

# Renal resistive index by transesophageal and transparietal echo-doppler imaging for the prediction of acute kidney injury in patients undergoing major heart surgery

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## Abstract

**Background** Acute kidney injury (AKI) following major heart surgery (MHS) is associated with early decrease in renal blood flow and worsened prognosis. Doppler-derived renal resistive index (RRI), which reflects renal vascular resistance, may predict the development of AKI in patients undergoing MHS.

**Methods** We studied 60 consecutive patients (mean age 69.5 years, range 30–88, 41 males) undergoing MHS. We measured RRI, both at the renal sinus and intraparenchymally, by transesophageal echo-Doppler ultrasound (TE-ED<sub>us</sub>) at anesthesia induction and at the end of surgery in all patients. Additionally, we measured RRI by external transparietal echo-Doppler ultrasound (TP-ED<sub>us</sub>) at the following time points: anesthesia induction, end of surgery, 4 and 24 h from cardiopulmonary bypass (CPB) start. We also measured serum neutrophil gelatinase associated lipocalin (NGAL) at the same time points.

**Results** AKI [serum creatinine (sCr) increase  $\geq 0.3$  mg/dl vs. baseline within 72 h] developed in 23/60 (38.3 %) patients, with two requiring dialysis. Systemic hemodynamic parameters were similar in the patients who developed AKI (AKI+) and in those who did not (AKI–). Intraparenchymal RRI at end-surgery was significantly higher in AKI+ compared to AKI– patients, both at TE-ED<sub>us</sub> and TP-ED<sub>us</sub> (TE-ED<sub>us</sub> mean difference,  $p = 0.004$ ; TP-ED<sub>us</sub> mean difference,  $p = 0.013$ ; difference between TE-ED<sub>us</sub> and TP-ED<sub>us</sub> results,  $p = 0.066$ ), although the predictive performance was limited with both methods (area under the curve [AUC] of the receiver-operator characteristics: 0.71 and 0.70 for TE-ED<sub>us</sub> and TP-ED<sub>us</sub>, respectively). Serum NGAL values were higher in AKI+ than in AKI– patients (anesthesia induction,  $p = 0.037$ ; end-surgery,  $p = 0.007$ ; 4 h from CPB start,  $p = 0.093$ ; 24 h from CPB start,  $p = 0.024$ ). However, combining RRI with serum NGAL at end-surgery did not provide a clear-cut advantage in predicting AKI.

**Conclusions** In patients undergoing MHS, increased echo-Doppler ultrasound-derived RRI at end-surgery is significantly associated with the risk of AKI, but has limited practical utility for identifying the patients who will develop AKI.

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**Keywords** Acute kidney injury · Resistance, vascular · Echocardiography, transesophageal · Doppler ultrasound imaging · Heart surgery

## Introduction

Acute kidney injury (AKI) is a frequent postoperative complication in patients undergoing major heart surgery (MHS); its incidence varies according to the different definitions, but

reaches 30 %, with 1–5 % of the patients requiring renal replacement therapy (RRT) [1–15]. Mortality is 50–70 % in the latter group [1–14], yet even minor increases in serum creatinine (sCr) may impact negatively on outcomes [15–17].

Kidney hypoperfusion due to intrarenal vasoconstriction during cardiopulmonary bypass (CPB) and aortic cross clamping (ACC) plays a pivotal role in the development of AKI after MHS [18, 19]. Changes in intrarenal resistance can be tracked by renal Doppler ultrasonography [20, 21]. Intriguingly, two recent studies [22, 23] reported that the renal resistive index (RRI), obtained by transparietal echo-Doppler ultrasound (TP-ED<sub>us</sub>) soon after the end of surgery, predicted accurately the occurrence of AKI in the early postoperative period. However, technical limitations may be encountered with TP-ED<sub>us</sub> (e.g. poor kidney visualization due to improper patient positioning and/or interference with the surgical field). Conversely, the transesophageal echo-Doppler ultrasound (TE-ED<sub>us</sub>) technique offers a unique opportunity to obtain a good kidney visualization during the entire surgical time [24].

In the present study, in 60 patients undergoing MHS we tested whether RRI, as assessed with TE-ED<sub>us</sub> and TP-ED<sub>us</sub> at the end of surgery, as well as in the early postoperative period with the latter technique, could predict the subsequent occurrence of AKI.

## Methods

### Patients

This study was conducted at the Cardiac Surgery Unit of the University Hospital of Parma, Italy, where approximately 650 interventions are performed each year. We enrolled 60 consecutive patients undergoing MHS between June 1st and October 31st 2014 for coronary artery disease (CAD), valvular heart disease (VHD) or combined CAD and VHD. Exclusion criteria were previous esophageal surgery, esophageal diseases, atrial fibrillation, emergent cardiac surgery, end-stage renal disease requiring dialysis, known renal artery stenosis, and kidney malformations. AKI was defined as sCr increase  $\geq 0.3$  mg/dl within 72 h of surgery. Additionally, AKI stage 2 was defined as sCr increase 2.0–2.9 times the preoperative value, and AKI stage 3 as sCr increase  $\geq 3.0$  times the preoperative value or need for RRT.

All patients provided written informed consent. The study protocol was approved by the local Ethics Committee (Comitato Etico per Parma).

### Hemodynamic measurements

After anesthesia induction, a Swan-Ganz catheter, a transesophageal ultrasonography probe, a Foley catheter,

and temperature probes (esophageal and bladder) were inserted. During mechanical ventilation, partial pressure of arterial carbon dioxide (PaCO<sub>2</sub>) was kept between 4.7 and 5.3 kPa. Non-pulsatile CPB (Medtronic Century System, Medtronic, Sesto San Giovanni, Italy) was performed with constant flow rate at 2.4 l/min/m<sup>2</sup>, mean arterial pressure (MAP) at 50–70 mmHg and body temperature at 32–34 °C.

Cardiac output, mean pulmonary artery pressure, pulmonary wedge pressure, central venous pressure (Swan-Ganz catheter), systolic/diastolic and mean systemic arterial pressure (radial artery catheter) were measured at anesthesia induction, at the end of surgery, at 4 h and at 24 h from CPB start. Systemic vascular resistances and pulmonary vascular resistances were derived as  $80 \times (\text{mean systemic arterial pressure} - \text{central venous pressure}) / \text{cardiac output}$  and  $80 \times (\text{mean pulmonary artery pressure} - \text{pulmonary wedge pressure}) / \text{cardiac output}$ , respectively, at the same time points.

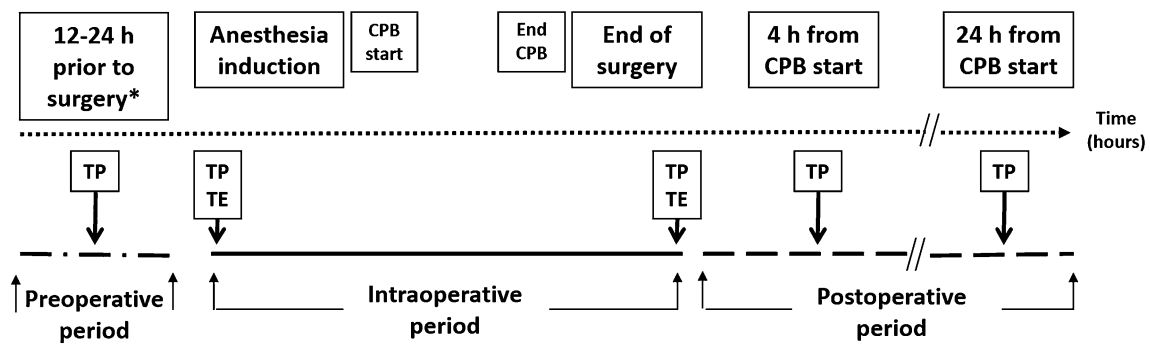
### Renal ultrasonography

The details of renal echo-Doppler examination through the transesophageal and the transparietal techniques are reported separately in the Online Resource. Briefly, RRI was assessed by TE-ED<sub>us</sub> at the level of the renal sinus (*renalsinus*-RRI) and at the level of the interlobar/arcuate arteries (*intrarenal*-RRI) at anesthesia induction and at the end of surgery. *Intrarenal*-RRI was also assessed by TP-ED<sub>us</sub> at anesthesia induction, at the end of surgery, at 4 h and at 24 h from CPB start. In a portion of the study population (n = 32) we were also able to assess baseline *intrarenal*-RRI by TP-ED<sub>us</sub> 12–24 h prior to surgery, depending on the scheduled time of patients' admission. The timing and modes of echo-Doppler ultrasound assessment of RRI are depicted in Fig. 1.

Since *intrarenal*-RRI values at TP-ED<sub>us</sub> did not differ significantly between the two kidneys at any time point (Table 1s in the Online Resource), they were pooled and averaged at each time point.

### Laboratory measurements

Routine laboratory measurements were performed by standard analytical methods. sCr values were measured on the surgery day in the morning, and at the time of the patient's arrival in the intensive care unit (ICU), then at 24 h after CPB start, and daily thereafter. Serum neutrophil gelatinase associated lipocalin (NGAL) was measured by a fluorescence immunoassay (Triage NGAL, Alere S.r.l., Scorzè, Italy) at anesthesia induction, at the end of surgery, at 4 h and at 24 h after CPB start.



$$\text{Renal resistive index} = \frac{\text{peak systolic velocity} - \text{end diastolic velocity}}{\text{peak systolic velocity}}$$

by pulsed Doppler interrogation of flow velocity at the level of interlobar or arcuate arteries (with the TP and TE approach) or at the level of the main renal artery trunk at renal sinus (with the TE approach)

**Fig. 1** Scheme of the timing and modes of echo-Doppler ultrasound assessment of renal resistive index. *TE* transesophageal echo-Doppler approach, *TP* transparietal echo-Doppler approach. *Asterisk* TP echo-

Doppler ultrasound assessment of intraparenchymal renal resistive index was also assessed 12–24 h prior to surgery in 32 patients, depending on the time of admission

**Statistical analysis**

Demographic, anthropometric, ultrasonography and laboratory data are reported as mean ± standard deviation (SD) or median (range), as appropriate. Two-sample differences in continuous variables were compared by the *t* test or the Mann–Whitney test, as appropriate, while differences in categorical variables were compared by the Pearson’s Chi-squared test. Within-subject changes in parameters were examined by the paired *t* test.

Multivariable logistic models were used to examine the relation between the ultrasonography indexes or their combination with serum NGAL and the incidence of AKI, whereas ordinary least square regression models were used to examine the relation of the ultrasonography indexes with serum NGAL (log-transformed) and MAP. The regression coefficients of the renal resistive indexes were expressed per 1 standard deviation unit. Forward-stepwise selection estimation (*p* < 0.05 for addition to the model) was used to identify independent predictors among the following variables: age, gender, diabetes, type of surgery, preoperative sCr, CPB time, ACC time, intraoperative fluid balance, and need for transfusions. The discriminatory ability of resistive indexes and serum NGAL in predicting the occurrence of AKI was evaluated by the area under the receiver

operating characteristic curve (AUC). A two-tailed *p* value of <0.05 was considered statistically significant.

We calculated that a sample of 60 patients would yield 90 % power to detect a 0.11 difference in intrarenal RRI (two-sided alpha 0.05) and 80 % power to detect a 0.20 difference in AUC for the discrimination between AKI+ and AKI– patients (one-sided alpha 0.025). Details of power and sample size calculation are provided in the Online Resource. All statistical analyses were performed with SPSS version 21 (SPSS, Chicago, IL, USA).

**Results**

**Patients**

Patients’ general characteristics are reported in Table 1 (left column). Sixty-seven percent had peripheral vascular disease; 48 % had left ventricular dysfunction, defined as ejection fraction <0.50, and 17 % had had an acute myocardial infarction in the 6 months preceding surgery. In line with this high vascular risk profile, one-third of the patients had underlying chronic kidney disease (CKD), defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m<sup>2</sup>. Although *intrarenal*-RRI values at

**Table 1** Baseline characteristics of study patients

	All patients	Patients w/o AKI (n = 37)	Patients with AKI (n = 23)	p
Age, years	69.5 (12.4)	69.2 (11.1)	70.0 (14.5)	0.80
Male sex, n (%)	41 (68.3)	26 (70.3)	15 (65.2)	0.68
BMI, kg/m <sup>2</sup>	26.0 (4.2)	25.7 (4.3)	26.5 (4.0)	0.44
Active smoker, n (%)	25 (41.7)	15 (40.5)	10 (43.5)	0.82
Hypertension, n (%)	41 (68.3)	24 (64.5)	17 (73.9)	0.46
Diabetes, n (%)	16 (26.7)	9 (24.3)	7 (30.4)	0.62
PVD, n (%)	40 (66.7)	23 (62.2)	17 (73.9)	0.22
AMI in the previous 6 months, n (%)	17 (28.3)	8 (21.6)	9 (39.1)	0.14
EF < 50 %, n (%)	29 (48.3)	18 (48.6)	11 (47.8)	0.87
Logistic EuroSCORE (dimensionless) <sup>o</sup>	7 (1–15)	7 (1–12)	7 (2–15)	0.13
Baseline serum creatinine, mg/dl	1.1 (0.3)	1.0 (0.3)	1.2 (0.4)	0.036
eGFR, ml/min/1.73 m <sup>2o</sup>	67.5 (27.0–128.0)	72.0 (36.0–128.0)	63.0 (27.0–121.0)	0.039
eGFR < 60 ml/min/1.73 m <sup>2</sup> , n (%)	20 (33.3)	9 (24.3)	11 (47.8)	0.063
Type of surgery				
CABG, n (%)	20 (33.3)	11 (29.7)	9 (39.1)	0.45
Valvular, n (%)	29 (48.4)	19 (51.4)	10 (43.5)	0.55
Mixed, n (%)	11 (18.3)	7 (18.9)	4 (17.4)	0.88

Data are reported as mean (SD), unless otherwise specified

<sup>o</sup> Median (range)

AKI acute kidney injury, AMI acute myocardial infarction, BMI body mass index, CABG coronary artery bypass grafting, EF ejection fraction, eGFR estimated glomerular filtration rate (4-variable MDRD equation), PVD peripheral vascular disease

baseline by TP-ED<sub>us</sub> were slightly higher in the patients with eGFR <60 ml/min/1.73 m<sup>2</sup> than in those with eGFR ≥60 ml/min/1.73 m<sup>2</sup>, this difference was not statistically significant (0.68 ± 0.03 vs. 0.63 ± 0.07, p = 0.10).

The type of MHS undergone was: coronary artery bypass grafting (CABG) in 34 % of patients, valvular surgery in 48 %, and combined CABG and valvular surgery in 18 %. Within the first 72 h of surgery, 23/60 patients (38.3 %) developed AKI. Among the 23 patients with AKI, peak sCr occurred on postoperative day 1 in 15 (65.2 %), on postoperative day 2 in 4 (17.4 %) and on postoperative day 3 in 4 (17.4 %). Two patients had AKI stage 2 and two had AKI stage 3. These latter two patients underwent RRT (sustained low-efficiency dialysis). Two patients (3.3 %) died, both in the AKI+ group. One patient was still under CPB after 4 h and died soon after arrival in the ICU. This patient was eliminated from further analyses, as he had no valid hemodynamic or Doppler data after anesthesia induction.

As shown in Table 1, there were no significant differences in baseline comorbidities among the patients with or without AKI; preoperative sCr was slightly yet significantly higher in AKI+ patients. There was no significant difference between baseline *intrarenal*-RRI by TP-ED<sub>us</sub> in AKI+ vs. AKI– patients (0.66 ± 0.06 vs. 0.64 ± 0.07, p = 0.34).

As shown in Table 2, no significant differences were observed between AKI+ and AKI– patients regarding the overall duration of surgery, ACC time, CPB time, type of surgery, and need for intraoperative vasopressors; overall, AKI+ patients had a greater need for transfusions and a slightly more positive intraoperative fluid balance (Table 2).

### Systemic hemodynamics

Mean arterial pressure values during surgery and in the postoperative period were slightly but not significantly lower in AKI+ patients (p = 0.086) (Fig. 1s in the Online Resource). There was no significant difference in the overall duration of hypotensive episodes (MAP <60 mmHg) during CPB (Table 2). The change in MAP at end-surgery (value at end-surgery minus value at baseline) was also similar between AKI+ and AKI– patients (Table 2).

No significant differences between AKI+ and AKI– patients were detected in hemodynamic invasive indexes at the pre-specified time points (anesthesia induction: cardiac index [CI] 1.9 ± 0.5 vs. 1.7 ± 0.5 l/min/m<sup>2</sup>, p = 0.33; systemic vascular resistance index [SVRI] 3086 ± 1102 vs. 3293 ± 1143 dyne s/cm<sup>5</sup>/m<sup>2</sup>, p = 0.47; pulmonary capillary wedge pressure [PCWP] 15.8 ± 4.7 vs.

**Table 2** Intra/postoperative variables

	All patients	Patients w/o AKI (n = 37)	Patients with AKI (n = 23)	p
Surgery time, min	255 (80)	242 (60)	275 (102)	0.12
CPB time, min (°)	118 (60 to 190)	110 (60 to 190)	130 (75 to 517)	0.64
Aortic cross clamping time, min (°)	83 (30 to 180)	81 (30 to 180)	90 (39 to 150)	0.94
Mean CPB flux (ml/kg/h)	61 (7)	61 (8)	59 (6)	0.28
MAP during CPB (mmHg)	69 (7)	69 (6)	69 (7)	0.91
Time with MAP < 60 mmHg, min (°)	15 (0 to 105)	0 (0 to 90)	15 (0 to 105)	0.78
ΔMAP at end-surgery vs. anesthesia induction, mmHg (°)	3 (−59 to 34)	2 (−59 to 34)	3 (−18 to 14)	0.46
Patients with intraoperative need for amines, n (%)	23 (38.3)	14 (37.8)	9 (39.1)	0.36
Treated with dopamine, n (%)	2 (3.3)	1 (2.7)	1 (4.3)	1.00
Treated with dobutamine, n (%)	17 (28.3)	10 (27.0)	7 (30.4)	0.78
Treated with noradrenaline, n (%)	16 (26.7)	10 (27.0)	6 (26.1)	0.94
Intraoperative fluid balance (ml) (°)	2200 (700 to 4800)	2100 (950 to 4050)	2700 (700 to 4800)	0.046
Need for transfusions, n (%)	37 (61.7)	19 (51.4)	18 (78.3)	0.037
Time on ventilator, h (°)	18 (9 to 768)	18 (11 to 78)	19 (9 to 768)	0.11

Data are reported as mean (SD), unless otherwise specified

° Median (range)

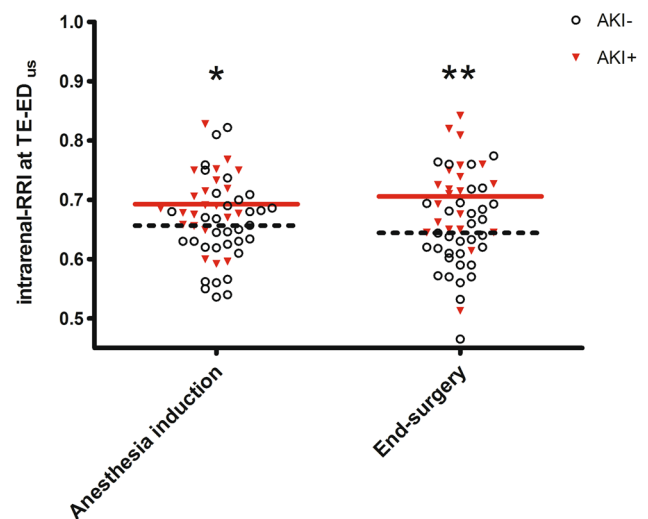
AKI acute kidney injury, CPB cardiopulmonary bypass, MAP mean systemic arterial pressure

13.3 ± 4.1 mmHg, p = 0.071; central venous pressure [CVP] 9.7 ± 2.7 vs. 9.1 ± 2.9 mmHg, p = 0.37. Two hours from CPB start: CI 2.8 ± 0.6 vs. 2.8 ± 0.6 l/min/m<sup>2</sup>, p = 0.78; SVRI 1738 ± 464 vs. 1906 ± 558 dyne s/cm<sup>5</sup>/m<sup>2</sup>, p = 0.34; PCWP 17.1 ± 4.3 vs. 15.0 ± 3.3 mmHg, p = 0.11; CVP 14.3 ± 3.8 vs. 12.5 ± 2.4 mmHg, p = 0.16. Four hours from CPB start: CI 2.6 ± 0.9 vs. 2.5 ± 0.6 l/min/m<sup>2</sup>, p = 0.76; SVRI 2202 ± 932 vs. 2835 ± 3309, dyne s/cm<sup>5</sup>/m<sup>2</sup>, p = 0.34; PCWP 14.8 ± 4.9 vs. 13.6 ± 4.6 mmHg, p = 0.50; CVP 12.6 ± 3.5 vs. 12.3 ± 4.4 mmHg, p = 0.59. Twenty-four hours after CPB start: CI 2.8 ± 0.6 vs. 2.8 ± 0.6 l/min/m<sup>2</sup>, p = 0.98; SVRI 1745 ± 369 vs. 1875 ± 817 dyne s/cm<sup>5</sup>/m<sup>2</sup>, p = 0.15; PCWP 13.0 ± 6.0 vs. 12.9 ± 5.2 mmHg, p = 0.74; CVP 15.8 ± 22.2 vs. 11.0 ± 6.1 mmHg, p = 0.91).

**Resistive indexes in the intra- and postoperative period**

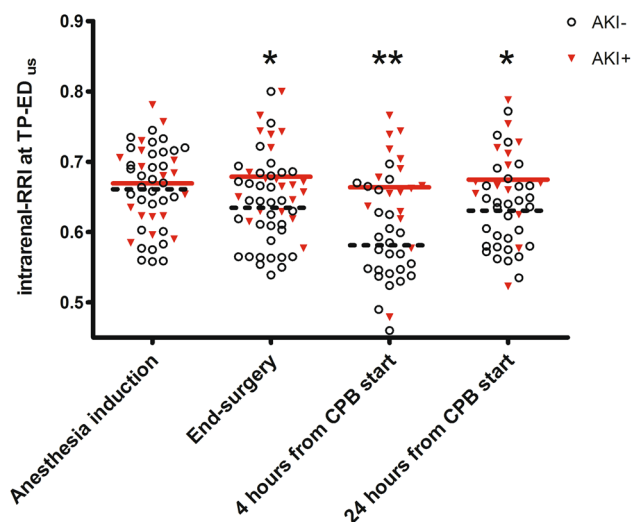
Intraclass correlation coefficient and coefficient of variation of TP-ED<sub>us</sub> measurements were 98.6 % (95 % confidence interval: 97.3–99.3) and 1.0 % (0.8–1.3), respectively. While we observed a trend towards a decrease of RRI values during the early postoperative period compared to those at anesthesia induction in the patients who did not develop AKI, this trend was not apparent in the patients who developed AKI, at either TE-ED<sub>us</sub> (Fig. 2) or

TP-ED<sub>us</sub> (Fig. 3). However, percent changes in RRI values relative to anesthesia induction did not differ significantly between AKI+ and AKI− patients at end-surgery

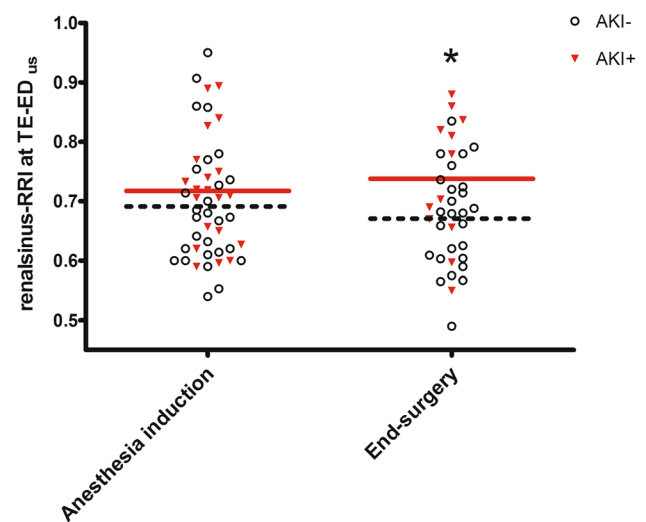


**Fig. 2** Intraparenchymal renal resistive index (intrarenal-RRI) at transesophageal echo-Doppler ultrasound (TE-ED<sub>us</sub>) during the intraoperative period. *Black open circles*, patients who did not develop acute kidney injury within the first 72 h of the postoperative period (AKI−); *red filled triangles*, patients who developed acute kidney injury within the first 72 h of the postoperative period (AKI+). *Dashed lines* represent mean intrarenal-RRI value for AKI− patients; *solid lines* represent mean intrarenal-RRI value for AKI+ patients. \*\*p < 0.01; \*p = 0.053, AKI+ vs. AKI− patients (color figure online)





**Fig. 3** Intraparenchymal renal resistive index (intrarenal-RRI) at transparietal echo-Doppler ultrasound (TP-ED<sub>us</sub>) during the intraoperative period. *Black open circles* patients who did not develop acute kidney injury within the first 72 h of the postoperative period (AKI-); *red filled triangles* patients who developed acute kidney injury within the first 72 h of the postoperative period (AKI+). *Dashed lines* represent mean intrarenal-RRI value for AKI- patients; *solid lines* represent mean intrarenal-RRI value for AKI+ patients. CPB cardiopulmonary bypass. \*\* $p < 0.01$ ; \* $p < 0.05$ , AKI+ vs. AKI- patients (color figure online)



**Fig. 4** Renal resistive index at renal sinus (renalsinus-RRI) at transesophageal echo-Doppler ultrasound (TE-ED<sub>us</sub>) during the intraoperative period. *Black open circles*, patients who did not develop acute kidney injury within the first 72 h of the postoperative period (AKI-); *red filled triangles*, patients who developed acute kidney injury within the first 72 h of the postoperative period (AKI+). *Dashed lines* represent mean renalsinus-RRI value for AKI- patients; *solid lines* represent mean renalsinus-RRI value for AKI+ patients. \* $p < 0.05$  AKI+ vs. AKI- patients (color figure online)

(difference of change in *renalsinus-RRI*, *intrarenal-RRI* at TE-ED<sub>us</sub> and *intrarenal-RRI* at TP-ED<sub>us</sub>,  $p = 0.48$ ,  $p = 0.48$ , and  $p = 0.56$ , respectively) or in the subsequent postoperative period (difference of change in *intrarenal-RRI* at 4 h and 24 h from CPB start at TP-ED<sub>us</sub>,  $p = 0.17$  and  $p = 0.93$ , respectively). At end-surgery *intrarenal-RRI* values were significantly higher in AKI+ than in AKI- patients, measured by either TE-ED<sub>us</sub> ( $p = 0.004$ ; Fig. 2) or TP-ED<sub>us</sub> ( $p = 0.013$ ; Fig. 3). At 4 h from CPB start the difference between AKI+ and AKI- patients measured by TP-ED<sub>us</sub> was even more evident ( $p = 0.005$ ; Fig. 3). *Intrarenal-RRI* values by TE-ED<sub>us</sub> at anesthesia induction were also marginally higher in AKI+ than in AKI- patients ( $p = 0.053$ ; Fig. 2), while no difference was observed by TP-ED<sub>us</sub> ( $p = 0.64$ ; Fig. 3). *Intrarenal-RRI* values obtained with TE-ED<sub>us</sub> and TP-ED<sub>us</sub> did not differ significantly, either at end-surgery or anesthesia induction ( $p = 0.066$  and  $p = 0.70$ , respectively). *Renalsinus-RRI* differences between AKI+ and AKI- patients showed a pattern similar to that of *intrarenal-RRI* ( $p = 0.043$  and  $p = 0.38$  at end-surgery and anesthesia induction, respectively; Fig. 4). End-surgery *intrarenal-RRI* was marginally higher in the patients who received than in those who did not receive vasopressors during surgery ( $p = 0.045$ ), while no differences were observed in the other renal echo-Doppler indexes between these two groups (Table 2s in the Online Resource).

A significant negative correlation was found in AKI+ patients between MAP and *intrarenal-RRI* measured by either TE-ED<sub>us</sub> ( $r = -0.35$ ,  $p = 0.012$ ) or TP-ED<sub>us</sub> ( $r = -0.43$ ,  $p = 0.001$ ); a similar negative correlation with MAP was found for *renalsinus-RRI* in this group ( $r = -0.37$ ,  $p = 0.021$ ). In AKI- patients, a negative correlation with MAP was found only for *intrarenal-RRI* by TP-ED<sub>us</sub> ( $r = -0.25$ ,  $p = 0.015$ ) and *renalsinus-RRI* ( $r = -0.31$ ,  $p = 0.027$ ).

#### Relation between resistive indexes and NGAL

Serum NGAL values increased progressively from anesthesia induction to 4 h after CPB start, and then decreased at 24 h after CPB start, both in AKI+ and in AKI- patients. However, serum NGAL values were higher in the former group (anesthesia induction:  $131.1 \pm 75.6$  vs.  $103.3 \pm 76.3$  ng/ml,  $p = 0.037$ ; 2 h from CPB start:  $305.8 \pm 155.1$  vs.  $214.9 \pm 134.7$  ng/ml,  $p = 0.007$ ; 4 h from CPB start:  $298.2 \pm 174.0$  vs.  $246.9 \pm 188.1$  ng/ml,  $p = 0.093$ ; 24 h from CPB start:  $264.3 \pm 225.2$  vs.  $148.4 \pm 96.1$  ng/ml,  $p = 0.024$ ). Serum NGAL (log-transformed) significantly correlated with both *intrarenal-RRI* ( $r = 0.20$ ,  $p = 0.025$ ) and *renalsinus-RRI* ( $r = 0.21$ ,  $p = 0.032$ ) measured by TE-ED<sub>us</sub> but not with *intrarenal-RRI* measured by TP-ED<sub>us</sub> ( $r = 0.04$ ,  $p = 0.61$ ).

## Predictive ability of resistive indexes for the development of AKI

At univariate regression analysis, preoperative sCr, end-surgery *intrarenal*-RRI by either TE-ED<sub>us</sub> or TP-ED<sub>us</sub>, and *intrarenal*-RRI at 4 and 24 h after CPB start by TP-ED<sub>us</sub> were significantly associated with the subsequent development of AKI (Table 3s in the Online Resource). Logistic EuroSCORE, intraoperative fluid balance and need for transfusion were also marginally associated with the development of AKI (Table 3s in the Online Resource). After adjusting for preoperative sCr, logistic EuroSCORE, intraoperative fluid balance and need for transfusion, end-surgery *intrarenal*-RRI measured by either TE-ED<sub>us</sub> [adjusted odds ratio (adjOR) 2.58 (1.28–5.20),  $p = 0.008$ ] or TP-ED<sub>us</sub> [adjOR 2.15 (1.13–4.10),  $p = 0.020$ ] were associated with the development of AKI; *intrarenal*-RRI at 4 h [adjOR 3.45 (1.56–7.64),  $p = 0.002$ ] and 24 h [adjOR 2.12 (1.03–4.36),  $p = 0.042$ ] from CPB start measured by TP-ED<sub>us</sub> were also associated with AKI development at multivariable logistic regression analysis. Forcing MAP for inclusion into the multivariable regression model produced only modest changes in the point estimates for end-surgery *intrarenal*-RRI by TE-ED<sub>us</sub> [adjOR 2.28 (1.14–4.57),  $p = 0.020$ ] and end-surgery *intrarenal*-RRI by TP-ED<sub>us</sub> [adjOR 1.95 (1.02–3.73),  $p = 0.043$ ], while the association of *intrarenal*-RRI at 4 h ( $p = 0.26$ ) and 24 h ( $p = 0.073$ ) from CPB start with AKI was no longer significant.

Receiver-operator curve (ROC) analysis for AKI prediction of end-surgery *intrarenal*-RRI was AUC 0.71 (0.56–0.86) and 0.70 (0.55–0.84) for TE-ED<sub>us</sub> and TP-ED<sub>us</sub>, respectively; therefore these indexes had only limited accuracy in discriminating between AKI+ and AKI– patients, without a difference between the two techniques ( $p = 0.86$ ). In fact, a cut-off value of 0.67 for end-surgery *intrarenal*-RRI at TE-ED<sub>us</sub> had 67 % sensitivity and 64 % specificity for the identification of AKI + patients; the corresponding sensitivity and specificity for the same cut-off at TP-ED<sub>us</sub> was 50 % and 71 %, respectively.

End-surgery serum NGAL had similar accuracy in discriminating between AKI + and AKI– patients at ROC analysis [AUC 0.71 (0.58–0.85)]. A cut-off value of 225 ng/ml for end-surgery serum NGAL had 73 % sensitivity and 65 % specificity for the identification of AKI+ patients.

The patients with both *intrarenal*-RRI at TE-ED<sub>us</sub> above 0.67 and serum NGAL above 225 ng/ml had a higher risk of developing AKI in the postoperative period at multivariable regression analysis [adjOR 11.33 (2.67–48.14),  $p = 0.001$ ]. However, the combination of end-surgery *intrarenal*-RRI at TP-ED<sub>us</sub> and serum NGAL values was not significantly associated with increased AKI risk [adjOR 5.04 (0.96–26.39),  $p = 0.055$ ].

Compared with AKI– patients, end-surgery *intrarenal*-RRI values measured by TE-ED<sub>us</sub> were significantly higher in those who developed AKI stage 2 or 3 ( $p = 0.002$ ) and in those who developed AKI stage 1 ( $p = 0.034$ ), while the difference between the latter two groups was not significant ( $p = 0.077$ ) (Fig. 2s in the Online Resource). After adjusting for preoperative sCr, logistic EuroSCORE, intraoperative fluid balance and need for transfusion, the association of end-surgery *intrarenal*-RRI by TE-ED<sub>us</sub> with risk of AKI stage 2 or 3 did not reach formal statistical significance [adjOR 7.27 (0.90–58.61),  $p = 0.063$ ]. Similarly, the combination of end-surgery *intrarenal*-RRI above 0.67 by either TE-ED<sub>us</sub> or TP-ED<sub>us</sub> and serum NGAL above 225 ng/ml was not associated with risk of AKI stage 2 or 3 ( $p = 0.089$  and  $p = 0.99$ , respectively).

## Discussion

The main finding of this study is that an early increase in intrarenal vascular resistance, as assessed by *intrarenal*-RRI at the end of surgery by either TE-ED<sub>us</sub> or TP-ED<sub>us</sub>, is significantly associated with the development of AKI within the first 72 h of the postoperative period in patients undergoing MHS.

Our data are in partial agreement with previous results obtained by other groups [22, 23] that performed TP-ED<sub>us</sub> at the time of patients' arrival in the ICU soon after the end of the surgical procedure; additionally, Guinot et al. [23] repeated TP-ED<sub>us</sub> at 6 h after ICU admission and on postoperative day 1. We used both the TE-ED<sub>us</sub> and the TP-ED<sub>us</sub> techniques at fixed time points intraoperatively and in the subsequent 24 h to investigate more accurately the time-course of intrarenal vascular resistance in parallel to systemic hemodynamic changes. However, at variance with the findings of those investigators, in our study end-surgery *intrarenal*-RRI by either TE-ED<sub>us</sub> or TP-ED<sub>us</sub> had limited accuracy in predicting AKI. One possible explanation for this discrepancy may reside in a greater baseline AKI risk in the population studied by Bossard et al. [22]. In fact, all patients had at least two risk factors for AKI (age >60 years, peripheral artery disease, advanced carotid stenosis, diabetes, valvular or combined surgery, intra-aortic balloon counterpulsation); moreover, one-third of the patients who developed AKI required RRT. Conversely, baseline patients' characteristics in Guinot et al.'s study [23] and in our own were remarkably similar; also, only 2 out of 21 (9.5 %) and 2 out of 23 (8.7 %) AKI patients in the former and in our study, respectively, required RRT.

The different definitions of AKI employed in these three studies may also partially explain the different accuracy of *intrarenal*-RRI in predicting postoperative AKI. Moreover, Guinot et al. [23] defined transient AKI as recovery from

AKI within 3 days after surgery, and found that *intrarenal*-RRI actually decreased on ICU admission compared with preoperative values in the patients either with transient AKI or no AKI, while they tended to increase in the patients with persistent AKI. Other investigators [25] observed higher mean intrarenal RRI values on admission in critically ill patients who subsequently developed persistent compared with transient AKI. Similarly, in our study RRI values decreased at the end of surgery in most of the patients who did not develop AKI, whilst they tended to increase in most of the patients who did. This observation may suggest an ongoing stronger vasoconstriction, decreased kidney perfusion and/or tubular damage in the latter group, as opposed to milder perturbations in intrarenal hemodynamics and preserved perfusion in the former group. In the same conceptual framework, the patients with AKI showing relatively low RRI values (i.e.  $<0.67$ ) at end-surgery and at 4 h from CPB start may have been those with milder hypoperfusion and/or undergoing earlier recovery. Since we did not perform echo-Doppler assessment of RRI later than 24 h from CPB start, we could not address this issue; yet, as only two patients progressed to stage 3 AKI requiring RRT, most of our patients had in fact mild and transient AKI.

As we adopted a very sensitive definition of AKI, the inclusion of patients with mild and transient AKI in the overall AKI group may have dampened the predictive ability of end-surgery *intrarenal*-RRI in our study through a dilution effect. Moreover, in patients with septic shock [26] and severe sepsis or polytrauma [27], higher mean RRI values were observed on admission in those who developed advanced compared with milder stages of AKI. Furthermore, in these patients *intrarenal*-RRI on the admission day appeared as the variable providing the best discrimination for subsequent development of AKI stage 2 or 3 [27]. With only four patients developing AKI stage 2 or 3, our study had insufficient power to demonstrate a better discriminating performance of end-surgery *intrarenal*-RRI at TE-ED<sub>us</sub> in this subgroup compared to the overall population of AKI patients.

Because the majority of our patients developed mild and reversible AKI, a relevant question is whether higher end-surgery RRI in these patients may have been related to reversible kidney hypoperfusion. In AKI+ patients we found a significant inverse correlation between MAP and *renalsinus*-RRI, as well as between MAP and *intrarenal*-RRI by both TE-ED<sub>us</sub> and TP-ED<sub>us</sub>. As MAP values were slightly although not significantly lower in AKI+ than in AKI- patients, it could be hypothesized that higher RRI values at end-surgery may have reflected higher intrarenal vascular resistance, hence relative kidney hypoperfusion, simply due to hemodynamic instability in the former group. However, a negative correlation between MAP and RRI

was reported previously in patients with AKI after MHS by some [22] but not other [23] investigators; in critically ill septic patients a weak inverse correlation between MAP and RRI was found both in patients with and without AKI by one group [27], whereas Dewitte et al. [28] observed this correlation only in patients without AKI. Moreover, forcing MAP in the multivariable regression model did not affect significantly the ORs for AKI of *intrarenal*-RRI at either TE-ED<sub>us</sub> or TP-ED<sub>us</sub> in our study.

Apart from decreased MAP, decreased CI and/or increased CVP may have also caused kidney hypoperfusion; however, CI rose after anesthesia induction, without significant differences between AKI+ and AKI- patients. Although higher CVP values may have caused increased RRI values, via increased intrarenal interstitial pressure and decreased arterial distensibility [29], we did not observe any significant differences in CVP values between AKI+ and AKI- patients at any time point. Furthermore, no significant correlations between invasive systemic hemodynamic indexes and RRI were reported in previous studies [23, 30].

Although we cannot exclude that transient kidney hypoperfusion due to hemodynamic instability may have partially accounted for higher end-surgery RRI values in our AKI patients, the early and persistent increase of plasma NGAL values in AKI+ compared with AKI- patients suggests that tubular injury was more likely responsible. This hypothesis is also supported by the significant correlation between *renalsinus*-RRI and *intrarenal*-RRI at TE-ED<sub>us</sub> and plasma NGAL in the overall patient population.

Inasmuch as CPB induces both a strong inflammatory response and an activation of the coagulation cascade [31–36], it may play an important role in the pathogenesis of AKI in the perioperative period in patients undergoing MHS. In fact, previous studies have reported an upregulation of adhesion molecules in leukocytes and vascular endothelium [37, 38], increased levels of interleukin (IL)-6, IL-8 and tumor necrosis factor (TNF)- $\alpha$  [31, 36], and the induction of a pro-thrombotic state [9, 36]. Unfortunately, we did not measure plasma levels of inflammatory cytokines, that may have helped in the interpretation of results in view of the association of systemic inflammatory response with cardiac surgery-induced AKI. Along the same lines of reasoning, increased plasma NGAL plasma levels in our AKI patients may have reflected upregulation due more to a pronounced systemic inflammatory response rather than to tubular damage. In fact, increased plasma NGAL levels have been reported in a canine sepsis model [40], as well as in adult [41, 42] and pediatric critically ill patients with sepsis [43]; however, none of the patients in the present study had clear-cut clinical and/or laboratory signs of severe sepsis.



The combination of end-surgery *intrarenal*-RRI and serum NGAL offered no clear-cut advantage in the prediction of AKI in the postoperative period compared with either variable evaluated separately. In fact, although in the patients who had both end-surgery *intrarenal*-RRI higher than 0.67 by TE-ED<sub>us</sub> and serum NGAL higher than 225 ng/ml we detected a statistically significant association with AKI risk, confidence intervals were wide; moreover, this association was not observed for the combination of end-surgery *intrarenal*-RRI by TP-ED<sub>us</sub> and serum NGAL. Thus, with respect to the development of AKI in the postoperative period in patients undergoing MHS, in our study the predictive accuracy of Doppler indexes of intrarenal resistance, serum NGAL, or their combination was limited.

Finally, the issue of the potential detrimental effects of fluid overload (FO) on kidney function in patients undergoing MHS should be taken into account when indirect measures of intrarenal resistance are being evaluated as a tool to predict AKI. Indeed, many retrospective studies [reviewed in 44] have pointed to an association between FO and deterioration of kidney function in surgical and critically ill patients. A systematic review that analyzed the results of randomized controlled trials of patients undergoing major surgery [45] showed a statistically robust association between a judicious fluid resuscitation (i.e. avoiding unnecessary excess fluid administration) and decreased AKI risk. In view of the possibility that interstitial edema brought about by systemic venous congestion may decrease renal perfusion pressure and blood flow [46] and thus increase intrarenal resistance, increased end-surgery RRI in AKI patients in our study might have reflected the significantly higher intraoperative fluid balance in this group (Table 2). However, as the association of *intrarenal*-RRI with the risk of AKI remained significant in a multivariable model that included intraoperative fluid balance, we believe that the mild FO *per se* in our AKI patients could not explain this association.

Several limitations of this study must be acknowledged. This was a single-center study enrolling a relatively low number of patients, and only two developed dialysis-requiring AKI; as stated previously, this low event rate resulted in insufficient power to investigate the predictive performance of RRI towards advanced AKI. Moreover, given its relatively small patient number and the very low incidence of dialysis-requiring AKI, this study did not allow to discriminate between functional albeit complex hemodynamic events and more severe hypoperfusion causing tubular damage. Also, long-term patient follow-up was not performed. Thus, we cannot establish whether increased end-surgery *intrarenal*-RRI by either TE-ED<sub>us</sub> or TP-ED<sub>us</sub> associated with mild and transient AKI may bear

prognostic value for the long-term (i.e. 1 year) survival or progression to CKD.

Notwithstanding these limitations, by incorporating ultrasound examinations at fixed time points intraoperatively and in the subsequent 24 h, our experimental protocol was designed to detect the earliest signs of AKI, well before a clinically significant increase in sCr. Although we did not find, as others did [47], significant differences in intraoperative *intrarenal*-RRI values obtained by TE-ED<sub>us</sub> or TP-ED<sub>us</sub>, in our study RRIs assessed with either approach proved to be insufficiently accurate and therefore of limited practical utility for AKI prediction in patients undergoing MHS. However, in view of the above limitations, the results of the present study should be considered as preliminary, and await confirmation from further investigations enrolling larger cohorts of critically ill patients undergoing MHS; in particular, these findings would be strengthened by studies with a larger number of patients developing dialysis-requiring AKI. Thus, further larger-scale studies enrolling heart surgery patients at risk for the development of AKI are needed before routine intraoperative echo-Doppler ultrasound examination may be proposed in this setting.

#### Compliance with ethical standards

**Conflict of interest** The Authors declare that they have no conflict of interest to disclose regarding the intellectual content of the present paper.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

#### References

1. Conlon PJ, Stafford-Smith M, White WD et al (1999) Acute renal failure following cardiac surgery. *Nephrol Dial Transplant* 14:1158–1162
2. Mangano CM, Diamondstone LS, Ramsay JG, Aggarwal A, Herskowitz A, Mangano DT (1998) Renal dysfunction after myocardial revascularization: Risk factors, adverse outcomes and hospital resource utilization. *Ann Intern Med* 128:194–203
3. Gailunas P Jr, Chawla R, Lazarus JM, Cohn L, Sanders J, Merrill JP (1980) Acute renal failure following cardiac operations. *J Thorac Cardiovasc Surg* 79:241–243
4. Ostermann ME, Taube D, Morgan CJ, Evans TW (2000) Acute renal failure following cardiopulmonary bypass: a changing picture. *Intensive Care Med* 26:565–571
5. Andersson LG, Ekroth R, Bratteby LE, Hallhagen S, Wesslen O (1993) Acute renal failure after coronary surgery—a study of incidence and risk factors in 2009 consecutive patients. *Thorac Cardiovasc Surg* 41:237–241

6. Zanardo G, Michielon P, Paccagnella A et al (1994) Acute renal failure in the patient undergoing cardiac operation. Prevalence, mortality rate, and main risk factors. *J Thorac Cardiovasc Surg* 107:1489–1495
7. Mangos GJ, Brown MA, Chan WY, Horton D, Trew P, Whitworth JA (1995) Acute renal failure following cardiac surgery: incidence, outcomes and risk factors. *Aust N Z J Med* 25:284–289
8. Antunes PE, Prieto D, Ferrao de Oliveira J, Antunes MJ (2004) Renal dysfunction after myocardial revascularization. *Eur J Cardiothorac Surg* 25:597–604
9. Yeboah ED, Petrie A, Pead JL (1972) Acute renal failure and open heart surgery. *Br Med J* 1:415–418
10. Bhat JG, Gluck MC, Lowenstein J, Baldwin DS (1976) Renal failure after open heart surgery. *Ann Intern Med* 84:677–682
11. Hilberman M, Myers BD, Carrie BJ, Derby G, Jamison RL, Stinson EB (1979) Acute renal failure following cardiac surgery. *J Thorac Cardiovasc Surg* 77:880–888
12. Corwin HL, Sprague SM, DeLaria GA, Norusis MJ (1989) Acute renal failure associated with cardiac operations. A case-control study. *J Thorac Cardiovasc Surg* 98:1107–1112
13. Schmitt H, Riehl J, Boseila A et al (1991) Acute renal failure following cardiac surgery: pre- and perioperative clinical features. *Contrib Nephrol* 93:98–104
14. Chertow GM, Levy EM, Hammermeister KE, Grover F, Daley J (1998) Independent association between acute renal failure and mortality following cardiac surgery. *Am J Med* 104:343–348
15. Lassnigg A, Schmidlin D, Mouhieddine M, Bachmann LM, Druml W, Bauer P, Hiesmayr M (2004) Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. *J Am Soc Nephrol* 15:1597–1605
16. Bihorac A, Yavas S, Subbiah S et al (2009) Long-term risk of mortality and acute kidney injury during hospitalization after major surgery. *Ann Surg* 249:851–858
17. Mehta RH, Honeycutt E, Patel UD et al (2010) Impact of recovery of renal function on long-term mortality after coronary artery bypass grafting. *Am J Cardiol* 106:1728–1734
18. Urzua J, Troncoso S, Bugeo G et al (1992) Renal function and cardiopulmonary bypass: effect of perfusion pressure. *J Cardiothorac Vasc Anesth* 6:299–303
19. Provenchere S, Plantevefe G, Hufnagel G et al (2003) Renal dysfunction after cardiac surgery with normothermic cardiopulmonary bypass: incidence, risk factors, and effect on clinical outcome. *Anesth Analg* 96:1258–1264
20. Norris CS, Barnes RW (1984) Renal artery flow velocity analysis: A sensitive measure of experimental and clinical renovascular resistance. *J Surg Res* 36:230–236
21. Petersen LJ, Petersen JR, Ladefoged SD, Mehlsen J, Jensen HA (1995) The pulsatility index and the resistive index in renal arteries in patients with hypertension and chronic renal failure. *Nephrol Dial Transplant* 10:2060–2064
22. Bossard G, Bourgoin P, Corbeau GG, Huntzinger J, Beydon L (2011) Early detection of postoperative acute kidney injury by Doppler renal resistive index in cardiac surgery with cardiopulmonary bypass. *Br J Anaesth* 107:891–898
23. Guinot PG, Bernard E, Abou Arab O, Badoux L, Diouf M, Zogheib E, Dupont H (2013) Doppler-based renal resistive index can assess progression of acute kidney injury in patients undergoing cardiac surgery. *J Cardiothorac Vasc Anesth* 27:890–896
24. Garwood S, Davis E, Harris SH (2001) Intraoperative transesophageal ultrasonography can measure renal blood flow. *J Cardiothorac Vasc Anesth* 15:65–71
25. Darmon M, Schortgen F, Vargas F, Liazydi A, Schlemmer B, Brun-Buisson C, Brochard L (2011) Diagnostic accuracy of Doppler renal resistive index for reversibility of acute kidney injury in critically ill patients. *Intensive Care Med* 37:68–76
26. Lerolle N, Guerot E, Faisy C, Bornstain C, Diehl J-L, Fagon J-Y (2006) Renal failure in septic shock: predictive value of Doppler-based renal arterial resistive index. *Intensive Care Med* 32:1553–1559
27. Schnell D, Derudder S, Harrois A, Pottecher J et al (2012) Renal resistive index better predicts the occurrence of acute kidney injury than cystatin C. *Shock* 38:592–597
28. Dewitte A, Coquin J, Meissignac B, Joannès-Boyou O et al (2012) Doppler resistive index to reflect regulation of renal vascular tone during sepsis and acute kidney injury. *Crit Care* 16:R165
29. Murphy ME, Tublin ME (2000) Understanding the Doppler RI: impact of renal arterial distensibility on the RI in a hydronephrotic ex vivo rabbit kidney model. *J Ultrasound Med* 19:303–314
30. Schnell D, Camous L, Guyomarc'h S et al (2013) Renal perfusion assessment by renal Doppler during fluid challenge in sepsis. *Crit Care Med* 41:1214–1220
31. Cremer J, Martin M, Redl H et al (1996) Systemic inflammatory response syndrome after cardiac operations. *Ann Thorac Surg* 61:1714–1720
32. Taylor KM (1996) SIRS—the systemic inflammatory response syndrome after cardiac operations. *Ann Thorac Surg* 61:1607–1608
33. Karkouti K, Beattie WS, Wijeyesundera DN et al (2005) Hemodilution during cardiopulmonary bypass is an independent risk factor for acute renal failure in adult cardiac surgery. *J Thorac Cardiovasc Surg* 129:391–400
34. Kumar AB, Suneja M (2011) Cardiopulmonary bypass-associated acute kidney injury. *Anesthesiology* 114:964–970
35. Paparella D, Yau TM, Young E (2002) Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. *Eur J Cardiothorac Surg* 21:232–244
36. Scarscia G, Rotunno C, Simone S et al (2015) Acute kidney injury in high-risk cardiac surgery patients: roles of inflammation and coagulation. *J Cardiovasc Med (Hagerstown)*. doi:10.2459/JCM.0000000000000343
37. Galinanes M, Watson C, Trivedi U, Chambers DJ, Young CP, Venn GE (1996) Differential patterns of neutrophil adhesion molecules during cardiopulmonary bypass in humans. *Circulation* 94 (9Suppl):II 364-9
38. Asimakopoulos G, Taylor KM (1998) Effects of cardiopulmonary bypass on leukocyte and endothelial adhesion molecules. *Ann Thorac Surg* 66:2135–2144
39. Parolari A, Mussoni L, Frigerio M et al (2005) Increased prothrombotic state lasting as long as one month after on-pump and off-pump coronary surgery. *J Thorac Cardiovasc Surg* 130:303–308
40. Cortellini S, Pelligand L, Syme H, Chang YM, Adamantos S (2015) Neutrophil gelatinase-associated lipocalin in dogs with sepsis undergoing emergency laparotomy: a prospective case-control study. *J Vet Intern Med* 29:1595–1602
41. Otto GP, Hurtado-Oliveros J, Chung HY et al (2015) Plasma neutrophil gelatinase-associated lipocalin is Primarily related to inflammation during sepsis: a translational approach. *PLoS One* 10:e0124429
42. Vanmassenhove J, Glorieux G, Lameire N, Hoste E, Dhondt A, Vanholder R, Van Biesen W (2015) Influence of severity of illness on neutrophil gelatinase-associated lipocalin performance as a marker of acute kidney injury: a prospective cohort study of patients with sepsis. *BMC Nephrol* 16:18
43. Wheeler DS, Devarajan P, Ma Q, Harmon K, Monaco M, Cvijanovich N, Wong HR (2008) Serum neutrophil gelatinase associated lipocalin (NGAL) as a marker of acute kidney injury in critically ill children with septic shock. *Crit Care Med* 36:1297–1303

44. Prowle JR, Echeverri JE, Ligabo EV, Ronco C, Bellomo R (2010) Fluid balance and acute kidney injury. *Nat Rev Nephrol* 6:107–115
45. Prowle JR, Chua H-R, Bagshaw SM, Bellomo R (2012) Clinical review: volume of fluid resuscitation and the incidence of acute kidney injury – a systematic review. *Crit Care* 16:230
46. Herrler T, Tischler A, Meyer A et al (2010) The intrinsic renal compartment syndrome: new perspectives in kidney transplantation. *Transplantation* 89:40–46
47. Karamaz A, Arslantas MK, Cinel I (2015) Renal resistive index measured by transesophageal echocardiography: comparison with translumbar ultrasonography and relation to acute kidney injury. *J Cardiothorac Vasc Anesth* 29:875–880