Title: Histidine metabolism after Bretschneider cardioplegia in cardiac surgical patients

Short title: Histidine metabolism after Bretschneider cardioplegia

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Summary

Background: Bretschneider (histidine-tryptophan-ketoglutarate) solution with its high histidine concentration (198 mM) is one of many cardioplegic solutions, which are routinely used for cardiac arrest. The aim of this study was to evaluate the physiological biochemical degradation of administered histidine to histamine and its major urinary metabolite N-methylimidazole acetic acid.

Material and methods: A total number of thirteen consecutive patients scheduled for elective isolated coronary artery bypass grafting with cardiopulmonary bypass were enrolled in the prospective observational designed study at the Department of Thoracic and Cardiovascular Surgery between 04/2016 and 06/2016. Patients received 1.7 l Bretschneider solution on average. Before and at the end of operation as well as in the postoperative course, urine samples were gathered from the urinary catheter bag which were analyzed.

Results: During the operative period, urinary histidine concentration significantly increased from 29 µmol/mmol creatinine to 9609 µmol/mmol creatinine. Postoperatively, histidine excretion reduced while histamine as well as N-methylimidazole acetic acid excretion rose significantly.

Discussion: Patients showed elevated levels of histidine, histamine as well as N-methylimidazole acetic acid in urine, but no unmanageable hemodynamic instability possibly arising from the histamine's biological properties. Chemically modified histidine might reduce uptake and metabolization while maintaining the advantages of buffer capacity.

Key words: urine, catabolism, N-methylimidazole acetic acid, catecholamines

Introduction

Bretschneider (histidine-tryptophan-ketoglutarate, HTK) solution is frequently used for the induction of cardioplegic arrest in cardiac surgery (Careaga *et al.* 2001). The high histidine concentration of 198 mM in Bretschneider solution was shown to buffer acidosis in the ischemic period (Scrascia *et al.* 2011). This way, the prolonged existence of anaerobic glycolysis is favored, which would be otherwise inhibited by an acidic milieu. As previously shown, plasma histidine concentration increases after Bretschneider administration, followed by immediate catabolism resulting in increased plasma concentrations of other amino acids, urea and ammonia (Teloh *et al.* 2016). In general, the histidine's decarboxylation yielding histamine is supposed to constitute a minor pathway (0.5%) of its total degradation (Maslinski 1975). Nevertheless, due to the high histidine amount (about 300 mmol) incorporated in the context of cardioplegic arrest with Bretschneider solution (Teloh *et al.* 2016), at least a transient increase of histamine is assumed after induction of cardioplegia. Histamine itself undergoes rapid catabolism, having a half-life of maximal three minutes (Ferreira *et al.* 1973, Kuefner *et al.* 2002, Lorenz and Doenicke 1978, Lorenz *et al.* 1982). The main histamine's urinary degradation product is N-methylimidazole acetic acid (Granerus 1968, Schayer 1959). Little is known about the metabolism of histidine to histamine and its cardiovascular effects after Bretschneider cardioplegia. Therefore, this study will demonstrate intra- and early postoperative plasma concentrations of histidine, histamine and its major urinary metabolite N-methylimidazole acetic acid.

Material and Methods

Study design and patient population

A total number of thirteen consecutive patients scheduled for elective isolated coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB) were enrolled in the prospective observational designed study at the Department of Thoracic and Cardiovascular Surgery

between 04/2016 and 06/2016. The study was approved by the local Medical Ethics Committee and confirms to the principles of the Declaration of Helsinki. All individuals gave written informed consent. Acute myocardial infarction, cardiogenic shock, concomitant cardiac diseases and procedures or participation in other clinical trials were exclusion criteria.

Standard CPB was established with ascending aortic and two-stage venous cannulation. Heparin was administered to achieve an activated coagulation time > 460 s. A mean volume of 1.2 l 0.9% NaCl solution was used for priming and de-airing of the heart-lung machine tubes and membrane oxygenator (Medtronic Affinity fusion oxygenator system with integrated arterial filter and venous reservoir; Medtronic, Santa Rosa California). For induction of cardioplegic arrest, cold crystalloid Bretschneider cardioplegia (Custodiol, Dr. Franz Koehler Chemie, Bensheim, Germany, 1.7 l ± 0.3 l on average) was infused antegradely. Myocardial protection was supplemented by topical cooling. The mean arterial blood pressure (MAP) was regulated by phenylephrine titration into the extracorporeal circuit and noradrenaline administered via the central venous catheter. The internal left thoracic artery and saphenous veins were the preferred grafts.

Patient characteristics

Median patients' age was 74 (58; 76) years, body surface area was 1.90 (1.78; 1.98) m^2, and 85% of the patients were male. Median cardiopulmonary bypass time was 97 (83; 100) min with 56 (53; 59) min cross-clamp time and they received three grafts on average each.

Sample collection

Immediately after urinary catheter installation, a urine sample was obtained as baseline. At the end of the operative procedures, a second sample was taken from the total collected urine volume. Further urine samples were taken 8h, 32h, and 56h postoperative from the volume having been excreted during the past eight hours.

Histamine Enzyme-Linked Immunosorbent assay (ELISA)

The ELISA kit was purchased from DRG Instruments GmbH (Marburg, Germany). Before the actual analysis was started, the probes had to be acylated with the reagents provided with the test. Of the acylated probes, 25 µl were pipetted into the appropriate wells of the microtiter strips and 100 µl of histamine antiserum was added. The plate was covered with adhesive foil and subsequently incubated on a shaker (600 rounds per minute (rpm)) for three hours at room temperature. After incubation had ended, the plate was washed four times by adding 300 µl wash buffer each. Subsequently, 100 µl of enzyme conjugate was pipetted into all wells and incubated for 30 minutes at room temperature on a shaker (600 rpm). Again, the plate was washed four times with 300 µl wash buffer each. After having pipetted 100 µl substrate solution into each well, the plate was incubated for 30 minutes on a shaker (600 rpm) at room temperature. Of the stop solution, 100 µl were added and absorbance was immediately read at 450 nm.

Urine samples were previously diluted at a ratio of 1:10 with ultrapure water at the following times: postoperative and 8h postoperative.

Hemodynamic effects of cardioplegia

For hemodynamic monitoring, each patient had an arterial line for mean arterial pressure (MAP) measurement, central venous catheter for drug administration and central venous pressure (CVP) measurement, and Swan-Ganz catheter for cardiac output (CO) and pulmonary artery pressure (PAP) measurement. Hemodynamic changes during or early after cardioplegia administration were measured by relative changes of MAP compared to MAP at onset of cardioplegia.

Histidine measurements

Quantification of histidine concentration in urine was conducted as described previously (Teloh *et al.* 2016). In short, after deproteinization, the sample was diluted with reagent buffer at the ratio of 1:1 of which 50 µl were analyzed by liquid chromatography (biochrom 30+, biochrom, Cambridge, UK).

N-methylimidazole acetic acid measurements

Analysis of N-methylimidazole acetic acid was conducted using liquid chromatography (Agilent 1100, Agilent Technologies, Ratingen, Germany) with tandem mass spectrometry (API 4000QTRAP, ABSciex, Darmstadt, Germany). Before analysis, samples were deproteinized by adding organic solvent and subsequent dilution with the aqueous mobile phase. Quantification was realized with the help of reversed phase chromatography using methyl alcohol and aqueous acetic acid as mobile phase. Ionization was achieved by electro spray in positive mode and subsequent detection with multiple reaction monitoring.

Statistical analysis

All data are expressed as mean ± standard deviation (SD) unless otherwise stated. Medians are given with 25% and 75% quartiles, respectively, in brackets. Comparisons among different time points were performed using one-way repeated measurement analysis of variance (ANOVA) followed by the Dunnett's multiple comparison test. A p value < 0.05 was considered significant.

Results

Urinary histidine concentration increased significantly from an initial value of 29 µmol/mmol creatinine to 9609 µmol/mmol creatinine at the end of the operation (Figure 1). During the postoperative course, it decreased to 4406 µmol/mmol creatinine 8h postoperative, and 324 µmol/mmol creatinine 32h postoperative to finally reach almost baseline conditions with 52 µmol/mmol creatinine 56h postoperative. Urinary histamine concentration increased

significantly from an initial value of 10 ng/ml to 87 ng/ml at the end of the operation (Figure 2). In the postoperative course, it steadily decreased to reach baseline conditions 56h postoperative. The initial value of N-methylimidazole acetic acid in urine was 1.8 mg/g creatinine (Figure 3). During the postoperative course, it increased to peak 32h postoperative (5.1 mg/g creatinine). Within the next 24 hours (until 56h postoperative), it declined to reach 3.4 mg/g creatinine.

Immediately after cross-clamping and antegrade root-cardioplegia infusion (and before therapeutic catecholamine administration), MAP decreased from the respective individual level by 30% on average for every patient (data not shown). Since the degree of decrease, its moment as well as its duration were individual for every patient, mean MAP values decreased only from 60 mmHg to 55 mmHg. Subsequently, the mean noradrenalin infusion rate was increased from 0.050 µg/kg/min before cardioplegia administration to 0.069 µg/kg/min after cardioplegia administration, and the amount of phenylephrine increased from 0.150 µg/kg/min to 0.506 µg/kg/min within the same time intervals (Figure 4, Table 1). Mean MAP decreased even during this enhanced catecholamine administration.

Discussion

The substance with the main buffer capacity in Bretschneider solution is histidine with a high concentration of 198 mM. As demonstrated previously, plasma histidine concentration distinctly increased from a physiological value of 70 µM to reach 20000 µM immediately after induction of cardioplegic arrest (Teloh *et al.* 2016). After incorporation of total 300 mmol histidine, a plasma concentration of 60000 µM would have been expected. However, only about one third of the histidine was detectable in plasma in this study. Hence, in the present study, we focused on the histidine's metabolism after Bretschneider cardioplegia administration.

Since only one third of the incorporated histidine was detectable, we therefore assume that about two thirds have been transported into the cells by system L amino acid transporters in the plasma membrane of cells of several tissues. This transport system is unspecific with a K_M value for histidine of approximately 30 µM (Bauza and Lagunoff 1983, del Amo *et al.* 2008). Once within the cells, two major pathways, depending on the tissue specific enzymes, are known for histidine degradation: either deamination to glutamate via urocanic acid, mainly in liver and skin by histidase and subsequently urocanase (Taylor *et al.* 1991, Virmani and Widhalm 1993), or transamination in the liver to finally aspartate (Greenberg 1969). Additionally, histidine can be decarboxylated giving the biogenic amine histamine. Histidine decarboxylase (K_M value of $2\text{-}4 \cdot 10^{-4}$ M for histidine) is responsible for most histamine synthesized in the human body (Beaven 1982). Under physiologic conditions, this metabolic pathway is supposed to be small (0.5%) compared to the total amount of degraded histidine (Beaven 1982, Maslinski 1975). Assuming that reaction rate of histidine decarboxylation via histidine decarboxylase increases with substrate concentration until saturation is reached, this pathway might gain importance in situations with increased plasma histidine concentrations.

Cells with histidine decarboxylase activity like mast cells, basophiles, macrophages, lymphocytes, neutrophils, and enterochromaffin-like cells are able to produce histamine, but many of them lack the specific granules for storage. Only mast cells and basophils possess these secretory granules (Cabut and Haegermark 1968, Schayer 1956, Shahid *et al.* 2010). The remaining cell types release generated histamine immediately after synthesis into the blood, where it is incorporated by competent cells via the organic cation transporter 3 (OCT3; K_M value for histamine of 200 µM (Grundemann *et al.* 1999)). Once within the cell, vesicular monoamine transporter 2 (VMAT2) mediates granule storage (Shahid *et al.* 2010). This way, histamine is either stored by mast cells and basophils in addition to the amount produced endogenously, or is taken up by organs for degradation purposes.

The histamine's degradation starts immediately, resulting in an extremely short half-life, which is indicated by times of maximal three minutes at body temperature (Ferreira *et al.* 1973, Kuefner *et al.* 2002, Lorenz and Doenicke 1978, Lorenz *et al.* 1982). As part of histamine catabolism, approximately one third is metabolized via the secretory enzyme diamine oxidase to imidazole acetaldehyde and imidazole acetic acid afterwards via aldehyde dehydrogenase, and the remaining two thirds via the intracellular enzyme N-methyltransferase to N-methylhistamine and finally N-methylimidazole acetic acid via monoamine oxidase (Granerus 1968, Schayer 1956). Since imidazole acetic acid is a metabolite of both histamine and histidine via independent routes (Granerus *et al.* 1983, Holm-Bentzen *et al.* 1987), it is insufficient to serve as a parameter for histamine degradation in the present context. Moreover, in humans, methylation constitutes the primary route for histamine (Schayer 1956) and thus, N-methylimidazole acetic acid is the major urinary metabolite (Granerus *et al.* 1983, Holm-Bentzen *et al.* 1987). Therefore, we measured N-methylimidazole acetic acid in urine as well.

In the previous study, renal histidine excretion rate was 7% (Teloh *et al.* 2016), according to the known physiological excretion rate of 5% (Lingard *et al.* 1973, Silbernagl and Volkl 1977). The percentage excretion rate remained thus almost unchanged, although the total plasma histidine concentration was significantly higher compared to the physiological level due to the administration of 300 mmol histidine by Bretschneider cardioplegia. This result was confirmed in the present study with urinary values of 29 µmol histidine/mmol creatinine preoperative and 9609 µmol histidine/mmol creatinine postoperative (Figure 1). Despite the minor contribution of histidine decarboxylation yielding histamine under physiologic conditions, and the low renal histamine clearance rate of only 1%-3% (Beall 1967, Beaven 1982, Bruce *et al.* 1976, Kaliner *et al.* 1982, Skoner *et al.* 2001), urinary histamine concentration increased almost by the factor of nine in the present study and exceeded the

physiological level of 3 ng/ml – 30 ng/ml (Figure 2) (Bruce *et al.* 1976, Myers *et al.* 1981). In the further postoperative course, it steadily decreased. Also, the obtained N-methylimidazole acetic acid values 8h and 32h postoperative were significantly elevated compared to baseline conditions and were therefore above the reference interval of 0.6 mg/g creatinine – 3.4 mg/g creatinine (Figure 3) (Tsuruta *et al.* 1987). These results indicate an increased plasma histidine concentration and consecutive metabolism to histamine after Bretschneider cardioplegia administration for the first approximately two postoperative days.

The systemic effects of histamine are variable depending on the species, dose, route of administration, anatomic location, and tone of the vessel (Levi *et al.* 1991). Histamine causes constriction of cardiac and pulmonary arteries and dilation of capillaries in peripheral organs with loss of peripheral resistance and consecutively blood pressure suppression (Akar *et al.* 1984, Beaven 1976, Levi *et al.* 1991). In the microcirculatory system, histamine increases vascular permeability mediated by histamine receptors 1 and 2 (Levi *et al.* 1982, Maintz and Novak 2007).

After initiation of cardiac arrest by antegrade administration of cold Bretschneider solution, MAP decreased, although norepinephrine and phenylephrine infusion rates were increased significantly (Figure 4, Table 1). Although the decrease in MAP and the concomitant increased need for vasoconstrictive drugs was obviously correlated to cardioplegia administration and is a known phenomenon, it could have also been caused by CPB initiation earlier. In addition, endogenous histamine might have been released from either mast cells or basophils in the context of anesthesia, surgical trauma, and blood transfusions as was already demonstrated in the past (Doenicke *et al.* 1973, Roher *et al.* 1982), leading to elevated systemic plasma histamine levels. The use of extracorporeal circulation with its exogenous surfaces, to which the blood is exposed, leads to activation of the contact, extrinsic and intrinsic coagulation, as well as the complement system (Downing and Edmunds 1992,

Misoph and Babin-Ebell 1997, Omar *et al.* 2015). Together with myocardial ischemia during the operation as well as the release of natriuretic peptides, these are all triggers for endogenous histamine liberation (Downing and Edmunds 1992, Lorenz *et al.* 1991, Shahid *et al.* 2010).

The contribution of these factors and consequently the respective share of endogenous (i.e. stored) and exogenous (resulting from histidine degradation) histamine cannot be differentiated in quantitative terms. Due to the prolonged renal excretion of histamine (Figure 2) and its major urinary metabolite N-methylimidazole acetic acid (Figure 3) in the postoperative course, it must be concluded that the body was indeed confronted with a certain amount of histamine. To quantify the exact amount of histamine arising from histidine metabolism in the current setting, labeling of the histidine, most probably radioactively, would be necessary. Since this would be unethical, the obtained parameters should be compared to those from patients receiving other cardioplegia solutions without histidine instead. The corresponding trial will also serve the purpose to validate the present data by increasing patient numbers.

In conclusion, patients having received Bretschneider solution for induction of cardiac arrest displayed elevated levels of histidine, histamine as well as its major urinary metabolite N-methylimidazole acetic acid in urine. Systemic cardiovascular effects potentially caused or intensified by histamine could have been managed by phenylephrine and noradrenaline doses. Due to the histidine's advantages as regards its buffer capacity thereby diminishing myocardial acidosis during the ischemic period (i.e. cross-clamping), one might chemically modify histidine while retaining its buffer capacity to aggravate its incorporation into cells. This way, its potential metabolization resulting in histamine formation could be reduced.

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This manuscript is dedicated to Dr. Dr. Herbert de Groot who passed away suddenly and unexpectedly on May 10 2016.

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Table

Table 1: Mean values of all patients as regards arterial blood pressure, phenylephrine, and noradrenaline before (-10 to -1 minutes) and after (0 to 10 minutes) cardioplegia administration

	Mean before cardioplegia administration (-10 to -1 minutes)	**Mean after cardioplegia administration (0 to 10 minutes)**	**p-value**
Mean arterial blood pressure (mmHg)	60 ± 1	55 ± 1	< 0.01
Phenylephrine (µg/kg/min)	0.150 ± 0.065	0.506 ± 0.085	< 0.01
Noradrenaline (µg/kg/min)	0.050 ± 0.002	0.069 ± 0.006	< 0.05

Figure legends

Figure 1 Urinary histidine excretion before and after the operation as well as in the postoperative course. * $p < 0.05$, **** $p < 0.0001$

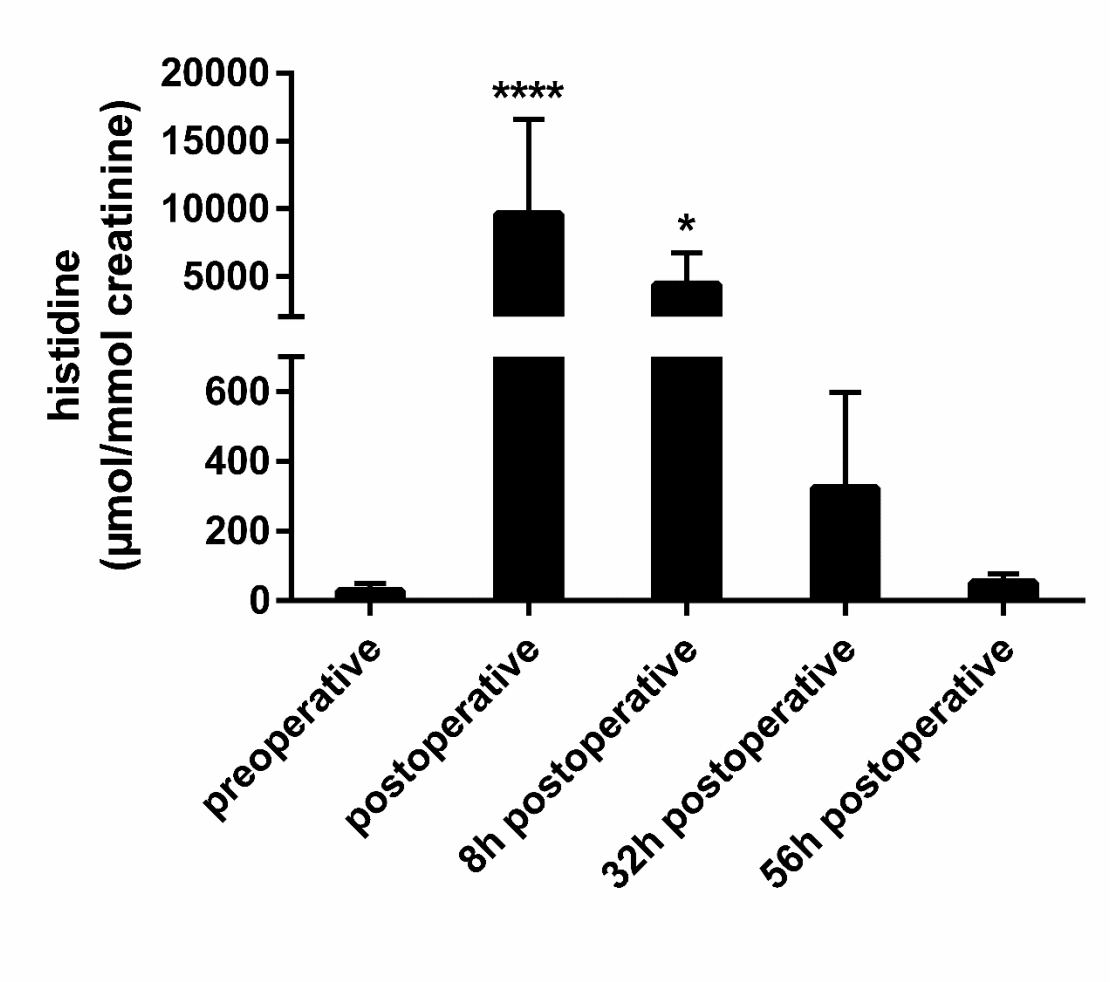
Figure 2 Urinary histamine excretion before and after the operation as well as in the postoperative course. ** $p < 0.01$, *** $p < 0.001$

Figure 3 Urinary N-methylimidazole acetic acid excretion before and after the operation as well as in the postoperative course. * $p < 0.05$, *** $p < 0.001$, **** $p < 0.0001$

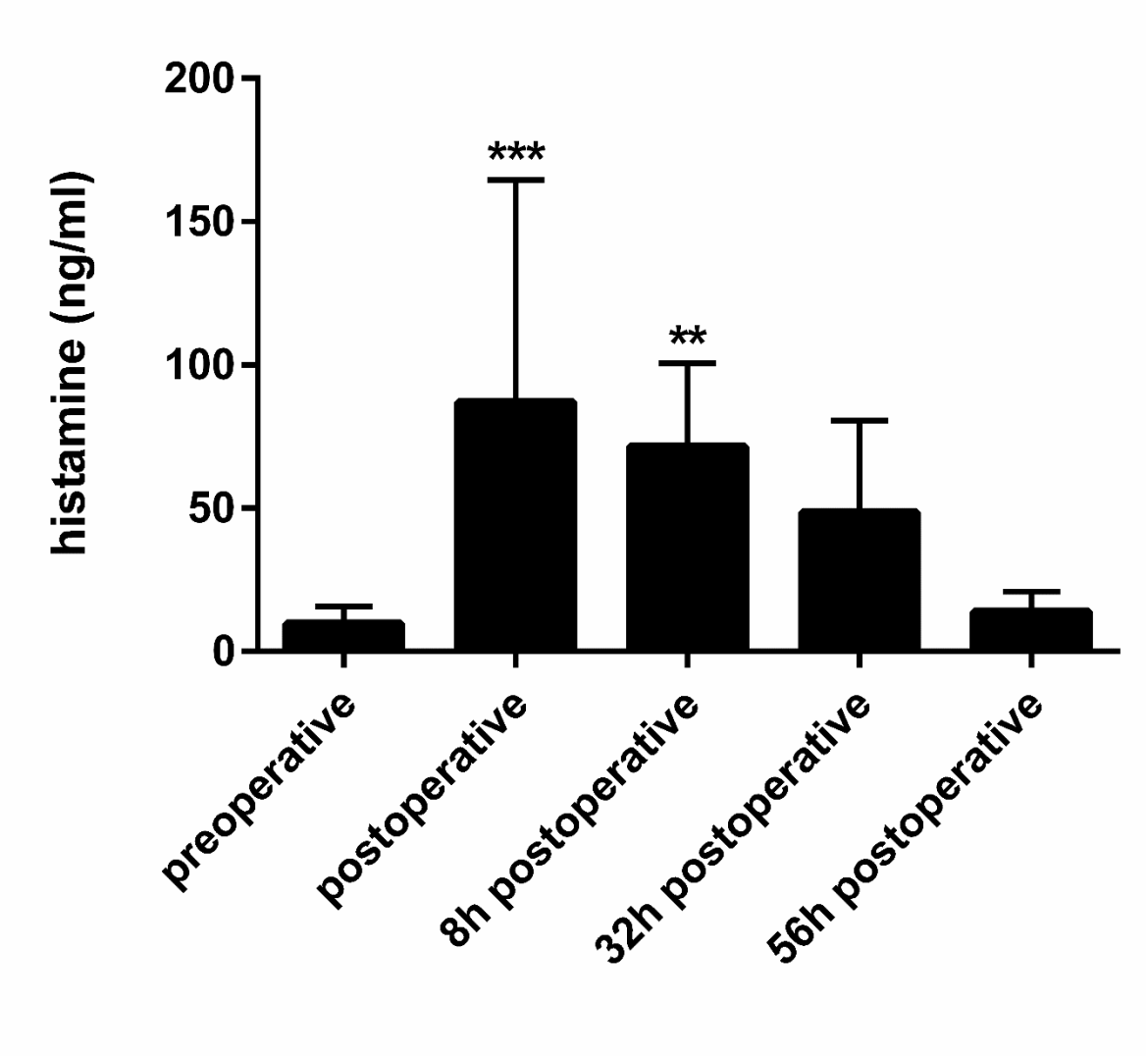
Figure 4 Amounts of phenylephrine and noradrenaline administered and their influence on mean arterial blood pressure (MAP) before and during the first minutes after start of cardioplegia administration.

Figures

Figure 1



1 Figure 2


200
150
100
50
0
histamine (ng/ml)
***
**
preoperative
postoperative
8h postoperative
32h postoperative
56h postoperative

2

3

Figure 3

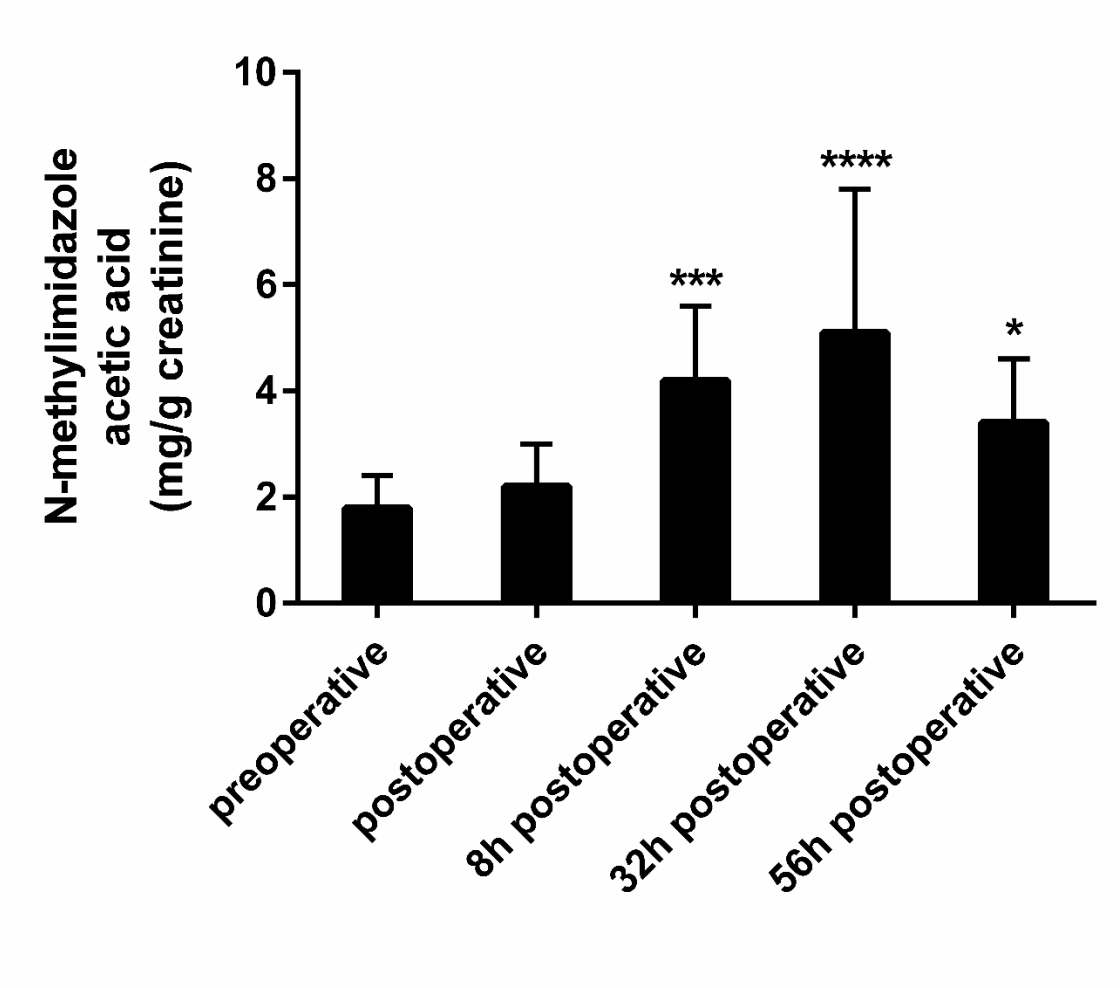
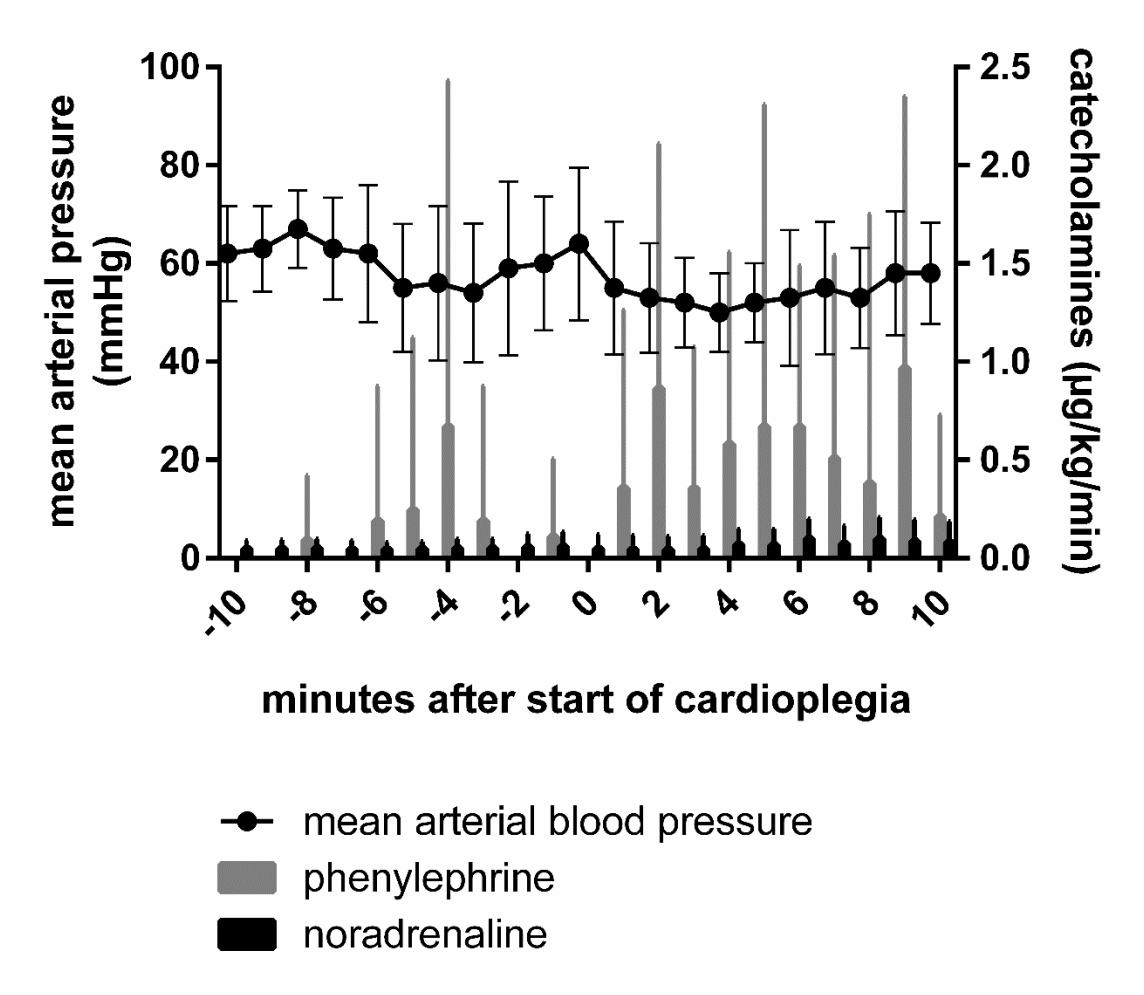

N-methylimidazole acetic acid (mg/g creatinine)
10
8
6
4
2
0
***
****
*
preoperative
postoperative
8h postoperative
32h postoperative
56h postoperative

Figure 4


mean arterial pressure (mmHg)
100
80
60
40
20
0
catecholamines (µg/kg/min)
2.5
2.0
1.5
1.0
0.5
0.0
-10
-8
-6
-4
-2
0
2
4
6
8
10
minutes after start of cardioplegia
mean arterial blood pressure
phenylephrine
noradrenaline