Original Paper

Evaluation of Nephroprotective Efficacy of Hypoxic Preconditioning in Patients Undergoing Coronary Artery Bypass Surgery

Zhaneta V. Vesnina^{a, c} Yury B. Lishmanov^{a, c} Ekaterina A. Alexandrova^b
Evgeniy A. Nesterov^c

^aLaboratory of Nuclear Medicine and ^bDepartment of Cardiovascular Surgery, Federal State Budgetary Scientific Institution 'Research Institute for Cardiology', and ^cNational Research Tomsk Polytechnic University, Tomsk, Russian Federation

Key Words

Hypoxic preconditioning · Coronary artery bypass grafting · Dynamic renal scintigraphy · Neutrophil gelatinase-associated lipocalin

Abstract

Background: Nonpulsatile blood flow plays an important role in the pathogenesis of renal dysfunction in patients with extracorporeal circulation. In our opinion, hypoxic preconditioning (HP) can be used to protect kidneys from postsurgical dysfunction. The aim of this study was to evaluate nephroprotective efficacy of HP in myocardial revascularization with extracorporeal circulation. **Methods:** The randomized, controlled trial was performed in 63 patients undergoing coronary artery bypass grafting (CABG). Thirty-three patients were subjected to HP during CABG; 30 patients were included in the comparison group. All patients underwent dynamic renal scintigraphy with ^{99m}Tc-diethylenetriaminepentaacetic acid and were subjected to measuring the concentration of lipocalin in blood serum before and after CABG. **Results:** After CABG, the mean values of the total glomerular filtration rate (GFR) and GFR for each kidney significantly decreased only in patients of the comparison group. Significant increases in the concentration of serum neutrophil gelatinase-associated lipocalin occurred 5 h after surgery both in the group with HP (70.65 ± 46.71 to 127.58 ± 98.46 ng/ml) and in the comparison group (65.01 ± 38.64 to 171.65 ± 89.91 ng/ml). At the same time, the mean difference values between pre- and postoperative lipocalin levels were 56.94 ± 51.75 ng/ml in the study group and 106.64 ± 51.27 ng/ml in the comparison group; these differences were highly statistically significant ($p = 0.004$). **Conclusion:** The results of our study showed that (i) HP exerts nephroprotection in patients undergoing on-pump CABG, and (ii) determination of the lipocalin-2 level can be used for early diagnosis of acute kidney injury in cardiac surgery patients.

© 2016 S. Karger AG, Basel

Dr. Zhaneta Vesnina, PhD
Laboratory of Nuclear Medicine
Federal State Budgetary Scientific Institution 'Research Institute for Cardiology'
Kievskaya Street, 111a, RU–634012, Tomsk (Russian Federation)
E-Mail zhvesnina@mail.ru

Introduction

Acute renal injury (AKI) is a common complication of cardiac surgery [1–5]. According to the available literature [2], renal failure occurs in 7.7% of the patients after coronary artery bypass surgery with extracorporeal circulation; 1.4% of the patients receive dialysis. In-hospital mortality and the duration of hospitalization are significantly higher in patients with renal failure than in other patients [2]. Evidence suggests that surgical trauma can trigger systemic inflammatory response, characterized by an increase in circulating cytokines, microvascular damage, and severe immune dysfunction [3]. Systemic inflammatory response can lead to acute renal failure in cardiac surgery patients [4]. Moreover, nonpulsatile blood flow plays an important role in the pathogenesis of renal dysfunction in patients with extracorporeal circulation. It causes increased levels of circulating catecholamines and inflammatory mediators, release of free hemoglobin from the damaged erythrocytes [2] as well as macro- and microembolism of the kidneys, leading to renal vasoconstriction, ischemic damage of renal parenchyma, and corresponding decreases in the renal blood flow and the glomerular filtration rate (GFR) by 25–75% [5]. Therefore, the search for new, highly efficacious methods for the prevention of renal dysfunction in patients undergoing cardiac surgery is an important task of present-day cardiology. In our opinion, hypoxic preconditioning (HP) can be used to protect kidneys from ischemic injury and postsurgical dysfunction in surgical interventions on the heart.

The phenomenon of HP consists in an increased tolerance of the organs and tissues to long-term hypoxia (ischemia) due to one or several preceding sessions of hypoxia and reoxygenation [6]. The term ‘hypoxic preconditioning’ was coined in 1992 by the research group of Prof. H.F. Downey from Texas [7]. Even the earliest works dedicated to this problem demonstrated that HP contributes to an increase in cardiac tolerance to ischemia and reperfusion [7]. Besides, data showed that ischemic and HP increases resistance of the kidneys to ischemic injury, reducing the degree of functional and structural renal abnormalities caused by ischemia/reperfusion [8, 9]. In the available literature, there is a lack of publications regarding the renoprotective efficacy of HP in human subjects.

As known, diagnostic criteria of acute renal dysfunction are based on the values of serum creatinine concentrations and the amount of excreted urine. However, these parameters do not enable early detection of AKI [10]. Some authors believe that the most promising markers for early diagnosis of AKI are those that are associated not only with abnormal renal filtration function and injury of kidney parenchyma but also with cellular proliferation, apoptosis, abnormal immune response, and inflammation [11, 12]. One of these markers is neutrophil gelatinase-associated lipocalin (NGAL), a protein associated with gelatinase in the neutrophils. In the presence of ischemic and toxic injury of the kidneys, the expression of NGAL is increased multifold in the cells of tubular epithelium; NGAL concentrations in blood plasma and excretion with urine increase 24–48 h before the rise in the creatinine level [13]. Increases in the NGAL concentration in blood and urine are found as soon as 2–6 h after cardiac surgeries and indicate the early stage of postoperative AKI with a sensitivity of 90% [14]. Having said this, the levels of NGAL in blood plasma and urine have a similar diagnostic and prognostic significance for AKI [15].

Unlike other diagnostic methods such as laboratory tests, radiopaque contrast-enhanced urography, and ultrasound study, radioisotope renal scintigraphy detects abnormalities in the renal function at early stages of the disease. It is a physiological, easily reproducible, and minimally invasive diagnostic method [16]. However, the available literature does not present data regarding the use of scintigraphic methods for studying the efficacy of various nephroprotective approaches in cardiac surgery.

The present study was designed to evaluate the nephroprotective efficacy of HP in myocardial revascularization with extracorporeal circulation.

Table 1. Clinical and intraoperative data of the patients enrolled in the study

Variables	Study group	Comparison group	p
Male, n	33	30	
Age, years	56.24±6.71	58.16±7.89	NS
NYHA class, n			
I	3	2	
II	23	22	
III	7	6	
AMI in anamnesis	29 (88)	27 (90)	
Coronary arteries with stenosis >50%	3.05±0.94	3.05±1.22	NS
LVEF	45.95±11.84	43.79±14.91	NS
ACEi/ARB treatment	33 (100)	30 (100)	
Cardiopulmonary bypass time, min	132.11±51.99	140.11±45.42	NS
Cross-clamp time, min	84.45±42.95	95.26±35.79	NS
Intraoperative perfusion pressure, mm Hg	71.96±8.75	71.33±7.04	NS
Grafts per patient	2.90±1.02	2.74±1.15	NS
LV plasty	7 (21.2)	9 (30)	
IABP use	1 (3)	1 (3.3)	
Use of LITA graft	31 (94)	27 (90)	
Use of RITA graft	2 (6)	2 (6.7)	

Data are presented as mean ± standard deviation or n (%), unless otherwise indicated. NS = Nonsignificant; study group: patients with HP; comparison group: patients without HP. p = Significance of differences between groups; AMI = acute myocardial infarction; LVEF = left ventricular ejection fraction; IABP = intra-aortic balloon pump; LITA = left internal thoracic artery; RITA = right internal thoracic artery.

Material and Methods

Patient Selection

A total of 63 patients (all male, mean age 57.62 ± 7.50 years) who had first-time coronary artery bypass grafting (CABG) were enrolled in the study. Patients were randomized into two groups: the study group included patients who received HP during CABG (n = 33), and the comparison group comprised patients without nephroprotection (n = 30). The clinical profiles of the matched patients were comparable and are described in table 1. All consecutive patients were examined after informed consent had been obtained. All patients underwent dynamic renal scintigraphy with ^{99m}Tc-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) before and 6–7 days after CABG and were subjected to measuring the concentration of lipocalin in blood serum prior to CABG and 5 h after the beginning of the operation.

Clinical Data

Collected data included: gender, age, New York Heart Association (NYHA) class, prior myocardial infarction, angiotensin-converting enzyme inhibitor (ACEi)/angiotensin II receptor blocker (ARB) treatment, and the number of damaged coronary arteries. The factors recorded intraoperatively included: duration of cardiopulmonary bypass, cross-clamp time, perfusion pressure, number of grafts, surgical left ventricular (LV) plasty, placement of a balloon pump, and the use of left or right internal thoracic artery grafts (table 1). The patients of both groups preoperatively received a background therapy with ACEi/ARBs to achieve target values of blood pressure (table 1). No clinically significant episodes of perioperative hypotension were documented in the study; blood pressure changes were comparable in both groups in the perioperative period and during cardiopulmonary bypass perfusion (table 1).

Renal Function Evaluation

Dynamic renal scintigraphy with ^{99m}Tc-DTPA was performed in a sitting position of the patients whose back faced a detector of the gamma-camera so that the heart and the kidneys were within the field of view. The radiopharmaceutical was introduced intravenously at a dose of 30–40 mBq (0.8–1.0 mCi) and a volume

of 1.0–1.5 ml. To calculate GFR, syringe activity was recorded before and after the infusion of the radiopharmaceutical. Results of dynamic renal scintigraphy consisted in a series of scintigrams with the renal images taken at different time intervals. Based on native scintigraphic images, the areas of interest were selected for both kidneys, the heart, and the background; the ‘activity-time’ curves were created.

The following parameters were calculated in the course of the study: total GFR (ml/min) and GFRs for each kidney; blood clearance (min) as half-time of radiopharmaceutical excretion from blood; half-time of radiotracer drainage from renal collecting system (min; separately for the left and right kidneys); half-time of radiotracer drainage from renal parenchyma (separately for the left and right kidneys), and cortical retention index for the radiopharmaceutical (separately for the left and right kidneys).

All scintigraphic studies were performed with gamma camera Philips Forte (Philips Medical Systems, Best, The Netherlands). The low energy collimators were used for data collection. Images were recorded in 64×64 and 128×128 pixel matrices on the special-purpose computer. The differential discriminator window was set to $140 \text{ keV} \pm 10\%$ photopeak for the studies with ^{99m}Tc . Processing of the acquired scintigrams was performed using JetStream® Workspace Release 3.0 software package (Philips Medical Systems).

The Method of HP

HP was performed as follows: after the beginning of the cardiopulmonary bypass and cessation of artificial ventilation of the lungs, before the placement of aortic clamp, a 10-min hypoxemia session was delivered by introducing a low-oxygen gaseous mix (21–22% of O_2) into the oxygenator with a subsequent 5-min period of reoxygenation before global ischemia. This gaseous mix provided a decrease in PaO_2 to 30–35 mm Hg and SaO_2 to 55–65%. This procedure increased the resistance of the vital organs to ischemic and reperfusion stress and, therefore, decreased the number and severity of postoperative complications [6].

Laboratory Methods

Serum NGAL (s-NGAL) was tested by the Human Lipocalin-2/NGAL ELISA kit (ELISA; BioVendor Laboratory Medicine, Inc., Brno, Czech Republic). The principle of the technique was based on quantitative solid phase immunoenzyme sandwich analysis. The Cockcroft-Gault equation [17] was used to calculate pre- and postoperative creatinine clearance.

Statistical Analysis

Statistical analysis was performed with STATISTICA software (version 8.0.360.0., StatSoft Inc., Tulsa, Okla., USA). Categorical patient demographics and characteristics were expressed as numbers and percentages. Data are presented as mean $\pm$ standard deviation. Statistical comparison of quantitative data was performed by the unpaired Mann-Whitney U test. To evaluate the significance of differences between dependent samples, the nonparametric Wilcoxon rank sum test was used. To detect the presence of correlation relationships between data, the Spearman rank correlation coefficient was used. For all statistical evaluations, differences in data with p values <0.05 were considered statistically significant.

Results

Before surgery, initial abnormalities in the renal function were absent in 13 patients, including 4 (12%) and 9 (30%) patients from the study and comparison groups, respectively. A reduction of varying degree in GFR in one or two kidneys was found in 18 (54.5%) of the patients of the study group and in 21 patients (70%) of the comparison group. Only 7 individuals (4 and 3 patients in the study and comparison groups, respectively) had chronic diseases of the kidneys in the past medical history.

In our study, the mean value of lipocalin-2 in all patients before surgical treatment was $67.76 \pm 6.8 \text{ ng/ml}$, which exceeded the corresponding mean value in individuals without cardiovascular diseases [18]. Moreover, we observed a reverse correlation relationship between the levels of s-NGAL and the LV ejection fraction ($R = -0.37$, $p = 0.02$). Statistical analysis also allowed to detect the presence of the inverse relationship between GFR and lipocalin levels in the study patients in the preoperative period ($R = -0.28$, $p = 0.046$).

Table 2. Scintigraphic parameters of renal functional activity in patients with coronary artery disease before and after CABG

Parameters	Study group			Comparison group		
	before CABG	after CABG	p	before CABG	after CABG	p
Total GFR, ml/min	104.13±5.91	102.26±6.41		105.45±11.75	97.27±13.11	0.001
Blood clearance, min	16.88±2.32	18.90±3.12		18.30±3.17	22.34±3.27	0.001
GFR left, ml/min	45.77±7.26	46.09±6.56		48.28±7.01	45.15±8.68	0.004
GFR right, ml/min	58.42±5.94	56.18±7.03	0.015	57.01±6.83	52.12±7.71	0.001
T _{1/2} left, min	16.84±5.73	20.96±13.66		12.81±3.74	17.08±5.98	0.001
T _{1/2} right, min	15.89±3.76	18.56±10.02		12.70±7.22	16.50±8.92	
T _{1/2} left parenchyma, min	22.66±3.39	24.45±3.76		19.46±4.23	23.39±8.17	0.02
T _{1/2} right parenchyma, min	21.01±6.20	20.95±4.50		16.95±4.92	22.07±8.91	0.001
CRI left	40.33±7.28	38.40±6.39		44.39±5.71	38.20±9.75	0.002
CRI right	45.26±9.27	42.72±7.24		47.89±7.28	39.84±9.60	0.001

Data are presented as mean ± standard deviation. Study group: patients with HP; comparison group: patients without HP. T_{1/2} = Half-time of indicator drainage from the renal collecting system and parenchyma; CRI = cortical retention index; p = significance of differences compared with preoperative value.

Table 2 shows that statistically significant changes in the values of functional activity of the kidneys after CABG were observed only in patients of the comparison group except for the half-time value of the right kidney. Indeed, there was a significant reduction in the mean values of total GFR and GFR for each kidney as well as statistically significant increases in the blood clearance and the half-life periods of the indicator for the renal collecting system of the left kidney and for the parenchyma of both kidneys. Pronounced renal dysfunction (decrease in the total GFR by ≥15% compared with the initial level) due to nonpulsatile blood flow occurred in 35% of the patients in the comparison group; an insignificant decrease in the filtration activity was found in 5 patients (16.7%). The obtained data accord with the results of several studies investigating the effects of artificial circulation on the renal function [5, 19].

Besides, half-time of the drainage of the radiopharmaceutical from the renal parenchyma and cortical delay index on both sides significantly changed in the comparison group (table 2). Moreover, adverse changes in the parenchyma half-time and the cortical delay index were observed in 16 (53.3%) and 18 (60%) patients of the comparison group, respectively. Taking into account that these parameters characterize the processes that occur at a level higher than that of the renal collecting system and excretion activity in the nephron, the abnormalities in these parameters can be considered as a sign of reduction in the renal blood flow and disturbance of the renal microcirculation causing functional abnormalities in the renal parenchyma.

In patients of this group, we observed increases in the mean value of half-life periods for the renal collecting system on both sides (insignificant on the right) (table 2). In the postoperative period, abnormal kidney evacuator function was found in 13 patients of the comparison group (43%) where, in the majority of cases (10 patients), the postoperative values of the indicator half-life exceeded the upper limit of normal by 9.2 min on average.

Table 3 demonstrates that significant increases in the concentration of s-NGAL occurred 5 h after surgery both in the group with HP and in the comparison group relative to the preoperative value (from 70.65 ± 46.71 to 127.58 ± 98.46 ng/ml and from 65.01 ± 38.64 to 171.65 ± 89.91 ng/ml, respectively). Statistical analysis revealed direct correlation between the duration of artificial circulation and the changes in the levels of s-NGAL in cardiac surgery patients of both groups (R = 0.39 and R = 0.37, p = 0.02 and p = 0.03, for the study and comparison groups, respectively).

Table 3. The parameters of functional activity of the kidneys and the levels of lipocalin in patients with coronary artery disease before and after CABG

Parameters	Before CABG		After CABG	
	study group	comparison group	study group	comparison group
Clearance of creatinine, ml/min	104.24±34.39	100.79±32.76	93.29±31.67**	83.37±37.95**
GFR, ml/min	104.13±5.91	105.45±11.45	102.26±6.41	97.27±13.11 ^{#,*}
Lipocalin, ng/ml	70.65±46.71	65.01±38.64	127.58±98.46*	171.65±89.91 ^{#,*}

Data are presented as mean ± standard deviation. Study group: patients with HP; comparison group: patients without HP.

[#] Significant differences between the groups ($p < 0.05$); * and ** significant differences compared with the preoperative values ($p < 0.01$ and $p < 0.05$, respectively).

Fig. 1. Increase in the blood serum concentration of s-NGAL in patients undergoing cardiac surgery.

At the same time, it is worthy to note that an increase in the blood serum concentration of s-NGAL was significantly more pronounced in the comparison group than in the study group (171.65 ± 89.91 ng/ml vs. 127.58 ± 98.46 ng/ml, $p = 0.02$) (fig. 1). The mean difference values between pre- and postoperative lipocalin levels were 56.94 ± 51.75 ng/ml in the study group and 106.64 ± 51.27 ng/ml in the comparison group; these differences were highly statistically significant ($p = 0.004$). Table 3 shows that creatinine clearance also significantly decreased in both groups (the decrease was more pronounced in the comparison group). However, no significant intergroup differences were present in the postoperative values ($p = 0.26$).

Discussion

Several works aimed at studying the diagnostic and prognostic roles of NGAL as a marker of renal dysfunction and demonstrated that lipocalin levels significantly correlate with serum creatinine, creatinine clearance, and GFR calculated using The Modification of Diet in Renal Disease (MDRD) Study equation, particularly in patients with chronic renal diseases, in

patients before and after coronary angiography, and in children who underwent on-pump cardiac surgery [14, 20]. However, in our study, we did not find such a relationship. It may be due to the fact that the plasma NGAL levels are associated not only with the morphologic and functional states of renal tubules but also with other functions of this protein. In particular, NGAL is involved in the recovery of damaged epithelium as a protein of the acute phase of inflammation as well as in remodeling of atherosclerotic plaques and myocytes in the presence of myocardial damage [12]. In all these cases, the plasma NGAL level increases. On the other hand, blood concentration of creatinine is affected by age, gender, muscle mass, circulating blood volume, the presence of creatinine metabolism abnormalities, and many other factors [21].

Abnormal glomerular filtration and the increased lipocalin-2 level in the preoperative period indicate the development of cardiorenal syndrome caused by chronic heart failure [22]. Indeed, it was known that the renal functional reserve can decrease at early stages of heart failure (NYHA I) even in the cases of clinically asymptomatic LV dysfunction [23]. There is also evidence that the levels of s-NGAL are associated with cardiovascular diseases. Indeed, Choi et al. [18] demonstrated that mean s-NGAL levels were 82.6 ± 38.7 ng/ml in patients with angiographically confirmed coronary artery stenosis versus 43.8 ± 27.8 ng/ml in the control group. The authors believe that changes in the s-NGAL level can be useful for the evaluation of cardiovascular disease risk because they are independently associated not only with coronary atherosclerosis but also with insulin resistance and systolic blood pressure.

The observed increase in the s-NGAL level in cardiac patients during the first hours after surgery agrees with data of other researchers. Mishra et al. [14] observed an elevation of the lipocalin level in blood plasma 2 h after the beginning of cardiopulmonary bypass surgery in children independently of whether they developed acute kidney injury afterwards. In addition, in patients without signs of abnormal kidney function, an increase in the lipocalin level was also significant relative to the preoperative values, though it manifested in a considerably smaller degree than in patients in whom acute kidney injury was diagnosed later. The authors also found a correlation between the duration of surgery and changes in the NGAL level [14].

In the context of extracorporeal circulation, nonpulsatile blood flow triggers a cascade of proinflammatory reactions increasing the levels of circulating catecholamines and mediators of inflammation and acute-phase response including lipocalin [4, 12]. There is evidence that the early rise in the level of NGAL in blood plasma 2–6 h after cardiac surgery is caused by the lipocalin release into the circulation due to the inflammatory neutrophil activation triggered by surgery [14]. The other adverse side effect of extracorporeal circulation consists in the renal macro- and microembolism leading to renal vasoconstriction and ischemic injury of renal parenchyma, which, in turn, leads to the expression of lipocalin as a marker of acute kidney injury [4, 14, 20]. Data at the molecular level demonstrated that the presence of injured renal tubular epithelium quickly activates NF- κ B, which stimulates the transcription of the NGAL gene [24] and elevates its plasma level due to the augmented synthesis in the liver, lungs, neutrophils, macrophages, and the cells of the immune system [14].

Several regimes and approaches for ischemic preconditioning have been developed for patients undergoing open heart surgery: for example, two cycles of 2-minute ischemia following 3-minute reperfusion before cross-clamping the ascending aorta, the procedure being repeated once [25].

In our work, we used an alternative approach to HP to protect vital organs of patients undergoing on-pump cardiac surgery. In our opinion, our approach avoids the main disadvantage of the classic method, namely the necessity of repeated aortic compressions increasing the risk of trauma of the atherosclerotically damaged aorta and triggering the release of atheromatous masses into the blood stream with subsequent embolism of various organs including the heart and the brain.

In summary: (i) HP exerts nephroprotection in patients undergoing on-pump CABG and (ii) the determination of lipocalin-2 level can be used for early diagnosis of acute kidney injury as well as for the evaluation of the efficacy of various approaches to nephroprotection in cardiac surgery patients.

Study Limitations

The main limitation of this study was the relatively small size of the study population. We do not have data on the long-term observation of these patients. It might be reasonable to evaluate study parameters after 0.5 and 1 year of follow-up.

Acknowledgment

This work was supported by a grant from the Russian Science Foundation (No. 14-15-00178).

Statement of Ethics

The study protocol complied with the Declaration of Helsinki and was approved by the Ethics and Research Committee of the Federal State Budgetary Scientific Institution ‘Research Institute for Cardiology’. All patients gave their informed written consent.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

References

- Gaffney AM, Sladen RN: Acute kidney injury in cardiac surgery. *Curr Opin Anaesthesiol* 2015;28:50–59.
- Mangano CM, Diamondstone LS, Ramsay JG, Aggarwal A, Herskowitz A, Mangano DT: Renal dysfunction after myocardial revascularization: risk factors, adverse outcomes, and hospital resource utilization. *Ann Intern Med* 1998;128:194–203.
- Ni Choileain N, Redmond HP: Cell response to surgery. *Arch Surg* 2006;141:1132–1140.
- Abu-Omar Y, Ratnaunga C: Cardiopulmonary bypass and renal injury. *Perfusion* 2006;21:209–213.
- Mazzarella V, Gallucci MT, Tozzo C, Elli M, Chiavarelli R, Marino B, et al: Renal function in patients undergoing cardiopulmonary bypass operations. *J Thorac Cardiovasc Surg* 1992;104:1625–1627.
- Maslov LN, Lishmanov IuB, Kolar F, Portnichenko AG, Podoksenov IuK, Khaliulin IG, et al: Hypoxic preconditioning is a phenomenon increasing tolerance of cardiomyocytes to hypoxia-reoxygenation (in Russian). *Neurosci Behav Physiol* 2012;42:380–391.
- Shizukuda Y, Mallet RT, Lee SC, Downey HF: Hypoxic preconditioning of ischaemic canine myocardium. *Cardiovasc Res* 1992;26:534–542.
- Timsit MO, Gadet R, Ben Abdennebi H, Coudas R, Petruzzio P, Badet L: Renal ischemic preconditioning improves recovery of kidney function and decreases alpha-smooth muscle actin expression in a rat model. *J Urol* 2008;180:388–391.
- Toosy N, McMorris ELJ, Grace PA, Mathie RT: Ischaemic preconditioning protects the rat kidney from reperfusion injury. *BJU International* 1999;84:489–494.
- Bellomo R, Kellum J, Ronco C: Acute renal failure: time for consensus. *Intensive Care Med* 2001;27:1685–1688.
- Tong Z, Wu X, Ovcharenko D, Zhu J, Chen CS, Kehr JP: Neutrophil gelatinase-associated lipocalin as a survival factor. *Biochem J* 2002;391:441–448.
- Schmidt-Ott KM, Mori K, Li JY, Kalandadze A, Cohen DJ, Devarajan P, Barasch J, et al: Dual action of neutrophil gelatinase-associated lipocalin. *J Am Soc Nephrol* 2007;18:407–413.
- Mori K, Lee HT, Rapoport D, Drexler IR, Foster K, Yang J, et al: Endocytic delivery of lipocalin-siderophore-iron complex rescues the kidney from ischemia-reperfusion injury. *J Clin Invest* 2005;115:610–621.
- Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, et al: Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. *Lancet* 2005;365:1231–1238.

- 15 Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A: Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis* 2009;54:1012–1024.
- 16 Britton KE, Maisey MN: Renal disease; in Maisey MN, Britton KE, Collier BD (eds): *Clinical Nuclear Medicine*. London, Chapman & Hall Medical, 1998, pp 389–424.
- 17 Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31–41.
- 18 Choi KM, Lee JS, Kim EJ, Baik SH, Seo HS, Choi DS, et al: Implication of lipocalin-2 and visfatin levels in patients with coronary heart disease. *Eur J Endocrinol* 2008;158:203–207.
- 19 Mangos GJ, Brown MA, Chan WY, Horton D, Trew P, Whitworth JA: Acute renal failure following cardiac surgery: incidence, outcomes and risk factors. *Aust N Z J Med* 1995;25:284–289.
- 20 Dent CL, Ma Q, Dastrala S, Bennett M, Mitsnefes MM, Barasch J, et al: Plasma neutrophil gelatinase-associated lipocalin predicts acute kidney injury, morbidity and mortality after pediatric cardiac surgery: a prospective uncontrolled cohort study. *Crit Care* 2007;11:R127.
- 21 Branten AJW, Vervoort G, Wetzels JWM: Serum creatinine is a poor marker of GFR in nephrotic syndrome. *Nephrol Dial Transplant* 2005;20:707–711.
- 22 McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW: Renal insufficiency and heart failure. *Circulation* 2004;109:1004–1009.
- 23 Magri P, Rao MAE, Cangianiello S, Bellizzi V, Russo R, Mele AF, et al: Early impairment of renal hemodynamic reserve in patients with asymptomatic heart failure is restored by angiotensin II antagonism. *Circulation* 1998;98:2849–2854.
- 24 Meldrum KK, Hilw K, Meldrum DR, Crone JA, Gearhart JP, Burnett AL: Simulated ischemia induced renal tubular cell apoptosis through a nuclear factor- κ B dependent mechanism. *J Urol* 2002;168:248–252.
- 25 Wu ZK, Tarkka MR, Pehkonen E, Kaukinen L, Honkonen EL, Kaukinen S: Ischaemic preconditioning has a beneficial effect on left ventricular haemodynamic function after a coronary artery bypass grafting operation. *Scand Cardiovasc J* 2000;34:247–253.