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Inhibition of xanthine oxidase improves myocardial contractility in patients with ischemic cardiomyopathy

Stephan Baldus[a,*,1], **Kai Müllerleile**[a,1], **Phil Chumley**[b], **Daniel Steven**[a], **Volker Rudolph**[a], **Gunnar K. Lund**[a], **Hans-Jürgen Staude**[c], **Alexander Stork**[d], **Ralf Köster**[a], **Jan Kähler**[a], **Christian Weiss**[a,2], **Thomas Münzel**[a,2], **Thomas Meinertz**[a], **Bruce A. Freeman**[b,3], and **Thomas Heitzer**[a]

a *Heart Center, Department of Cardiology, University Hospital Hamburg–Eppendorf, Martinistrasse 52, Hamburg 20246, Germany*

b *Center for Free Radical Biology, University of Alabama at Birmingham, Birmingham, AL 35233, USA*

c *Department of Pharmacy, University Hospital Hamburg–Eppendorf, Hamburg 20246, Germany*

d *Department of Radiology, University Hospital Hamburg–Eppendorf, Hamburg 20246, Germany*

Abstract

Reactive oxygen species, in particular superoxide, have been closely linked to the underlying pathophysiology of ischemic cardiomyopathy: superoxide not only mediates mechanoenergetic uncoupling of the myocyte but also adversely impacts on myocardial perfusion by depleting endothelial-derived nitric oxide bioavailability. Xanthine oxidase generates superoxide upon oxidation of hypoxanthine and xanthine and has been detected in cardiac myocytes and coronary endothelial cells of patients with ischemic heart disease. Here we investigated the effects of oxypurinol, a xanthine oxidase inhibitor, on myocardial contractility in patients with ischemic cardiomyopathy. Twenty patients (19 males, 66±8 years) with stable coronary disease, severely suppressed systolic function (left ventricular ejection fraction 22±2%), and nonelevated uric acid plasma levels received a single intravenous dose of oxypurinol (400 mg). Cardiac MRI studies, performed before and 5.2±0.9 h after oxypurinol administration, revealed a reduction in end-systolic volumes (−9.7±4.2%; p=0.03) and an increase in left ventricular ejection fraction (+17.5±5.2%; p=0.003), whereas 6 patients (6 males, 63±3.8 years, ejection fraction 26±5%) who received vehicle only did not show significant changes in any of the parameters studied. Oxypurinol improves left ventricular function in patients with ischemic cardiomyopathy. These results underscore the significance of reactive oxygen species as important pathophysiological mediators in ischemic heart failure and point toward xanthine oxidase as an important source of reactive species that serve to modulate the myocardial redox state in this disease.

Keywords

Nitric oxide; Superoxide; Hydrogen peroxide; Heart failure; Endothelial function; Reactive oxygen species; Myocardial infarction; Free radicals

Impaired contractility of cardiac myocytes is a central feature of ischemic heart failure. Pathophysiologically, impaired myocyte function has been closely linked to alterations in inter-

* Corresponding author. Fax: +49 40 42803 2967. E-mail address: baldus@uke.uni-hamburg.de (S. Baldus).
[1]These authors contributed equally to this work.
[2]Current address: Department of Cardiology, University Hospital Mainz, Mainz, Germany.
[3]Department of Pharmacology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15263, USA.

and subcellular signaling cascades in the contractile apparatus itself as well as coronary conductance and resistance vessels [1]. Reactive oxygen-containing species centrally affect myocardial homeostasis: In particular, excess generation of superoxide and hydrogen peroxide serves to mediate the pathophysiology of depressed myocardial function. For example, superoxide and hydrogen peroxide lower calcium responsiveness of stunned cardiac myofilaments by modifying redox-sensitive proteins like the L-type calcium channel, the ryanodine receptor, the calcium ATPase, and mitochondrial respiratory complexes [2–4]. Moreover, superoxide reacts at diffusion-limited rates with other free radicals, particularly with NO to form the potent oxidant peroxynitrite [5]. Peroxynitrite has been shown to activate metalloproteinases, which cause myocardial injury by degradation of troponin I [6,7]. Impairment of endothelial bioavailability by reaction of NO with superoxide also attenuates vasodilation and adversely impacts on organ perfusion [8,9].

Multiple enzyme systems emerge as potential candidates for generation of reactive oxygen species in the failing human heart, such as the leukocyte-derived NADPH oxidase and $gp91^{phox}$ homologues, uncoupled NO synthases, mitochondrial respiratory chain-generated superoxide, and xanthine oxido-reductase [10–13]. Xanthine oxidoreductase, when transferred into its oxidase form xanthine oxidase (XO), generates super-oxide and hydrogen peroxide upon conversion of xanthine to hypoxanthine and hypoxanthine to uric acid, respectively. Vascular and myocyte-localized XO is increased in patients with coronary artery disease, and circulating XO levels are upregulated in congestive heart failure [14,15]. XO inhibition in hyperuricemic patients with dilated and ischemic cardiomyopathy leads to an improvement of vascular NO bioavailability [16,17], and local infusion of allopurinol into the coronary circulation in patients with dilated cardiomyopathy lowered myocardial oxygen consumption [15].

Given the above observations, we hypothesized that XO inhibition by oxypurinol may translate into increased myocardial contractility in patients with ischemic cardiomyopathy. To test this, patients with coronary artery disease (CAD), severely suppressed left ventricular function, and normal uric acid levels underwent cardiac MRI studies, the accepted standard for assessment of left ventricular function [18,19], before and after intravenous administration of oxypurinol.

Materials and methods

The study was approved by the Hamburg Medical Board, the Bundesinstitut für Arzneimittel und Medizinprodukte, and the local health care department. To participate in the study every patient had to give written informed consent. The trial included patients with angiographically documented CAD and a left ventricular ejection fraction below 35%. Main exclusion criteria were unstable coronary artery disease or myocardial infarction within 2 weeks before study entry, significant valvular disease, hypotension, uncontrolled hypertension, creatinine 1.5 times the upper limit of normal, hyperuricemia (>351 μM in women and >422 μM in men), current allopurinol intake or known allopurinol intolerance, and intravenous heparin within 24 h of the study. All patients had to be eligible for cardiac MRI studies.

Oxypurinol (400 mg · 100 ml^{-1}) was infused into the femoral vein at 26 mg · min^{-1}. The study medication was prepared aseptically on-campus by dissolving oxypurinol (Cardiome Pharmaceuticals, Vancouver, BC, Canada) in glucose 5% and sodium hydroxide (0.07 N) to a final pH of 9.7. All solvated oxypurinol was used within 8 h of preparation. Before and after infusion of oxypurinol blood was drawn and plasma was frozen at −80°C until analysis of oxypurinol plasma levels.

MR imaging protocol

To assess left ventricular function all patients underwent cardiac MRI studies before and after oxypurinol administration. The studies were performed with a 1.5-T scanner (Magnetom Symphony; Siemens Medical Systems, Erlangen, Germany) equipped with Quantum gradients (30 mT/m) using a phased array four-element body surface coil. An ECG-gated segmented true fast imaging with steady-state precision sequence was used for cine-MRI. Typical imaging parameters were as follows: repetition time 3.6 ms, echo time 1.8 ms, flip angle 60°, slice thickness 8 mm, field-of-view 350 × 306 mm^2, matrix 256×139, pixel spacing 1.4×2.2 mm^2. For identification of the cardiac axes, scout images in the coronal, sagittal, and transversal planes were acquired. A cine loop in the long-axis four-chamber plane was followed by short-axis cine loops, perpendicular to the long-axis plane. Short-axis slices were obtained at 10-mm intervals, covering the entire left ventricle from the mitral valve to the apex.

Image analysis

Image analysis was performed using the public domain NIH Image program (version 1.62; U.S. National Institutes of Health) and analyzed by an independent investigator blinded to patient identity, date of examination, and treatment. Left-ventricular endocardial and epicardial contours were manually traced in end-diastole and end-systole, whereas papillary muscles were traced separately. End-diastolic and end-systolic left-ventricular volumes were calculated by summing the areas contained by the endocardial borders as previously [20,21] (Fig. 1). Stroke volume was defined as the difference between end-diastolic and end-systolic volume, ejection fraction was defined as stroke volume divided by end-diastolic volume. Left-ventricular mass was determined by multiplication by the specific gravity of the myocardium (1.05). Intraobserver variability, as assessed in six patients undergoing consecutive cardiac MRI studies with the same pathology, was 1.1%.

Assessment of plasma levels of oxypurinol, xanthine, hypoxanthine, and uric acid and XO activity

Xanthine oxidase activity was determined by measurement of uric acid formation via HPLC with electrochemical detection. A chromatography elution scheme, using a 25×5-mm C18 column, was devised to permit the baseline resolution of added xanthine, uric acid, and oxypurinol. This consisted of a 30-min isocratic elution with KH_2PO_4 (300 mM, adjusted to pH 4.0):methanol:acetonitrile: tetrahydrofuran (97.9:1:1:0.1, v/v). The flow rate was 1 ml/min and the column temperature was maintained at 30°C. An eight-channel electrochemical CoulArray detector (ESA Chelmsford, USA) with applied potentials of 0, 120, 220, 300, 575, 700, 800, and 900 mV was used for purine oxypurinol detection. Every five samples, an internal standard mixture of oxypurinol, xanthine, and uric acid was resolved chromatographically for calculating inhibitor and purine concentrations in patient plasma. All samples were run in duplicate and averaged and the means were combined for statistical analysis. The potentially confounding effects of plasma uricase activity were separately determined by addition of known concentrations of uric acid to plasma samples. Subsequent plasma analysis by HPLC–diode array detection revealed no detectable loss of uric acid over time.

Statistical analysis

All parameters are given as mean values±SEM. Differences between parameters before and after oxypurinol were assessed by applying the paired Student *t* test. Differences of $p<0.05$ were considered statistically significant.

Results

A total of 20 patients (67±2 years, 95% male) received the study medication (Table 1). All patients tolerated the study protocol and none of the patients experienced adverse reactions after oxypurinol infusion. Most patients had experienced q wave myocardial infarctions (85%) and all patients presented with NYHA class III (70%) and IV (30%), respectively. The majority of the patients were diagnosed for hyperlipoproteinemia and hypertension and 40% of the population were diabetic. The patient population was under standard therapy for heart failure with 95% taking oral diuretics including 50% receiving spironolactone, 93% receiving ACE inhibitors or AT-1 receptor blockers, and 92% on beta blockers.

Baseline cardiac MRI revealed highly increased end-systolic and end-diastolic volumes (247 ±24 and 309±25 ml, respectively; Table 2) and severely suppressed left-ventricular function (ejection fraction 22+2%).

Upon infusion of oxypurinol, plasma levels of oxypurinol increased from 1.59±1.47 to 118 ±8.78 μmol/L ($p<0.001$). No significant changes were observed in levels of purine metabolites such as xanthine (0.62±0.55 μM vs. 1.0±1.02 μM after oxypurinol, $p>0.05$), hypoxanthine (3.12±4.9 μM vs. 5.56± 6.02 μM after oxypurinol, $p>0.05$), and uric acid (27.4± 6.5 μM vs. 30.9±7.1 μM after oxypurinol, $p>0.05$). In addition, plasma xanthine oxidase activity remained unchanged after infusion of oxypurinol (0.06±0.01 vs. 0.09±0.02 μU/mg protein; $p=0.4$).

Cardiac MRI, performed 25±5.7 h after baseline MRI and 5.2 ± 1.3 h after oxypurinol administration, revealed a reduction in end-systolic volume (−9.7±4.2; $p=0.03$) and a nonsignificant decline in end-diastolic volume (−5.6±4.5%, $p=0.2$), which translated into a significantly increased left ventricular ejection fraction (+17.8±5.1%, $p=0.003$) in the presence of an unchanged left ventricular mass (+1.8±3.2%; $p=0.6$; Fig. 2). There was a trend toward an increase in mean aortic pressure after administration of oxypurinol (91.9 mm Hg vs. 97.3 mm Hg, $p=0.055$). The heart rate during baseline and follow-up MRI remained unchanged (77 ±17/min vs. 76±18/min, $p>0.05$).

Six consecutive patients with ischemic cardiomyopathy (male, $n=6$, age 63±3.8 years, ejection fraction 25.5±4.7%) who received infusion of the vehicle instead of oxypurinol revealed unchanged end- systolic (−1.4±1.9%; $p=0.5$) and end-diastolic volumes (−2.3±1.2%, $p=0.1$) with no alteration of ejection fraction (−1.1±6.3%, $p=0.9$) and unchanged left ventricular mass (−2.7±3.5%; $p=0.4$; Fig. 2).

Discussion

The principal finding of the current study is that xanthine oxidase inhibition exerts positive inotropic effects in patients with ischemic cardiomyopathy. Administration of the XO inhibitor oxypurinol lowered end-systolic volumes and increased ejection fraction by 18%.

The depression of myocardial contractility in patients with ischemic cardiomyopathy is no longer viewed as solely the consequence of a loss of structurally intact myocytes, rather is much more appreciated as a disease involving impaired myocyte and vascular redox signaling pathways. Among these, the imbalance between NO and reactive oxygen species such as superoxide and hydrogen peroxide has emerged as a central contributor to depression of myocardial function [22,23]. Xanthine oxidase has also now emerged as a potential source of superoxide and hydrogen peroxide in heart failure, given its upregulation in both vascular and myocardial compartments in this disease [14,15,24].

The modulation of myocardial contractility after xanthine oxidase inhibition has been extensively investigated in animal models of heart failure: In myocytes from a rodent model

of heart failure, myocardial oxypurinol administration significantly increased twitch tension and exerted a positive inotropic effect [25]. In a canine pacing-induced heart failure model, allopurinol also increased myocardial contractility and reduced myocardial oxygen requirement [26–28].

Initial clinical studies examining the effects of XO inhibition revealed attenuated oxygen consumption and increased myocardial efficiency in individuals with dilated cardiomyopathy and decreased reperfusion injury. There was also improved endothelial function as a consequence of preserved NO bioavailability in patients with CAD and preserved left ventricular function, as well as in individuals with ischemic and dilated cardiomyopathy [9, 14,15,24].

The current study now adds importantly to these initial observations by demonstrating for the first time that systemic XO inhibition by oxypurinol decreases left end-systolic and end-diastolic volumes as revealed by cardiac MRI. Importantly, these effects were seen in patients with nonelevated uric acid levels, suggesting that systemic levels of purine metabolites are not necessarily reflecting local distribution of purine-oxidizing enzymes.

In addition, the effect of oxypurinol was observed in patients, almost all of whom received standard therapy for heart failure—in particular ACE inhibitors, AT-1 blockers, and beta blockers—suggesting that XO inhibition may represent an adjunct treatment strategy in this disease. The increase in ejection fraction has to be considered modest compared to classical positive inotropic agents routinely used in current practice, such as levosimendan or dobutamine [29,30]. However, given the underlying mechanisms of XO inhibition, namely the increase in cardiac NO bioavailability, the increase in myocardial contractility may be just one aspect of net potential anti-inflammatory benefits deriving from this treatment strategy in heart failure.

The fact that infusion of the vehicle did not alter myocardial performance further reinforces the notion that the effects of oxypurinol on cardiac contractility reflect inhibition of the enzyme and reduced generation of reactive oxygen species. Of note, we did not observe changes in circulating xanthine oxidase activity. Furthermore, plasma oxypurinol levels did not exceed those measured in previous studies examining patients with coronary disease and preserved left ventricular function despite the fact that the dose of oxypurinol was doubled (400 mg iv vs. 200 mg iv in the previous trial). Potential explanations are increased body volumes in the current trial and a different extent of local XO deposition, which may have influenced plasma distribution of the drug.

Importantly, the effects of oxypurinol were not accompanied by an increase in heart rate, as opposed to other inotropic agents such as dobutamine, phosphodiesterase inhibitors, and levosimendan [31,32]. This underscores the concept that the positive inotropic effects do not simply reflect endogenous release of catecholamines, but rather are linked to inducing a reduced bioavailability of reactive oxygen species. Given recent ex vivo observation of a markedly attenuated capacity of oxypurinol to inhibit cell-associated and glycosaminoglycan-immobilized XO [33], the role of XO in the depression of cardiac function during ischemic heart failure may still be underestimated.

Certainly, the current study is limited by its nonrandomized design and its overall small size. However, given the significant decrease in end-systolic volumes and the profound increase in ejection fraction upon a single dose of oxypurinol, this pharmacological intervention emphasizes the significance of reactive oxygen species as critical mediators of impaired contractility in patients with ischemic cardiomyopathy. Moreover, xanthine oxidase emerges as a primary source of oxidant stress in the failing heart. Whether these “reverse remodeling”

effects of XO inhibition will translate into an adjunct, antioxidant treatment strategy in patients with ischemic heart disease remains to be evaluated in larger clinical trials.

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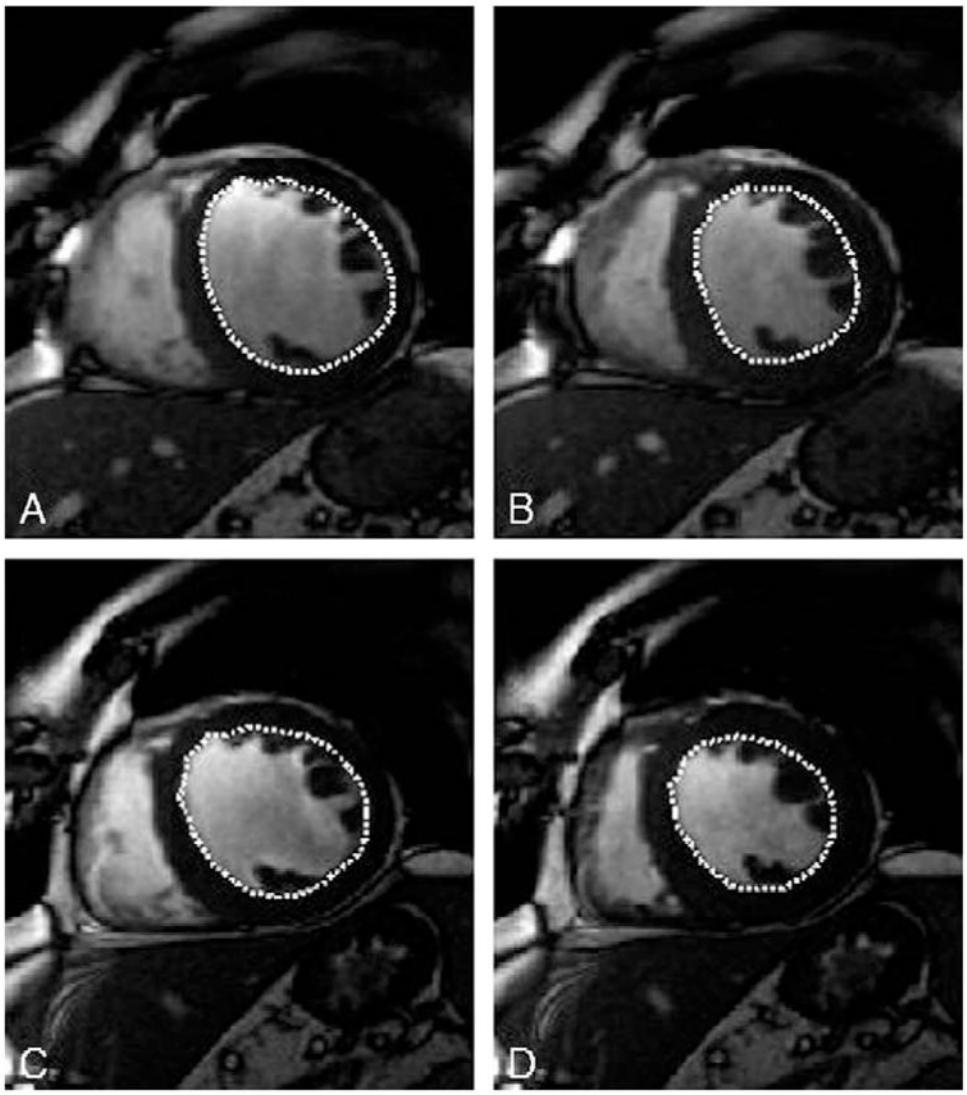
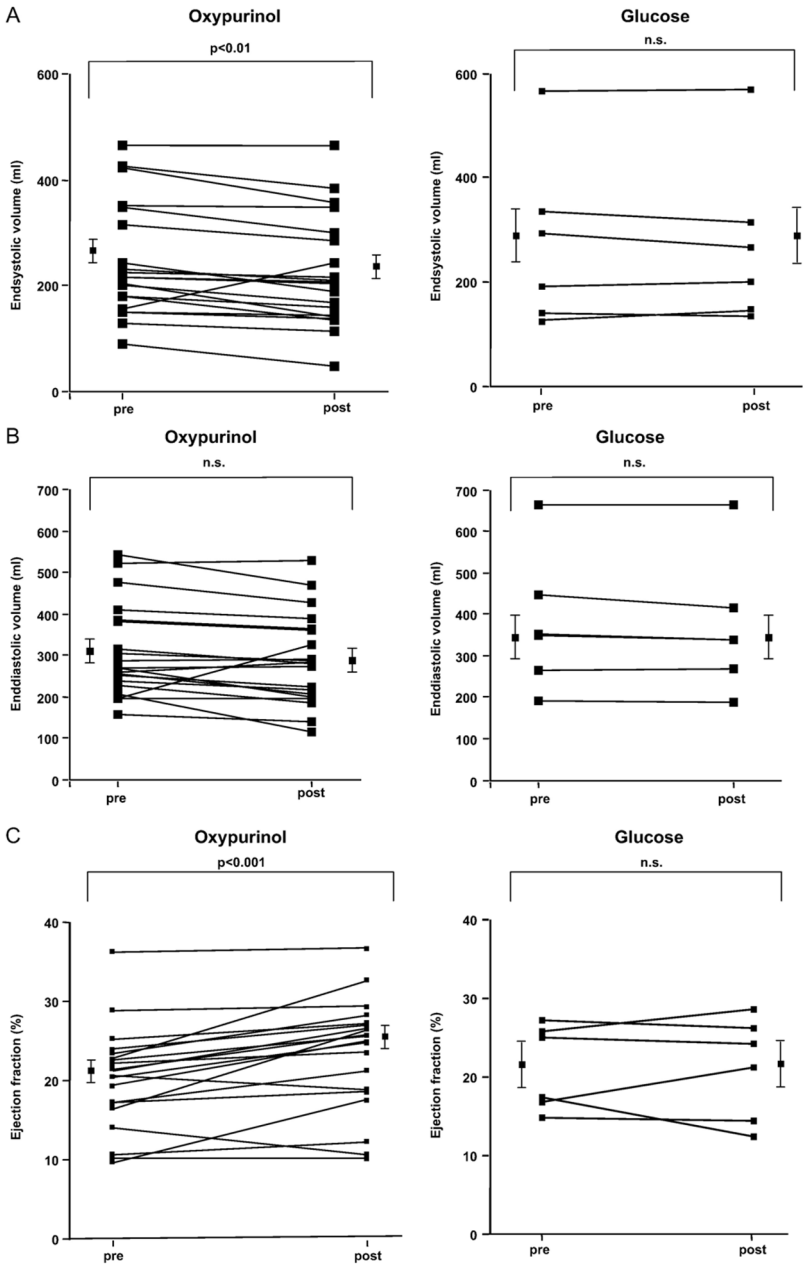


Fig. 1.

Assessment of left-ventricular volumes by cine-MRI. Endo- and epicardial borders were manually traced in all slices in end-diastole and end-systole, papillary muscles were traced separately. After administration of oxypurinol, MR imaging was repeated with corresponding slice orientations. (A) Diastolic endocardial borders in a midventricular slice before administration of oxypurinol. (B) Systolic endocardial borders in a midventricular slice before administration of oxypurinol. (C) Diastolic endocardial borders in a midventricular slice after administration of oxypurinol. (D) Systolic endocardial borders in a midventricular slice after administration of oxypurinol.



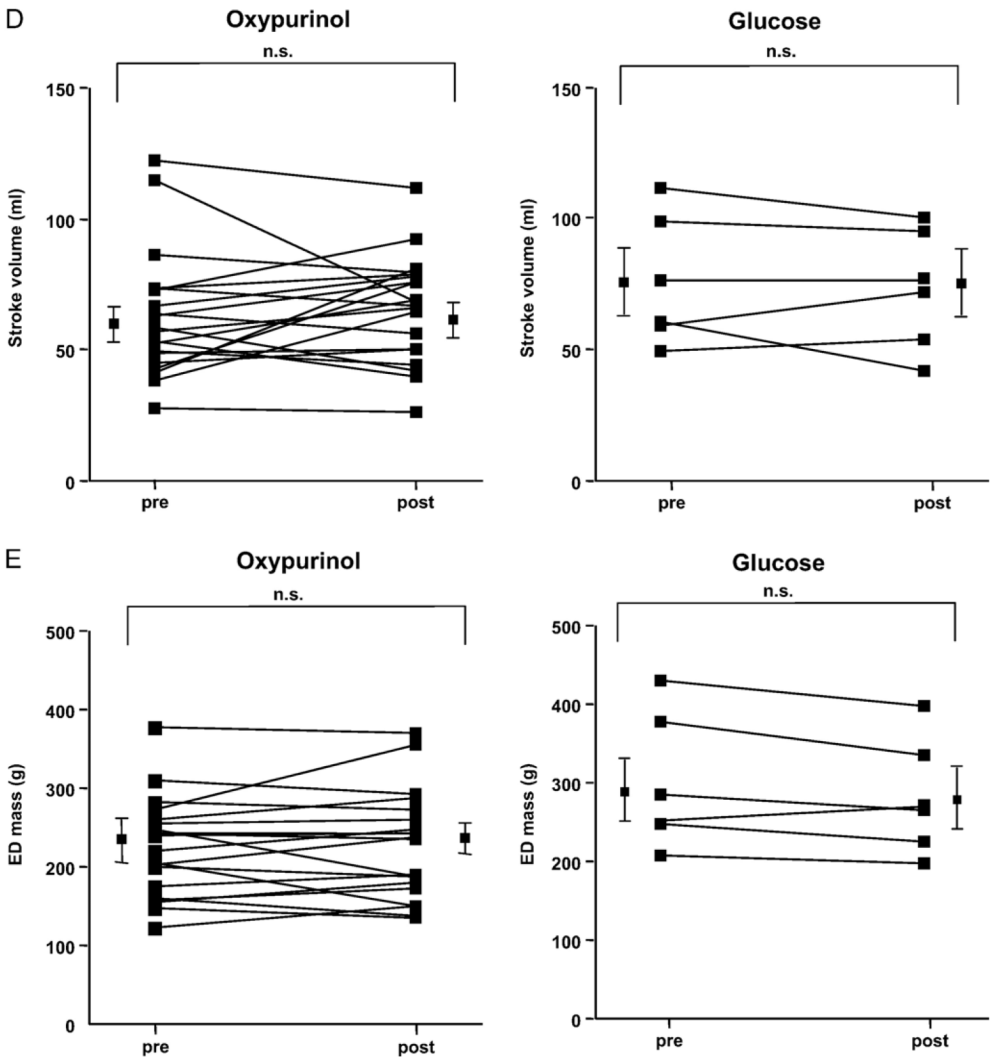


Fig. 2.

Evaluation of myocardial contractility in response to oxypurinol using cardiac MRI. (A–E) Cardiac MRI was performed in 20 patients before and after administration of oxypurinol (400 mg iv) as well as in 6 patients who received the vehicle only (glucose). Values are given for every patient before and after treatment with mean values±SEM being displayed separately.

Table 1

Baseline clinical characteristics

***N*=20**	**(%)**
Age (±SD; years)	67±2
Sex, male/female	m:19 (95); w:1 (5)
NYHA III; IV	14 (70); 6 (32)
Q wave myocardial infarction	17 (89)
Body mass index (kg/m^2)	26±4
Diabetes mellitus	8 (42)
Hypertension	14 (73)
Hyperlipoproteinemia	14 (73)
Smoker	12 (63)

Table 2

Baseline hemodynamic and cardiac MRI measurements

***N*=20**	
Heart rate	74±14
Ejection fraction (%)	22±2
End diastolic volume (ml)	309±25
End systolic volume (ml)	247±24
Stroke volume (ml)	63±6
End diastolic mass (g)	227±14