Türk Göğüs Kalp Damar Cerrahisi Dergisi 2013;21(3):610-615
doi: 10.5606/tgkdc.dergisi.2013.7164

Original Article / Özgün Makale

An evaluation of renal functions in pulsatile and non-pulsatile cardiopulmonary bypass in the elderly

Yaşlılarda pulsatil ve nonpulsatil kardiyopulmoner baypasta böbrek fonksiyonlarının değerlendirilmesi

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Background: This study aims to evaluate the effects of pulsatile and non-pulsatile cardiopulmonary bypass techniques on renal functions in elderly.

Methods: Between January 2011 and June 2011, 41 patients aged above 70 years who underwent coronary artery bypass grafting (CABG) in our clinic were enrolled in the study. Patients were randomly divided into two groups according to the perfusion technique: pulsatile and non-pulsatile flow. Preoperative, post-cardiopulmonary bypass and at third day following surgery, creatinine, cystatin C, blood urea nitrogen values, urine output during cardiopulmonary bypass and the incidence of acute kidney injury were recorded.

Results: At third day following operation, cystatin C, creatinine and blood urea nitrogen values were significantly lower in pulsatile flow group. A significant difference was observed between the groups in terms of urine output during cardiopulmonary bypass and the incidence of acute kidney injury.

Conclusion: Pulsatile flow cardiopulmonary bypass is a simple and safe method which may prevent acute kidney injury in elderly.

Key words: Acute kidney injury; cystatin C; non-pulsatile flow; pulsatile flow.

Amaç: Bu çalışmada yaşlı hastalarda pulsatil ve non-pulsatil kardiyopulmoner baypas tekniklerinin böbrek fonksiyonları üzerindeki etkileri değerlendirildi.

Çalışma planı: Ocak 2011 - Haziran 2011 tarihleri arasında kliniğimizde koroner arter baypas greftleme (KABG) yapılan 70 yaş üzeri 41 hasta çalışmaya alındı. Hastalar uygulanan perfüzyon tekniğine göre randomize olarak pulsatil ve non-pulsatil akım gruplarına ayrıldı. Hastaların ameliyat öncesi, kardiyopulmoner baypas sonrası ve ameliyat sonrası 3. gün kreatinin, sistatin C, kan üre azot değerleri, kardiyopulmoner baypas sırasında idrar çıkış miktarı ve akut böbrek hasarı görülme sıklığı kaydedildi.

Bulgular: Hastaların ameliyat sonrası 3. gün sistatin C, kreatinin ve kan üre azot değerleri pulsatil akım grubunda anlamlı derecede daha düşüktü. Kardiyopulmoner baypas süresince hastaların idrar çıkışı ve akut böbrek hasarı görülme sıklığı gruplar arasında anlamlı düzeyde farklı bulundu.

Sonuç: Pulsatil akımlı kardiyopulmoner baypas yaşlı hastalarda akut böbrek hasarını önleyebilen basit ve güvenli bir yöntemdir.

Anahtar sözcükler: Akut böbrek hasarı; sistatin C; nonpulsatil akım; pulsatil akım.

Acute kidney injury (AKI) occurs following coronary artery bypass grafting (CABG) surgery at an incidence rate ranging from 0.6-10%.[1,2] Approximately, 20% of these patients need dialysis, which carries a high mortality risk.[3-5] The etiology of AKI after CABG is multifactorial and complex. However, it may occur following off-pump CABG when extracorporeal circulation is a major risk factor for postoperative renal failure. The factors related to cardiopulmonary bypass (CPB) that contribute to AKI include aortic

Available online at
www.tgkdc.dergisi.org
doi: 10.5606/tgkdc.dergisi.2013.7164
QR (Quick Response) Code

Received: May 23, 2012 *Accepted:* November 28, 2012

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cross-clamping time, CPB time, low perfusion pressure, nonpulsatile blood flow, and hemodilution along with the use of centrifugal pumps, use of protamine, generation of emboli, and formation of free oxygen radicals. However, the induction of a massive systemic proinflammatory response might be the greatest contributor. Recent studies have revealed that postoperative systemic proinflammatory response is more significant with on-pump CABG than off-pump CABG.[6,7]

Advanced age is considered to be an independent risk factor for renal disease, even in the absence of other comorbidities. In addition, previous studies have revealed higher incidence rates of acute renal failure in the elderly.[8,9] Although the strong association between age and kidney function has been proven, it is not clear what portion of this relationship is due to the higher prevalence of risk factors for renal disease at older ages, such as diabetes mellitus (DM), vascular disease, and hypertension.[10] Changes in renal structure and function in the aging process prevent the kidneys from adapting to acute ischemic injuries since older kidneys have a decreased vasodilatation capacity when maximally stimulated and a greater sensitivity to volume depletion.[11]

In this study, we aimed to compare the pulsatile and nonpulsatile flow CPB techniques in terms of postcardiac surgical renal impairment in patients older than 70 years. We used the nephelometric cystatin C measurement for renal function assessment based on two meta-analyses that concluded that cystatin C was superior to creatinine for this purpose.[12,13]

PATIENTS AND METHODS

This prospective, randomized study was composed of 41 consecutive patients (32 males, 9 females; mean age 73.6±2.5 years; range 70 to 81 years) older than 70 years old who underwent an on-pump CABG grafting operation between April 2010 and July 2010. Local ethics committee approval was obtained along with the informed consent of each participant. The preoperative functional status of the patients was evaluated in accordance with the New York Heart Association (NYHA) classification, and operative risk was calculated with the logistic EuroSCORE model. Furthermore, transthoracic echocardiography (TTE) was performed on all patients by the same cardiologist.

The sample size was calculated using a power analysis. The mean functional capacity was 2.4±0.7, and the mean logistic EuroSCORE was 2.4±02. The patients' mean ejection fraction (EF) was determined to be 52.8%±14.6% according to the modified Simpson formula.

The same surgical team operated on all of the patients, who were randomly divided into two groups. Nonpulsatile CPB was performed on 21 patients (group NP), and pulsatile flow CPB was performed on 21 others (group P). The patients' preoperative characteristics are summarized in Table 1.

We evaluated the preoperative renal function of each patient by examining the serum creatinine, cystatin C, and blood urea nitrogen (BUN) levels. Renal function tests were repeated following CPB and on the third postoperative day with samples that were obtained from the central venous catheter (CVC).

The cystatin C levels were measured via particle-enhanced immunonephelometric assay with a BN™ II nephelometer (Siemens AG, Erlangen, Germany) using frozen plasma stored at –20 °C. The assay range was 0.195-7.330 mg/L, with the normal range being 0.53-0.95 mg/L.

Acute kidney injury in our patients was defined as an absolute increase in the serum creatinine of greater than or equal to 0.3 mg/dl (≥26.4 μmol/l), a percentage

Table 1. Preoperative characteristics of the patients

	Group NP (n=21)			Group P (n=20)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Gender							
Male	17	80.9		16	80		NS
Age (year)			73.8±2.5			73.2±1.9	NS
Smoking history		57			50		NS
Hypertension		38.10			40		NS
Left ventricular ejection fraction (%)			52.6±11.3			52.8±13.8	NS
Logistic EuroSCORE			2.3±0.2			2.4±0.2	NS
New York Heart Association FC class			2.3±0.7			2.4±0.9	NS

NP: Nonpulsatile; P: Pulsatile; SD: Standard deviation; FC: Functional class. NS: Not significant.

increase in the serum creatinine of 50% (a 1.5-fold increase from the baseline), a reduction in urine output (documented oliguria of less than 0.5 ml/kg per hour for more than six hours) greater than or equal to 03 mg/dl, postoperative serum creatinine levels greater than or equal to a 50% increase according to the criteria of the AKI Network (AKIN).[14]

Exclusion criteria

Patients with a history of renal disease, DM, uncontrolled hypertension, impaired left ventricle function (LVEF <50), and valvular heart disease were excluded from the study. All of the participants were elective subjects; emergent cases were not included. Additionally, those who had undergone coronary angiography within the previous two weeks were also excluded.

Anesthetic technique

The standard technique was used for all of the patients. Routine monitorization was composed of electrocardiography and invasive arterial pressure monitoring via radial artery catheterization, and central venous catheterization along with the use of a pulse oximeter, a capnograph, an esophageal temperature probe. Sevoflurane (Sevorane® Abbott Laboratories. Abbott Park, IL, U.S.A.) was used for gas anesthesia, but fractioned midazolam and pancuronium were used while performing the CPB.

Operative technique

Extracorporeal circulation was established with a two-stage cannulation of the aorta, and myocardial protection was achieved by antegrade blood cardioplegia and moderate hypothermia (32 °C). The left internal thoracic artery (LITA) was anastomosed to the left anterior descending artery (LAD) in all patients. Proximal anastomoses were done via aortic side-clamping.

Extracorporeal circulation

Cardiopulmonary bypass was instituted with standard ascending aorta to right atrium (two-stage venous) cannulation. We used a Stockert S3 roller pump (Sorin Group Deutschland GMBH, München, Germany) with a pulsatile control module for extracorporeal circulation.

Nonpulsatile flow

Standard linear flow CPB was performed with the aim of achieving 60-80 mmHg mean pressure.

Pulsatile flow

The CPB was initiated with the nonpulsatile mode in the usual fashion, but in group P, the pulsatile flow was started just after aortic cross-clamping. After unclamping the aorta, the flow pattern was transformed back to the nonpulsatile form.

Statistical analysis

Statistical analysis was performed with SPSS for Windows version 11.5 software (SPSS Inc., Chicago Illinois, USA), and all data was presented as mean ± standard deviation. A paired t-test was used for comparing the preoperative and postoperative scores, and Student's t-test (independent sample test) was used for comparing the groups. The Bonferroni test was performed as a post hoc test for pairwise comparison of group differences, and the Kolmogorov-Smirnov test was applied to assess normal distribution. Correlation calculations were done using Pearson's chi-square test for data with normal distribution, whereas Spearman's rank correlation test was utilized for data not suitable for normal distribution. A p value of <005 was considered to be significant.

RESULTS

The demographic characteristics of patients were compared between the two groups, and there was no significant differences with regard to age, gender, history of hypertension and smoking, the mean LVEF, the mean logistic EuroSCORE, or the mean functional capacity (p>0.05) (Table 1).

The operative variables were found to be similar between the groups. The mean number of anastomosis prodedures was 3.1±0.7 in group NP and 3±0.4 in group P (p>0.05). Furthermore, the CPB time and aortic cross-clamp time were nearly identical (76.8±27.9 versus 78.6±20.5 and 45.9±23.5 versus 51.6±15.7, respectively; p>0.05) (Table 2).

The mean total of transfused red blood cell units was 2.1±1.6 in group NP and 2.2±1.3 in group P, but this difference was not significant.

The preoperative serum creatinine and cystatin C values were similar between the groups. In group P, the serum creatinine was slightly higher, but the cyctatin c did not change after being weaned from CPB. In group NP, the serum creatinine levels did not change, but the cystatin C levels were slightly lower after CPB. However, once again, this difference was not significant (Figures 1 and 2).

The preoperative and post-CPB mean BUN values were also similar between the groups, but it was significantly higher in group NP on the postoperative third day (18.9±4.0) than in group P (14.8±2.6) (p<0.05).

Table 2. Operative data of the study groups

	Group NP	Group P	
	Mean±SD	Mean±SD	*p*
Mean number of anastomoses	3.14±0.7	3±0.35	NS
Cardiopulmonary bypass time (minutes)	76.81±27.92	78.60±20.49	NS
Cross clamp time (minutes)	45.86±23.48	51. 6±15.71	NS
Mean perfusion pressure (mmHg)	63.14±14.71	64.35±13.50	NS

NP: Nonpulsatile; P: Pulsatile; SD: Standard deviation; NS: Not significant.

Perioperative diuresis was also compared between groups, and the total urine output was significantly higher in group P (828.6±500.4) than in group NP (1025±344.2) ($p<0.05$).

The serum creatinine levels increased in group NP but did not change in group P on the postoperative third day, and the difference was significant (1.2±0.2 vs. 0.9±0.1, respectively; $p<0.05$). Similarly, the cystatin C levels increased significantly in group NP but were unchanged in group P (1.0±0.2 vs. 0.8±0.2, respectively; $p<0.05$) (Table 3).

Postoperative AKI occurred in seven patients in group NP (33.3%) and two patients in group P (10%) ($p<0.05$).

DISCUSSION

Although various studies have compared pulsatile and nonpulsatile flow, there is still no consensus concerning the indications and advantages of these techniques. Theoretically, pulsatile flow may provide better microcirculation and tissue perfusion than nonpulsatile flow due to its physiological nature. Peripheral vascular resistance is one of the major determinants that affects tissue perfusion during CPB, and pulsatile flow provides lower peripheral vascular resistance and higher blood supply than nonpulsatile flow.[15,16] This might be explained by various mechanism. For example, pulsatile flow triggers the vasomotor reflex and reduces the vasomotor discharge; thus, peripheral vascular resistance is also reduced. Another possible mechanism is involves hormonal modulations in which higher catecholamine levels and lower thromboxane cause reduced peripheral vascular resistance. Pulsatile flow also increases the endothelium-derived nitrous oxide synthesis and reduces endothelin 1 and interleukin 8, both of which enhance peripheral tissue circulation and organ function. Additionally, pulsatile flow creates enough hydraulic energy to exceed that produced by the small arterioles and the precapillary sphincter systolic pressure, thereby maintaining a high microcirculation. These beneficial effects indirectly cause reduced lactic acid, elevated blood pH levels, and increased tissue oxygenation.

Pulsatility provides more physiological hemodynamic energy levels compared with nonpulsatile flow. Cardiopulmonary bypass flow creates an energy gradient which is more important to tissue perfusion than the pressure gradient. This gradient was defined as energy equivalent pressure (EEP) by Shepard et al.[17] in 1966. Shepard's formula makes it possible to compare EEP with the mean arterial pressure (MAP). The difference between EEP and MAP is the extra energy generated by CPB. In the normal

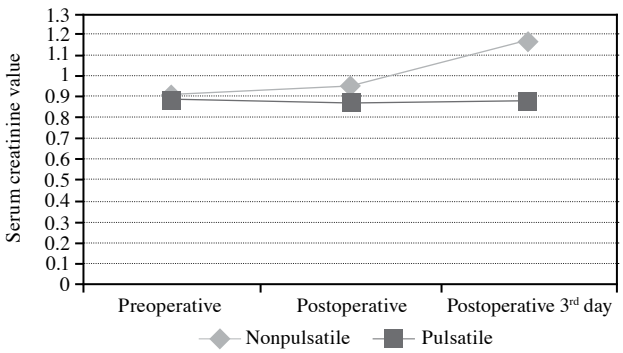

Figure 1. Serum creatinine values (mg/dl) of the study groups measured preoperatively, at the termination of cardiopulmonary bypass, and on the postoperative third day.

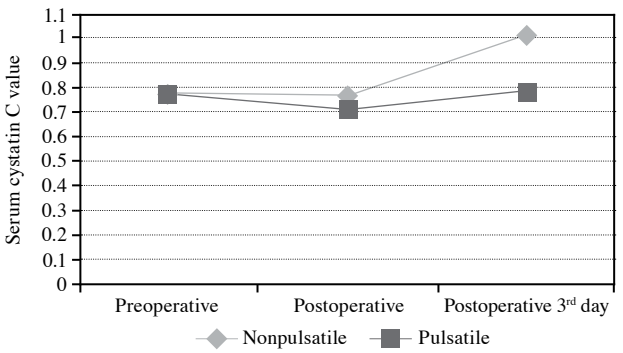

Figure 2. Serum cystatin C values (mg/L) of study groups measured preoperatively, at termination of cardiopulmonary bypass and on postoperative third day.

Table 3. Comparison of renal function tests between the study groups

	Group NP	Group P	
	Mean±SD	Mean±SD	*p*
Creatinine 1 (mg/dl)	0.9±0.2	0.9±0.2	NS
Creatinine 2 (mg/dl)	1.0±0.1	0.9±0.2	NS
Creatinine 3 (mg/dl)	1.2±0.2	0.9±0.1	<0.05
Cystatin C 1 (mg/L)	0.8±0.2	0.8±0.2	NS
Cystatin C 2 (mg/L)	0.8±0.1	0.7±0.2	NS
Cystatin C 3 (mg/L)	1.0±0.2	0.8±0.2	<0.05
Blood urea nitrogen 1 (mg/dl)	15.2±2.5	15.0±3.7	NS
Blood urea nitrogen 2 (mg/dl)	15.2±3.4	13.9±3.7	NS
Blood urea nitrogen 3 (mg/dl)	18.9±4.0	14.8±2.6	<0.05

NP: Nonpulsatile; P: Pulsatile; SD: Standard deviation; NS: Not significant; 1: Preoperative; 2: After cardiopulmonary bypass; 3: Postoperative 3rd day.

human heart, the difference between EEP and MAP is approximately 10%. This difference decreases to 3-5% with the pulsatile roller pump and only 0-1% with the nonpulsatile pump.[18] Additionally, systemic vascular resistance during the aortic cross-clamping was lower during pulsatile CPB, and this leads to improvement in energy transmission. Therefore, these results clearly show that pulsatile flow generates significantly higher hemodynamic energy and tissue perfusion than nonpulsatile flow.

Although the advantages of pulsatile flow have been reported in various studies, the use of pulsatile CPB is still not widespread. One of the most important factors limiting pulsatile flow usage is that pulsatile flow may cause hemolysis. Recently, however, Silistreli et al.[19] reported that this type of flow does not cause clinically significant hemolysis. In our study, we did not observe significant hemolysis or thrombocytopenia, and the number of transfused erythrocyte cell units was also similar in our two groups.

The pathophysiology of AKI following cardiac surgery is multifactorial. Perioperative renal hypoperfusion and the presence of endogenous and exogenous nephrotoxins along with microembolisms may cause glomerular and tubular injury, especially in the presence of comorbidities such as preoperative renal disease, advanced age, left ventricular dysfunction and DM. Therefore, AKI is an interaction of several pathophysiological mechanisms, including patient-related factors, the effects of CPB, the systemic inflammatory response syndrome, and microembolization. The factors related to CPB are nonpulsatility, duration of CPB, hypothermia, and free hemoglobin release.

Previous studies revealed that pulsatile flow could possibly protect renal function in patients who undergo cardiac surgery;[20,21] however, other studies have emphasized the similarity of the pulsatile and nonpulsatile techniques in terms of the clinical benefits.[22] Ji and Undar,[23] reported that the blood flow into the kidneys was four times higher with pulsatile CPB. Kim et al.[16] concurred by stating that renal oxygen consumption increases at two hours and that the oxygenation of the renal cortical and medullar tissues increases during pulsatile flow. In our study, we observed a significantly higher incidence of AKI in group NP, but no patient required hemodialysis. In addition, we observed significantly higher urine output in group P. Furthermore, the CPB, aortic cross-clamp times, mean CPB pressure were similar between the groups. The difference in renal functions between the groups was considered to be dependent on pulsatility and flow energy dynamics.

It is well known that there is a correlation between advanced age and AKI in cardiac surgery patients.[8,24] Given that advanced age is not a preventable risk factor, the management of preventable factors becomes more important in elderly patients in order to protect renal functions following cardiac surgery. Currently, various tests are being used to accomplish this. The glomerular filtration rate (GFR) seems to be the best parameter since it declines with aging. However, several studies have reported that cystatin C is a better marker for measuring the GFR than creatinine.[12] We analyzed both cystatin C and serum creatinine with regard to the monitorizaion of renal functions, and the renal protective effect of pulsatility was clearly shown. On the postoperative third day, the mean creatinine clearance, mean cystatin C, and BUN values were significantly higher in group NP, but the mean diuresis during CPB was higher in group P. Additionally, the incidence of AKI occurrence was higher in group NP.

Conclusion

Pulsatile flow is a simple, safe CPB technique, and its more physiological and protective nature provides better tissue perfusion. Although it has been claimed that pulsatile flow causes hemolysis, recent studies have shown that this is not the case.

Acute kidney injury following cardiac surgery is common in the elderly, and pulsatile flow CPB may protect renal functions better than nonpulsatile flow. Therefore, we recommend this technique to prevent AKI, especially for patients of advanced age.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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