Associations of Methylarginines and Homoarginine With Diastolic Dysfunction and Cardiovascular Risk Factors in Patients With Preserved Left Ventricular Ejection Fraction

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ABSTRACT

Background: Asymmetric dimethylarginine (ADMA), symmetric dimethylarginine (SDMA), and homoarginine are considered to modulate nitric oxide synthesis. We evaluated whether ADMA, SDMA, and homoarginine are associated with diastolic dysfunction.

Methods and Results: We investigated primary care patients at cardiovascular risk with preserved left ventricular ejection fraction from the multicenter DIAST-CHF study. We measured serum concentrations of ADMA, SDMA, and homoarginine and performed standardized echocardiographic examinations. Among 1,396 patients (mean age 65.3 ± 8.3 y, 54.6% women), diastolic dysfunction was ruled out in 261 patients (18.7%). Mild and moderate/severe grades of diastolic dysfunction were present in 900 (64.5%) and 235 (16.8%) study participants, respectively. After adjustments for cardiovascular risk factors, ADMA and SDMA were positively and homoarginine negatively associated with N-terminal pro–B-type natriuretic peptide and midregional pro-adrenomedullin ($P < .05$ for all). Lower homoarginine levels were associated with diastolic dysfunction, and higher ADMA and SDMA levels were associated with the severity of diastolic dysfunction ($P < .05$ for all).

Conclusions: Higher levels of ADMA and SDMA and lower levels of homoarginine are associated with an adverse cardiovascular risk profile and diastolic dysfunction. Further studies should clarify the potential of these amino acid derivatives for the therapy of cardiovascular diseases. (*J Cardiac Fail 2014;20:923–930*)

Key Words: Homoarginine, methylarginines, diastolic dysfunction, cardiovascular risk.

Identification and characterization of novel risk factors for heart failure and cardiovascular diseases is important to improve diagnostic and therapeutic approaches.[1,2] Exploration of potential treatment targets for diastolic dysfunction is of particular importance because there exists no proven beneficial treatment for these patients yet, when symptoms have developed, they have a similar poor prognosis compared with patients with systolic dysfunction.[3,4]

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Accumulating evidence argues for a pivotal role of amino acids and its derivatives in metabolic and cardiovascular pathophysiology.[5] In this context, it has been shown that the methylarginines asymmetric dimethylarginine (ADMA) and its stereoisomer symmetric dimethylarginine (SDMA) are associated with increased cardiovascular risk.[6−14] ADMA is an endogenous inhibitor of nitric oxide (NO) synthase and can thereby contribute to NO deficiency, which exerts deleterious effects on myocardial function.[6,7] SDMA may also adversely affect NO metabolism by interference with membrane transport of arginines, which are the precursors for NO.[15,16] In contrast, the amino acid derivative homoarginine may increase NO levels by serving as a substrate for NO synthase or by inhibiting arginine degradation by the enzyme arginase.[17,18] In line with this, low homoarginine levels are significantly associated with fatal cardiovascular events.[19−25] These data were derived from patients referred to coronary angiography, chronic kidney disease patients, patients with heart failure, and stroke patients.[19−25] Interestingly, the proposed key enzyme for homoarginine synthesis, arginine:glycineamidinotransferase (AGAT), was found to be significantly upregulated in the myocardium of heart failure patients.[17,26,27] Considering that AGAT is also crucial for the synthesis of the energy metabolite guanidinoacetate, which is further converted to creatine, it was hypothesized that increased AGAT expression in the heart aims to compensate energy depletion in states of myocardial dysfunction.[27]

Earlier studies have already shown that high levels of ADMA and SDMA as well as homoarginine deficiency are all associated with parameters of heart failure including systolic dysfunction.[6−15,22,23,27,28] It is, however, largely unknown whether these biomarkers are related to diastolic dysfunction and biochemical parameters of heart failure (N-terminal pro−B-type natriuretic peptide [NT-proBNP] and midregional pro-adrenomedullin [MR-proADM]) in patients with preserved ejection fraction. To address these issues, we measured ADMA, SDMA, and homoarginine in a large cohort of primary care patients derived from the noninterventional DIAST-CHF study (Diagnostic Trial on Prevalence and Clinical Course of Diastolic Dysfunction and Diastolic Heart Failure).[29−31] Our main aim was to evaluate whether methylarginines and homoarginine levels are associated with diastolic dysfunction, NT-proBNP, and MR-proADM. Additional analyses were performed to evaluate associations of methylarginines and homoarginine with renal function, because the kidney plays a major role for ADMA, SDMA, and homoarginine metabolism.[6−9,15−17]

Methods

Study Population

Detailed information on study concept, design, and examinations of the DIAST-CHF study have been published previously.[29,30] In brief, the DIAST-CHF study is a multicenter observational trial on risk factors and outcome of diastolic dysfunction and is part of the nationwide German Competence Network Heart Failure project.[29,30] Study participants were referred by primary care physicians and were examined in 2004−2005. Patients aged 50−85 years with ≥1 risk factor for diastolic heart failure (history of hypertension, diabetes mellitus, sleep apnea syndrome, or atherosclerotic disease) and/or previously diagnosed congestive heart failure were prospectively included into the study. Heart failure was diagnosed in accordance with recent European Society of Cardiology guidelines and Framingham diagnostic criteria. There were no further predefined exclusion criteria apart from inability to participate or consent. The present work was restricted to study participants with preserved left ventricular (LV) function, ie, LV ejection fraction (LVEF) >50%, and to those with available data for classification of diastolic function. The study complied with the Declaration of Helsinki. Each of the study participants gave written informed consent, and we obtained approval for the study from all local Ethics Committees.

Baseline examinations were described in detail in previous reports and included blood samplings, several questionnaires on, eg, medical history and current drug intake, physical examinations (ie, measurement of body mass index and blood pressure, electrocardiography, and a 6-minute walk test), and comprehensive echocardiography.[29,30]

Echocardiography

Echocardiographic examinations were performed according to guidelines of the American Society of Echocardiography and with the use of a Hewlett-Packard Sonos 5500 (Hewlett-Packard, Andover, Massachusetts). In detail, diastolic function was classified based on tissue Doppler techniques, including determinations of peak velocities of early (E) and late (A) diastolic mitral inflow and early (e′) and late (a′) tissue Doppler velocity waves, E-wave deceleration time, and peak systolic (S) and diastolic (D) pulmonary vein flow velocity. Tissue Doppler values represent medial mitral annular velocities. These echocardiographic examinations were performed only by physicians experienced in the technique and with the use of a prespecified standard operating procedure. Furthermore, an echocardiography core laboratory of the Competence Network Heart Failure at the University of Essen reviewed randomly chosen examinations to ensure data quality.

LV mass index was calculated according to the Devereux formula indexed to body surface area and left atrial volume index was calculated with the use of the ellipsoid model. LV hypertrophy was classified in women with LV mass index >95 g/m^2 and in men with LV mass index >115 g/m^2.[31] Ratios of E/A, E/e′, and S/D were calculated as diastolic functional parameters. Diastolic dysfunction was classified according to a previously published prespecified algorithm of the DIAST-CHF study protocol and includes the following stages: normal diastolic function (E/A ≥1, E/e′ <10, S/D ≥1, E/A with Valsalva maneuver ≥1), mild diastolic dysfunction (E/A <1), moderate diastolic dysfunction (1 ≤ E/A < 2, and 1 of the following: E/e′ ≥10, S/D < 1, E/A ;Valsalva <1), and severe diastolic dysfunction (E/A ≥2, and 1 of the following: E/e′ ≥10, S/D < 1).[29,30]

Laboratory Methods

Blood collections were performed in the fasting state and after 15 minutes at rest. Samples were stored at −80°C until analyses. ADMA, SDMA, and homoarginine were measured 5−6 years after blood sampling. Serum homoarginine was measured with the