

Rationale and design of the SMART Heart study

A prediction model for left ventricular hypertrophy in hypertension

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Left ventricular hypertrophy (LVH) is an independent risk factor for the development of heart failure, coronary heart disease and stroke. LVH develops in response to haemodynamic overload, e.g. hypertension. LVH was originally thought to start as an adaptive and beneficial response required to normalise wall stress. However, this concept has been challenged by recent animal experiments suggesting that any degree of LVH is detrimental for the preservation of cardiac function and survival. If confirmed in humans, these findings imply that an increase in LV mass should be prevented, e.g. by lifestyle or pharmacological interventions. To facilitate and optimise interventions, the SMART Heart study was recently set up to develop a prediction model, also involving single nucleotide polymorphism data, for the identification of subjects at high risk of developing LVH in hypertension. For this purpose 1000 subjects with chronic hypertension will undergo cardiac

MR imaging. In addition, this study allows the extrapolation of animal experimental genetic research into the human situation. (*Neth Heart J* 2007;15:295-8).

Keywords: hypertrophy, MRI, single nucleotide polymorphism (SNP), risk prediction, delayed enhancement

Left ventricular hypertrophy (LVH) develops in response to increased biomechanical stress, e.g. high blood pressure. Large population studies have provided evidence that LVH confers increased risk for stroke, myocardial infarction, heart failure and cardiovascular death.¹ This association was found both in samples of the general population, such as the Framingham study^{2,3} and the Second National Health And Nutrition Examination Survey Epidemiological Follow-up Study (NHANES-II),⁴ and in groups of patients who were already suffering from a symptomatic vascular disease, e.g. the Heart Outcomes Prevention Evaluation (HOPE) study.⁵ Also over a shorter period of time, LVH has been associated with an increased risk of LV dysfunction developing.⁶ LVH can have a concentric morphology, i.e. increased mass in the absence of dilation, or an eccentric morphology, i.e. increased mass with dilation. However, evidence as to whether concentric or eccentric morphology is associated with worse prognosis is contradictive.⁷⁻⁹ Importantly, pharmacological treatment can induce regression of both concentric and eccentric LVH, which is associated with improved prognosis.¹⁰ Interestingly, in the Losartan Intervention For Endpoint (LIFE) study the angiotensin-II receptor type 2 antagonist losartan induced more LVH regression than the β -blocker atenolol.¹¹ In addition, it was observed that LV dysfunction ameliorated upon LVH regression in both treatment arms.¹²

LVH was originally thought to be required for the normalisation of wall stress in haemodynamic overload.¹³ This concept of 'adaptive hypertrophy' is now

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being challenged by a large number of animal experiments, consistently suggesting that any degree of LVH is detrimental for LV function and survival.¹ In a landmark paper, Esposito et al. demonstrated that the genetic inhibition of the LV hypertrophic response to surgically increased aortic pressure did indeed result in increased LV wall stress compared with wild-type animals who developed LVH.¹⁴ However, while wild-type animals developed LV dilation and dysfunction, the genetically altered animals did not. If confirmed in humans, this notion implies prognostic benefit from LVH inhibition, e.g. by lifestyle changes, by pharmacological blood pressure lowering and/or by pharmacological intervention in molecular pathways involved in LVH. Specifically, hypertensive patients at high risk of developing LVH may need different drugs compared with those with a low risk of developing LVH. Such a view necessitates the identification of patients at high risk for LVH development. For this purpose, the SMART Heart study aims to develop a prediction model for LVH development, also involving single nucleotide polymorphism (SNP) data. Because hypertension is the most prevalent stimulus for LVH development, SMART Heart focuses on hypertensive subjects.

We aim to detect SNPs in genes in the calcineurin, NFAT and MEF2 pathways, which our group have demonstrated to be involved in LVH in animal studies.¹⁵⁻¹⁷ These data come from animal studies yet extrapolation towards patient populations is warranted. Therefore, as a secondary aim SMART Heart allows the extrapolation of animal data to the human situation, by evaluating the relation of SNPs in the pathways mentioned above in humans. In addition, it may point to a possible role for other genes, which have not yet been studied.

Design of the SMART Heart study

Aim

The first aim of the SMART Heart study is to develop a prediction model, also involving SNP data in the calcineurin, NFAT and MEF2 pathways, for LVH development in hypertensive subjects.

Secondly, SMART Heart aims to facilitate the extrapolation of animal experimental data on molecular pathways involved in LVH development.

Thirdly, the evaluation of SNPs across quartiles of LV mass index may point to a possible role for other genes, which have not yet been studied.

Population

SMART (Secondary Manifestations of ARterial disease) is a large single-centre prospective cohort study among patients newly referred to the University Medical Centre Utrecht with clinically manifest atherosclerotic vessel disease, or marked risk factors for atherosclerosis.¹⁸ Detailed information on medical history, including medication use, has been obtained from the

participants of the SMART study together with extensive measurements of cardiovascular risk factors, including an ECG. A DNA sample has been stored for all participants. In addition, all participants are being followed for the occurrence of cardiovascular events, including myocardial infarction, stroke and cardiovascular death. To date, over 6000 patients have been enrolled.

To address the objectives of the SMART Heart study 1000 patients with long-standing (i.e. ≥ 3 years) hypertension, but free of known coronary or valvular disease, will be selected for cardiac MR imaging. Hypertension is defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or antihypertensive treatment based on self report and blood pressure measurements at baseline of the SMART study. Additional exclusion criteria for the SMART Heart study are severe concomitant illness, morbid obesity (BMI >40 kg/m²), and contraindications to MRI examination. All SMART Heart participants will be asked to complete a modified SMART questionnaire on medical (family) history, and medication on the day of examination and resting blood pressure, height and weight will be recorded.

Cardiac imaging

All subjects will undergo cardiac MRI (CMR), and in a randomly selected subgroup strain/strain-rate echocardiography will be performed. CMR is the most

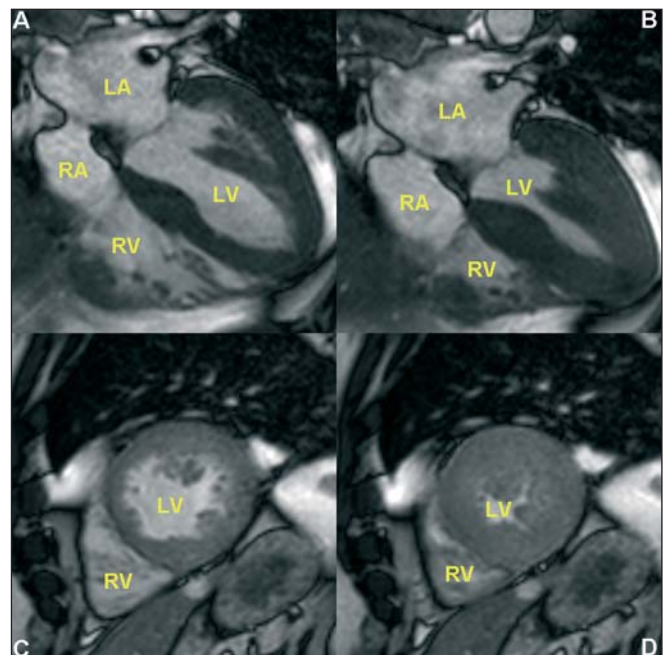


Figure 1. Cardiac MRI images in a subject with increased LV mass. A-B. Four-chamber view demonstrating the four cardiac chambers, in end-diastole (A) and end-systole (B). C-D. Short-axis view demonstrating the ventricles, in end-diastole (C) and end-systole (D). LA=left atrium, RA=right atrium, LV=left ventricle, RV=right ventricle.

accurate noninvasive method for obtaining anatomical information.¹⁹ Compared with standard echocardiography, variability with CMR measurement of ventricular mass is three times smaller. Smart Heart will use 1.5 T Philips Achieva MRI scanners (Philips Medical Systems, Best, the Netherlands). In a 30-minute CMR protocol, LV mass, LV end-diastolic and end-systolic volumes and left atrial volume will be measured using a steady state free precession (SSFP) pulse sequence for optimal blood-myocardium contrast (figure 1).

These measurements are performed on serial short-axis views, using dedicated software (ViewForum, Philips Medical Systems). LV mass will be analysed as a continuous variable. Subjects with an LV mass index in the highest quartile will be considered cases. Ejection fraction and cardiac output are calculated from end-diastolic and end-systolic volumes. Increased left atrial volume was previously suggested as a marker of LV diastolic dysfunction, and was found to be associated with increased cardiovascular risk.²⁰ A bolus of gadolinium contrast medium (0.2 mmol/kg) will be administered intravenously for delayed enhancement scans (inversion recovery-T1 pulse) in several planes covering the entire LV. Fibrotic areas in the LV will be identified (figure 2), thus enabling the detection and semiquantification of previous (silent) myocardial infarctions,²¹ and the differentiation between various forms of non-ischaemic LVH.²²

Strain/strain-rate echocardiography will be used to study regional abnormalities in myocardial deformation.²³ Smart Heart will use a Vivid 7 machine (GE Vingmed ultrasound, Horten, Norway) with a 2.5 MHz ultrasound probe. Earlier studies have defined different strain and strain-rate patterns of the longitudinal and radial fibres in both normal and diseased myocardium. A decrease in peak strain, an increase in time-to-peak strain and the presence of postsystolic thickening is considered abnormal. Furthermore, by comparing the strain and strain-rate

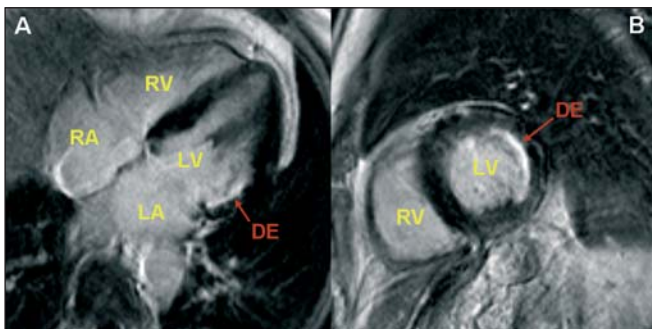


Figure 2. Cardiac MR images using the delayed enhancement (DE) technique. A fibrotic area (arrow) is seen in the four-chamber (A) and short-axis (B) view. This is most likely a silent myocardial infarction. LA=left atrium, RA=right atrium, LV=left ventricle, RV=right ventricle.

curves, it is possible to distinguish between ischaemic and nonischaemic causes of postsystolic thickening.²⁴ Furthermore, tissue Doppler and Doppler echocardiography will be used to evaluate LV diastolic function.²⁵

SNP analysis

Single nucleotide polymorphism (SNP) analysis will be used to develop the prediction model and for further aetiological studies on the genetic background of LVH, as described above.

To cover the total genetic variation in the genes mentioned above we will search for new genetic variations, through the available databases (such as dbSNP: www.ncbi.nlm.nih.gov/SNP) and Celera (www.celeradiscoverysystem.com) and our own research (sequencing). The final selection will be based on the haplotype block structure of the available SNPs. Across quartiles of LV mass index genes will be measured at the Hubrecht laboratory using DHPLC and sequencing techniques. Within those groups SNPs will be determined. Comparison of SNPs will be performed using standard regression techniques. In the final analyses, regression techniques will be applied to adjust for potential confounding factors.

Prediction model development

The prediction model will evaluate traditional risk factors, such as age, gender, previous cardiovascular events, blood pressure level, cholesterol level, diabetes and medication use, with the individual genetic profile, on the presence of increased LV mass index on MRI. Subjects with an LV mass index in the highest quartile will be considered cases. The most common genetic variation is the SNP, a DNA sequence variation occurring when a single nucleotide is replaced by another. Such a variation must occur in at least 1% of the population to be considered a SNP. The characteristics that relate to LV mass index with a p value of <0.157 will be evaluated in a multivariable model to assess the contribution of each risk factor separately. Next, model shrinkage techniques will be applied to adjust for over-optimism of the obtained model. Then a prediction rule will be developed. Next, using c-statistic the ability of the prediction rule to correctly identify those who do and those who do not develop an LV mass index in the highest quartile will be examined. Next a risk score will be compared with the risk of developing an LV mass index in the highest quartile to determine a cut-off point above which we feel that the risk of an LV mass index in the highest quartile is clearly increased, and the number of false-positives (high risk, but no increased LV mass development) is low. Validation of the prediction rule in a different study population will be addressed in the future.

Sample size calculation

For the aetiological question on genetics and LVH the sample size consideration was based on several assumptions. Using the highest quartile of LV mass

index as cases, the prevalence of cases is 25%. For most genes involved in LVH, the prevalence of SNPs is unknown. Therefore, with the prevalence of SNP B for gene A, the BB variant is assumed to be around 5%, whereas an AB variant is estimated to be 30%, making allele frequencies of 80% As and 20% Bs. Thirdly, the power of the study is set at 80% and alpha is set at 0.05. With a sample size of 1000 hypertensive subjects and the above-mentioned assumptions, we will be able to demonstrate a difference in allele frequencies of 12.5% or an 8% difference in prevalence of BB variant.

For the prognostic research question, i.e. the prediction of subjects at risk of LVH, we expect 250 cases and 700 controls using the highest quartile of LV mass index as cases. That is a sufficiently large sample size to develop a prediction rule.

Timelines

It is expected that on average 40 patients per month will complete the imaging protocol. Thus, inclusion of patients will be completed in 2 to 2.5 years time.

Conclusion

The SMART Heart study aims to develop a model for the early prediction of the development of LVH in hypertension. In addition, SMART Heart aims at extending the knowledge on the genetic background of LVH in humans.

The SMART Heart cohort will comprise the largest number of subjects to date in which detailed CMR data are combined with traditional risk factors and genetic data. A prediction model will enable the clinician to assess the risk of LVH developing for the individual patient. In addition, the contribution of SMART Heart to the aetiological understanding of the genetic background of LVH may produce new strategies for LVH inhibition. ■

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