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Plasma asymmetric dimethylarginine, L-arginine and Left Ventricular Structure and Function in a Community-based Sample

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Abstract

Objective—Increasing evidence indicates that cardiac structure and function are modulated by the nitric oxide (NO) system. Elevated plasma concentrations of asymmetric dimethylarginine (ADMA; a competitive inhibitor of NO synthase) have been reported in patients with end-stage renal disease. It is unclear if circulating ADMA and L-arginine levels are related to cardiac structure and function in the general population.

Methods—We related plasma ADMA and L-Arginine (the amino acid precursor of NO) to echocardiographic left ventricular (LV) mass, left atrial (LA) size and fractional shortening (FS) using multivariable linear regression analyses in 1,919 Framingham Offspring Study participants (mean age 57 years, 58 % women).

Results—Overall, neither ADMA or L-arginine, nor their ratio was associated with LV mass, LA size and FS in multivariable models ($p > 0.10$ for all). However, we observed effect modification by obesity of the relations of ADMA and LA size (p for interaction $p = 0.04$): ADMA was positively related to LA size in obese individuals (adjusted- $p = 0.0004$ for trend across ADMA quartiles) but not in non-obese people.

Conclusion—In our large community-based sample, plasma ADMA and L-arginine concentrations were not related to cardiac structure or function. The observation of positive relations of LA size and ADMA in obese individuals warrants confirmation.

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Keywords

ADMA; L-Arginine; Biomarker; Hypertrophy; Epidemiology

Introduction

Substantial epidemiological data suggest that higher left ventricular (LV) mass is associated with increased cardiovascular morbidity and mortality [1]. The major clinical determinants of LV mass include age, sex, height, weight and blood pressure [2].

In this context, increasing experimental evidence suggests that cardiac structure (including LV mass) and function are strongly modulated by the nitric oxide (NO) system [3,4]. NO is generated from L-arginine by NO synthase (NOS), plays a crucial role in the maintenance of vascular homeostasis [5], and is the major mediator of endothelium-dependent vasodilation [5]. Of note, all three isoforms of NOS (the neuronal, inducible and endothelial isoforms encoded by the *NOS1*, *NOS2*, and *NOS3* genes, respectively) are expressed in the heart, including in cardiomyocytes [4]. Mice lacking the *NOS3* gene (*NOS3*^{-/-}) or the *NOS1* gene (*NOS1*^{-/-}) display age-associated increased ventricular stiffness and cardiac hypertrophy [3, 6]. In experimental models of chronic pressure overload, the *NOS3*^{-/-} mice demonstrate a more pronounced hypertrophic response and worse cardiac systolic and diastolic function [7]. On a parallel note, in response to isoproterenol-infusions, transgenic mice that over express *NOS3* demonstrate less LV hypertrophy (LVH) compared to their wild-type counterparts [8].

Consistent with the experimental data noted above, limited clinical evidence also supports a role for the NO system in LVH. ADMA (asymmetric dimethylarginine), an endogenous competitive inhibitor of the NO synthase and an emerging cardiovascular risk factor [9], has been linked to adverse LV remodeling in patients with end-stage renal disease (ESRD) [10]. Specifically, circulating ADMA concentrations were significantly increased in ESRD patients, especially so in those with LVH or LV systolic dysfunction [10]. Based on the aforementioned experimental and clinical evidence, we postulated that higher circulating concentrations of ADMA and lower concentrations of L-arginine (the amino acid precursor of NO) may be associated with higher LV mass and a greater prevalence of LV systolic dysfunction in unselected people in the general population. To test this hypothesis, we related plasma concentrations of ADMA and L-arginine to echocardiographic measures of LV structure and function in a large community-based sample.

Methods

Study Sample

The Framingham Offspring Study was initiated in 1971 with the enrolment of 5,124 participants, who were the offspring of the original cohort participants and the spouses of the offspring [11]. Offspring cohort participants undergo routine examinations at the Heart Study clinic approximately every four years. At each Heart Study visit, participants undergo anthropometric measurements, medical history and physical examination, and laboratory assessment of traditional cardiovascular risk factors.

Of 3,532 attendees at the sixth examination cycle (1995–1998), 1,613 individuals were excluded from the present investigation for the following reasons: prevalent myocardial infarction or heart failure (n=415; both conditions can affect LV measurements), missing or inadequate LV echocardiographic measurements (n=1,172), missing ADMA (n=21), and serum creatinine >2 mg/dl (n=5). After these exclusions, 1,919 individuals (1,122 women) remained eligible for the present investigation. Clinical, echocardiographic and biochemical

characteristics of participants included in the present analysis and those with missing covariates or missing echocardiographic data are displayed in **online** supplementary Table 1. Those individuals with missing echocardiographic data or covariates were older, heavier, more likely to be diabetic, more often on antihypertensive treatment and had a higher prevalence of increased LV mass; the higher vascular risk profile of individuals with missing imaging data has been reported consistently in epidemiological studies [12].

Written informed consent has been obtained from all participants and the study protocols were approved by the Boston University Medical Center Institutional Review Board.

Echocardiographic Methods

At the sixth examination cycle, attendees underwent routine M-mode and two-dimensional transthoracic echocardiography with Doppler colour flow imaging using a Sonos 1000 Hewlett-Packard machine. Digital M-mode frames were used to measure the end-diastolic LV septal (SWT) and posterior wall (PWT) thicknesses, and LV internal dimensions at end-diastole (LVEDD) and end-systole (LVESD), and the left atrial (LA) size at end-systole according to the recommendations of the American Society of Echocardiography. LV mass was calculated as $0.8[1.04(LVEDD+PWT+SWT)^3-(LVEDD)^3]+0.6$ [13]. LV fractional shortening (FS), an indicator of LV systolic function, was calculated as $(LVEDD-LVESD)/LVEDD$. Significant valve disease was defined as greater than mild degree of stenosis or regurgitation of the aortic or mitral valves on Doppler echocardiography.

Measurements of Plasma ADMA and L-arginine Concentrations

Concentrations of plasma ADMA and L-arginine were measured by using a fully validated commercially available high throughput liquid chromatography-tandem mass spectrometry assay (DLD Diagnostika, Hamburg, Germany) [14], with an intra-assay coefficient of variation (CV) of 3.2% and 2.2%, for ADMA and L-arginine, respectively, and an inter-assay CV of < 5% for both.

Statistical analyses

Means and standard deviations are presented to summarize continuous clinical, echocardiographic and biochemical characteristics and percentages are presented for categorical characteristics. We evaluated the distributional properties of L-arginine and ADMA graphically. We used multiple linear regression analysis to relate plasma L-arginine and ADMA concentrations to LV mass, LA size and FS (each biomarker considered separately in relation to each echocardiographic variable). The biomarkers were modeled as continuous non-transformed variables (given their normal distribution). We did not observe effect modification by sex upon formal statistical testing for an interaction between each biomarker and sex for each echocardiographic measurement. Accordingly, all analyses were performed for pooled sexes. Two sets of multivariable models were constructed: Model 1 adjusted for age, sex and height; model 2 adjusted for age, sex, weight, height, systolic blood pressure (BP), antihypertensive treatment, total/high-density lipoprotein cholesterol ratio, diabetes, smoking status, and presence of significant valve disease on Doppler colour flow imaging (fully-adjusted model). Diabetes was defined as a fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L) or treatment with oral antidiabetic medications or insulin. We also used analysis of covariance to estimate means of the echocardiographic measures across quartiles of plasma ADMA and L-arginine adjusted for key clinical covariates. We evaluated effect modification by age (dichotomized at the median), diabetes (yes/no), and obesity (body mass index ≥ 30 kg/m²; yes/no) by incorporating corresponding interaction terms into the multivariable model 2. We modeled BMI as a binary trait (obesity) because it is a clinically useful category.

We defined several secondary analyses *a priori*. We repeated our analyses modeling the L-arginine/ADMA ratio as the independent variable. Given sex- and height-related differences in the distribution of LV mass, we repeated analyses modeling LV mass indexed to height as the dependent variable. Also, although primary analyses focused on LV mass, LA size and FS to minimize the extent of multiple testing, we conducted additional analyses relating ADMA to the two components used to calculate LV mass, i.e., LV wall thickness (LVWT; sum of SWT and PWT), and to LVEDD. Additionally, whereas the primary analyses modeled LV mass and FS as continuous variables, we also evaluated two additional phenotypes: increased LV mass (defined as a value exceeding the sex-specific 80th percentile) and LV systolic dysfunction (defined as FS<0.29, or mild or greater systolic dysfunction on visual assessment in multiple views [corresponding to ejection fraction less than 50%]). For these analyses, we used multivariable logistic regression to estimate odds ratios for increased LV mass or LV systolic dysfunction relative to a one-SD increment in each biomarker (covariates as in models 1 and 2 above).

Results

The baseline characteristics of our study sample are shown in Table 1. Our sample was middle-aged to elderly, included slightly more women than men, and had a moderately high prevalence of antihypertensive treatment and smoking. The prevalence of LV systolic dysfunction was lower in women compared with men.

Associations of plasma ADMA, L-arginine and their ratio with LV structure and function

Table 2 displays the relations of plasma ADMA, L-arginine concentrations and their ratio to echocardiographic measurements in our sample. In both sets of regression models, neither ADMA nor L-arginine (or their ratio) was related to LV mass, FS or LA size (Table 2). Likewise, adjusted mean values for each of these echocardiographic variables did not differ by quartiles of ADMA or L-arginine (Table 3). In analyses of LV mass indexed to height and separate analyses of its two components (LVEDD, LVWT), the lack of association of ADMA and L-arginine with echocardiographic measures was maintained (data not shown). Analyses of binary echocardiographic traits (increased LV mass and LV systolic dysfunction) further corroborated the lack of association of ADMA and L-arginine with cardiac structure and function.

We did not observe any effect modification by age, sex or diabetes. However, we observed a significant statistical interaction of ADMA with obesity ($p=0.04$) for LA size, but not for LV mass or FS. Analyses stratified by obesity status revealed a positive association between plasma ADMA and LA size in obese individuals ($\beta=0.06$ per one-SD increment in ADMA modeled as a continuous variable, $p=0.005$; $p=0.0004$ for trend across ADMA quartiles; Figure 1) but not in non-obese people ($\beta=0.006$ per one-SD increment in ADMA modeled as a continuous variable, $p=0.64$; $p=0.80$ for trend across ADMA quartiles; Figure 1).

Additional adjustment for antihyperlipidemic medications, aspirin, and hormone replacement therapy in women revealed similar results ($\beta=0.06$ per one-SD increment in ADMA; $p=0.005$). ADMA concentrations explained only a small proportion of the interindividual variability in LA size in obese individuals (partial $R^2=0.019$) but its effect was comparable to that of height (partial $R^2=0.021$), age (partial $R^2=0.023$) and valve disease (partial $R^2=0.022$). Antihypertensive treatment (partial $R^2=0.030$) and hormone replacement therapy (partial $R^2=0.052$) explained a larger proportion of the interindividual variability of LA size in obese individuals. In exploratory analyses, ADMA was not related to LV mass and FS in either obese or non-obese individuals.

Given the overall lack of association of biomarkers evaluated and LV structure and function in our sample, we examined our statistical power to detect associations with our sample size. If ADMA or L-arginine were dichotomized at the median, our study has 80% power to detect a difference in LV mass as small as 5.6 g, a difference in LA size as small as 0.07 cm and a difference in FS as small as 0.01 between the two groups at an alpha level of 0.05.

Discussion

Substantial experimental evidence suggests that cardiac remodeling and function are regulated by the NO system [4,15–17]. Increasing clinical data also suggest that ADMA, a competitive endogenous inhibitor of the NOS, is an novel cardiovascular disease risk factor [9]. Recently, ADMA levels were positively associated with LV hypertrophy and systolic dysfunction in a moderate-sized sample of patients with ESRD [10]. In the present analysis of a large community-based sample, we did not observe statistically significant associations of plasma ADMA or L-arginine with echocardiographic LV mass, LA size, or LV systolic function overall. However, we observed effect modification by obesity of the relations of ADMA and LA size. We observed a positive association of ADMA concentrations and LA size in individuals with obesity, but not in non-obese people. Although this finding has to be considered as hypothesis-generating and needs confirmation in independent cohorts, the observation of a positive association of plasma ADMA and LA size in obese is consistent with the notion that ADMA may represent a marker for structural alterations in the heart in high-risk individuals. It is interesting that most of the studies reporting associations of plasma ADMA and cardiovascular outcomes including mortality were performed in patients with established cardiovascular or renal disease, or in critically ill patients in intensive care units [18–20].

ADMA is a non-specific inhibitor of all NOS isoforms, which may each differentially affect cardiovascular remodeling. Furthermore, vascular resistance and compliance are modulated by multiple mechanisms and defects in one system (e.g., the NO pathway) might be compensated by other pathways (e.g., the endothelium-derived hyperpolarizing factor [EDHF] pathway) [21], in relatively healthy individuals. By contrast, inhibition of the NOS (through ADMA) might have more profound consequences (leading to vascular and ventricular remodeling) in high-risk patients. In line with this assumption, Zoccali et al. observed an association between ADMA levels and LVH and systolic dysfunction in patients with ESRD [10], who are known to have a high burden of cardiovascular disease [22]. Associations of ADMA with LA size or diastolic function were not assessed in that study [10].

In our analyses, however, we found no association of ADMA or L-arginine with LV mass or FS in individuals with obesity. This might be explained by the fact that enlarged LA size is an early marker of diastolic dysfunction that is associated with adverse cardiovascular outcomes [23] and might antedate structural and functional alterations of the LV in obese people [24].

Indeed, individuals with obesity are prone to both atrial and ventricular remodeling [24]. Clinical and community-based studies have consistently shown, that obesity is associated with enlarged LA size [25], diastolic dysfunction [26] and an increased risk for heart failure [27]. Also, ADMA concentrations are increased in obesity [28]. Of note, several cardiovascular conditions [29], including obesity [30] and renal disease [31] are characterized by increased oxidative/nitrosative stress. On a parallel note, heightened oxidative stress reduces the activity of the major enzyme dimethylarginine dimethylaminohydrolase (DDAH) [29], which degrades ADMA. A lower activity of DDAH might explain elevated ADMA concentrations in various cardiovascular conditions that have been reported in clinical studies [10,32] and might also constitute an important pathophysiological link between the NO system and cardiovascular risk, including atrial remodeling.

Strengths and limitations

The large community-based sample and the routine assessment of echocardiographic measures and ADMA/L-arginine (blinded to results of each other) are strengths of our investigation. However, we acknowledge several limitations. We evaluated an ambulatory cohort of relatively healthy, white, middle-aged individuals of European descent. Caution must be exercised in extrapolating these results to other samples. We did not assess LV diastolic function directly, and it is conceivable that plasma ADMA is associated with LV diastolic dysfunction in the community. Given the cross-sectional design of our investigation, we cannot rule out that nitrosative stress may contribute to LV/LA remodeling longitudinally. Since we are measuring circulating ADMA and L-arginine concentrations we cannot exclude the possibility that nitrosative damage may contribute to LV remodeling at the local tissue level. Also, a significant proportion of attendees were excluded due to missing/inadequate imaging data. This is an unavoidable limitation of large epidemiological cohort studies [12]. Certain medications including inhibitors of the renin-angiotensin system and oral hypoglycaemic agents can affect ADMA levels [33,34]. We, therefore, adjusted for use of antihypertensive medications and antidiabetic medications (as part of the diabetes definition) in our multivariable analyses.

Conclusions

Overall, plasma ADMA and L-arginine concentrations were not related to cardiac structure or function in our large community-based sample. Given the number of tests performed in the present analyses, the observation of positive relations of LA size and ADMA in obese individuals is hypothesis-generating and warrants confirmation in other studies. If replicated, our observation would suggest that a potential mechanism by which obesity may increase LA size is via its association with higher ADMA levels. One could speculate then that measures to reduce oxidative stress in obese people (including weight loss) may reverse atrial remodeling. This premise would warrant additional verification in intervention studies evaluating effects of weight loss on cardiac remodeling in obese people.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Multivariable adjusted least squares means of left atrial size according to ADMA quartiles in obese and non-obese individuals.

Abbreviations used: ADMA, asymmetric dimethylarginine; LA, left atrial.

Models were adjusted for: age, sex, height, weight, systolic blood pressure, hypertension treatment, total/high-density lipoprotein cholesterol ratio, diabetes status, smoking status, presence of valve disease

Table 1
Characteristics of the study sample.

	Women (N=1,122)	Men (N=797)
A. Clinical Features		
Age, years	58±9	57±9
Height, m	1.62±0.06	1.75±0.06
Weight, kg	69.5±13.6	86.0±12.9
Systolic BP, mm Hg	125±20	129±17
Diastolic BP, mm Hg	74±9	78±9
Hypertension treatment, %	20	24.9
Smoking, %	14.8	13.4
Diabetes, %	4.9	7.4
B. Echocardiographic Features		
LV mass, g	141.0±30.1	192.5±41.5
Left atrial size, mm	3.7±0.4	4.2±0.5
Fractional shortening	0.38±0.05	0.36±0.05
Increased LV mass, %*	17.5	17.6
LV systolic dysfunction, %	2.2	4.3
Valve disease, %	3.2	4.8
C. Biochemical Features		
Total cholesterol, mg/dL	211±39	200±36
HDL cholesterol, mg/dL	59±16	44±12
ADMA, μmol/L	0.53±0.13	0.54±0.12
L-arginine, μmol/L	77±20	79±22
Arginine/ADMA	150±46	153±46

Values are means ± SD or %.

Abbreviations used: BP, blood pressure; LV, left ventricular; HDL, high-density lipoprotein; ADMA, asymmetric dimethylarginine.

* values are less than 20% because the top quintile was defined based on the largest sample prior to exclusions.

Table 2
Association of plasma ADMA, L-arginine levels and their ratio with LV mass, left atrial size and fractional shortening.

	Continuous Variables					Binary Variables				
	LV mass		Left atrial size		p	Fractional shortening		Increased LV mass		p
	beta (SE)	p	beta (SE)	p		beta (SE)	p	OR (95% CI)	p	
ADMA, $\mu\text{mol/L}$	0.06 (0.72)	0.93	0.016(0.01)	0.10	0.001 (0.001)	0.28	1.08(0.94,1.23)	0.28	0.90(0.68,1.21)	0.49
L-Arginine, $\mu\text{mol/L}$	0.818(0.718)	0.25	-0.00076(0.0096)	0.94	0.00089 (0.0012)	0.46	1.10(0.97,1.25)	0.15	0.95(0.73,1.25)	0.72
Arginine/ADMA	0.619(0.714)	0.39	-0.0089 (0.0095)	0.35	0.000067 (0.0012)	0.96	1.02(0.90,1.16)	0.77	1.00(0.78,1.29)	0.99

SD for ADMA: 0.13; SD for L-arginine: 20.1; SD for L-Arginine/ADMA ratio: 45.8

Abbreviations used: ADMA, asymmetric dimethylarginine; LV, left ventricular; SE, standard error; OR, odds ratio; CI, confidence interval; SD, standard deviation.

Models were adjusted for: age, sex, height, weight, systolic blood pressure; hypertension treatment, total/high-density lipoprotein cholesterol ratio, diabetes status, smoking status, presence of valve disease.

Beta for continuous traits, ORs and CIs are relative to one-SD increment in marker concentrations.

Table 3
Adjusted* means of LV mass, left atrial size and fractional shortening by quartiles of plasma ADMA, L-arginine levels and their ratio.

	LV mass		p-value	Left atrial size		p-value	Fractional shortening		p-value
	Adjusted Mean			Adjusted Mean			Adjusted Mean		
ADMA									
Q1	163			3.92			0.376		
Q2	161		0.78	3.90		0.13	0.373		0.30
Q3	162			3.90			0.374		
Q4	162			3.96			0.379		
L-Arginine									
Q1	163			3.93			0.373		
Q2	162		0.14	3.93		0.68	0.374		0.39
Q3	160			3.90			0.378		
Q4	164			3.92			0.375		
L-Arginine/ADMA									
Q1	161			3.95			0.376		
Q2	162		0.76	3.91		0.20	0.375		0.58
Q3	163			3.89			0.373		
Q4	163			3.93			0.378		

Abbreviations used: ADMA, asymmetric dimethylarginine; LV, left ventricular.

* Models were adjusted for: age, sex, height, weight, systolic blood pressure, hypertension treatment, total/high-density lipoprotein cholesterol ratio, diabetes status, smoking status, presence of valve disease.