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Derivation and Evaluation of Age-Specific Multivariate Reference Regions to Aid in Identification of Abnormal Filling Patterns

The HUNT and VaMIS Studies

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ABSTRACT

OBJECTIVES This study aimed to derive age-specific multivariate reference regions (MVRs) able to classify subjects into those having normal or abnormal filling patterns and to evaluate the prognostic impact of this classification.

BACKGROUND The integration of several parameters is necessary to diagnose disorders of left ventricular (LV) filling because no single measurement accurately describes the complexity of diastolic function. However, no generally accepted validated multiparametric algorithm currently exists.

METHODS A cohort of 1,240 apparently healthy subjects from HUNT (the Nord-Trøndelag Health Study) with measured early (E) and late (A) mitral inflow velocity and early mitral annular diastolic tissue velocity (e′) were used to derive univariate 95% reference bands and age-specific MVRs. Subsequently, the prognostic impact of this MVR-based classification was evaluated by Cox regression in a community-based cohort (n = 726) and in a cohort of subjects with recent acute myocardial infarction (n = 551). Both evaluation cohorts were derived from VaMIS (the Västmanland Myocardial Infarction Study).

RESULTS Univariate reference bands and MVRs are presented graphically and as regression equations. After adjustment for sex, age, hypertension, body mass index, diabetes, prior ischemic heart disease, LV mass, LV ejection fraction, and left atrial size, the hazard ratio associated with abnormal filling patterns in the community-based cohort was 3.5 (95% confidence interval: 1.7 to 7.0; $p < 0.001$) and that in the acute myocardial infarction cohort was 1.8 (95% confidence interval: 1.1 to 2.8; $p = 0.011$).

CONCLUSIONS This study derived age-specific MVRs for identification of abnormal LV filling patterns and showed, in a community-based cohort and in a cohort of patients with recent acute myocardial infarction, that these MVRs conveyed important prognostic information. An MVR-based classification of LV filling patterns could lead to more consistent diagnostic algorithms for identification of different filling disorders. (J Am Coll Cardiol Img 2017;■:■-■)

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ABBREVIATIONS AND ACRONYMS

A = late mitral inflow velocity

AFP = abnormal filling pattern

AMI = acute myocardial infarction

BSA = body surface area

CB = community-based

CI = confidence interval

DDF = diastolic dysfunction

DT = deceleration time

E = early mitral inflow velocity

e′ = early mitral annular diastolic tissue velocity

FPAS = filling pattern abnormality score

HFpEF = heart failure with preserved ejection fraction

HR = hazard ratio

LV = left ventricular

LVMi = left ventricular mass indexed for body surface area

MVR = multivariate reference region

NFP = normal filling pattern

Systolic heart failure and asymptomatically reduced left ventricular (LV) systolic function are clinical entities for which a high degree of consensus exists on diagnostic criteria (1). The opposite holds true for heart failure with preserved ejection fraction (HFpEF) and for diastolic dysfunction (DDF), the diagnostic criteria for which are constantly debated and revised (2–6).

Several echocardiographic measurements and derived parameters reflect, in various degrees, different aspects of LV filling. However, these parameters all have their individual shortcomings with regard to accuracy, reproducibility, and/or feasibility (7,8). The proposed solution to the shortcomings of individual measurements has been to use a multiparametric integrative approach (1,8). Several multiparametric classification schemes have been proposed to aid in identifying subjects with HFpEF or DDF, but the concordance among these methods has been shown to be poor, thus indicating that further work is needed (9). Notably, multiparametric diagnostic schemes presented in recommendations are frequently formulated on the basis of expert consensus and theoretical considerations rather than on clinical studies (10). We believe this to be a consequence of the scarcity of studies exploring how multiparametric diagnostic schemes could be constructed. Within the field of clinical chemistry, multivariate reference regions (MVRs) have been developed to facilitate identification of abnormal patterns on multivariate test profiles for arterial blood gases (11), thyroid function (12), and insulin-like growth factors (13). An MVR for interpretation of echocardiographic Doppler data could function as a simple and intuitive test to identify subjects with filling disorders.

In this study, we aimed to derive an MVR with the ability to classify subjects into those having a normal filling pattern (NFP) or an abnormal filling pattern (AFP) and evaluate the prognostic impact of such a classification.

METHODS

DERIVATION COHORT. HUNT3 (the third phase of the Nord-Trøndelag Health Study) was used as the derivation cohort. This cohort was described in detail previously (14). Briefly, 94,194 people from the general population were invited to participate in HUNT3, and 50,839 (54%) accepted the invitation. A subsample of subjects free of cardiovascular disease, hypertension, and diabetes was selected by random sampling (n = 1,296) for an echocardiographic substudy. Subjects whose echocardiograms revealed arrhythmia, valvular disease, or any kind of myocardial disease (n = 30) were excluded. The echocardiographic measurements used in the present study were early mitral annular diastolic tissue velocity, measured by pulsed tissue Doppler, averaged for the lateral and septal wall (e′), early mitral inflow velocity (E), and late mitral inflow velocity (A). Subjects with missing values for A, E, or e′ (n = 26) were excluded, thereby leaving 1,240 subjects to form the derivation cohort. The study was approved by the Regional Committee for Medical Research Ethics and was conducted according to the principles of the second Declaration of Helsinki. Written informed consent was obtained from all participants. Data on the intraobserver and interobserver variability of the derivation cohort were published earlier (14).

EVALUATION COHORTS. The evaluation cohorts were derived from VaMIS (the Västmanland Myocardial Infarction Study); the inclusion criteria and study protocol were reported previously (15,16). Briefly, subjects hospitalized for acute myocardial infarction (AMI) between November 2005 and May 2011 were included in VaMIS. For each included patient, a control subject was recruited from the general population. From the Swedish Population Register in which all Swedish citizens are registered, a subject of the same sex with the nearest date of birth and living in the same municipality as the VaMIS patient was identified and invited to participate. All subjects underwent clinical examination, echocardiographic examination, and blood sampling. LV mass was calculated from the LV wall thickness and diameter and was indexed for body surface area (BSA) as left ventricular mass indexed for body surface area (LVMi) (17). LV ejection fraction was categorized from biplane Simpson measurements in subjects with adequate image quality and otherwise by visual estimation into the following categories: ≥55%; 45% to 54%; 35% to 44%; 25% to 34%; and <25%. Left atrial volume was measured by monoplane Simpson in the apical 4-chamber view and indexed for BSA. Reproducibility in the evaluation cohorts was tested by repeat measurement in a random subset of 22 subject by 2 observers (P.H. and J.S.), including 1 who performed the original measurements (P.H.). The intraobserver and interobserver coefficients of variation for E, A, and e′ were <5.2% for all. VaMIS was approved by the Ethics Committee of Uppsala University, Sweden. All participants gave written informed consent.