m/s) Estimated RA pressure (mmHg) Estimated PA systolic pressure (mmHg) Inferior vena cava respiratory variation (normal, <50%, absent)

4CH, apical four-chamber view; A, late mitral valve inflow wave during atrial contraction; a′, myocardial tissue velocity during atrial contraction; d, diastole; E, early mitral valve inflow; d, diastole; I, indexed for body surface area; e′, myocardial tissue velocity early diastolic wave; LA, left atrium; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; LVOT, left ventricular outflow tract; PA, pulmonary artery; PV, pulmonary vein; RA, right atrium; RVEDD, right ventricular end diastolic diameter; RVOT, right ventricular outflow tract; s, systole.

due to obstructive coronary artery disease and defects in the global myocardial perfusion reserve due to coronary microvascular disease.

Measurements questionnaires

Quality of life measurements are to be assessed with validated instruments: the EuroQol-5 dimensions, the Kansas City cardiomyopathy questionnaire, and the Minnesota living with heart failure questionnaire. To screen for excessive daytime sleepiness, we will use the Epworth Sleepiness Scale version 1.0.

Screening for obstructive sleep apnoea

Screening for sleep disorders and obstructive sleep apnoea is performed at inclusion by the SOMNOcheck micro CARDIO (Weinman, Hamburg, Germany), self-applied by the study participants at home before bedtime. The ambulatory overnight cardio-respiratory polygraphy recording will measure apnoea/hypopnea, desaturation, and arousal indices.

Peripheral venous blood and urine sampling

Peripheral blood and urine will be collected after overnight fasting with no ingestion of caffeine or nicotine within at least 12 h. Clinical routine analyses of plasma and urine will be performed directly, but for future analysis of biomarkers and DNA extraction, aliquots of whole blood, plasma, and serum will be stored at −80°C in the Stockholm Medical Biobank until further analysis. This ensures a standardized handling of biomaterial with high security and traceability also for long-term storage. In the PREFERS Hypertension study, we plan to analyse the same panel of biomarkers as for the PREFERS HF study,[16] which will enable a comparison between the two cohorts. Here, we focus on biomarkers indicative of various pathophysiological mechanisms relevant to HFpEF, including those reflecting myocardial fibrosis, inflammation, and endothelial dysfunction, as listed in *Table 4*.

Outcome measures

Mortality data outside hospital and incident admission to hospital due to HF will be obtained by merging the Swedish

Table 4 Examples of blood biomarkers planned to be assessed in plasma

Function/pathophysiology	Examples of biomarkers	Method
Endothelial dysfunction	Soluble E-selectin, ICAM-1, VCAM-1, allantoin, ADMA, SDMA, calprotectin, arginin, endothelial microparticles (EMPs)	Immunoassays and flow cytometry (microparticles)
Inflammation	HsCRP, TNF-α, interleukin-6, E-selectin, ICAM-1, VCAM-1, YLK-40, GDF15	Immunoassays
Myocardial function and markers of fibrosis	Troponins, natriuretic peptides, sST2, galectin-3, titin (fragment), collagen split products PICP, CITP-I, MMPs (1, 2, and 9), IGFBP2	Immunoassays

ADMA, asymmetrical dimethyl arginin; CITP I, C-terminal telopeptide of collagen I; GDF15, growth differentiation factor 15; hsCRP, High sensitive C-reactive protein; ICAM-1, intracellular adhesion molecule type 1; IGFBP2, insulin-like growth factor-binding protein 2; MMP, Matrix metalloproteinase; PICP, carboxyterminal propeptide of type 1 procollagen; SDMA, symmetrical dimethyl arginin; sST2, soluble ST2; TNF-α, tumour necrosis factor-α; VCAM-1, vascular cell adhesion molecule type 1; YLK-40, chitinase-3-like protein 1.

cause of death register and the Swedish national inpatient register. The unique personal identification number of all Swedish citizens will ascertain complete follow-up.

Primary endpoint and statistical power

As a proxy for HFpEF development, our overall aim is to investigate if change in diastolic cardiac function E/e′ or left atrial (LA) volume index after 1 year is associated to BP at baseline. Therefore, the primary endpoint in this study is either mean change of E/e′ of 2 or more or mean change of LA volume index of 4 mL/m^2 or more after 1 year. These assumptions are based on a cross-sectional analysis of a big cohort from Olmsted County, Minnesota, where clear-cut differences were shown for these echocardiographic variables in patients with hypertension, HFpEF, and healthy controls.[17] To reach 80% power at a two-sided level of significance of 0.05, the present study planned to recruit 250 patients and 60 healthy controls, including 20% drop outs.

Discussion

In the present study, we hypothesize that hypertension might be a pivotal upstream pathophysiological phase that initiates the deterioration over time (*Table 1*). Uncomplicated hypertension may start the evolution of extracellular changes and myocardial fibrosis that might be an early mechanism in the transition from hypertension to HHD and subsequent HF. Early signs of myocardial fibrosis might be the initial step that leads to decreased LA and LV compliance, which may start with deteriorated LA strain, followed by increased filling pressure, LA enlargement, and subsequent reduced global longitudinal strain with LVEF >50% and HF symptoms (HFpEF). However, the timeline as well as the upstream pathophysiological mechanisms for transition from hypertension to HHD need to be elucidated. Most likely, signs of myocardial fibrosis could be found early in patients with hypertension. Our rationale is that there may be subjects more prone to disease than others, and it is important not only to identify them early but also to find new strategies to prevent or delay disease progress. Therefore, we aim to perform a longitudinal study on the transition from uncomplicated hypertension to symptomatic HFpEF using clinical, extensive imaging, and biomarker parameters. Cardiac imaging modalities as echocardiography and CMR are keys to describe both functional and structural changes during this transition. In addition, biomarkers reflecting myocardial fibrosis, inflammation, and endothelial dysfunction could be used as early non-invasive measures and could lead to new treatment strategies.

Timeline

To monitor the transition from hypertension to HHD and impaired diastolic function, we plan to examine our study cohort at inclusion and after 1 and 6 years. Even though our patients might not develop HFpEF within 6 years, our power calculation is made to detect clinically relevant changes and signs of increased LV filling pressure, as a proxy for HFpEF. Beyond analyses of underlying pathophysiological mechanisms in both cardiac imaging data and blood biomarkers during the study period, we have the opportunity to later analyse outcome measures, by merging our database with the national registries for incident HF and admission to hospital.

Blood pressure measurements and pulse wave velocity

Large artery stiffening is associated to systolic hypertension and age-dependent increase in pulse pressure, and PWV is the gold standard to measure large artery stiffness.[24] In addition, elevated arterial stiffness is also associated to cardiovascular disease and mortality.[25] In a cross-sectional study, subjects with hypertension and HFpEF had elevated arterial stiffness compared with people with normal BP.[17]

Furthermore, Framingham data have shown that greater aortic stiffness is associated with increased risk of HF.[26] Most likely, elevated PWV reflects both the duration of hypertension and the effects of antihypertensive treatment, but still, the association of central aortic stiffness with incident HHD and HFpEF physiology over time is not well described. PWV might be one relevant and easily available marker of disease progression.

Electrocardiogram

A conventional 12-lead ECG will be assessed at each follow-up, but to extend the protocol, we will also analyse advanced ECG parameters.[20] ECG information occurring with signs of LVH and increased LV mass predicts adverse clinical outcome.[27] Using advanced ECG parameters may increase both sensitivity and specificity when analysing signs of LVH[28] as well as other signs of HHD. These ECG findings, common in hypertension patients, may be reversible with effective pharmacological antihypertensive treatment.[29] However, a conventional 12-lead ECG has limited sensitivity for detecting increased LV mass because myocardial mass and diffuse fibrosis have opposing effects upon ECG voltage measures of LVH. Consequently, myocardial fibrosis may disguise the ECG signs of increased LV mass.[30]

Echocardiography and cardiac magnetic resonance

Hypertension affects cardiac function through the interplay between the LV performance and the arterial system, the ventricular–arterial coupling. The left ventricle wall thickens in response to neurohormonal activation, increased afterload, and cytokines, which all are associated with arterial hypertension. HFpEF patients have also been suggested to have a subtle systolic dysfunction not reflected in ejection fraction but LV contractility.[31] Interestingly, LV longitudinal strain is impaired in both HHD and HFpEF[32] and is also associated to prognosis in HFpEF.[31] To further investigate the ventricular–arterial coupling, we plan to assess measures of elevated filling pressure and PWV over time in the present study. LA enlargement reflects cardiac structural remodelling and is an early sign of HHD.[33] Usually, LA enlargement is found before the development of LVH and LA enlargement is up to three-fold more common in patients with hypertension compared with healthy controls.[34] LA mechanical deterioration or LA dysfunction is also often found before structural changes occur. Recently, LA global strain has been demonstrated as a feasible method to evaluate LA function and an inverse relationship between LA–global strain and diastolic LV filling pressures has been shown[35].

We will use an advanced protocol for CMR that give us opportunity to investigate cardiac diastolic function and to gain our knowledge regarding pathophysiological mechanisms. We will perform a complete evaluation of the LV diastolic function, according to the updated international echocardiographic guidelines. In addition, we will use a quantitative perfusion mapping during rest and adenosine stress to confirm or exclude ischaemic coronary artery disease and to obtain quantitative measurements of microvascular function or the myocardial perfusion reserve, corresponding to the coronary flow reserve.[36] Late gadolinium enhancement is the reference standard for non-invasive imaging of myocardial scar and focal fibrosis. With this non-invasive method, changes in the myocardium over time may be assessed.[22,37] Previously, both LV global longitudinal strain, measured with echocardiography, and extra-cellular volume, measured with CMR, have been demonstrated able to discriminate between HHD and HFpEF.[38] CMR is therefore one way to find early signs of myocardial fibrosis.

Biomarkers reflecting myocardial fibrosis, inflammation, and endothelial dysfunction

Myocardial fibrosis is characterized by excessive deposition of collagen type I and collagen cross-linking (CCL) and is involved in LV stiffening and diastolic dysfunction. Still, clinical evaluation of myocardial extracellular matrix and fibrosis is difficult; until now, the gold standard has been myocardial tissue biopsies—an invasive procedure not without risks. The measurement of fibrosis markers in the circulation has evolved as an alternative strategy, which we will analyse and relate to the findings obtained by the different cardiac imaging methods.

Cardiac fibroblasts are central for the synthesis of collagen and matrix metalloproteinase (MMP), fibrinolytic enzymes that degrades collagens. Interestingly, collagen type I synthesis and degradation can be assessed indirectly in the circulation, by measuring the degradation products procollagen type 1 c-terminal propeptide and collagen type I C-terminal telopeptide, respectively.[11] We have earlier demonstrated that the collagen split product procollagen type 1 c-terminal propeptide is related to other markers of HF, such as brain natriuretic peptide, LV size, and diastolic function in HFrEF.[39] Furthermore, the degree of myocardial CCL determines collagen's resistance to degradation by MMP-1, and excessive CCL is associated with hospitalization for HF in hypertensive patients. In addition, the serum collagen type I C-terminal telopeptide: MMP-1 ratio has been demonstrated to identify patients with increased CCL.[40] Other interesting biomarkers of HF and remodelling are suppression of tumourigenicity-2 and galectin-3 (Gal-3). Plasma levels of suppression of tumourigenicity-2 are higher in patients with HFpEF than in patients with HFrEF but have similar effect on predicting prognosis in both patient groups.[41] Gal-3 is expressed by

activated macrophages and plays a regulatory role in inflammation and cardiac fibrosis in animal studies.[42] Interestingly, human data from the Framingham study have shown that increased circulating levels of Gal-3 are associated to incident HF.[43]

The transition from hypertension to HHD and HF is characterized by increased levels of natriuretic peptides, where N terminal pro brain natriuretic peptide is associated to increased LV wall stress. However, myocardial fibrosis, inflammation, and coronary artery disease may have a central pathophysiological role in disease progression.[12] Other HFpEF co-morbidities, mainly obesity and diabetes mellitus, induce a pro-inflammatory state, which starts and maintains a chronic activation of reactive oxygen species, which limits the bioavailability of nitric oxide in cardiomyocytes. Interestingly, nitric oxide is important for endothelial function, which probably has a central role in the pathophysiology of HFpEF. The endothelium regulates vasomotor tonus and communicates closely with nearby smooth muscle cells that regulate BP. Furthermore, hypertension has been suggested to promote inflammation, and endothelial dysfunction in hypertensive patients correlates with biomarkers of inflammation including tumour necrosis factor α, interleukin 6, C-reactive protein, E-selectin, vascular cell adhesion molecule 1, and intercellular adhesion molecule 1.[12] The pro-inflammatory state may result in an impaired microvascular and macrovascular functions and might cause downstream reactions that stiffen cardiomyocytes through hypophosphorylation of titin and increased collagen deposition, causing LV dysfunction and HFpEF.[12]

Conclusions

Because hypertension is usually managed at primary health care centres, the present study is built upon a scientific collaboration between hospital and primary care. We aim to characterize and study the timeline and the transition from uncomplicated hypertension to HHD and HFpEF in subjects with primary hypertension using advanced cardiac imaging techniques and bioinformatics. Further, we want to find cardiac imaging variables and biomarkers to explain and monitor disease progression and identify phenotypes prone to develop HHD and HFpEF. Ultimately, the present study may contribute to finding new treatment strategies of hypertension in order to prevent HFpEF. The results will guide and support health care providers in both hospital and primary care to provide an optimal and individualized treatment, which may change and ultimately improve living conditions for a large patient group.

Conflicts of interest

None declared.

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