Effects of an Acute Dose of L-Arginine during Coronary Angiography in Patients with Chronic Renal Failure

A Randomized, Parallel, Double-Blind Clinical Trial

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Key Words

Renal failure · Contrast media · L-Arginine · Angiography

Abstract

Background: Contrast media (CM) are nephrotoxic and might further worsen renal function in patients with chronic renal failure. L-Arginine, the substrate of nitric oxide, protects kidney function and may improve endothelial function in patients with coronary artery disease. **Hypothesis:** Acute administration of L-arginine in a subset of patients with combined coronary artery disease and impaired kidney function during coronary angiography might prevent superimposed acute renal failure. **Methods:** A double-blind study of patients with mild/moderate chronic renal failure (Cr >1.7 mg/dl) undergoing coronary angiography (meglumine ioxaglate) was conducted. Patients received either L-arginine (300 mg/kg) or placebo and were followed for 48 h. Cardiac hemodynamic parameters, renal function and nitric oxide production were sequentially recorded. **Results – Primary and Secondary:** Both groups experienced a decrease of creatinine clearance 48 h following the procedure ($p <$

0.05). Creatinine levels slightly increased following the administration of L-arginine ($p < 0.05$) but not in the placebo treated group. No changes of systemic and cardiac pressures, total peripheral resistance or cardiac output were recorded within and between the treatment and placebo groups. **Conclusion:** CM injection causes an impairment of renal function. Addition of intravenous L-arginine during cardiac catheterizations in patients with chronic renal failure does not prevent CM-induced nephrotoxicity and does not affect endothelial dysfunction in the particular population studied by the authors, i.e. patients with coronary artery disease (CAD) of various degrees, or suspicion of CAD and chronic mild renal failure.

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Introduction

Contrast media (CM) are nephrotoxic, especially in patients with impaired renal damage, and often result in an acute superimposed renal failure [22]. CM detrimental effects are caused by direct cytotoxicity of both ionics and

nonionics and by hyperosmolarity (ionics) [9, 24]. Intravascular administration of CM can produce acute hemodynamic changes characterized by an increase in renal vascular resistance and a decrease in the glomerular filtration rate [21]. CM might as well induce pathophysiologic changes in the kidney, such as hypoxic tubular injury [20]. Ultimately, these effects might cause contrast nephrotoxicity [27]. It is estimated that CM-induced nephrotoxicity is the third leading cause of renal failure in hospitalized patients [2].

In order to protect the high-risk population of patients with chronic renal failure from CM-induced nephrotoxicity various approaches were used, such as hydration and mannitol [29], calcium channel blockers, adenosine antagonists, theophylline [20], acetylcysteine [30] and based on preliminary studies in animals and a weighty theoretical background, treatment with *L*-arginine [28].

L-Arginine is the natural precursor of nitric oxide (NO), a molecule participating in regulation of kidney function. NO might improve endothelial function in patients with coronary artery disease [6]. Since chronic renal failure patients have a low NO production [3] and accumulate natural inhibitors of NO synthesis [5], it is assumed that the addition of NO precursors to chronic renal failure patients may be beneficial. In animal models administration of *L*-arginine increases glomerular filtration rate [19] and is renoprotective in a radiocontrast-induced renal failure model in rats [28]. In humans, a controversy exists, since *L*-arginine dietary intake prevents an age-related reduction of renal function [25] and on the other hand acute *L*-arginine administration does not improve arterial endothelial function in renal failure [8]. The role of *L*-arginine bolus addition in heart disease is not clearly defined either, since it was reported to improve myocardial perfusion in a subset of patients with angina pectoris [13] but it does not increase the exercise capacity in patients with chronic heart failure [18].

Accordingly we investigated the efficacy of intravenous *L*-arginine as a potentially protective agent during coronary angiography in a selected subset of patients with coronary artery disease and chronic renal failure.

Patients and Methods

Study Design and Patient Entry Criteria

A total of 42 patients with chronic renal failure (creatinine >1.7 mg/dl) (table 1), scheduled for cardiac catheterization were enrolled in the study. The study was designed to demonstrate whether *L*-arginine improves clinical safety of angiographic procedure in high-risk chronic renal failure patients and was conducted as a ran-

Table 1. Patients' characteristics (mean $\pm$ SEM)

	Placebo (n = 21)	<i>L</i> -Arginine (n = 21)
Age	72 $\pm$ 7	69 $\pm$ 16
Males	15	16
Angina degree	2.7	2.9
Prior MI	13	10
Hypertension	16	14
Diabetes	4	7
Hyperlipidemia	12	14
Creatinine	2.41 $\pm$ 0.9	2.58 $\pm$ 0.7
Creatinine clearance	35.7 $\pm$ 4	32.10 $\pm$ 3
Mean CM injected volume, ml	147	182

Values are given as mg/dl for creatinine and ml/min for creatinine clearance. No statistically significant differences in clinical characteristics exist between the placebo and treatment groups.

domized, single-center, double-blind trial, comparing pre-angiographic injection of *L*-arginine versus placebo, 0.9% saline. The study conformed to the principles outlined in the Declaration of Helsinki and the protocol was approved by the institutional Research and Ethics Committee.

Protocol

All patients signed an informed consent. Diagnostic coronary angiography was performed via the right femoral approach. All patients received a hydration protocol of 100 cm³/h 0.45% saline 12 h prior and post procedure. Routine coronary premedication included diazepam 2.5 mg i.v. and nitroglycerin 300 μ g prior to the procedure. The study drug, 20 g *L*-arginine diluted in 200 ml saline, was infused into a peripheral vein over a period of 20–30 min prior to the angiographic examination. The coronary arteries were imaged with manual injections of 8–10 ml contrast medium using pre-shaped catheters. A total of about 150–180 ml of contrast medium (meglumine ioxaglate, Guerbet, France) was used. The left ventricle was visualized by the injection of 30 cm³ of contrast medium via a pigtail catheter and cardiac parameters were assessed. All cardiac parameters were measured after *L*-arginine administration and prior to CM injection. The patients were followed in-hospital for 72 h. Daily laboratory determination of SMAC and creatinine clearance were performed. Plasma and urine nitrite and stable metabolites of nitric oxide (NO) were determined as previously described [3]. No statistically significant differences in baseline clinical characteristics were found between the placebo and treatment groups (table 1).

Statistical Analysis

The results are presented as mean $\pm$ SEM. Comparisons were made using the ANOVA on ranks for inter- and intragroup assessment and paired t test as required (SigmaStat, Jandel, Java).

Table 2. Influence of *L*-arginine administration on patients' hemodynamic functions

	Placebo	Arginine
Systolic BP 0	164±5.5	171±4.7
Systolic BP 10	159±5.7	164±4.3
Systolic BP 20	157±5.9	162±5.1
Diastolic BP 0	70.2±2.0	72±2.2
Diastolic BP 10	69.6±2.2	70±2.5
Diastolic BP 20	69.3±2.2	70±2.8
SP 0	166±5.7	182±7.2
SP 10	161±6.1	176±6.5
SP 20	160±5.8	178±8.6
EDP 0	18.8±2.4	21±1.8
EDP 10	17.8±2.2	19.5±1.4
EDP 20	17.1±2.0	20.4±1.6
CO 0	4.5±0.2	4.4±0.2
CO 10	4.4±0.2	4.5±0.2
CO 20	4.4±0.2	4.6±0.3
TPR 0	1,915±77	2,072±156
TPR 10	1,939±79	1,959±130
TPR 20	1,993±98	2,021±172

Comparisons were made within and between the treatment groups. Values are given as mm Hg for blood pressure and [(dyn-s)/cm²] for peripheral resistance. '0' time refers to measurements prior to *L*-arginine infusion. '10' and '20' refers to time in minutes after onset of *L*-arginine infusion.

Results

Patients' hemodynamic data following *L*-arginine administration is presented in table 2. No differences for placebo and *L*-arginine treatments were observed within each group or between groups for intraventricular pressure, systemic blood pressure, total peripheral resistance or cardiac output. Within 48 h from treatment the creatinine levels were elevated in the *L*-arginine treated group ($p < 0.05$), but not in the placebo-saline administered patients (table 3). Urinary creatinine excretion did not differ between the treatment and placebo groups (data not shown). Creatinine clearance decreased in both treated and untreated groups within 48 h as compared to pre-angiography values ($p < 0.05$, fig. 1a). The serum BUN did not differ between and within groups (fig. 1b).

The blood and urinary NO were without a significant change during the first 24 h after the procedure in the placebo-treated group. Following the *L*-arginine injection, blood NO, but not urinary NO, was significantly higher in the *L*-arginine-treated group immediately after the injection of arginine at the start of the cardiac procedure ($p < 0.05$, table 3).

Table 3. Influence of *L*-arginine administration on creatinine and nitric oxide concentrations (mean ± SEM)

Serum creatinine, mg/ml	Placebo	<i>L</i> -Arginine
Baseline	2.41±0.2	2.58±0.2
24 h	2.40±0.3	2.66±0.1
48 h	2.36±0.2	2.81±0.2*
Blood NO '0'	42.1±10.7	54.9±7.0
Blood NO 24 h post-procedure	42.6±8.8	37.6±5.2*
Urinary NO '0'	674±199	841±272
Urinary NO 24 h post-procedure	518±119	573±129

Values are given as mg/dl for creatinine and μmol/mg creatinine for NO. Statistical comparisons were made within and between the treatment groups. * $p > 0.05$ only for serum creatinine as compared to *L*-arginine baseline.

Fig. 1. Renal function of chronic renal failure patients after injection of contrast medium. a Creatinine clearance as compared to baseline of treated and untreated groups (* $p > 0.05$). b BUN levels with or without *L*-arginine treatment.

Discussion

The present study demonstrates that in a subset of patients with combined coronary artery disease and mild-to-moderate chronic renal failure diagnostic angiography with ionic CM causes a decreased renal function. The administration of *L*-arginine during angiography prior to CM did not affect cardiac hemodynamics, nor did it prevent a CM-induced renal deterioration. The *L*-arginine-treated patients, unlike placebo-treated, had a slight increase of serum creatinine within 48 h from the catheterization procedure. However, none of the 42 subjects experienced acute renal failure necessitating dialysis treatment. This can be attributed to an appropriate pre- and post-angiography hydration protocol.

The rationale of the study is that contrast dyes reduce release of NO from endothelial cells of the renal vasculature [17]. Because exogenous sources of NO could in theory restore NO to the kidney, this maneuver may block a reduction in renal blood flow and thereby reduce the incidence of contrast nephropathy. At the molecular level, CM-induced damage might be related to changes of intracellular pH [9], mitochondrial dysfunction [15] or to direct apoptotic effects [33]. Vacuolization of cells is a preapoptotic sign in kidney and heart cells [1, 7] and it was reported in renal cells due to exposure to CM [31]. It is known that CM is involved in direct inhibition of NO production by endothelial cells [17] and reduces cortical NOS activity [16]. CM induces signs of subclinical nephrotoxicity in subjects with normal kidney function, altering markers of glomerular [11] tubular damage [12].

L-Arginine, the substrate of NO production, is supposedly deficient or its production is inhibited in coronary artery disease, contributing to endothelial dysfunction. This hypothesis leads to the assumption that provision of *L*-arginine could be a key element in endothelial function improvement [4]. *L*-Arginine infusion was reported to induce changes of diastolic blood pressure, cardiac output and peripheral vascular resistance in some studies, but not by others [14]. Our study sample did not show any significant acute hemodynamic changes due to *L*-arginine injection. We have employed about 0.3 g/kg *L*-arginine dose and the lack of hemodynamic changes cannot be attributed to a sub-optimal *L*-arginine dosage. Other studies indicated that *L*-arginine was physiologically effective already at 0.1 g/kg and elevated the renal plasma flow within 30 min of injection [26], due to its vasodilator effect and modulation of tubular sodium reabsorption.

The pathophysiologic changes induced by CM and their deleterious effects on the kidney have been amply described [21]. CM injection causes a hypoperfusion state due to renal vasoconstriction to be followed by further renal parenchymal hypoxia, resulting in a 12–27% risk renal nephrotoxicity in patients with impaired renal function. Unlike animal models, human studies demonstrate that administration of *L*-arginine in chronic renal failure patients does not improve renal function [10, 32]. We previously demonstrated a beneficial effect of *L*-arginine supplementation on preventing CM-induced acute renal failure in rats [28], and further inquired whether this finding can be duplicated in human subjects. The possible effect of *L*-arginine is to increase the systemic and intrarenal NO production (a possible increase of eNOS). Since a decreased NO production was documented in chronic renal failure patients, administration of *L*-arginine is supposed to have a beneficial effect in preventing the CM-induced superimposed acute renal failure. Our *L*-arginine treated subjects did not demonstrate a protective effect of *L*-arginine, as evidenced by a 48-hour post-catheterization creatinine clearance decrease and even a slight increase of creatinine levels as compared to baseline values.

Few data reports examine endothelial dysfunction in the particular population studied by us, i.e. patients with coronary artery disease of various degrees and chronic renal failure. *L*-Arginine does not improve renal function in chronic renal failure patients, possibly due to the initial lack of significant endothelial dysfunction in these patients [8]. The lack of response in renal function does not seem to be due to the minimal acid load received by the *L*-arginine-treated group (200 ml of saline vehicle at pH 5.5). A possible explanation to the inefficacy of *L*-arginine might be related to a high intraglomerular pressure (hyperfiltration state) existent in chronic renal failure resulting in no further NO production and no further haemodynamic effects due to addition of *L*-arginine. This may also explain an enhanced outer medullar NOS activity during CM administration as reported previously [16]. In addition, it was shown that administration of CM inhibits the NO production [17]. This might further explain the lack of improvement with *L*-arginine and the decrease in kidney function in the *L*-arginine treated group, a failure which might have been overcome by even higher doses of *L*-arginine injection. An alternative explanation to the elevation in creatinine in the arginine-treated group might be related to metabolites of arginine which can be converted to creatinine [23, 23].

Our study is limited by the lack of comparison of effects with different doses of *L*-arginine, the need to use other types of CM, e.g. nonionics and the relatively small sample of patients. The administration of a bolus of *L*-arginine might not be sufficient to be effective and a prolonged infusion might be preferable. In summary, there is

place for further clinical studies to investigate the lack of effect of *L*-arginine as a cytoprotector in patients with combined chronic renal failure and coronary artery disease undergoing coronary angiography. The in vitro/animal studies might not be relevant to clinical improvement in patients with both diseases who receive ionic CM.

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