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Source / Izvornik: **International Journal of Cardiology, 2018, 261, 109 - 113**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

https://doi.org/doi:10.1016/j.ijcard.2018.03.037

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:706387

International Journal of Cardiology 261 (2018) 109–113

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Serum concentrations of asymmetric and symmetric dimethylarginine are associated with mortality in acute heart failure patients

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ARTICLE INFO

Article history:
Received 13 November 2017
Received in revised form 5 March 2018
Accepted 9 March 2018
Available online 11 March 2018

Keywords:
Acute heart failure
Prognostic biomarkers
Acute heart failure
ADMA
SDMA
Mortality

ABSTRACT

Background: Serum concentrations of asymmetric (ADMA) and symmetric (SDMA) dimethylarginine are established predictors of total and cardiovascular mortality. However, the predictive capacity of ADMA and SDMA for hospital and 3-months mortality of patients with acute heart failure (AHF) is unknown.
Methods & results: Out of 152 included AHF patients, 79 (52%) were female, and the mean patient age was 75.2 ± 10.3 years. Hospital and three-month mortality rates were 14.5% and 27.4%, respectively. Serum ADMA and SDMA levels at admission, determined by reversed phase high performance liquid chromatography, were higher in patients having at least one of the three signs implying venous volume overload (enlarged liver, ascites, peripheral edema), a consequence of right-sided heart failure, compared to patients without those signs. Univariable logistic regression analyses revealed a significant positive association of ADMA and SDMA concentrations with hospital mortality [odds ratio (OR) and 95% confidence interval (CI) per standard deviation (SD) increase: 2.22 (1.37–3.79), $p = 0.002$, and 2.04 (1.34–3.18), $p = 0.001$, respectively], and 3-months mortality [2.06 (1.36–3.26), $p = 0.001$, and 2.52 (1.67–4.04), $p < 0.001$, respectively]. These associations remained significant after adjusting for age, sex, mean arterial pressure, low-density lipoprotein cholesterol, glomerular filtration rate, and N-terminal pro-brain natriuretic peptide.
Conclusions: We conclude that ADMA and SDMA concentrations are associated with hospital and 3-month mortality and are increased by venous volume overload in AHF patients.

1. Introduction

Despite achievements in prevention, diagnosis and treatment, heart failure (HF) is still a frequent cause of death and disability worldwide [1]. HF is defined by the European Society of Cardiology (ESC) as an abnormality of cardiac structure and function, resulting in failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues [2,3]. Acute heart failure (AHF) denotes the rapid onset of, or changes in, symptoms and signs of HF [3]. Accurate prognostic biomarkers are crucial for risk assessment, timely and appropriate therapeutic interventions and the overall management of AHF.

Asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA) are products of intracellular proteolysis of proteins containing methylated arginines [4]. Serum concentrations of ADMA and SDMA are determined by the rate of their release from the cells, tissue degradation and the rate of renal elimination [4]. Both ADMA and SDMA exert a negative effect on vascular nitric oxide (NO) bioavailability [5], implicating their role in the cardiovascular pathophysiology related to endothelial dysfunction [6,7]. In line with this, both ADMA and SDMA have been found to independently predict total

Abbreviations: HF, heart failure; AHF, acute heart failure; ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine; NO, nitric oxide; NT-proBNP, N-terminal pro-brain natriuretic peptide; GFR, glomerular filtration rate; MAP, mean arterial pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NYHA, New York Heart Association Functional Classification; CRP, C-reactive protein; (IL-6), interleukin-6; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; ESC, European Society of Cardiology; eNOS, endothelial nitric oxide synthase.

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https://doi.org/10.1016/j.ijcard.2018.03.037
0167-5273/

and cardiovascular mortality [8–10]. In addition, it has been shown that ADMA levels are predictive for disease progression and adverse long-term outcomes in chronic systolic HF patients [11].

2. Theory

Since it is known that ADMA and SDMA are associated with the cardiovascular pathophysiology as well as mortality, but the association with AHF mortality has not yet been studied, the aim of the present study was therefore to examine the predictive capacity of ADMA and SDMA for hospital and 3-months mortality in AHF patients.

3. Methods

3.1. Study design and patients

We previously reported on study design, inclusion and exclusion criteria as well as patient characteristics for our AHF cohort [12,13]. Written informed consent was obtained from each patient and the study was conducted in adherence to the ethical guidelines of the Declaration of Helsinki [14], as reflected in a priori approval by the Ethics Committees of the University Hospital Centre Sisters of Charity, Zagreb, Croatia and the Medical University of Graz, Austria. All patients were treated according to the ESC Guidelines for AHF [3,15].

3.2. Laboratory procedures

The collection of blood samples, standard laboratory methods, and the determination of the N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) concentration were described in our previous reports on our AHF cohort [13,16]. ADMA and SDMA levels were determined according to our previous work [8,9]. The concentration of fibrinogen was determined with a blood coagulometer (BCS XP, Siemens, Germany). The levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined with Architect c8000, Abbott 2013 (Chicago, IL, USA).

3.3. Statistical analyses

Categorical data are shown as absolute and relative frequencies, whereas continuous data are summarized as median and range (minimum to maximum) due to the skewed distribution of many of the laboratory parameters. Patients with and without signs of venous volume overload were compared by the Mann-Whitney *U* test and Fisher's exact test. Correlations between ADMA, SDMA and various laboratory and clinical parameters were determined by the Spearman correlation coefficient. Univariable and multivariable logistic regression analyses were used to examine the impact of ADMA and SDMA levels on hospital and 3-month mortality. In the multivariable analyses, we adjusted for age, sex, NT-proBNP, GFR, mean arterial pressure (MAP) as well as low-density lipoprotein (LDL) cholesterol and checked the variance inflation factor to prevent multi-collinearity among the covariates. Results are presented as odds ratio (OR) and the respective 95% confidence interval (CI) per standard deviation (SD) increase. Presentation on the SD scale is warranted because ADMA and SDMA values were normally distributed. R version 3.4.2 was used for all statistical analyses.

4. Results

4.1. Patients' clinical characteristics and laboratory parameters

The patients' baseline characteristics have been described elsewhere [12]. Out of 152 included patients, 79 (52%) were female and the mean (SD) age was 75.2 ± 10.3 years. According to the New York Heart Association Functional Classification (NYHA), 11 (7.2%) patients belonged to class 2, 83 (54.6%) to class 3, and 58 (38.2%) to class 4. Frequent comorbidities were hypertension (89.5%), type 2 diabetes mellitus (51.7%), hyperlipidemia/hypertriglyceridemia (39.5%), and hypercholesterolemia (38.8%). Regarding previous medication 41 (27%) of patients were treated with statins, 67 (45%) with β-blockers, 86 (57%) with angiotensin-converting enzyme inhibitors (ACEI), and 25 (16.6%) with amlodipine. Worsening of chronic HF occurred in 105 (69.1%) patients and 61 (42.4%) had a preserved ejection fraction. Regarding signs at admission reflecting venous volume overload as a consequence of right-sided HF, 53 (34.9%) patients had an enlarged liver, 21 (13.8%) had ascites, and 105 (69.1%) had a peripheral edema (with possible overlaps); 110 (72.4%) patients had at least one of the signs and 11 (7.2%) had all three. Median (range) length of hospitalization was 9 (0.0–85.0) days. Twenty-two (14.5%) patients died in the hospital; the number increased to 40 (27.4%) three months after admission. Median and range for ADMA and SDMA levels were 0.8 (0.5–1.4) μmol/L and 1.4 (0.5–4.3), respectively; fibrinogen concentration was 3.6 (1.1–12.1) g/L and the levels of ALT and AST were 23.0 (6.0–623.0) U/L and 27.0 (10.0–666.0), respectively. Other laboratory parameters have been reported previously [16].

4.2. Impact of venous volume overload on serum levels of laboratory parameters and MAP

To examine whether venous volume overload, a consequence of right-sided HF, affects serum levels of ADMA, SDMA, various laboratory parameters, and MAP, we compared their levels in patients with at least one of the three signs implying venous volume overload (enlarged liver, ascites or peripheral edema) to those without. As shown in Table 1, the concentrations of ADMA, SDMA, and CRP were significantly higher in patients with signs whereas the concentrations of total serum proteins, fibrinogen, total cholesterol, LDL cholesterol, HDL-cholesterol, triglycerides, and MAP were significantly decreased. The kidney function markers, GFR, urea, and creatinine as well as serum albumin, a marker for the biosynthetic capacity of the liver, and NT-proBNP, a marker for HF severity, as well as ALT and AST were similar in patients with and without signs.

4.3. Correlation of ADMA and SDMA concentrations with laboratory and clinical parameters

As shown in Table 2 the concentrations of ADMA and SDMA were positively correlated with patients' age and negatively with MAP, GFR and fibrinogen. SDMA, (but not ADMA), was further positively correlated with urea, creatinine and NT-proBNP and negatively with the serum protein concentration, as well as the total and HDL cholesterol serum levels. No significant correlation with either ADMA or SDMA was observed for body mass index (BMI), interleukin-6 (IL-6), C-reactive protein (CRP), AST, ALT, serum albumin, LDL cholesterol, triglycerides, left ventricular ejection fraction (LVEF), and length of

Table 1
Laboratory parameters and MAP in patients with or without sign(s) implying volume overload.

	No sign (N = 42)	Sign(s) (N = 110)	p-Value
ADMA (μmol/L)	0.7 (0.5–1.2)	0.9 (0.5–1.4)	**0.001**
SDMA (μmol/L)	1.1 (0.5–2.6)	1.5 (0.5–4.3)	**0.002**
GFR (ml/min/1.73 m^2)	50.6 (19.6–105.7)	51.0 (15.0–104.8)	0.517
Urea (mmol/L)	8.0 (3.0–64.0)	8.0 (3.0–41.0)	0.063
Creatinine (μmol/L)	48.0 (18.6–138.0)	47.0 (6.0–151.0)	0.534
NT-proBNP (ng/mL)	8.3 (0.7–70.0)	9.6 (0.2–70.0)	0.214
ALT (U/L)	23.0 (7.0–145.0)	23.0 (6.0–623.0)	0.610
AST (U/L)	24.0 (14.0–369.0)	28.0 (10.0–666.0)	0.843
IL-6 (pg/mL)	19.2 (0.4–300.0)	21.4 (1.2–300.0)	0.968
CRP (μg/mL)	4.5 (0.2–71.6)	11.5 (0.5–247.4)	**0.004**
Protein (g/L)	71.5 (36.0–87.0)	66.0 (31.0–86.0)	**<0.001**
Fibrinogen (g/L)	3.8 (2.4–12.1)	3.5 (1.1–9.4)	**0.003**
Albumin (g/L)	39.5 (24.0–72.0)	40.0 (21.0–62.0)	0.580
Total cholesterol (mmol/L)	4.5 (2.5–9.1)	3.8 (1.7–8.5)	**0.001**
LDL-cholesterol (mmol/L)	2.7 (1.3–6.3)	2.2 (0.8–6.1)	**0.004**
HDL-cholesterol (mmol/L)	1.1 (0.4–2.3)	0.9 (0.3–3.6)	**0.027**
Triglycerides (mmol/L)	1.2 (0.6–4.3)	1.0 (0.5–3.2)	**0.002**
MAP (mm Hg)	109.2 (65.0–158.3)	100.0 (53.3–160.0)	**0.034**

Data are presented as median and range (minimum to maximum). Differences between patients without any sign and those with at least one of the three signs implying venous volume overload (enlarged liver, peripheral edema, ascites) were tested with the Mann-Whitney *U* test; significant differences are depicted in bold.
ADMA, asymmetric dimethylarginine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; GFR, glomerular filtration rate; IL-6, interleukin-6; LDL, low-density lipoprotein; HDL, high-density lipoprotein; MAP, mean arterial pressure; NT-proBNP, N-terminal pro brain natriuretic peptide; SDMA, symmetric dimethylarginine.

Table 2
Correlation analyses of ADMA and SDMA concentrations with clinical and laboratory parameters.

	ADMA (μmol/L)			SDMA (μmol/L)		
	r	p-Value	N	r	p-Value	N
Age (years)	0.28	**0.001**	131	0.26	**0.002**	137
BMI (kg/m^2)	−0.10	0.250	131	−0.17	0.054	137
GFR (ml/min/1.73 m^2)	−0.20	**0.021**	130	−0.66	<**0.001**	136
Urea (mmol/L)	0.13	0.137	130	0.51	<**0.001**	136
Creatinine (mol/L)	0.07	0.397	130	0.56	<**0.001**	136
NT-proBNP (pg/mL)	0.15	0.094	126	0.50	<**0.001**	131
AST (U/L)	−0.07	0.426	128	0.08	0.370	134
ALT (U/L)	−0.15	0.096	127	−0.06	0.504	133
IL-6 (pg/mL)	−0.01	0.876	131	0.17	0.053	137
CRP (μg/mL)	0.02	0.785	129	0.14	0.094	135
Protein (g/L)	−0.11	0.227	129	−0.24	**0.006**	134
Fibrinogen (g/L)	−0.25	**0.005**	126	−0.24	**0.006**	132
Albumin (g/L)	−0.08	0.357	128	−0.13	0.121	134
Total cholesterol (mmol/L)	−0.14	0.113	131	−0.25	**0.003**	137
LDL-cholesterol (mmol/L)	−0.08	0.373	131	−0.16	0.068	137
HDL-cholesterol (mmol/L)	−0.17	0.060	131	−0.22	**0.009**	137
Triglycerides (mmol/L)	0.01	0.919	131	−0.06	0.506	137
MAP (mm Hg)	−0.21	**0.016**	131	−0.33	<**0.001**	137
LVEF (%)	0.05	0.549	122	−0.17	0.052	127
Length of hospitalization (days)	−0.02	0.785	129	0.15	0.081	135

Data are presented as Spearman correlation coefficient r, p-value, and number of available samples; significant correlations are depicted in bold.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; GFR, glomerular filtration rate; HDL, high-density lipoprotein; IL-6, interleukin 6; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro brain natriuretic peptide; SDMA, symmetric dimethylarginine.

hospitalization. Finally, ADMA and SDMA levels were positively correlated with each other ($r = 0.47$, $p < 0.001$).

4.4. Logistic regression analyses

The association of ADMA and SDMA with hospital and 3-month mortality in AHF patients was examined by logistic regression analyses (Table 3). The univariable analyses showed a significant positive association of both ADMA and SDMA levels with hospital and 3-month mortality. Importantly, these associations remained significant even after adjusting for age, sex, NT-proBNP, GFR, MAP and LDL cholesterol, the clinical and laboratory parameters that are known to be associated with mortality in HF patients.

5. Discussion

It is well established that accurate prognostic biomarkers are crucial for risk assessment, efficient therapeutic intervention, and overall management of HF. Previous studies highlighted both ADMA and SDMA as independent risk markers for total and cardiovascular mortality and cardiovascular disease [8,10]. However, no study to date has examined the association of ADMA and SDMA with mortality in AHF patients.

The present study shows, for the first time, that high serum levels of ADMA or SDMA are independently associated with both hospital and 3-months mortality in AHF patients.

Furthermore, we show that ADMA and SDMA levels are increased in patients with signs implying venous volume overload (enlarged liver, peripheral edema, ascites), a consequence of right-sided HF. Given that different pathophysiological states and medication affect ADMA and SDMA serum levels, the baseline serum levels of these metabolites in our AHF patients reflect not only the impact of the AHF pathophysiology, but also, at least in part, the impact of the associated comorbidities and medication [5]. In the present study, comorbidities and prior medication were neither associated with mortality nor did they affect the association of ADMA and SDMA with mortality (Supplementary Tables 1–3).

The crucial role of endothelium-derived NO in the maintenance of a normal cardiac function and the inhibition of adverse ventricular remodeling is well established [17,18]. In line with this, it has been shown that administration of NO improves the left ventricle diastolic function in HF patients [19] and that chronic inhibition of the endogenous NO production is associated with severe myocardial fibrosis in animal models [20]. Accordingly, the well-documented diminishing effect of ADMA and SDMA on the vascular NO bioavailability, due to inhibition of the endothelial nitric oxide synthase (eNOS) activity by ADMA and the interference of SDMA with the utilization of the eNOS substrate L-arginine [4,5], may well explain the link between ADMA, SDMA and AHF mortality. Additionally, considering that HDL function, including the activation of the eNOS/NO pathway [21], is attenuated by methylated arginine species [22], it is conceivable that ADMA and SDMA exert deleterious effects through HDL dysfunction. Moreover, increased ADMA and SDMA levels in AHF patients with signs implying venous volume overload, a condition associated with venous congestion as well as hemodynamic and metabolic perturbations [23], suggest an association of ADMA and SDMA with a more severe stage of AHF. This additionally supports the association of ADMA and SDMA with mortality. Indeed, an increase (albeit not statistically significant) in hospital (16.4% vs. 9.5%, $p = 0.439$) and 3-month mortality (31.7% vs. 16.7%, $p = 0.069$) was observed in patients with at least one sign, compared to patients without.

In line with previous studies, we observed a strong association of SDMA and a less profound association of ADMA with parameters indicating renal function [24]. In contrast to the reported association of venous volume overload with impaired renal function [25], we did not observe that the markers of kidney function (including GFR, urea and creatinine), were altered by venous volume overload (Table 1). This indicates that venous volume overload defined by the presence of enlarged liver, ascites or peripheral edema, was not accompanied by renal congestion or that the degree of renal congestion was insufficient to affect renal function.

The negative association of SDMA, but not of ADMA, with serum proteins, as well as total and HDL-cholesterol might be a consequence of a positive association of SDMA with the severity of HF, which is known to

Table 3
Univariable and multivariable logistic regression analyses of hospital and 3-month mortality for ADMA and SDMA.

	Unadjusted			Adjusted[a]		
	OR (95% CI)	p-Value	Events/N	OR (95% CI)	p-Value	Events/N
Hospital mortality						
ADMA (μmol/L)	2.22 (1.37–3.79)	0.002	20/131	2.15 (1.17–4.29)	0.019	19/125
SDMA (μmol/L)	2.04 (1.34–3.18)	0.001	21/137	1.83 (1.01–3.39)	0.045	20/130
3-month mortality						
ADMA (μmol/L)	2.06 (1.36–3.26)	0.001	34/126	2.28 (1.38–3.98)	0.002	32/120
SDMA (μmol/L)	2.52 (1.67–4.04)	<0.001	37/132	1.88 (1.14–3.28)	0.017	35/125

OR and CI are presented on the SD scale (increase per 1 SD); SDs for ADMA and SDMA are 0.17 and 0.81 μmol/L, respectively.
[a] The model was adjusted for age, sex, NT-proBNP, GFR, MAP and LDL-cholesterol. ADMA, asymmetric dimethylarginine; CI, confidence interval; GFR, glomerular filtration rate; LDL, low-density lipoprotein; MAP, mean arterial pressure; NT-proBNP, N-terminal brain natriuretic peptide; OR, odds ratio; SD, standard deviation; SDMA, symmetric dimethylarginine.

be positively associated with metabolic impairment and a catabolic dominance [23]. Indeed, SDMA, (but not ADMA) levels, were strongly positively correlated with NT-proBNP, an established marker for the severity of HF (Table 2).

It is conceivable that intestinal congestion, and thereby accompanied intestinal edema, as well as an impaired nutrient absorption, together with a diminished biosynthetic activity of the congested liver, underlie the decreased circulating proteins and lipids in our patients with venous volume overload. This would be in line with a previous study suggesting that hepatic congestion, a consequence of right-sided HF, rather than hypo-perfusion, causes liver dysfunction [26].

Since in the present study ALT and AST levels were similar in patients with and without signs, it seems that venous volume overload was not associated with any hepatocyte damage, but rather with an impaired hepatic biosynthetic activity.

Interestingly, in contrast to decreased levels of total serum proteins and fibrinogen, the levels of albumin, a marker for nutritional status and the biosynthetic capacity of the liver, were not altered in patients with signs (Table 1). Unaltered albumin levels probably reflect the contribution of certain compensating mechanisms, namely the net transfer of extravascular albumin into the intravascular pool, and the decreased albumin catabolic rate, which are both operative for albumin [27,28], but not fibrinogen [29], when biosynthetic capacity of the liver is diminished.

Quite opposite to what was found for serum proteins and lipids, the levels of ADMA and SDMA were increased in patients with at least one sign implying volume overload. Several potential mechanisms may explain this observation: First, increased ADMA and SDMA levels have previously been observed in various pathophysiological conditions associated with increased protein-turnover [30,31]. An increased rate of protein-turnover, likely caused by limited delivery of nutrients due to intestinal edema and impaired intestinal absorption, may in turn explain increased ADMA and SDMA levels in AHF patients with signs. Second, it might be that tissue congestion augments the methylation rate of arginine residues in cellular proteins, or the release of ADMA and SDMA into the circulation. Importantly, increased gene and protein expression of the ADMA-degrading enzyme, dimethylaminohydrolases-1, was observed in end-stage failing human hearts upon ventricular unloading following the support with a left ventricular assist device [32]. This finding strongly supports the notion that the decreased expression and activities of ADMA- and SDMA-degrading enzymes in the congested tissue might be responsible for increased ADMA and SDMA serum levels when there is a venous volume overload, as observed in our patients with signs. Accordingly, it is likely that the alleviation of congestion by diuretics decreased ADMA and SDMA levels in our AHF patients upon hospitalization. Furthermore, other pharmacological interventions, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or some statins, are capable of decreasing ADMA levels [5] and were used for treatment of our AHF patients. Therefore, it is conceivable that either one or a combination of these pharmacological approaches might have affected ADMA and SDMA levels and consequently the effect thereof on mortality. However, medication on the first and second day of hospitalization was neither associated with mortality nor did it affect the association of ADMA and SDMA with mortality (Supplementary Tables 4–7).

We found that ADMA and SDMA were not significantly correlated with IL-6 or CRP serum levels, but were negatively correlated with fibrinogen (Table 2), an acute phase protein that was itself positively correlated with CRP ($r = 0.33$, $p < 0.001$) and IL-6 ($r = 0.22$, $p = 0.007$). This suggests that in our AHF patients both ADMA and SDMA levels were not affected by the patients' inflammatory status. Accordingly, the negative correlations of both ADMA and SDMA with fibrinogen conceivably reflect that they are regulated into opposite directions by venous volume overload, a state that was accompanied by increased CRP levels in the present study (Table 1).

5.1. Study limitations

There are several limitations to our present study: The design does not allow us to draw conclusions about cause and effect for the pathophysiological processes involved in the regulation of ADMA and SDMA serum levels. Furthermore, we cannot provide a mechanistic explanation on how ADMA and SDMA affect mortality. In addition, by defining venous volume overload solely as the presence of signs implying volume overload, we were unable to test the impact of the extent of volume overload, as would have been possible with data on the right ventricle end diastolic diameter or the diameter of the right atrium. Finally, the moderate number of participants ($n = 152$) in this monocentric study influences the statistical power of our analyses. Therefore, further large studies are needed to confirm our results.

6. Conclusions

Based on our results, we conclude that serum concentrations of both ADMA and SDMA are associated with hospital and 3-month mortality and are increased by venous volume overload in AHF patients.

Funding

This research was supported by the Austrian Science Foundation [P27166-B23 to SF] and the Jubilee Foundation of the Austrian National Bank [15858 to SF]. The funders had no roles in the design of the study, data collection, analysis, and interpretation, report writing or article submission.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.03.037.

References

[1] V.L. Roger, Epidemiology of heart failure, Circ. Res. 113 (6) (2013) 646–659.
[2] K. Dickstein, A. Cohen-Solal, G. Filippatos, J.J. McMurray, P. Ponikowski, P.A. Poole-Wilson, A. Stromberg, D.J. van Veldhuisen, D. Atar, A.W. Hoes, A. Keren, A. Mebazaa, M. Nieminen, S.G. Priori, K. Swedberg, E.S.C.C.f.P. Guidelines, ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM), Eur. Heart J. 29 (19) (2008) 2388–2442.
[3] J.J. McMurray, S. Adamopoulos, S.D. Anker, A. Auricchio, M. Bohm, K. Dickstein, V. Falk, G. Filippatos, C. Fonseca, M.A. Gomez-Sanchez, T. Jaarsma, L. Kober, G.Y. Lip, A.P. Maggioni, A. Parkhomenko, B.M. Pieske, B.A. Popescu, P.K. Ronnevik, F.H. Rutten, J. Schwitter, P. Seferovic, J. Stepinska, P.T. Trindade, A.A. Voors, F. Zannad, A. Zeiher, E.S.C.C.f.P. Guidelines, ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC, Eur. Heart J. 33 (14) (2012) 1787–1847.
[4] X. Liu, L. Hou, D. Xu, A. Chen, L. Yang, Y. Zhuang, Y. Xu, J.T. Fassett, Y. Chen, Effect of asymmetric dimethylarginine (ADMA) on heart failure development, Nitric Oxide 54 (2016) 73–81.
[5] Y.L. Tain, C.N. Hsu, Toxic Dimethylarginines: Asymmetric Dimethylarginine (ADMA) and Symmetric Dimethylarginine (SDMA), Toxins (Basel) 9 (3) (2017).
[6] C.D. Goonasekera, D.D. Rees, P. Woolard, A. Frend, V. Shah, M.J. Dillon, Nitric oxide synthase inhibitors and hypertension in children and adolescents, J. Hypertens. 15 (8) (1997) 901–909.
[7] K. Krzyzanowska, F. Mittermayer, N. Shnawa, M. Hofer, J. Schnabler, Y. Etmuller, S. Kapiotis, M. Wolzt, G. Schernthaner, Asymmetrical dimethylarginine is related to renal function, chronic inflammation and macroangiopathy in patients with Type 2 diabetes and albuminuria, Diabet. Med. 24 (1) (2007) 81–86.

[8] A. Meinitzer, J.T. Kielstein, S. Pilz, C. Drechsler, E. Ritz, B.O. Boehm, B.R. Winkelmann, W. Marz, Symmetrical and asymmetrical dimethylarginine as predictors for mortality in patients referred for coronary angiography: the Ludwigshafen Risk and Cardiovascular Health study, Clin. Chem. 57 (1) (2011) 112–121.
[9] A. Meinitzer, U. Seelhorst, B. Wellnitz, G. Halwachs-Baumann, B.O. Boehm, B.R. Winkelmann, W. Marz, Asymmetrical dimethylarginine independently predicts total and cardiovascular mortality in individuals with angiographic coronary artery disease (the Ludwigshafen Risk and Cardiovascular Health study), Clin. Chem. 53 (2) (2007) 273–283.
[10] S. Schlesinger, S.R. Sonntag, W. Lieb, R. Maas, Asymmetric and symmetric dimethylarginine as risk markers for total mortality and cardiovascular outcomes: a systematic review and meta-analysis of prospective studies, PLoS One 11 (11) (2016), e0165811.
[11] W.H. Tang, W. Tong, K. Shrestha, Z. Wang, B.S. Levison, B. Delfraino, B. Hu, R.W. Troughton, A.L. Klein, S.L. Hazen, Differential effects of arginine methylation on diastolic dysfunction and disease progression in patients with chronic systolic heart failure, Eur. Heart J. 29 (20) (2008) 2506–2513.
[12] I. Potocnjak, V. Degoricija, M. Trbusic, S.D. Teresak, B. Radulovic, G. Pregartner, A. Berghold, B. Tiran, G. Marsche, S. Frank, Metrics of high-density lipoprotein function and hospital mortality in acute heart failure patients, PLoS One 11 (6) (2016), e0157507.
[13] B. Radulovic, I. Potocnjak, S. Dokoza Teresak, M. Trbusic, N. Vrkic, D. Malogorski, N. Starcevic, M. Milosevic, S. Frank, V. Degoricija, Hypochloraemia as a predictor of developing hyponatraemia and poor outcome in acute heart failure patients, Int. J. Cardiol. 212 (2016) 237–241.
[14] A. World Medical, World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects, JAMA 310 (20) (2013) 2191–2194.
[15] C.W. Yancy, M. Jessup, B. Bozkurt, J. Butler, D.E. Casey Jr., M.H. Drazner, G.C. Fonarow, S.A. Geraci, T. Horwich, J.L. Januzzi, M.R. Johnson, E.K. Kasper, W.C. Levy, F.A. Masoudi, P.E. McBride, J.J. McMurray, J.E. Mitchell, P.N. Peterson, B. Riegel, F. Sam, L.W. Stevenson, W.H. Tang, E.J. Tsai, B.L. Wilkoff, F. American College of Cardiology, G. American Heart Association Task Force on Practice, 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, J. Am. Coll. Cardiol. 62 (16) (2013) e147–239.
[16] I. Potocnjak, V. Degoricija, M. Trbusic, G. Pregartner, A. Berghold, G. Marsche, S. Frank, Serum concentration of HDL particles predicts mortality in acute heart failure patients, Sci. Rep. 7 (2017), 46642.
[17] R. King, M. Esmail, S. Mahon, J. Dingley, S. Dwyer, Use of nitric oxide for decompensated right ventricular failure and circulatory shock after cardiac arrest, Br. J. Anaesth. 85 (4) (2000) 628–631.
[18] R. Rastaldo, P. Pagliaro, S. Cappello, C. Penna, D. Mancardi, N. Westerhof, G. Losano, Nitric oxide and cardiac function, Life Sci. 81 (10) (2007) 779–793.
[19] C.M. Matter, L. Mandinov, P.A. Kaufmann, G. Vassalli, Z. Jiang, O.M. Hess, Effect of NO donors on LV diastolic function in patients with severe pressure-overload hypertrophy, Circulation 99 (18) (1999) 2396–2401.
[20] H. Tomita, K. Egashira, Y. Ohara, M. Takemoto, M. Koyanagi, M. Katoh, H. Yamamoto, K. Tamaki, H. Shimokawa, A. Takeshita, Early induction of transforming growth factor-beta via angiotensin II type 1 receptors contributes to cardiac fibrosis induced by long-term blockade of nitric oxide synthesis in rats, Hypertension 32 (2) (1998) 273–279.
[21] C.G. Santos-Gallego, J.J. Badimon, R.S. Rosenson, Beginning to understand high-density lipoproteins, Endocrinol. Metab. Clin. N. Am. 43 (4) (2014) 913–947.
[22] T. Speer, L. Rohrer, P. Blyszczuk, R. Shroff, K. Kuschnerus, N. Krankel, G. Kania, S. Zewinger, A. Akhmedov, Y. Shi, T. Martin, D. Perisa, S. Winnik, M.F. Muller, U. Sester, G. Wernicke, A. Jung, U. Gutteck, U. Eriksson, J. Geisel, J. Deanfield, A. von Eckardstein, T.F. Luscher, D. Fliser, F.H. Bahlmann, U. Landmesser, Abnormal high-density lipoprotein induces endothelial dysfunction via activation of Toll-like receptor-2, Immunity 38 (4) (2013) 754–768.
[23] W. Doehner, M. Frenneaux, S.D. Anker, Metabolic impairment in heart failure: the myocardial and systemic perspective, J. Am. Coll. Cardiol. 64 (13) (2014) 1388–1400.
[24] J.T. Kielstein, S.R. Salpeter, S.M. Bode-Boeger, J.P. Cooke, D. Fliser, Symmetric dimethylarginine (SDMA) as endogenous marker of renal function—a meta-analysis, Nephrol. Dial. Transplant. 21 (9) (2006) 2446–2451.
[25] J.F. Gnanaraj, S. von Haehling, S.D. Anker, D.S. Raj, J. Radhakrishnan, The relevance of congestion in the cardio-renal syndrome, Kidney Int. 83 (3) (2013) 384–391.
[26] R.K. Seeto, B. Fenn, D.C. Rockey, Ischemic hepatitis: clinical presentation and pathogenesis, Am. J. Med. 109 (2) (2000) 109–113.
[27] W.P. James, A.M. Hay, Albumin metabolism: effect of the nutritional state and the dietary protein intake, J. Clin. Invest. 47 (9) (1968) 1958–1972.
[28] M.A. Rothschild, M. Oratz, S.S. Schreiber, Albumin metabolism, Gastroenterology 64 (2) (1973) 324–337.
[29] A.S. McFarlane, D. Todd, S. Cromwell, Fibrinogen catabolism in humans, Clin. Sci. 26 (1964) 415–420.
[30] E.B. Marliss, S. Chevalier, R. Gougeon, J.A. Morais, M. Lamarche, O.A. Adegoke, G. Wu, Elevations of plasma methylarginines in obesity and ageing are related to insulin sensitivity and rates of protein turnover, Diabetologia 49 (2) (2006) 351–359.
[31] K. Caglar, M.I. Yilmaz, A. Sonmez, E. Cakir, A. Kaya, C. Acikel, T. Eyileten, M. Yenicesu, Y. Oguz, C. Bilgi, C. Oktenli, A. Vural, C. Zoccali, ADMA, proteinuria, and insulin resistance in non-diabetic stage I chronic kidney disease, Kidney Int. 70 (4) (2006) 781–787.
[32] Y. Chen, S. Park, Y. Li, E. Missov, M. Hou, X. Han, J.L. Hall, L.W. Miller, R.J. Bache, Alterations of gene expression in failing myocardium following left ventricular assist device support, Physiol. Genomics 14 (3) (2003) 251–260.