Prediction of Extensive Myocardial Fibrosis in Nonhigh Risk Patients With Hypertrophic Cardiomyopathy

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In nonhigh risk patients with hypertrophic cardiomyopathy (HC), the presence of extensive late gadolinium enhancement (LGE_{ext}) at cardiovascular magnetic resonance (CMR) imaging has been proposed as a risk modifier in the decision process for implantable cardioverter defibrillator implantation. With a pretest risk of about 10%, a strategy that alters the likelihood of LGE_{ext} could markedly affect efficacious CMR imaging. Our aim was to study the potential of clinical variables and biomarkers to predict LGE_{ext}. In 98 HC patients without any clear indication for implantable cardioverter defibrillator implantation, we determined the discriminative values of a set of clinical variables and a panel of biomarkers (hs-cTnT, NTproBNP, GDF-15, and Gal-3, CICP) for LGE_{ext}, that is, LGE ≥15% of the left ventricular mass. LGE_{ext} was present in 10% (10/98) of patients. The clinical prediction model contained a history of nonsustained ventricular tachycardia, maximal wall thickness and reduced systolic function (c-statistic: 0.868, p <0.001). Of all biomarkers, only hs-cTnT was associated with LGE_{ext}, in addition to the improved clinical model of diagnostic accuracy (p = 0.04). A biomarker-only strategy allowed the exclusion of LGE_{ext} in half of the cohort, in case of a hs-cTnT concentration less than the optimal cutoff (Youden index; 8 ng/L—sensitivity 100%, specificity 54%). In conclusion, in this nonhigh risk HC cohort, the pretest likelihood of LGE_{ext} can be altered using clinical variables and the addition of hs-cTnT. The promising findings with the use of hs-cTnT only call for new initiatives to study its impact on efficacious CMR imaging in a larger HC population, either with or without additional use of clinical variables. **(Am J Cardiol 2018;00:1−7)**

Hypertrophic cardiomyopathy (HC) is a major cause of sudden cardiac death (SCD) with an incidence of <1% per year, which poses a major clinical challenge for its prediction.[1,2] Importantly, the highest absolute number of SCDs still occur in the large group of nonhigh risk HC patients without a clear indication for an implantable cardioverter defibrillator.[1−4] Recently, clinical experts have suggested to incorporate extensive late gadolinium enhancement (LGE) in clinical decision making for this category of HC patients.[5] As extensive LGE (≥15% of left ventricular [LV] mass) is only seen in about 10%,[6] a strategy based on easily obtainable characteristics that would alter the pretest likelihood, would be a more cost-effective approach than routine LGE cardiovascular magnetic resonance (CMR) imaging.[7,8] In addition to various clinical variables (e.g., LV mass, wall thickness, and nonsustained ventricular tachycardia [NSVT][9−11]) biomarkers like cardiac troponin, natriuretic peptides, and markers of collagen turnover have repeatedly been associated with LGE in HC.[12−19] In the previously mentioned clinical context, we aimed to identify predictors of extensive LGE between routinely assessed clinical variables and a broad panel of biomarkers in nonhigh risk HC patients. In addition, we demonstrate the predictive value of the addition of biomarkers in comparison to a prediction model with clinical variables only.

Methods

For this analysis, we selected nonhigh risk patients from a large cohort of HC patients who participated in a Dutch multicenter study on CMR imaging and biomarkers.[20] In short, adult HC patients from different hospitals were enrolled at 2 outpatient clinics (Radboud University Medical Center, Nijmegen and Albert Schweitzer Hospital, Dordrecht, The Netherlands) from 2008 to 2014. Patients had to fulfill the diagnostic criteria for HC according to the prevailing guidelines at the time of inclusion and should not

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have a history of coronary artery disease or septal reduction therapy. For this analysis, data on the extent of LGE had to be available. Furthermore, we selected HC patients who are considered not to be at high SCD risk based on the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines (i.e., low to intermediate risk HC patients). Accordingly, we excluded patients with a family history of SCD, extreme hypertrophy (≥30 mm) or a recent unexplained syncope (i.e., patients in whom ICD implantation is considered reasonable according to the latest AHA/ACC guidelines).[2] The study complies with the Declaration of Helsinki and the protocol was approved by the local ethical committees and conducted accordingly. All participants provided written informed consent.

CMR imaging was performed on 1.5 T CMR systems (Philips Achieva [Philips Healthcare, Best, The Netherlands] or Siemens Avanto [Siemens Health Care, Erlangen, Germany]) according to local imaging protocols, as previously described in more detail.[20] T1-weighted inversion-recovery imaging was performed to assess LGE 10 minutes after the administration of 0.2 mmol/kg contrast medium (Dotarem; Guerbet, Gorinchem, The Netherlands).

Images were analyzed with commercially available software (QMass 7.5, Medis, Leiden, The Netherlands) by three observers (FG, JB, and HD) unaware of the subjects' clinical information. The extent of LGE was scored visually according to a semi-quantitative score, previously validated in HC.[21] The definition of extensive LGE was met in case the LGE extent comprised ≥15% of the LV mass.

Blood samples were obtained by trained personnel and processed within 60 minutes after phlebotomy, and stored at −80°C until further analysis. Serum samples were used for the determination of the biomarkers (1) cardiac troponin T using the highly sensitive assay (hs-cTnT), (2) N-terminal-pro-B-type-natriuretic peptide (NTproBNP), (3) Galectin-3 (Gal-3), (4) soluble tumorigenicity suppressor2 (sST2), (5) growth differentiation factor-15 (GDF-15), and (6) C-terminal propeptide of type I collagen (CICP). Variability and performance in healthy controls and patients with heart failure have been published.[22] We refer to Appendix A for a detailed description of the assays.

Continuous variables are presented as means (±standard deviations) or medians (interquartile ranges) and were compared between patients with and without extensive LGE using a Student's t or Mann−Whitney U test, whichever is appropriate. Dichotomous variables were compared using a chi-square or Fisher's exact test, whichever appropriate. A p value of <0.05 was considered significant (two-sided). Then, multivariable regression analysis was performed. A stepwise forward approach was adopted to predict extensive LGE based on the likelihood-ratio-test (P-in, 0.05; P-out, 0.10). First, we constructed a model for prediction of extensive LGE with the clinical variables that differed between patients with and without extensive LGE ($p<0.10$; model 1). Second, we constructed model 2 for prediction of extensive LGE with the addition of the biomarkers that differed between patients with and without extensive LGE ($p<0.10$). To assess the calibration of the models, we used the Hosmer−Lemeshow goodness-of-fit statistical method. Receiver operating characteristic (ROC) analysis using c-statistics was performed to determine the area under the curve of both models, and of each biomarker variable included in model 2 separately. The cut-off value for the continuous variables was determined using the Youden index. Statistical analysis was performed with IBM SPSS Statistics 22 (IBM Corp, Armonk, New York).

Results

For the present analysis, 98 nonhigh HC patients selected from our total HC cohort of 141 HC patients were studied (61% male, age 55 ± 14 years) (Figure 1 and Table 1).[20] Most patients were a- or mildly symptomatic with 96 (98%) in New York Heart Association class I to II. The presence of LGE was demonstrated in 56 (57%) patients. In these 56 patients, the extent of LGE comprised 8% (interquartile ranges 3 to 13%) of the LV mass. In 10 (10%) patients the extent of LGE was ≥15%.

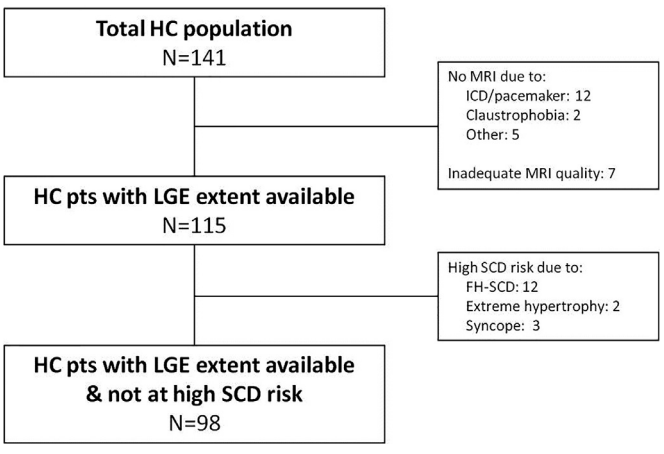

Figure 1. Flow chart of our HC study population.

Our total HC population comprised 141 HC patients. Twenty-six HC patients were excluded because there was no data available on LGE extent. Seventeen HC patients were excluded because they were considered to be at high SCD risk according to the ACC/AHA guidelines, in which an ICD implantation is considered reasonable.

ACC = American college of cardiology; AHA = American heart association; FH-SCD = family history of sudden cardiac death; HC = hypertrophic cardiomyopathy; ICD = implantable cardioverter defibrillator; LGE = late gadolinium enhancement; MRI = magnetic resonance imaging; SCD = sudden cardiac death.