

Diagnostic Value of Serum Asymmetric Dimethyl Arginine and Arginine Derivatives Levels in Distinguishing Potentially Life-Threatening Causes in Patients Presenting with Chest Pain to the Emergency Department

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Abstract

Aim: Chest pain a common complaint in the emergency department, often associated with serious cardiovascular conditions such as ischemic heart disease, pulmonary embolism, and aortic aneurysm. Rapid and accurate diagnosis is crucial. Asymmetric dimethylarginine (ADMA), an inhibitor of nitric oxide synthase, contributes to the pathogenesis of cardiovascular disease. Measuring serum ADMA and arginine levels may aid in distinguishing life-threatening conditions and in improving clinical decision-making. This study explores the diagnostic value of ADMA and arginine derivatives in patients presenting with chest pain, aiming to enhance early and effective medical intervention

Materials and Methods: Blood samples were collected from each participant and analyzed for serum ADMA and arginine levels using liquid chromatography-mass spectrometry. Patients were classified based on potentially life-threatening versus benign causes of chest pain. Serum ADMA and arginine levels were compared between the patient and control groups.

Results: A total of 219 participants were included in the study. For biochemical measurements, no significant differences were observed in levels of ADMA, symmetric dimethyl arginine, and NG-monomethyl-L-arginine, whereas arginine and the ratios differed significantly between groups.

Conclusion: The findings offer new approaches to improve early diagnosis and treatment processes. It is anticipated that the results will determine whether the levels of ADMA and arginine can serve as clinically useful adjuncts in the management of chest pain. This could enable the rapid and accurate differentiation of potentially fatal causes, ultimately improving patient management and outcomes.

Keywords: Arginine, ADMA, cardiovascular disease, biomarkers, chest pain

Introduction

Chest pain is one of the most common complaints encountered in emergency departments. It can be a sign of potentially life-threatening conditions, such as myocardial infarction, aortic aneurysm, and pulmonary embolism (PE). Consequently, the rapid and accurate assessment of patients presenting with chest pain is lifesaving. However, a diverse range of potential causes

complicates the diagnostic process. In recent years, biomarkers have made significant contributions to clinical practice, particularly the serum markers asymmetric dimethylarginine (ADMA) and arginine. ADMA is an endogenous inhibitor of nitric oxide synthase, and elevated ADMA levels are associated with vascular dysfunction and atherosclerosis (1). Arginine plays a pivotal role in nitric oxide production and supports vascular function. Both molecules may possess substantial diagnostic



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value in distinguishing cardiovascular events. High levels of ADMA may aid the early diagnosis of cardiovascular diseases, while examining arginine levels can provide insights into vascular function by reflecting nitric oxide levels (2).

This study aims to evaluate the diagnostic value of serum ADMA and arginine levels for differentiating potentially life-threatening causes of chest pain in patients presenting to the emergency department. Studies indicate that ADMA and arginine levels are vital for the diagnosis and management of cardiovascular events. For instance, the work of Zhou et al. (1) highlights the relationship between ADMA and coronary artery disease, demonstrating that elevated ADMA levels are associated with an increased risk of myocardial infarction (1). Numerous studies underscore the diagnostic significance of ADMA and arginine in identifying cardiovascular diseases (3,4).

In this context, evaluating serum ADMA and arginine levels alongside traditional biomarkers may improve the accuracy and effectiveness of diagnostic processes in the emergency department. The findings of this study are intended to contribute significantly to clinical diagnostic algorithms and decision-making processes for emergency medical interventions.

Materials and Methods

This prospective study was conducted between June and November 2016 with approval from the Selçuk University Faculty of Medicine Ethics Committee (decision number: 2016/147 date: 18.05.2016). The study included patients aged 18 years and older who presented with chest pain. Informed consent forms were obtained from all participants. Healthy volunteers without complaints who agreed to participate in the study and showed no pathological findings on physical examination were included as the control group. Patients who met one or more of the following exclusion criteria: chest pain lasting longer than 48 hours; pregnancy or breastfeeding; malignancy; trauma; chronic diseases; or thoracic or esophageal pathologies were excluded from the study. Demographic data, complaints, vital signs, and physical examination findings were recorded. Blood samples were collected from each participant and analyzed for serum ADMA and arginine levels using liquid chromatography-mass spectrometry (LC-MS). Patients were classified according to whether the cause of chest pain was potentially life-threatening (e.g., acute coronary syndrome (ACS), PE, aortic dissection) or benign. Serum ADMA and arginine levels were compared between the patient and control groups. Additionally, medication use, family history, electrocardiogram (ECG) findings, emergency department outcomes, and patients' final status were evaluated.

Quantitative Measurement of ADMA and Other Arginine Derivatives

The normal range for ADMA in adults is accepted to be 0.5-1.2 $\mu\text{mol/L}$. Serum samples were collected in gel tubes, centrifuged, and stored at -80°C . Plasma samples for measurement of ADMA, symmetric dimethyl arginine (SDMA), NG-monomethyl-L-arginine (L-NMMA), arginine, and citrulline were analyzed at the Selçuk University Faculty of Medicine Biochemistry Laboratory using the AB SCIEX API 3200 LC-MS/MS system. The analysis was conducted in positive-ion mode using Turbo Ion Spray electrospray ionization source on a Phenomenex Luna 50×4.6 mm, $5 \mu\text{m}$ C18 HPLC column. A gradient was established using two mobile phases: water containing 0.1% formic acid (pump A) and methanol containing 0.1% formic acid (pump B). Butanol containing 5% acetyl chloride was used for derivatization. Each sample was processed using prepared reagents, and internal standards were used as necessary (5).

Statistical Analysis

Data analysis was conducted using the SPSS 20.0 statistical software (IBM Inc., Chicago, IL) on the dataset compiled in Microsoft Excel. Descriptive statistics for all variables were calculated. The normality of the data was evaluated using the Kolmogorov-Smirnov test; most of the data did not conform to a normal distribution. Therefore, the Mann-Whitney U test was used to assess differences between two independent groups, and the Kruskal-Wallis test was used for comparisons among multiple groups. Pairwise comparisons were analyzed using the Wilcoxon signed-rank test.

Results

Of the 219 participants included in the study, 47.5% were in the patient group presenting with chest pain and 52.5% were in the control group. Of the participants, 58.4% were male. The cases were classified as ACS, non-specific chest pain (NSGA), PE, and other diagnoses, with NSGA (42.3%) and ACS (35.6%) being the most frequent. The demographic analysis showed similar average ages; the control group had a greater average height, whereas the case group's body mass index (BMI) was 2 kg/m^2 higher than that of the control group.

Regarding biochemical measurements, no significant differences were found among the levels of ADMA, SDMA, and L-NMMA, whereas arginine ($p < 0.001$) and the ratios (arginine/ADMA, $p < 0.001$; arginine/total methyl arginine, $p = 0.001$) showed significant differences between the groups. The arginine concentration in the patient group was approximately $111 \mu\text{mol/L}$, whereas in the control group it was $131 \mu\text{mol/L}$. The arginine/ADMA ratio was 403 and $131 \mu\text{mol/L}$ in the patient

and control groups, respectively (Table 1). All participants in the control group presented in autumn, whereas participants in the patient group presented similarly in summer and autumn. No significant differences were found in the levels of ADMA, SDMA, and L-NMMA. The rates of non-ST elevation myocardial infarction (NSTEMI) and STEMI were notable, and the similarity in pain presentation was 34%.

Cardiovascular risk factors were examined in the patient group: a history of angiography and smoking were present in 40.4%, hypertension in 42.3%, and a family history in 39.4%. Among the patients, 42.2% were discharged after examination, whereas angiography was performed in 33.7%. Among the ECG findings, ST depression was the most commonly observed (15.5%). Presentations occurred during daytime hours in 47.1% of cases. In the initial diagnosis grouping, NSGA (42.3%) and ACS (35.6%) rates were notable, while the PE rate was 8.7%. Troponin and creatine kinase-MB (CK-MB) levels were higher in the NSGA group than in the PE group. Among the arginine derivatives, ADMA levels were lowest in PE and highest in ACS. No mortality was observed in the emergency department; however, three patients died during hospitalization.

In patients with PE, L-NMMA levels were elevated ($p=0.013$). Simultaneously, SDMA and total methyl arginine increased in cases of cardiomegaly, whereas arginine and the arginine-to-total methyl arginine ratio decreased in cases of atelectasis. In fatal cases, D-dimer, ADMA, SDMA, and L-NMMA levels were elevated; aspartate aminotransferase was elevated in NSGA. D-dimer was significantly elevated in patients with STEMI. Troponin levels did not differ significantly among the groups, with measurements of 100 ng/mL in STEMI, 120 ng/mL in NSTEMI, and 165 ng/mL in unstable angina pectoris (USAP). Four hours later, decreases were observed in STEMI and USAP, while increases were noted in NSTEMI and other groups. CK-MB levels were elevated in NSTEMI and other groups. D-dimer levels were significantly elevated in

patients with STEMI. The arginine/ADMA ($p=0.017$) and arginine/total methyl arginine ($p=0.037$) ratios showed significant differences among the STEMI, NSTEMI, and USAP groups. Arginine/ADMA was 642 $\mu\text{mol/L}$ in STEMI, 318 $\mu\text{mol/L}$ in NSTEMI, and 176 $\mu\text{mol/L}$ in USAP. Arginine/total methyl arginine was 313 $\mu\text{mol/L}$ in STEMI, 187 $\mu\text{mol/L}$ in NSTEMI, and 104 $\mu\text{mol/L}$ in USAP. ADMA levels were elevated in NSTEMI and USAP but reduced in STEMI. SDMA concentrations were 314 $\mu\text{mol/L}$ in NSTEMI and 172 $\mu\text{mol/L}$ in STEMI. L-NMMA was elevated in USAP to 0.045 $\mu\text{mol/L}$. Citrulline concentration peaked at 23.78 $\mu\text{mol/L}$ in USAP. Total methylarginine values were similar in NSTEMI and USAP (both 0.700 $\mu\text{mol/L}$) (Table 2).

In patients with a history of angiography, levels of troponin, CK-MB, and D-dimer were lower, whereas levels of ADMA and total methyl arginine were higher. In patients with typical pain, CK-MB levels were significantly higher. SDMA levels were substantially higher in those with a history of heart failure ($p=0.040$). Smokers had lower citrulline levels ($p=0.038$), whereas physically active individuals had lower SDMA and total methylarginine levels ($p=0.045$ and $p=0.009$, respectively). In those with a history of hypertension, troponin and citrulline levels were elevated ($p=0.006$ and $p=0.009$, respectively). As the duration of the stay in the intensive care unit increased, SDMA levels rose while arginine levels decreased. A positive correlation was found between ADMA and total methyl arginine, whereas an inverse correlation was observed between ADMA and the arginine/ADMA ratio. The ROC analysis of the arginine-to-ADMA ratio demonstrated high diagnostic accuracy (area under the curve: 0.867) with a cutoff value of 218.15 $\mu\text{mol/L}$. Alcohol use was more common in the group with fatal cardiovascular disease ($p=0.019$). Most of the fatal cases were male and presented during daytime hours (Table 3, Figure 1).

Parameter	Patients (n=104)	Control (n=115)	p value
ADMA ($\mu\text{mol/L}$)	0.315 \pm 0.133	0.327 \pm 0.136	0.515
SDMA ($\mu\text{mol/L}$)	0.229 \pm 0.182	0.189 \pm 0.080	0.184
L-NMMA ($\mu\text{mol/L}$)	0.038 \pm 0.034	0.034 \pm 0.014	0.567
Arginine ($\mu\text{mol/L}$)	111.34 \pm 63.33	131.52 \pm 44.90	<0.001*
Citrulline ($\mu\text{mol/L}$)	18.76 \pm 15.37	19.44 \pm 11.33	0.103
Total methyl arginine ($\mu\text{mol/L}$)	0.583 \pm 0.261	0.551 \pm 0.182	0.556
Arginine/ADMA	403.19 \pm 318.09	131.75 \pm 44.91	<0.001*
Arginine/total methyl arginine	218.36 \pm 160.09	151.0 \pm 48.3	0.001*

*: $p<0.001$, ADMA: Asymmetric dimethylarginine, SDMA: Symmetric dimethyl arginine, L-NMMA: NG-monomethyl-L-arginine

Table 2. Biochemical findings of cardiac markers according to detailed diagnostic categories

Parameter	STEMI (n=11)	NSTEMI (n=22)	USAP (n=4)	Other (n=67)	p value
Troponin (ng/L)	98.38±250.5	121.32±298	164.9±186.2	130.4±330	0.703
CK-MB (ng/mL)	3.44±2.56	5.60±12.5	3.05±1.8	9.74±26.3	0.886
D-dimer (ng/mL)	2520±353	1963±2439	-	-	0.946
INR	1.31	1.27	-	-	0.984
ADMA (µmol/L)	0.254±0.12	0.328±0.14	0.381±0.12	0.315±0.13	0.384
SDMA (µmol/L)	0.172±0.04	0.314±0.36	0.273±0.11	0.208±0.10	0.150
L-NMMA (µmol/L)	0.034±0.01	0.041±0.02	0.045±0.01	0.038±0.04	0.942
Arginine (µmol/L)	139.6±104.7	102.5±65.7	68.17±40.8	112.5±54.8	0.151
Citrulline (µmol/L)	19.63±11.4	18.96±23.1	23.78±24.3	18.27±13.9	0.941
Total methyl arginine (µmol/L)	0.460±0.16	0.692±0.20	0.700±0.02	0.562±0.21	0.122
Arginine/ADMA	642.0±508.7 ^{a,b}	318.7±135.3 ^b	176.8±107.6 ^a	407.1±308.4	0.017 [*]
Arginine/total methyl arginine	313.3±210.3 ^{a,b}	187.8±88.9 ^b	104.1±75.3 ^a	227.1±163.9	0.037 [*]

Significant differences marked with asterisks. “a” and “b” represent groups with significant differences (comparison indicated in the table). CK-MB: Creatine kinase-MB; INR: International normalized ratio; ADMA: Asymmetric dimethylarginine; SDMA: Symmetric dimethyl arginine; L-NMMA: NG-monomethyl-L-arginine; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction.

Table 3. Differential diagnostic information determined for the arginine/ADMA ratio

Arginin/ADMA	Patients	Control	Total
>218.16	78	5	83
<218.15	26	110	136
Total	104	115	219
Sensitivity	75.0%	False negative	25.0%
Specificity	95.65%	False positive	4.34%
Positive predictive value	93.97%	Positive probability	1725%
Negative predictive value	80.88%	Negative probability	26.13%
Accuracy	85.84%		

ADMA: Asymmetric dimethylarginine

Discussion

This study investigated the relationship between arginine derivatives (ADMA, SDMA, L-NMMA) and cardiovascular diseases. Elevated plasma ADMA levels are an important risk factor for atherosclerosis and cardiovascular events. The finding of lower citrulline levels in smokers highlights the effects of smoking on metabolism. A positive correlation has been observed between age and ADMA levels, indicating that ADMA levels increase with age. The study by Cavusoglu et al. (6) indicates that high levels of ADMA and SDMA can serve as cardiovascular risk factors and are associated with potentially fatal cardiovascular events. These findings are consistent with previous studies (7,8).

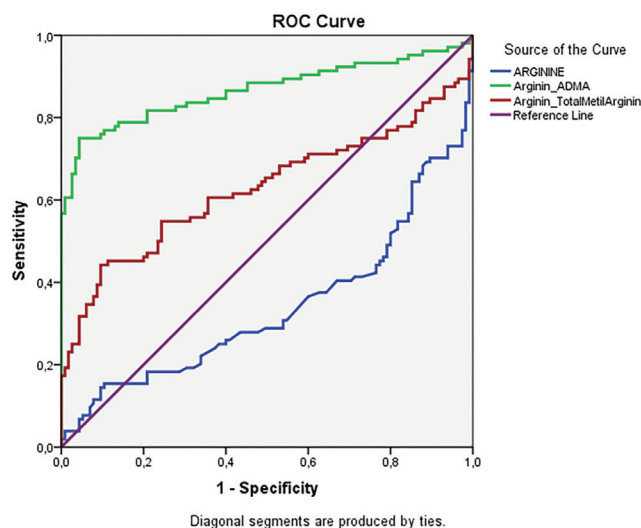


Figure 1. Results of ROC analysis for arginine and its ratios
ADMA: Asymmetric dimethylarginine

Previous research has examined the effects of arginine derivatives on cardiovascular disease. Borgeraas et al. (9) found that ADMA levels were higher in the low BMI group, indicating that arginine derivatives are associated with increased cardiovascular risk. In another study conducted by Borgeraas et al. (9), male gender and age were associated with ADMA levels in patients grouped by trans fatty acids. These findings align with the results of this study and strengthen the relationship between arginine and ADMA levels and cardiovascular diseases.

Previous studies have shown that ADMA and SDMA could serve as cardiovascular risk factors (10). Souza-Costa et al. (11) examined the effects of L-NMMA on pulmonary hypertension and provided evidence of a relationship between arginine derivatives and cardiovascular conditions. Böger et al. (3) emphasized the significance of the relationship between ADMA and cardiovascular diseases. In our study, elevated levels of ADMA were observed in patients with chest pain admitted to the emergency department. Cavusoglu et al. (6) also examined the relationship between ADMA and BMI, and found a significant association between obesity and elevated ADMA levels. Our study similarly demonstrates that ADMA is associated with BMI, hypertension, and other cardiovascular risk factors, consistent with previous studies.

Das et al. (12) examined the effects of hypertension and diabetes on ADMA levels and observed significantly elevated levels in patients with hypertension. Our study also found increases in arginine and SDMA levels in patients with a history of hypertension. Zoccali et al. (13) pointed out that inflammation increases ADMA levels; our study also demonstrated an association between inflammatory conditions and ADMA. Kumar et al. (14) examined the relationship between pulmonary hypertension and L-NMMA, indicating that L-NMMA could be used for clinical diagnosis. Lippi et al. (15) investigated the diagnostic value of arginine derivatives in ACS and noted the elevation of the arginine/ADMA ratio. These findings suggest that arginine derivatives may be important in clinical diagnosis.

A major limitation of this study is the small sample size in certain diagnostic subgroups, particularly the USAP group (n=4). This small subgroup size reduces the statistical power and limits the reliability of subgroup comparisons. Therefore, the findings related to USAP should be interpreted with caution and considered hypothesis-generating rather than definitive.

Study Limitations

The study's generalizability is limited by the small sample size and heterogeneous group composition. Larger population-based, long-term studies are needed to understand the value of arginine derivatives better. To reduce confounding, patients with conditions known to elevate ADMA independently of cardiovascular disease—such as renal failure, infection/sepsis, systemic inflammatory or autoimmune disorders, malignancy, and chronic liver disease—were excluded. This ensured that observed changes in ADMA and arginine metabolism primarily reflected cardiovascular pathology.

Conclusion

Elevated ADMA levels and an increased arginine/ADMA ratio have been identified as important biomarkers in the differential diagnosis of cardiovascular events and fatal conditions. Findings emphasize the connection between ADMA and factors such as inflammation, hypertension, and obesity, suggesting potential contributions to early diagnosis and treatment. The use of the arginine/ADMA ratio in diagnostic processes is recommended. This study highlights that these biomarkers could be critical tools in emergency management and lays the groundwork for future research.

Ethics

Ethics Committee Approval: The study was conducted between June and November 2016 and was approved by the Selçuk University Faculty of Medicine Ethics Committee (decision no: 2016/147, date: 18.05.2016).

Informed Consent: Informed consent forms were obtained from all participants.

Footnotes

Authorship Contributions

Concept: HSY., Design: HSY, AB., Data Collection or Processing: HSY, AB, AU., Analysis or Interpretation: HSY, AB, FA., Literature Search: HSY, AB, AU, MA, BT., Writing: HSY.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Zhou Z, Jing H, Tao Z, Choi H, Aboulfatova K, Moake J, et al. Effects of naturally occurring mutations in CUB-1 domain on synthesis, stability, and activity of ADAMTS-13. *Thromb Res.* 2009;124:323-7.
2. Cotter G, Kaluski E, Blatt A, Milovanov O, Moshkovitz Y, Zaidenstein R, et al. L-NMMA (a nitric oxide synthase inhibitor) is effective in the treatment of cardiogenic shock. *Circulation.* 2000;101:1358-61.
3. Böger RH. Association of asymmetric dimethylarginine and endothelial dysfunction. *Clin Chem Lab Med.* 2003;41:1467-72.
4. Pettersson A, Hedner T, Milsom I. Increased circulating concentrations of asymmetric dimethyl arginine (ADMA), an endogenous inhibitor of nitric oxide synthesis, in preeclampsia. *Acta Obstet Gynecol Scand.* 1998;77:808-13.
5. Schulze F, Wesemann R, Schwedhelm E, Sydow K, Albsmeier J, Cooke JP, et al. Determination of asymmetric dimethylarginine (ADMA) using a novel ELISA assay. *Clin Chem Lab Med.* 2004;42:1377-83.
6. Cavusoglu E, Ruwende C, Chopra V, Poludasu S, Yanamadala S, Frishman WH, et al. Relation of baseline plasma ADMA levels to cardiovascular morbidity and mortality at two years in men with diabetes mellitus referred for coronary angiography. *Atherosclerosis.* 2010;210:226-31.

7. Kielstein JT, Salpeter SR, Bode-Boeger SM, Cooke JP, Fliser D. Symmetric dimethylarginine (SDMA) as endogenous marker of renal function--a meta-analysis. *Nephrol Dial Transplant*. 2006;21:2446-51.
8. Valkonen M, Penttilä M, Saloheimo M. Effects of inactivation and constitutive expression of the unfolded- protein response pathway on protein production in the yeast *saccharomyces cerevisiae*. *Appl Environ Microbiol*. 2003;69:2065-72.
9. Borgeraas H, Hertel JK, Svingen GF, Pedersen ER, Seifert R, Nygård O, et al. Association between body mass index, asymmetric dimethylarginine and risk of cardiovascular events and mortality in norwegian patients with suspected stable angina pectoris. *PLoS One*. 2016;11:e0152029.
10. Hov GG, Aasarød KI, Sagen E, Åsberg A. Arginine, dimethylated arginine and homoarginine in relation to cardiovascular risk in patients with moderate chronic kidney disease. *Clin Biochem*. 2015;48:646-51.
11. Souza-Costa DC, Zerbini T, Metzger IF, Rocha JB, Gerlach RF, Tanus-Santos JE. L-Arginine attenuates acute pulmonary embolism-induced oxidative stress and pulmonary hypertension. *Nitric Oxide*. 2005;12:9-14.
12. Das UN, Repossì G, Dain A, Eynard AR. L-arginine, NO and asymmetrical dimethylarginine in hypertension and type 2 diabetes. *Front Biosci (Landmark Ed)*. 2011;16:13-20.
13. Zoccali C, Maas R, Cutrupi S, Pizzini P, Finocchiaro P, Cambareri F, et al. Asymmetric dimethyl-arginine (ADMA) response to inflammation in acute infections. *Nephrol Dial Transplant*. 2007;22:801-6.
14. Kumar R, Gupta N, Jain P. L-NMMA levels and their association with pulmonary hypertension. *Respir Med*. 2023;121:95-101.
15. Lippi G, Montagnana M, Salvagno GL, Guidi GC. Potential value for new diagnostic markers in the early recognition of acute coronary syndromes. *CJEM*. 2006;8:27-31.