*Prospective Clinical Research Report*

*Journal of* INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(6) 1–9

DOI: 10.1177/0300060520920439
journals.sagepub.com/home/imr
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# Increased symmetric dimethylarginine, but not asymmetric dimethylarginine, concentrations are associated with transient myocardial ischemia and predict outcome

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## Abstract

**Objective:** Asymmetric and symmetric dimethylarginines (ADMA and SDMA) are endothelial dysfunction markers. ADMA inhibits synthesis of nitric oxide. We aimed to analyze both markers in patients with coronary artery disease (CAD) who were referred for stress/rest myocardial perfusion scintigraphy (MPS).

**Methods:** All patients underwent a 2-day dipyridamole (DP) stress/rest protocol. Thereafter, patients with transient myocardial perfusion abnormality were followed up and their coronary blood flow was quantitatively assessed. Venous blood was taken before and after DP stress to measure markers.

**Results:** Baseline ADMA and SDMA concentrations were significantly higher in patients with CAD compared with healthy subjects. Pre- and post-stress SDMA concentrations were significantly higher in patients with transient myocardial perfusion abnormality compared with those with negative MPS results. However, ADMA and L-arginine concentrations were not significantly different between the two groups. None of the markers were significantly different between patients with angiographically proven low coronary flow and those with normal coronary flow. Pre-stress SDMA concentrations were an independent predictor of cardiovascular mortality during a 8-year follow-up.

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**Conclusions:** Elevated serum SDMA concentrations may be helpful for selecting high-risk patients with CAD if there is any doubt in interpreting MPS. SDMA concentrations may also predict cardiovascular outcome.

**Keywords**
Dipyridamole, coronary artery disease, asymmetric dimethylarginine, myocardial perfusion scintigraphy, L-arginine, cardiovascular mortality

Date received: 11 October 2019; accepted: 23 March 2020

## Introduction

Coronary artery disease (CAD) is the leading cause of death in Western countries.[1] Coronary arteriography is widely accepted as the gold standard for diagnosing CAD and evaluating the extent and severity of vessel stenosis[2] because of its superior spatial and temporal resolution.[1] Non-invasive diagnostic tests, such as single-photon emission computed tomography (SPECT), positron emission tomography, stress echocardiography, exercise electrocardiography, and multislice computerized tomography, can detect the consequences of ischemia (e.g., impaired cell membrane function, decreased perfusion, and impaired myocardial contractility). However, none of these techniques are perfect.[3] A highly sensitive non-invasive test to estimate the severity of CAD in stable patients is urgently required. Dipyridamole (DP) is a nonselective coronary vasodilator that is commonly used for stress perfusion cardiac imaging. This agent is safe and provides an effective means to diagnose stable CAD.[4]

Asymmetric dimethylarginine (ADMA) causes endothelial dysfunction by inhibiting endothelial nitric oxide synthase (NOS). Elevated plasma ADMA concentrations are a major risk factor for CAD and predict coronary events.[5] ADMA is metabolized by dimethylarginine dimethylaminohydrolases to citrulline and dimethylamine (DMA), and is partly excreted unchanged via the kidney.[6] Although the clinical role of ADMA has been clarified, the clinical role of its structural isomer symmetric dimethylarginine (SDMA) remains largely unclear.[7]

The present study aimed to investigate whether ADMA and/or SDMA concentrations in patients suffering from CAD are associated with transient myocardial perfusion abnormality. Patients were referred and scheduled for a DP stress test combined with myocardial perfusion scintigraphy (MPS) by cardiologists. Coronary angiography was later performed in part of the study population. We also aimed to examine the relationship between angiographically proven reduced coronary flow and transient myocardial perfusion defects based on DP-induced changes in serum ADMA and SDMA concentrations. Furthermore, we aimed to follow-up mortality data for clarifying the potential role of ADMA or SDMA in predicting death.

## Material and methods

The study protocol was approved by the Clinical Center's Regional and Institutional Research Ethics Committee, University of Pécs, Hungary. Written informed consent was obtained from each patient. Anonymous blood donors served as healthy controls.

### *Patients*

Patients who suffered from CAD and were scheduled for rest/stress (2-day protocol)

MPS by cardiologists were selected for this study after consent was obtained. Exclusion criteria were chronic renal failure (creatinine concentrations >120 μmol/L) and decline to participate in the study.

The medical history concerning previous coronary events, stroke/transient ischemic attack, diabetes, hypertension, dyslipidemia, current cigarette smoking, body mass index, and orally taken medication was obtained from all patients. A history of hypertension was defined as the use of antihypertensive drugs or blood pressure >140/90 on at least two separate occasions. Diabetes mellitus was defined as the use of anti-diabetic drugs or diet treatment only, or a fasting plasma glucose value ≥7.0 mmol/L.

## Blood sampling and DP

Venous blood samples were drawn before DP stress as baseline and at the end of DP infusion. Serum samples were frozen within 60 minutes and stored at −70°C until analysis.

*Determination of arginine derivatives.* The amino acid content of serum samples was retrieved by solid-phase extraction. Amino acids were quantified by high-performance liquid chromatography after derivatization in collaboration with the Department of Applied Chemistry at the University of Debrecen, Hungary.

Solid-phase extraction of the analytes was performed according to the procedure of Nonaka et al.[8] The dry residue was dissolved in 200 μL ultrafiltered deionized water (Milli-Q; Merck KGaA, Darmstadt, Germany) and derivatized according to Molnar-Perl et al.[9] Arginine and homoarginine were detected at $\lambda_{ex} = 337$ nm and $\lambda_{em} = 520$ nm, respectively, and $\lambda_{em} = 454$ nm was used for ADMA and SDMA. The baseline separation was achieved using a previously described method.[10]

*MPS protocol.* All patients underwent a 2-day stress SPECT protocol. Technetium-99m sestamibi (555–740 MBq) was intravenously injected at rest and during pharmacological stress. The pharmacological stress protocol was as follows.[11] DP (0.56 mg/kg) was intravenously infused during 4 minutes under continuous electrocardiographic monitoring. Technetium-99m sestamibi was injected 4 minutes after the end of the infusion. Contraindications to DP were a history of asthma or chronic obstructive pulmonary disease, second- or third-degree atrioventricular block, and systemic blood pressure <90/60 mm Hg. Patients were instructed to avoid xanthine-containing products for 24 hours before the test.

Image acquisition began 60 minutes after injection during pharmacological stress or at rest. A dual-head camera (Nucline Cardio-C dual head SPECT; Mediso, Budapest, Hungary) with a low-energy, high-resolution collimator was rotated in a circular orbit from 45° right anterior oblique to 135° left posterior oblique, and it acquired 32 projections (70 seconds/projection after stress or at rest). Transaxial sections were reoriented in three standard cardiac planes (short axis, and horizontal and vertical long axes). Anterior, anterolateral, anteroseptal, inferoseptal, inferior, and inferolateral segments of the left ventricular myocardium were analyzed in a midventricular short-axis slice. The apex was analyzed in a vertical long-axis slice. Images were visually interpreted by two experienced observers using a semiquantitative color scale, with each change in color representing an approximately 10% change in radiotracer uptake. Perfusion defects were reported as transient (decreased post-stress uptake, but normal at rest = ischemia), fixed (decreased uptake post-stress and at rest = infarction), or mixed (reduced post-stress uptake with 10% increase in uptake at rest, without reaching normal perfusion = infarction with associated ischemia).

*Coronary angiography follow-up*. Follow-up was obtained by hospital records using the findings of cardiac catheterization. Coronary blood flow was objectively evaluated by means of the Thrombolysis in Myocardial Infarction (TIMI) frame count (TFC). The TFC and corrected TFC (CTFC) for the left anterior descending coronary artery are simple clinical tools for assessing quantitative indices of coronary blood flow.[12]

*Statistical analysis*. Statistical analysis was performed using the SPSS software program, version 16.0 (Chicago, IL, USA). Continuous variables with a normal distribution are presented as mean and standard deviation or 95% confidence interval (CI). Comparison of categorical and continuous variables between the groups was performed by the chi-square test and independent sample *t*-test, respectively.

## Results

Forty-four patients with the diagnosis of CAD (mean age: $58 \pm 9$ years, male sex: $n = 18$) who were referred by a cardiologist were recruited for this prospective study. Baseline demographic characteristics, risk factors, and medication are shown in Table 1. Healthy blood donors without apparent cardiac symptoms served as controls ($n = 64$) (Table 2).

### *Myocardial perfusion scintigraphy*

All patients were examined by stress/rest MPS. Transient myocardial perfusion abnormality was detected in 31 (male sex: $n = 17$) patients. Baseline biomarker data of the patients in both groups are shown in Table 2. Patients with CAD had significantly higher ADMA and SDMA concentrations at baseline compared with controls (both $p = 0.01$). Pre-stress ($p = 0.04$) and post-stress serum SDMA ($p = 0.01$) concentrations were significantly higher in patients with transient myocardial perfusion abnormality as shown by MPS compared with those with negative MPS results (Table 3, Figure 1). However, serum L-arginine and ADMA concentrations were not significantly different between the two MPS subgroups (Table 3).

**Table 1.** Demographic and clinical data of patients with coronary artery disease.

| | Men<br>n = 18 | Women<br>n = 26 | p value |
|---|---|---|---|
| Age, years | 61 ± 8 | 58 ± 10 | NS |
| BMI, kg/m$^2$ | 28.8 ± 3.3 | 29.2 ± 4.0 | NS |
| Dipyridamole induced angina | 2 (11) | 12 (46) | <0.05 |
| Positive MPS | 17 (94) | 14(54) | <0.01 |
| Positive coronary angiography | 10/13 | 7/9 | NS |
| Smoking | 10 (55) | 6 (23) | <0.05 |
| Hypertension | 14 (78) | 23 (88) | NS |
| Diabetes | 4 (22) | 10 (38) | NS |
| Creatinine (μmol/L) | 79.4 ± 17.6 | 71.4 ± 10.8 | NS |
| Dyslipidemia | 14 (78) | 13 (50) | NS |
| Statin therapy | 14 (78) | 13 (50) | NS |
| Clopidogrel | 2 (11) | 2 (8) | NS |
| Aspirin | 12 (67) | 8 (31) | <.05 |

Values are presented as mean ± standard deviation or as number (%). The chi-square test and independent samples *t*-test were used for analysis.

BMI = body mass index, positive MPS = presence of transient ischemia by myocardial perfusion scintigraphy, NS = not significant.

**Table 2.** Demographic and baseline biomarker data in patients with CAD compared with healthy subjects.

| | Healthy subjects n = 64 | Patients with CAD n = 44 | p value |
|---|---|---|---|
| Age, years | 51 ± 3.4 | 58 ± 9.5 | NS |
| Male sex | 37 | 18 | NS |
| ADMA, μmol/l | 0.41 ± 0.09 | 0.80 ± 0.38 | 0.01 |
| SDMA, μmol/l | 0.37 ± 0.12 | 0.54 ± 0.17 | 0.01 |
| L-arginine, μmol/l | 88.17 ± 14.54 | 66.95 ± 42.81 | NS |

Values are mean ± standard deviation. The independent samples *t*-test was used for analysis.
NS = not significant, ADMA = asymmetric dimethylarginine, SDMA = symmetric dimethylarginine.

**Table 3.** Biomarkers measured at pre- and post-dipyridamole stress in patients with or without transient myocardial perfusion abnormality as shown by MPS.

| | Positive MPS n = 31 | Negative MPS n = 13 | p value |
|---|---|---|---|
| Pre-stress L-arginine, μmol/L | 72.2 ± 42.0 | 53.8 ± 45.1 | NS |
| Post-stress L-arginine, μmol/L | 70.5 ± 30.0 | 52.6 ± 33.2 | NS |
| Pre-stress ADMA, μmol/L | 0.80 ± 0.25 | 0.79 ± 0.61 | NS |
| Post-stress ADMA, μmol/L | 0.77 ± 0.24 | 0.73 ± 0.23 | NS |
| Pre-stress SDMA, μmol/L | 0.57 ± 0.18 | 0.43 ± 0.11 | 0.04 |
| Post-stress SDMA, μmol/L | 0.55 ± 0.17 | 0.40 ± 0.13 | 0.01 |

Values are mean ± standard deviation. The independent samples *t*-test was used for analysis.
MPS = myocardial perfusion scintigraphy, NS = not significant, ADMA = asymmetric dimethylarginine, SDMA = symmetric dimethylarginine. Positive MPS means the presence of transient ischemia by MPS and negative MPS means no perfusion defects.

## *Coronary angiography*

Twenty-two patients with transient myocardial perfusion abnormality (positive MPS) were scheduled for coronary angiography. Coronary flow was quantified objectively by two interventional cardiologists who were blinded to the biomarker characteristics of the patients using the TFC method. The retrospectively evaluated biomarker data showed no significant differences between patients with and those without angiographically proven stenosis involving any coronary artery based on the TFC.

## *Eight-year follow-up: cardiovascular mortality*

Six patients died because of cardiovascular reasons (1 from acute myocardial infarction, 2 from acute heart failure, 1 from in-stent restenosis, and 2 for other reasons) during 8 years of follow-up. Pre- and post-stress serum SDMA concentrations, but not ADMA concentrations, were significantly higher in patients who died compared with those who survived (median: 0.79 μmol/L, 95% CI: 0.61–0.86 vs 0.50 μmol/L, 0.44–0.61; and 0.76 μmol/L, 0.55–0.79 vs 0.48 μmol/L, 0.40–0.62; $p = 0.005$ and $p = 0.029$, respectively) during 8 years of follow-up. Additionally, pre-stress serum SDMA concentrations were strongly predictive of cardiovascular death with a cut-off value of serum SDMA concentrations of $\geq 0.592$ μmol/L (sensitivity of 83% and specificity of 76%). The receiver operating characteristic area under the curve was 0.864 (95% confidence interval: 0.721–1.006,

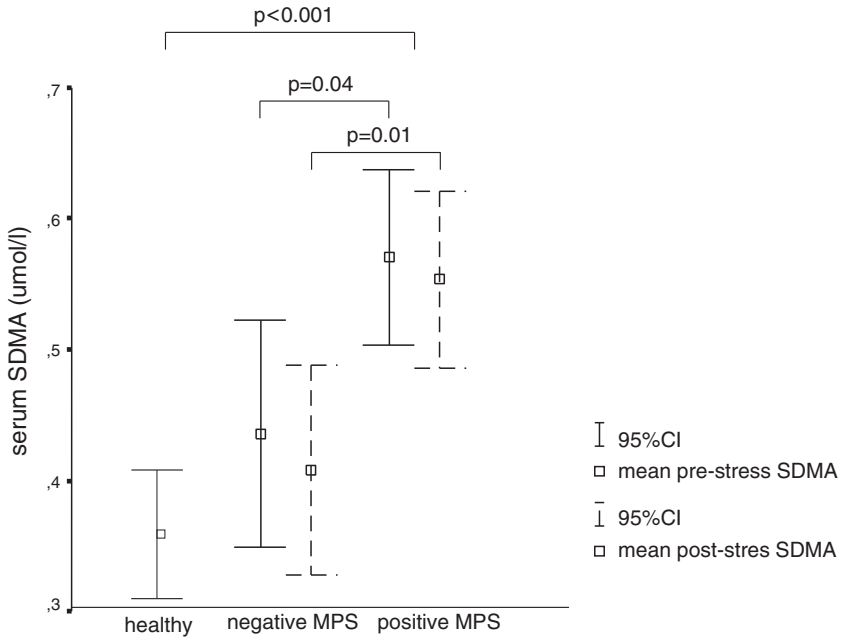


**Figure 1.** Comparison of pre- and post-stress SDMA concentrations in patients with coronary artery disease with positive (transient ischemia) and negative myocardial perfusion scintigraphy, and SDMA concentrations in healthy controls. Serum SDMA concentrations (mean, 95% CI) were examined in 64 healthy subjects and 44 patients with suspected coronary artery disease measured before (as baseline) and after dipyridamole stress (independent samples *t*-test, $p < 0.01$).
SDMA = symmetric dimethylarginine, CI = confidence interval.

$p = 0.005$). Binary logistic regression analysis including confounders, such as age, sex, and comorbidity (see Table 1), showed that serum pre-stress SDMA concentrations with an odds ratio of 9.1 ($p = 0.03$) were an independent predictor of cardiovascular mortality during the follow-up period.

## Discussion

In this study, we found that serum ADMA and SDMA concentrations were significantly higher in patients with CAD compared with healthy subjects. This finding is in accordance with a recent study in which the authors argued against an exclusive ADMA effect in mediating cardiovascular risk and emphasized that SDMA had similar diagnostic value in a large prospective cohort.[13] Additionally, SDMA was found to be a marker of the estimated glomerular filtration rate and the extent of CAD because it was eliminated by renal excretion.[13] However, the major route of ADMA elimination is hydrolytic degradation by dimethylaminohydrolases and it is only partly excreted by the kidney.[14] Importantly, SDMA does not directly inhibit NOS, but is a competitor of arginine transport. SDMA reduces endothelial nitric oxide synthesis, probably by limiting L-arginine supply to NOS.[14]

The major finding of the present study was that pre- and post-stress serum SDMA concentrations were significantly higher in patients with positive MPS than in those with negative MPS results. Recently, SDMA, but not ADMA, was

found to be an independent predictor of all-cause and cardiovascular mortality in a large multiethnic population-based cohort.[15] The question may be raised whether there is an association between L-arginine pathway metabolites and systemic infusion of DP. In this cohort, there were no significant differences between pre-and post-stress serum ADMA and SDMA concentrations, but post-stress samples were not examined at later time points. Although adenosine causes acute activation of p42/p44 mitogen-activated protein kinase and nitric oxide release,[16] the acute effect of the adenosine reuptake inhibitor DP on circulating ADMA and SDMA concentrations requires further investigation.

Our finding that patients with positive MPS had significantly higher pre- and post-stress SDMA concentrations compared with those with negative MPS results suggests that SDMA *per se* might be a predictor of an impaired coronary microcirculation. Accumulating evidence has recently suggested that increased SDMA concentrations in blood independently predict the risk for obstructive CAD and incident major adverse coronary events in stable patients.[17] Sustained elevation of SDMA concentrations independent from DP stress might be an adaptive mechanism to improve coronary flow reserve. This possibility is supported by the previous finding that systemic infusion of the NOS inhibitor N(G)-monomethyl-L-arginine improved coronary flow reserve, even in patients with CAD.[18] This suggests that adenosine-induced hyperemia in patients with CAD is constrained by a mechanism that can be relieved by systemic NOS inhibition with N (G)-monomethyl-L-arginine. Additionally, because we found that mean post-stress serum ADMA and SDMA concentrations were slightly decreased compared with baseline (Table 3), we speculate that a direct flow-mediated mechanism due to DP or adenosine was involved. DP works directly and generally on vessels by increasing blood flow and on the heart by increasing heart rate and the left ventricular ejection fraction, resulting in improved cardiac output.[19] However, stress-induced ischemia promptly causes a transient reduction of the left ventricular ejection fraction in high-risk patients with CAD.[20] Presumably, this temporary reduction in cardiac output does not significantly affect renal blood flow. Therefore, any change in urinary excretion of SDMA is not expected. Renal blood flow was decreased in spontaneous hypertensive rats after DP, but remained unchanged or slightly increased in normotensive rats.[21] Importantly, antihypertensive treatment of these rats completely restored the normal renal vascular response to DP.[21] Furthermore, intravenous infusion of ADMA increased mean arterial pressure and cardiac output in rats.[22]

A recent study showed that patients with slow coronary flow had significantly higher plasma ADMA concentrations and a lower L-arginine/ADMA ratio compared with participants with normal coronary flow.[23] In contrast, neither ADMA and SDMA nor L-arginine/ADMA and L-arginine/SDMA ratios were significantly different between patients with angiographically proven stenosis and patients with negative coronary angiography in our cohort. However, recent findings support a complex interplay of arginine metabolism and vascular function.[11,24,25] Because only half of the patients in our study underwent coronary angiography, and periprocedural blood samples for biomarkers were not taken again, retrospective evaluation of biomarkers might be a major limitation of our study.

Our study suggests that increased serum SDMA concentrations in combination with abnormal myocardial perfusion should be considered in addition to traditional risk factors in patients undergoing elective cardiac evaluation. Importantly, pre-stress

serum SDMA concentrations with a cut-off value of $\geq$0.592 µmol/L predicted cardiovascular death with a sensitivity of 83% and specificity of 76% in long-term follow-up in our study. In accordance with this finding, a previous study showed that high SDMA levels, but not ADMA levels, were associated with an increased prevalence of significantly obstructive CAD in stable patients undergoing cardiac evaluation.[17] An increased SDMA concentration may help to select high-risk patients with CAD if there is any doubt in interpretation of MPS. However, a post-stress reduction in serum SDMA concentrations in patients with cardiac risk factors, but without apparent myocardial perfusion abnormalities, indicates a potential therapeutic role of DP. Further study to examine the profile of metabolites of the L-arginine pathway in patients with stable CAD, who are on sustained-release DP/aspirin therapy, for determining its long-term benefit might be warranted.[20]

## Acknowledgements

The authors thank Attila Konyi MD, PhD for his support in follow-up of the enrolled patients.

## Declaration of conflicting interest

The authors declare that there is no conflict of interest.

## Funding

This work was supported by EFOP-3.6.3-VEKOP-16-2017-00009 at the University of Pecs.

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