Atorvastatin facilitates protection against contrast-induced nephropathy in patients undergoing coronary angiography via humoral mediators rather than altered renal hemodynamics

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Introduction

Contrast-induced acute kidney injury (CI-AKI) represents a frequently neglected complication of contrast agent use, which is associated with suboptimal treatment outcomes in the subset of patients with coronary artery disease (CAD) [1]. Despite the use of several well-established preventive measures [2], including peri-procedural hydration, limitation of contrast agent dose and the cessation of potentially nephrotoxic agents, the onset of CI-AKI is still common [3]. Recently, numerous studies have lent support to the notion that pre-procedural use of high-dose statins is associated with decreased risk of CI-AKI development [2, 4, 5]. Further reports exploring surrogate endpoints provided insight into the anti-apoptotic effect of statins towards renal tubular cells [6]. Although several molecular pathways have been suggested [6, 7], the effect of both atorvastatin and rosuvastatin on renal hemodynamics remains unknown. Also, the interplay between statins and humoral mediators of cell survival, including anti-apoptotic renalase [8], has not been investigated so far.

Aim

Therefore, the aim of the study was to evaluate the impact of a loading dose of atorvastatin on post-procedural renal hemodynamics and urinary renalase concentration in patients with CAD submitted to coronary angiography.

Material and methods

In this prospective, randomized, single-blind study, 67 statin-naive patients with stable angina scheduled for coronary angiography were randomized to atorvastatin at a dose of 80 mg administered 24 h prior to the procedure (study group; n = 33) or placebo (control group; n = 34). The research complied with the Declaration of Helsinki and was authorized by the local Ethics Committee. All the study participants gave their written informed consent to study enrollment. The primary inclusion criterion was the diagnosis of stable angina with either high pre-test probability of CAD or a positive treadmill electrocardiographic stress test or echocardiographic dobutamine test. The exclusion criteria included cardiogenic shock, pulmonary edema, acute or chronic respiratory failure (blood oxygen saturation < 90%), advanced heart failure with left ventricular ejection fraction (LVEF) < 35%, evidence of renal artery stenosis or hydronephrosis, severe valvular heart disease of any kind, high pulse pressure > 80 mm Hg, tachycardia > 100 bpm or bradycardia < 50 bpm, severe obesity (body mass index > 40 kg/m^2), active neoplastic disease, liver dysfunction (any hepatic aminotransferase > 3× upper reference limit), intolerance of statin or history of rhabdomyolysis or myositis or age < 18 years.

The baseline data were acquired through patients' interview and by means of a thorough review of former discharge summaries. Following inclusion in the study, patients were randomized to the study or control group using a flip of a coin technique. The venous blood samples were obtained prior to the procedure, as well as 24 and 48 h after the coronary angiography. Baseline blood samples were tested for a set of basic laboratory data and serum creatinine concentration (SCr), whereas 24-hour and 48-hour specimens were assayed only for

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SCr. The criteria of CI-AKI diagnosis comprised ≥ 50% relative or ≥ 0.3 mg/dl absolute increase of SCr at 48 h after the procedure.

Mid-stream urine samples were acquired within 24 h preceding the procedure and 6 h after coronary angiography. The urine samples were centrifuged for 15 min at 1000×g at 2–8°C within 15 min after acquisition and kept at the temperature of –80°C with no freeze-thaw cycles. Urine samples were assayed for renalase concentration using enzyme-linked immunosorbent assay (ELISA; Cloud-Clone Corp, Houston, USA) and adjusted to urinary creatinine concentration.

Table I. General characteristics of the study population

Variables	Median (1Q–3Q) or mean ± SD or *n* (%)
Age [years]	64 (57–71)
Male	42 (62.7)
Body mass index [kg/m^2]	29.5 ±4.9
Cigarette smoking	38 (56.7)
Arterial hypertension	64 (95.5)
Diabetes/IFG/IGT	26 (38.8)
Dyslipidemia	61 (91.0)
Atrial fibrillation	17 (25.4)
Peripheral artery disease	12 (17.9)
Total volume of contrast media [ml]	90 (60–150)
Left ventricular ejection fraction [%]	55 (50–60)
E/e'	8.98 ±3.473
Intima-media thickness [mm]	0.09 ±0.030
Hemoglobin [g/dl]	13.88 ±1.290
White blood cells [× 1000/mm^3]	6.85 ±1.424
Platelet count [× 1000/mm^3]	197 (177–258)
Mehran risk score [points]	2 (1–5)
Serum creatinine concentration [mg/dl]	0.88 (0.77–1.07)
eGFR [ml/min]	84.30 ± 20.411
Syntax score [points]	8 (2–24)
Left main disease	5 (7.5)
Referral for CABG	10 (14.9)
PCI ad hoc	23 (34.3)
CI-AKI rate	6 (8.9)

CABG – coronary artery bypass grafting, CI-AKI – contrast-induced acute kidney injury, eGFR – estimated glomerular filtration rate by modification of diet in renal disease formula (MDRD), IFG – impaired fasting glucose, IGT – impaired glucose tolerance, Q – quartile, SD – standard deviation, PCI – percutaneous coronary intervention.

Ultrasonographic parameters of renal blood flow in arcuate/interlobular arteries, including peak systolic (PSV) and end-diastolic velocity (EDV), augmentation index (AI), acceleration time (AT), renal resistive index (RRI) and pulsatility index (RPI), were acquired directly before and 1 h after the procedure using Vivid 7 (GE Healthcare) with a 5C probe (4.4–6.7 MHz). The arithmetic mean was calculated from 3 measurements in both kidneys in the case of all the assessed parameters. The exact methodology of intra-renal Doppler ultrasonography was described in a former publication [9].

Statistical analysis

Statistical analysis was performed using Statistica 10.0 (StatSoft Poland). Quantitative variables were expressed as mean and standard deviation or median and 1–3 quartile boundaries and qualitative parameters as number and percentage. A variable's type of distribution was verified using the Shapiro-Wilk test. Student's *t* test for unpaired samples was applied for normally distributed variables, whereas the Mann-Whitney *U* test was used for non-normally distributed parameters. All the variables with $p < 0.1$ in the univariate model were included in the multivariate regression model. A *p*-value of less than 0.05 was regarded as statistically significant. Based on the calculation of statistical power and sample size, the study population should comprise 44 subjects for RRI and 178 patients for Δrenalase in order to reach the statistical power of 80%. Still, the post-hoc statistical power was 13% for RRI and 93.5% for Δrenalase. One should conclude that the study is partially underpowered and its results should be interpreted with caution.

Results

Detailed characteristics of the study population are shown in Table I. Contrast-induced acute kidney injury occurred in 4 patients in the study (11.8%) and 2 patients in the control group (6.1%; $p = 0.35$). The comparison between the study and control group is presented in Table II. The analysis revealed that both pre- and post-procedural values of intra-renal blood flow parameters, including PSV, EDV, AT and AI, were comparable in both cohorts (Table II). Accordingly, the resultant RRI and RPI indices did not differ between study and control group either at baseline or at 1 h after contrast administration (Table II).

Patients in the study group were characterized by a smaller absolute (–1.08 vs. –2.05 µg/mg, $p = 0.0001$) and relative decrease of plasma-renalase (–36.1% vs. –50.6%, $p < 0.0001$) following the procedure (Table II). Patients in the study group were more likely to have Δrenalase < 25 percentile (OR = 5.0, 95% CI: 1.2–21.8, $p = 0.033$). Multivariate regression revealed that atorvastatin loading dose was the only independent predictor of renalase fluctuations ($b = 0.28$, $p = 0.03$; $R^2 = 0.42$, $p < 0.001$).

Table II. Renal function, intra-renal Doppler-derived hemodynamics and renalase concentration depending on the administration of atorvastatin loading dose

Variables	Atorvastatin (+) (n = 33)	Atorvastatin (–) (n = 34)	P-value
Age [years]	65 (59–70)	63.5 (55–71)	0.926[a]
Male	18 (54.6%)	24 (70.6%)	0.135[b]
Syntax score [points]	6 (1–24)	9 (3–24)	0.640[a]
CI-AKI rate	2 (6.1%)	4 (11.8%)	0.351[b]
SCr [mg/dl]:			
Baseline	0.87 (0.73–1.06)	0.91 (0.81–1.07)	0.243[a]
24 h postprocedural	0.88 (0.73–1.09)	0.98 (0.80–1.13)	0.301[a]
48 h postprocedural	0.92 (0.76–1.09)	1.00 (0.87–1.17)	0.163[a]
Renalase:			
Baseline [µg/mg*]	3.33 (3.20–3.91)	4.22 (3.58–4.86)	0.013[a]
Postprocedural [µg/mg*]	2.13 (1.91–2.40)	2.03 (1.85–2.21)	0.134[a]
Absolute Δ [µg/mg*]	–1.08 (–1.54– –0.87)	–2.05 (–2.69– –1.72)	0.0001[a]
Relative Δ [%]	–36.1 (–43.5– –27.2)	–50.6 (–57.2– –43.8)	< 0.000[a]
Intra-renal Doppler indices – preprocedural:			
RRI	0.63 ±0.062	0.62 ±0.067	0.555[c]
RPI	1.38 ±0.182	1.37 ±0.202	0.833[c]
PSV [m/s]	0.42 ±0.105	0.43 ±0.105	0.775[c]
EDV [m/s]	0.16 ±0.051	0.17 ±0.055	0.539[c]
AcT [ms]	55.5 (51.0–69.0)	64.8 (49.5–69.5)	0.658[a]
AI [m/s^2]	4.05 (3.58–4.50)	4.28 (3.48–4.55)	0.414[a]
Intra-renal Doppler indices – postprocedural:			
RRI	0.67 ±0.075	0.66 ±0.072	0.470[c]
RPI	1.52 ±0.165	1.48 ±0.221	0.394[c]
PSV [m/s]	0.45 ±0.085	0.46 ±0.095	0.794[c]
EDV [m/s]	0.15 ±0.045	0.16 ±0.053	0.425[c]
AcT [ms]	76 (65–94)	83.5 (66.5–107)	0.248[a]
AI [m/s^2]	3.44 (3.00–3.95)	3.62 (3.25–4.37)	0.280[a]

**Renalase concentration adjusted to urinary creatinine concentration, [a]Mann-Whitney U test, [b]Fisher's exact test, [c]Student's t test, CI-AKI – contrast-induced acute kidney injury, SCr – serum creatinine concentration, RRI – renal resistive index, RPI – renal pulsatility index, PSV – peak systolic velocity, EDV – end-diastolic velocity, AcT – acceleration time, AI – augmentation index.*

The rate of CI-AKI was also comparable in study and control groups (6.1% vs. 11.8%, p = 0.351); however, patients who developed contrast-induced nephropathy were characterized by higher pre-procedural RRI (0.68 vs. 0.62, p = 0.027) and RPI (1.54 vs. 1.36, p = 0.026), as well as post-procedural RRI (0.75 vs. 0.66, p = 0.002) and RPI values (1.76 vs. 1.47, p = 0.0004). Both pre- and post-procedural urinary renalase levels were comparable in CI-AKI and non-CI-AKI groups.

Discussion

The current study is the first to deliver evidence for the lack of a relationship between atorvastatin loading dose administered prior to coronary angiography and intra-renal blood flow parameters. Given the prior sound evidence of a protective effect of a loading dose of atorvastatin on the incidence of CI-AKI [10], our data indicate that atorvastatin exerts its beneficial effect probably by modulation of humoral mediators. We have previously

demonstrated that spillover of urinary renalase is significantly decreased following infusion of contrast media, especially in patients subsequently experiencing CI-AKI [11]. Consequently, the present study corroborates that a loading dose of atorvastatin leads to less severe urinary depletion of nephroprotective renalase (Table II). We may speculate that the less pronounced decrease of urinary renalase level is partially responsible for the preventive effect of atorvastatin towards CI-AKI [2, 4, 5, 10]. Based on a rat model, renalase was previously documented to reduce SCr elevation and oxidative stress, and to down-regulate tubular apoptosis and necrosis [8]. It should be noted that the impact of renalase on catecholamine metabolism has recently been disputed [12]; hence renalase depletion does not necessarily reflect the increase of catecholamine concentration and therefore does not translate into altered renal hemodynamics. However, recently published reports have underscored the role of renalase as a growth factor promoting cell survival via PMCA4b receptor stimulation and activation of the MAP kinase signaling pathway, especially with regard to renal tubular cells [13].

Atorvastatin was shown to interfere with intra-cellular signaling of tubular cells via up-regulation of heat shock protein 27 (Hsp27) [6] or inhibition of Rho/ROCK [7] or JNK/p38 MAP kinase [14], leading to suppression of contrast-mediated apoptosis. Irrespective of the underlying mechanism, the results of our study suggest that atorvastatin's effect on renal tubular cells may be interlinked with regulation of renalase expression.

Conclusions

Atorvastatin does not modify intra-renal blood flow reflected by Doppler-based parameters, but it leads to less pronounced depletion of anti-apoptotic renalase following contrast administration.

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Conflict of interest

The authors declare no conflict of interest.

References

1. Valle JA, McCoy LA, Maddox TM, et al. Longitudinal risk of adverse events in patients with acute kidney injury after percutaneous coronary intervention: insights from the National Cardiovascular Data Registry. Circ Cardiovasc Interv 2017; 10: e004439.
2. Su X, Xie X, Liu L, et al. Comparative effectiveness of 12 treatment strategies for preventing contrast-induced acute kidney injury: a systematic review and Bayesian Network Meta-analysis. Am J Kidney Dis 2017; 69: 69-77.
3. Gurm HS, Seth M, Kooiman J, Share D. A novel tool for reliable and accurate prediction of renal complications in patients undergoing percutaneous coronary intervention. J Am Coll Cardiol 2013; 61: 2242-8.
4. Lee JM, Park J, Jeon KH, et al. Efficacy of short-term high-dose statin pretreatment in prevention of contrast-induced acute kidney injury: updated study-level meta-analysis of 13 randomized controlled trials. PLoS One 2014; 9: e111397.
5. Liang M, Yang S, Fu N. Efficacy of short-term moderate or high-dose rosuvastatin in preventing contrast-induced nephropathy: a meta-analysis of 15 randomized controlled trials. Medicine (Baltimore) 2017; 96: e7384.
6. He X, Yang J, Li L, et al. Atorvastatin protects against contrast-induced nephropathy via anti-apoptosis by the upregulation of Hsp27 in vivo and in vitro. Mol Med Rep 2017; 15: 1963-72.
7. Su J, Zou W, Cai W, et al. Atorvastatin ameliorates contrast medium-induced renal tubular cell apoptosis in diabetic rats via suppression of Rho-kinase pathway. Eur J Pharmacol 2014; 723: 15-22.
8. Zhao B, Zhao Q, Li J, et al. Renalase protects against contrast-induced nephropathy in Sprague-Dawley rats. PLoS One 2015; 10: e0116583.
9. Wybraniec MT, Bożentowicz-Wikarek M, Chudek J, Mizia-Stec K. Pre-procedural renal resistive index accurately predicts contrast-induced acute kidney injury in patients with preserved renal function submitted to coronary angiography. Int J Cardiovasc Imaging 2017; 33: 595-604.
10. Quintavalle C, Fiore D, De Micco F, et al. Impact of a high loading dose of atorvastatin on contrast-induced acute kidney injury. Circulation 2012; 126: 3008-16.
11. Wybraniec MT, Bożentowicz-Wikarek M, Chudek J, Mizia-Stec K. Urinary renalase concentration in patients with preserved kidney function undergoing coronary angiography. Nephrology (Carlton) 2018; 23: 133-8.
12. Beaupre BA, Hoag MR, Moran GR. Renalase does not catalyze the oxidation of catecholamines. Arch Biochem Biophys 2015; 579: 62-6.
13. Wang L, Velazquez H, Chang J, Safirstein R, Desir GV. Identification of a receptor for extracellular renalase. PLoS One 2015; 10: e0122932.
14. He X, Li L, Tan H, et al. Atorvastatin attenuates contrast-induced nephropathy by modulating inflammatory responses through the regulation of JNK/p38/Hsp27 expression. J Pharmacol Sci 2016; 131: 18-27.