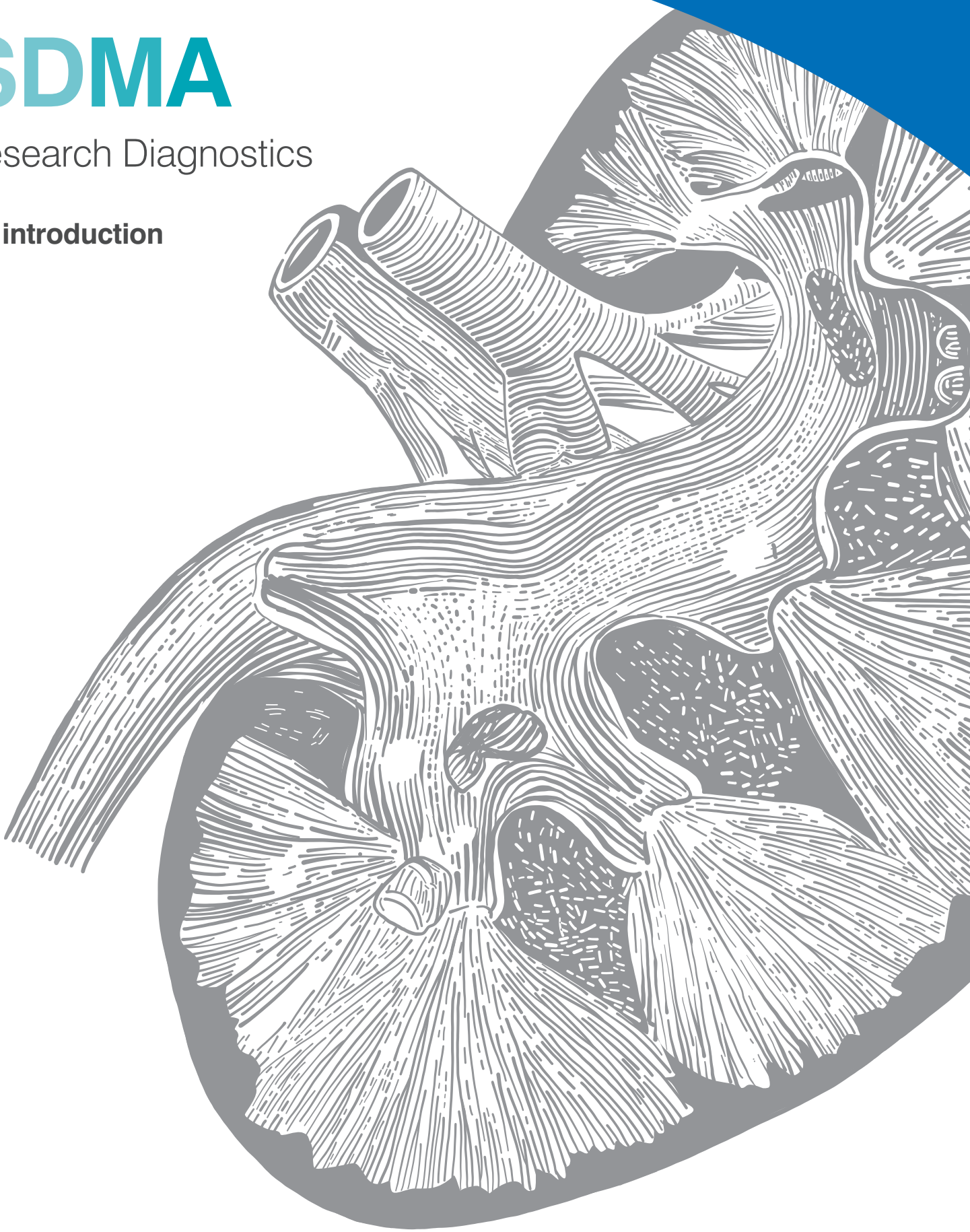
IDEXX **BioAnalytics**

# SDMA

## Research Diagnostics

### An introduction



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# What is **SDMA?**

## Serum symmetric dimethylarginine (SDMA)

SDMA stands for symmetric dimethylarginine. SDMA is an amino acid produced in the body when protein is broken down and then excreted through the kidneys. It is measured to detect kidney disease.

- SDMA is a methylated form of arginine in intracellular proteins of all nucleated cells
- SDMA is released into circulation when intracellular proteins are processed
- SDMA is xcreted by the kidneys
- Stable production of SDMA is part of daily cell activity
- It is a renal biomarker shown to correlate with glomerular filtration rate (GFR)

## An earlier indicator of renal failure

Historically, estimation of renal function has depended on blood urea nitrogen (BUN) and serum creatinine. Creatinine is a crude estimate of renal function as it doesn't elevate until significant (~75%) loss of function occurs. **SDMA identifies at only 40% loss of kidney function and as early as 25% loss.*** Compare this to creatinine testing which detects once 75% of kidney deterioration has occured and is an earlier indicator of renal failure than creatinine/BUN.

# Features and benefits

- SDMA is a marker for kidney function
- SDMA is earlier, more sensitive, and more reliable than creatinine
- SDMA correlates with GFR
- SDMA is a sensitive indicator of kidney function that **detects as little as 25% loss of function.**
- SDMA is more reliable than creatinine as an indicator of kidney function because it is not influenced by common confounding conditions.
- Compared to BUN, SDMA is a more reliable and sensitive indicator of kidney function in animals. BUN can be influenced by decreased production of urea in liver disease or anorexia and by increased production with high-protein meals or gastrointestinal bleeding. This contrasts with SDMA, which changes only with changes in GFR.
- SDMA is an earlier indicator of progressive kidney function loss, often increasing before other parameters.
- An increased SDMA may also serve as an indicator of concurrent diseases that may have a secondary impact on kidney function.

| Benefit | Mouse | Rat | Dog | NHP |
|---|---|---|---|---|
| Biomarker for kidney function | ● | ● | ● | |
| Correlates with GFR | ● | ● | ● | |
| Earlier indicator than Creatinine | | | ● | |
| More sensitive than Creatinine | | | ● | |
| Not subject to extrarenal factors | ● | ● | ● | |

# Testing methodologies

## Validation

- **SDMA has been validated in rats, and used in mice (basic science)** — LCMS
- **SDMA is validated in dogs, cats, and horses (clinical studies)**— LCMS, Beckman (Immunoassay), In house diagnostics (Immunoassay - Catalyst ®)
- **SDMA is highly correlated to GFR**
  Current methodology: Inulin, Iohexal, Creatinine Clearance, direct measurement
- **IDEXX SDMA was validated in rats** at the Reference Labs through a comparison to the gold standard method, liquid chromatography mass spectrometry.

## Sample submission

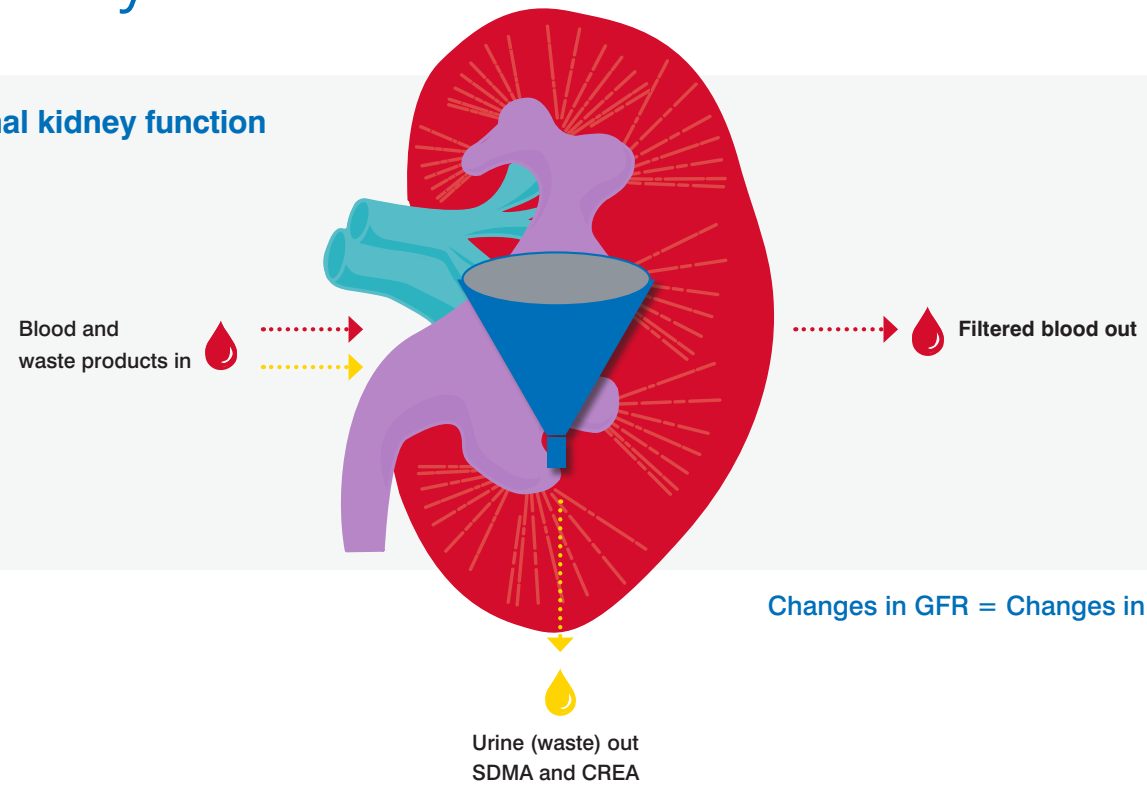
| Assay | Species | Platform | Sample Type | Sample Volume* |
|---|---|---|---|---|
| SDMA | Rat | LCMS | Serum, Plasma | 50 µL |
| SDMA | Mouse | LCMS | Serum, Plasma | 50 µL |
| SDMA | NHP | LCMS | Serum, Plasma | 100 µL |
| SDMA | Dog | LCMS | Serum, Plasma | 100 µL |
| SDMA | Cat | Beckman | Serum, Plasma | 100 µL |
| SDMA | Dog | Beckman | Serum, Plasma | 100 µL |
| SDMA | Rat | Beckman | Serum, Plasma | 100 µL |

* Minimum volume required

See the SDMA Directory of Services for complete requirements

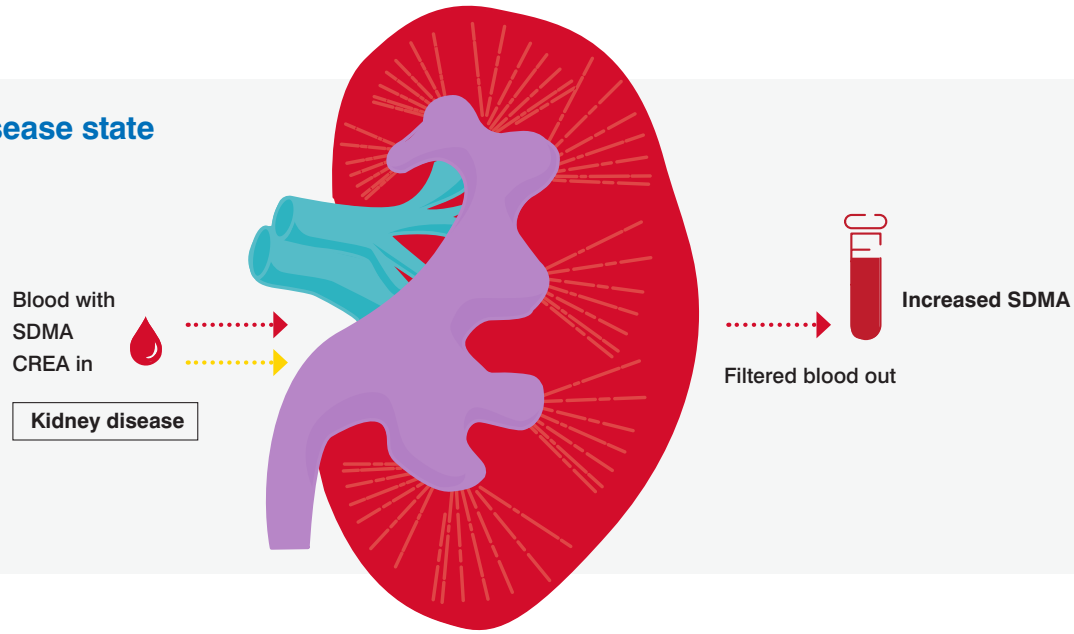
# Kidneys in action

## Normal kidney function




Changes in GFR = Changes in SDMA

## Kidney disease state




**Impaired GFR = Increased SDMA**

**Waste builds up in blood**
so less waste in urine

# Creatinine connection

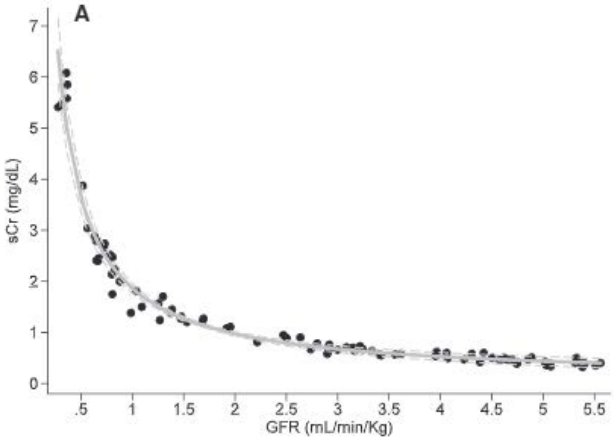
## Does SDMA replace creatinine in diagnosing kidney disease?

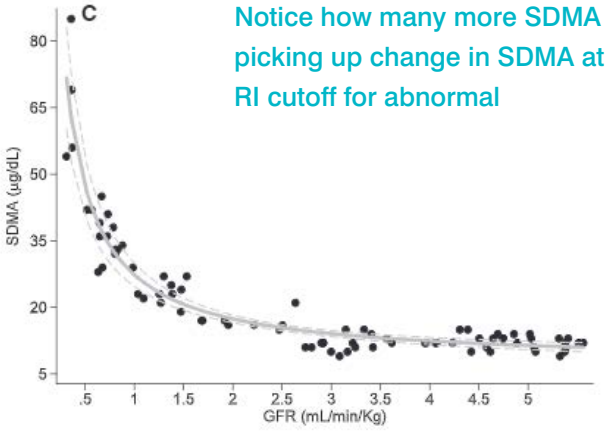
SDMA does not replace creatinine in diagnosing kidney disease. While SDMA is a more reliable tool to evaluate kidney function/GFR and results should be considered first, creatinine is still complementary to SDMA for evaluating kidney function. A complete kidney evaluation should consist of a thorough history, physical examination, and evaluation of a minimum database, including CBC, chemistry profile with SDMA and electrolytes, and complete urinalysis.

## How does SDMA compare to creatinine when assessing kidney function?

As compared to creatinine, SDMA is a more reliable and sensitive indicator of kidney function in animals. SDMA increases earlier than creatinine in dogs and cats with kidney disease. SDMA increases with as little as 25% loss of kidney function (average 40% loss of kidney function). Creatinine does not increase until up to 75% of kidney function is lost. Creatinine is a breakdown product of muscle and is therefore impacted by lean body mass, whereas SDMA is not.

## GFR in relation to SDMA and Creatinine




Notice how many more SDMA are picking up change in SDMA at the RI cutoff for abnormal

**GFR < 2 mL/min/kg this would be reduced or abnormal for canine species (3m-4ml/min/kg is normal GFR)**

# LCMS — the gold standard

### What is the gold standard method for measuring SDMA?

The gold standard methodology for measuring SDMA is Liquid Chromatography Mass Spectrometry (LCMS), which has shown good correlation with glomerular filtration rate.

### What is liquid chromatography mass spectrometry?

Mass spectrometry, often referred to as mass spec, is an advanced analytical technique that is becoming increasingly popular in bioresearch. In a nutshell, mass spec is used to accurately identify and quantify molecules within a sample.

It is not often used for clinical work; however, it is increasingly relied upon for academic research and by regulatory authorities such as the Food and Drug Administration (FDA).

### For which species has SDMA been validated and can it be run on other species?

SDMA has been validated at the Reference Labs for dogs, cats, horses, and rats.

Projects validating SDMA and establishing reference intervals for other species are ongoing. At the Reference Lab, SDMA results will be provided on routine non-species-specific chemistry profiles.

### How was the SDMA reference interval established for rats at the Reference Labs?

IDEXX SDMA was validated in rats at the Reference Labs through a comparison to the gold standard method, liquid chromatography mass spectrometry. Following validation, a reference interval study on clinically healthy adult rats was performed.

# Human clinical studies

## Is SDMA used in human research studies?

SDMA has been studied in human beings and has been shown to correlate with GFR and to be a more sensitive marker for detecting early loss of kidney function than creatinine or eGFR (estimated GFR) calculations. At this time SDMA is not used routinely in human medicine because traditional methods of measuring SDMA with liquid chromatography-mass spectrometry (LCMS) are not very practical. SDMA currently appears to only be used during human clinical studies. **IDEXX is the only company globally to have successfully developed a high-throughput assay for SDMA and has been partnering with Yale University to help bring this technology to human medicine.**

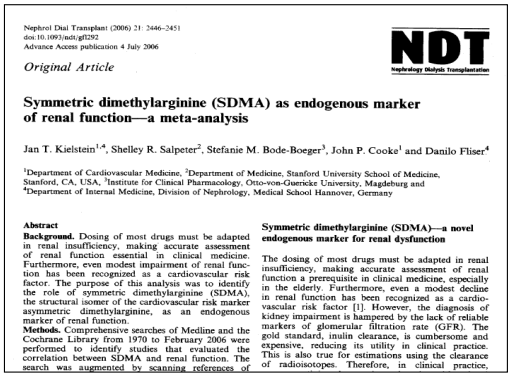
# Resources

**Literature review published in 2006**

- 18 studies N = 2,136 people
- SDMA correlated with inulin clearance
  - R = 0.85 (CI 0.76–0.91)
- SDMA correlated with creatinine
  - R = 0.75 (0.46–0.88)

**Updated Literature since 2006**

- SDMA and Sepsis
- SDMA



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NDT Nephrology Dialysis Transplantation

*Original Article*

**Symmetric dimethylarginine (SDMA) as endogenous marker of renal function—a meta-analysis**

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**Abstract**

**Background.** Dosing of most drugs must be adapted in renal insufficiency, making accurate assessment of renal function essential in clinical medicine. Furthermore, even modest impairment of renal function has been recognized as a cardiovascular risk factor. The purpose of this analysis was to identify the role of symmetric dimethylarginine (SDMA), the structural isomer of the cardiovascular risk marker asymmetric dimethylarginine, as an endogenous marker of renal function.
**Methods.** Comprehensive searches of Medline and the Cochrane Library from 1970 to February 2006 were performed to identify studies that evaluated the correlation between SDMA and renal function. The search was augmented by scanning references of

**Symmetric dimethylarginine (SDMA)—a novel endogenous marker for renal dysfunction**

The dosing of most drugs must be adapted in renal insufficiency, making accurate assessment of renal function a prerequisite in clinical medicine, especially in the elderly. Furthermore, even a modest decline in renal function has been recognized as a cardiovascular risk factor [1]. However, the diagnosis of kidney impairment is hampered by the lack of reliable markers of glomerular filtration rate (GFR). The gold standard, inulin clearance, is cumbersome and expensive, reducing its utility in clinical practice. This is also true for estimations using the clearance of radioisotopes. Therefore, in clinical practice,

**Link:** https://academic.oup.com/ndt/article/21/9/2446/1939355

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- Foundational Study
- Background – two main forms of dimethylarginine – ADMA And SDMA
- ADMA – associated with inflammatory condition, not a good marker of renal function.
- SDMA : Continual production from cells, increased with decreasing renal function
- SDMA rises with reduction in GFR

*Am J Physiol Heart Circ Physiol* 290: H209–H216, 2006.
First published August 19, 2005; doi:10.1152/ajpheart.00208.2005.

Asymmetrical dimethylarginine plasma clearance persists after acute total nephrectomy in rats

**Katari A. Carello,[1] Steven E. Whitesall,[1] Mary C. Lloyd,[1] Scott S. Billecke,[1] and Louis G. D'Alecy[1,2,3]**

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Submitted 3 March 2005; accepted in final form 15 August 2005

**Carello, Katari A., Steven E. Whitesall, Mary C. Lloyd, Scott S. Billecke, and Louis G. D'Alecy.** Asymmetrical dimethylarginine plasma clearance persists after acute total nephrectomy in rats. *Am J Physiol Heart Circ Physiol* 290: H209–H216, 2006. First published August 19, 2005; doi:10.1152/ajpheart.00208.2005.—Elevated plasma concentrations of symmetrical dimethylarginine (SDMA) and asymmetrical dimethylarginine (ADMA) are repeatedly associated with kidney failure. Both ADMA and SDMA can be excreted in urine. We tested whether renal excretion is necessary for acute, short-term maintenance of plasma ADMA and SDMA. Sprague-Dawley rats underwent sham operation, bilateral nephrectomy (NPX), ureteral ligation, or ureteral section under isoflurane anesthesia. Tail-snip blood samples (250 μl) were taken before and at 6- or 12-h intervals for 72 h after operation. Plasma clearance was assessed in intact and NPX rats. High-performance liquid chromatography determined SDMA and ADMA concentrations. Sodium, potassium, creatinine, blood urea nitrogen (BUN), and body weight were also measured. Forty-eight hours after NPX, SDMA increased 25 times (0.23 ± 0.03 to 5.68 ± 0.30 μM), whereas ADMA decreased (1.17 ± 0.08 to 0.73 ± 0.08 μM) by 38%. Creatinine and BUN increased, paralleling SDMA. Sham-operated animals showed no significant changes. Increased SDMA confirms continuous systemic production of SDMA and its obligatory renal excretion, much like creatinine. In contrast, decreased plasma ADMA suggests that acute total NPX either reduced systemic ADMA formation and/or systemic hydrolysis of ADMA increased 48-h post-NPX. However, plasma clearance of ADMA appeared unchanged 48 h after NPX. We conclude that renal excretory function is needed for SDMA elimination but not needed for acute, short-term ADMA elimination in that systemic hydrolysis is fully capable of clearing plasma ADMA.

ischemia may independently trigger the release of ADMA as suggested by indirect evidence for release of an endogenous NOS inhibitor in response to acute hindlimb ischemia (23–26). A recent review of Fliser et al. (19) traces the progression of ADMA, an innocent marker, to its current position as a leading candidate for a mediator of atherosclerotic complications in patients. In contrast, the physiological control, origins, and fates of this endogenous NOS inhibitor has yet to be fully defined.

In 1970, Kakimoto and Akazawa (27) first reported the natural occurrence of ADMA and symmetrical DMA (SDMA) in human urine and detected concentrations >30% higher than that of arginine in urine. In contrast, the plasma ADMA and SDMA concentrations they reported were <0.5% (0.3 μM) of the concentration of arginine (53.8 μM) in the plasma, reflecting a dramatic urinary concentrating effect on ADMA and SDMA and unequivocally demonstrating their renal excretion.

By 1976, intravenous injections of radiolabeled, methylated arginines were used to demonstrate that L-NMMA and ADMA were catabolized in some way, whereas SDMA was largely unchanged in urine excreted (39). Ogawa et al. (47) later identified an enzyme that hydrolyzed ADMA to citrulline. This enzyme, dimethylarginine dimethylaminohydrolase (DDAH), has been identified in the heart, brain, lung, liver, and skeletal muscle and has been shown to have particularly high activity in the kidney and pancreas (48). Although significant hydrolysis of SDMA in vivo has yet to be reported in the literature (47),

**Link:** https://www.physiology.org/doi/full/10.1152/ajpheart.00208.2005

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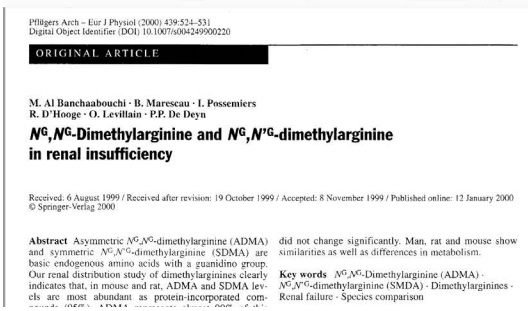
Mouse and Rat models

SDMA present in renal tissue and in plasma/serum

Nephrectomized rats can be used as models for renal pathology



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ORIGINAL ARTICLE

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**$N^G$,$N^G$-Dimethylarginine and $N^G$,$N'^G$-dimethylarginine in renal insufficiency**

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**Abstract** Asymmetric $N^G$,$N^G$-dimethylarginine (ADMA) and symmetric $N^G$,$N'^G$-dimethylarginine (SDMA) are basic endogenous amino acids with a guanidino group. Our renal distribution study of dimethylarginines clearly indicates that, in mouse and rat, ADMA and SDMA levels are most abundant as protein-incorporated com-

did not change significantly. Man, rat and mouse show similarities as well as differences in metabolism.

**Key words** $N^G$,$N^G$-Dimethylarginine (ADMA) · $N^G$,$N'^G$-dimethylarginine (SMDA) · Dimethylarginines · Renal failure · Species comparison

**Link:** https://www.ncbi.nlm.nih.gov/pubmed/10764210