ORIGINAL ARTICLE

The impact of prolonged intraoperative hypotension on postoperative outcome in surgical resection of renal tumors with cavo-atrial extension

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Abstract: Objectives – Surgical treatment with extracorporeal circulation represents often the only therapeutic option in patients with renal tumours with cavo-atrial venous extension. Intraoperative hypotension occurs in such surgical operations involving both significant blood loss and eventual embolic events. Its influence on the subsequent evolution of the patient depends on its level and duration. This study aims to identify the impact of prolonged intraoperative hypotension on postoperative outcome quntificated by the occurrence of severe complications (organ dysfunction and death), postoperative Acute Kidney Injury stage 3 (AKI 3) and neurological complications. **Methods –** The retrospective study included all the patients who underwent the complex surgery of radical nephrectomy with cavo-atrial thrombectomy under extracorporeal circulation in Prof. C.C. Iliescu Emergency Institute for Cardiovascular Diseases in Bucharest during 2004-2018. The medical records have been studied, after obtaining the approval of the ethical commitee of the institution regarding this study. The pacients who died intraoperatively were excluded from the statistical analysis. Prolonged intraoperative hypotension was defined as mean intraoperative blood pressure below 60 mm Hg for more than 20 cumulated minutes (pre-, intra- and post-extracorporeal circulation). Postoperative complications were graded according to Clavien Dindo classification, acute postoperative renal injury according to Kidney Disease Improving Global Outcomes (KDIGO) criteria and neurological complications included postoperative encephalopathy and acute stroke. **Results –** There were identified 30 consecutive patients undergoing nephrectomy with cavo-atrial thrombectomy using extracorporeal circulation. Only 28 patients were included in the study because there were two intraoperative death. Aplying Fisher exact test in the 2x2 contingency tables we found out that the presence of prolong intraoperative hypotension was associated with postoperative organ dysfunction and death (Clavien Dindo IV and V), but also with postoperative AKI 3 and neurological complications. **Conclusion –** Prolonged intraoperative hypotension correlates with severe postoperative complications. At the same time, it represents a risk factor in the occurrence of postoperative AKI 3 and neurological complications. That is why the medical team has to work together to minimize and reduce the duration of intraoperative hypotension.
Keywords: acute renal injury, arterial hypotension, neurological complications, severe complications.

Rezumat: Obiective – Tratamentul chirurgical cu ajutorul circulației extracorporeale reprezintă uneori singura opțiune terapeutică în cazul tumorilor renale cu extensie venoasă cavo-atrială. Hipotensiunea arterială intraoperatorie se întâlnește în cazul acestor intervenții chirurgicale ce presupun pierderi de sânge importante, dar și eventuale evenimente embolice. Influența acesteia asupra evoluției ulterioare a pacientului depinde de nivelul și de durata acesteia. Studiul de față își propune să identifice impactul hipotensiunii arteriale intraoperatorii prelungite asupra prognosticului postoperator cuantificat prin apariția complicațiilor severe (disfuncții de organ și deces), a injuriei renale acute stadiul 3 și a complicațiilor neurologice. **Metode –** Studiul retrospectiv a inclus toți pacienții supuși unei intervenții chirurgicale complexe, nefrectomie radicală cu extragerea trombului venos sub circulație extracorporeală în cadrul Institutului de Urgență pentru Boli Cardiovasculare „Prof. C.C. Iliescu", București, între 2004-2018. Au fost studiate documentele medicale ale pacienților după obținerea acordului comisiei de etică a institutului. Pacienții care au decedat intraoperator au fost excluși din analiza statistică. Hipotensiunea intraoperatorie prelungită este definită în această lucrare ca fiind tensiunea arterială medie intraoperatorie sub 60 mm Hg pentru o perioadă cumulată de peste 20 de minute (pre, intra și post circulație extracorporeală). Complicațiile postoperatorii au fost expuse conform clasificării Clavien Dindo, injuria renală acută postoperatorie conform criteriilor Kidney Disease Improving Global Outcome (KDIGO), iar complicațiile neurologice au cuprins encefaloptia postoperatorie

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și accidentul vascular acut. **Rezultate –** Au fost identificați 30 de pacienți consecutivi la care s-a practicat nefrectomia radicală cu trombectomie cavo-atrială sub circulație extracorporeală. Numai 28 de pacienți au fost înrolați în studiu, întrucât au existat 2 decese intraoperatorii. Aplicând testul exact Fisher în tabelele de contingență 2x2 am demonstrat că prezența hipotensiunii arteriale prelungite a fost asociată cu disfuncțiile de organ postoperatorii și deces (Clavien Dindo IV și V), dar de asemenea cu apariția injuriei renale acute severe și a complicațiilor neurologice. **Concluzie –** Hipotensiunea arterială intraoperatorie prelungită se corelează cu prezența complicațiilor postoperatorii severe. În același timp, reprezintă un factor de risc în apariția AKI 3 și a complicațiilor neurologice postoperatorii. De aceea, echipa medicală trebuie să conlucreze în vederea minimizării și a micșorării duratei hipotensiunii arteriale intraoperatorii.
Cuvinte cheie: complicații neurologice, complicații severe, hipotensiune arterială, injurie renală acută.

INTRODUCTION

The prevalence of kidney cancer is low[1,2]. Approximately 80% of these are renal cell carcinomas[2]. Some of them have venous extensions, including infra- or supradiaphragmatic inferior vena cava level or even in right atrium-1% of cases[3]. Their treatment consists in surgical intervention that aims at removing the primary tumor, as well as its extension. In the case of the supradiaphragmatic venous extension, with or without the involvement of the right atrium, surgical intervention involves excision of the involved kidney together with the tumor, but also the removal of the venous extension under extracorporeal circulation, with or without cross-clamping the ascending aorta, arresting the heart, in normothermia or moderate hypothermia. These complex surgeries involve an entire multidisciplinary team: urologists, surgeons, cardiac surgeons, anesthetists and intensive care physicians, cardiologists, perfusionists.

Major intraoperative risks are massive bleeding, but also embolic events with dramatic consequences. Thus, this study aims to identify the impact of prolonged intraoperative hypotension, defined as intraoperative mean blood pressure below 60 mmHg for more than 20 minutes during the pre-, intra- and post-cardiopulmonary bypass period, on the postoperative outcome: occurrence of postoperative severe complications (Clavien Dindo IV and V), postoperative AKI3 and neurological complications. The Clavien-Dindo classification[4] (Table1) is recommended and validated by the *European Association of Urology* as a standardized reporting method for postoperative complications[5].

PATIENTS AND METHODS

The retrospective study included all the patients who underwent complex surgery (radical nephrectomy with extraction of the venous thrombus under extracorporeal circulation) in Prof. C.C. Iliescu Emergency Institute for Cardiovascular Diseases in Bucharest during 2004-2018. The pacients who died intraoperatively were excluded from the study, because the endpoints are represented by postoperative complications.

The patients were previously diagnosed clinically and imagistically (echocardiography, computer tomography or magnetic resonance imaging, transesophageal echocardiography) with kidney tumor with venous extension in the supradiaphagmatic inferior vena cava and/or at atrial level by the urologists. Surgery is performed under general anesthesia with orotracheal intubation, with advanced noninvasive and invasive intraoperative monitoring, having at hand blood products, but also rapid infusion and cell saver devices for life-threatening bleeding. Transesophageal echocardiography was used for the location and description of venous thrombus in the inferior vena cava or right atrium during the intraoperative period, prior to initiating cardiopulmonary bypass, as well as for monitoring the patient after weaning from extracorporeal circulation, to highlight any possible remaining thrombi or possible embolization. The surgical interventions involved a mixed team: urologists, cardiac surgeons, anesthetists, perfusionists. The data, including mean arterial pressure measured using an intraarterial catheter, was recorded manually in the intraanesthetic monitoring charts at every 5-15 minutes, depending on the anesthetist. Postoperatively, the pacients were transported in ICU.

The study was performed with the approval of the ethical commitee of the institution in order to perform this retrospective study. The medical records were analyzed.

Prolonged intraoperative hypotension was defined in this study as the presence of a mean intraoperative blood pressure below 60 mm Hg for more than 20 minutes, cumulatively pre-, intra- and post-extracorporeal circulation.

For the quantification of postoperative complications, the Clavien-Dindo classification[4] was used. Those

Table 1. Clavien-Dindo classification

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for a pharmacological or surgical, endoscopic and radiological intervention. Antiemetics, antithermics, analgesics, diuretics, electrolytes and physiotherapy are allowed. It also includes wound infections treated at the patient's bed
Grade II	Requires drug treatments other than grade I. Includes transfusion and parenteral nutrition
Grade III -IIIa -IIIb	Requires surgical, endoscopic or radiological intervention Without general anesthesia With general anesthesia
Grade IV -IVa -IVb	Emergence of life-threatening complications, including neurological ones, requiring specific intensive care measures Single organ dysfunction (including dialysis) Multi-organ dysfunction
Grade V	Death

Table 2. KDIGO criteria for defining acute kidney injury (one of the following)

1. Increase in serum creatinine by >0.3 mg/dl in the last 48 hours
2. Increased serum creatinine ≥1.5 times the baseline, known or presumed to have occurred in the last 7 days
3. Diuresis <0.5ml/kg/h for 6 hours

Table 3. AKI Staging according to KDIGO:

AKI 1: Serum creatinine >1.5-1.9 times the baseline or increase ≥0.3 mg/ml or diuresis <0.5 ml/kg/h for 6-12 hours
AKI 2: Serum creatinine >2-2.9 times the baseline or diuresis <0.5 ml/kg/h for >12 hours
AKI 3: Serum creatinine >3 times the baseline or increase in serum creatinine by more than 4 mg/dl or initiation of kidney cleansing treatment or diuresis <0.3 ml/kg/h for ≥12 hours

graded IV and V in Clavien Dindo classification were considered in this study severe postoperative complications.

Post-operative acute kidney injury was diagnosed (Table 2) and staged (Table 3) according to KDIGO criteria[6], while postoperative neurological complications were diagnosed as postoperative encephalopathy (clinical diagnosis made by the intensivist and recorded in the medical sheets) or as a vascular accident (clinical and imaging diagnosis).

STATISTICAL ANALYSIS

The statistical analysis was performed using the IBM SPSS Statistics 20 software. The quantitative variables are expressed by mean and standard deviation. The grade of postoperative complications and postoperative AKI grade are ordinal variables. The data representing the number of patients with or without prolonged intraoperative hypotension was presented in 2x2 contingency tables, as a function of the occurrence or

Table 4. Preoperative characteristics of patients

Preoperative characteristics		Number of patients (%)
Sex	- men	19 (67.8%)
	- women	9 (32.2%)
Kidney tumor	- right	19 (67.9%)
	- left	9 (32.1%)
Venous extension level	- supradiaphragmatic inferior vena cava	12 (43.3%)
	- right atrium	16 (56.7%)
Comorbidities	-diabetes mellitus	4 (14.3%)
	-hypertension	21 (75%)
	-obesity	3 (10.7%)
	-heart failure	14 (50%)
Preoperative creatinine clearance		
	> 85 ml/min	10 (35.7%)
	50-85 ml/min	14 (50%)
	<50 ml/min	4 (14.3%)

not of severe postoperative complications, AKI 3 or postoperative neurological complications. In order to identify the statistical association of the category variables, we used the Fisher exact test, as it was not possible to use the Chi square test. This is because the contingency tables do not meet the requirement that the expected values should be more than 5 in more than 80% of the cells[7,8]. The degree of association between variables is done using the Cramer test and the Odds ratio[7,8]. Relative risk was also calculated. The Kendall tau test was used to test the statistical correlation between the category variables or between the category variable and the ordinal variables. The threshold of statistical significance is 95% ($p < 0.05$).

RESULTS

There were identified 30 consecutive patients who underwent radical nephrectomy with extraction of the venous thrombus under extracorporeal circulation in Prof. C.C. Iliescu Emergency Institute for Cardiovascular Diseases in Bucharest during 2004-2018. Intraoperatively, there were two deaths: one patient with massive intraoperative bleeding and one patient with major pulmonary embolism. Thus, only 28 of the pacients were analyzed in this study. Postoperatively, there were another four deaths (one patient with enteric infarction, two with multiple organ dysfunction and one patient with major bleeding).

The 28 patients aged 57.29+/-9.85 years old had the preoperative characteristics presented in table 4. The intraoperative data is presented in table 5.

The postoperative complications of the 28 surgery survivors graded through the Clavien Dindo classification are exemplified in the following table (Table 6).

Prolonged intraoperative hypotension was found in the case of 11(39.28%) patients. Vassopressors were used in 26 (92.85%) pacients, with higher doses and longer duration in the case of patients with prolong intraoperative hypotension. The following contingency table 2x2 presents the number of pacients with or without prolong intraoperative hypotension in the 2 groups of patients classified according to postoperative complications graded Clavien Dindo.

Between the two variables, namely the presence of prolonged intraoperative hypotension and the occurrence of severe postoperative complications (graded IV and V in Clavien Dindo classification) there is an association relationship ($p = 0.001$ exact Fisher test). The strong intensity of this relationship is given by the Cramer test (coefficient V 0.781, $p = 0.0\ 01$), but also the odds ratio OR=75 (CI 95%: 5.973, 941.79). The relative risk is 8.18. Kendall tau b correlation coefficient is 0.652 ($p=0.001$).

Table 5. Intraoperative data

Characteristics	
Extracorporeal circulation time (minutes)	71.6 ± 40.6
Ascending aortic cross-clamping • number of patients (%) • time (minutes)	 20 (71.4%) 41.5 ±19.8
Intraoperative blood loss (liters)	5.8± 4.5
Number of units of packed red blood cells	6.3 ± 4.9
Number of units of frozen fresh plasma	6 ±5.4
Cell saver - number of patients (%)	24 (85.7%)
Temperature management -number of patients (%) • normothermia • moderate hypothermia	 17 (60.7%) 11 (39.3%)

Table 6. Postoperative complications according to the Clavien-Dindo classification:

Clavien Dindo classification grade	Number of patients	Percentage of patients
I	7	25%
II	9	32.14%
III	0	0%
IV A	3	10.71%
IV B	5	17.85%
V	4	14.28%
Total	**28**	**100%**

Table 7. Contingency Table 2x2: Prolonged Intraoperative Hypotension- Severe postoperative complications graded Clavien- Dindo

Prolonged intraoperative hypotension	Clavien Dindo complications Number of patients		Total Number of patients
	I,II,III	IV,V	
Absent	15	2	17
Present	1	10	11
Total	**16**	**12**	**28**

Table 8. Distribution of the number of patients according to the characteristics of the postoperative kidney function

Postoperative kidney function	Percentage of patients	Number of patients
Normal	7.17%	2
AKI1	35.71%	10
AKI2	25.00%	7
AKI3	32.14%	9
Total	**100%**	**28**

Postoperative acute kidney injury was present in 26 (92.85%) patients, but only 9 (32.14%) had AKI 3 renal injuries. (Table 8).

The relationship between prolonged intraoperative hypotension and the occurrence of acute kidney injury AKI 3 is illustrated in the contingency table 2x2 (Table 9).

Fisher's exact test shows that the two variables, in this case, the presence of prolonged intraoperative hypotension and the postoperative occurrence of AKI 3 are dependent variables (p= 0.01). The Odds ratio is OR=13.12 (CI 95%: 1.924, 89.515) and the Cramer coefficient is 0.542 (p = 0.004), measuring this association as a medium-intensity one. The relative risk was 3.69. The correlation coefficient Kendall tau b is 0.542 (p = 0.005).

Regarding postoperative neurological complications, these were found in 7 (25%) patients, 2 of whom had a stroke diagnosed by imaging, while the rest had postoperative encephalopathy. The contingency table 2x2 below (Table 10) identifies patients considering 2 criteria: prolonged intraoperative hypotension as defined by the study, and the occurrence of postoperative neurological complications.

The two variables, prolonged intraoperative hypotension and the occurrence of postoperative neurological complications are dependent variables (p = 0.007, Fisher exact test). The intensity of the association between the variables is measured with Cramer coefficient of 0.549 (p= 0.004) and odds ratio OR=19.20 (CI 95%: 1.844, 199.937). Relative risk is 9.27. The correlation coefficient Kendall tau b is 0.549 (p=0.004).

DISCUSSION

Our study found a strong association between the intraoperative prolong hypotension and the occurrence of severe postoperative complications (Clavien-Dindo IV and V), postoperative AKI3 and postoperative neurological complications. Intraoperative prolong hypotension was defined as intraoperative mean arterial blood pressure below 60 mmHg for a duration greater than 20 minutes (cumulatively pre-, intra- and post- cardiopulmonary bypass).

Surgery to remove kidney tumors with venous extensions in the supradiaphragmatic inferior vena cava and/or in the right atrium level represents a major surgical intervention of a fairly high duration (6-8 hours), involving extracorporeal circulation, significant blood loss, embolic events, with major haemodynamic manifestations and hypotension. Early detection of the haemodynamic changes and a good venous access are mandatory[9]. The monitoring of the intraoperative hypotension is essential because its magnitude, expressed by value and duration, influences organ perfusion and consequently the postoperative evolution of the patients. The use of cardiopulmonary by-pass, which is often used in such surgery, seems to be safe from an oncologic perspective, but is known to be associated with the risk of bleeding, coagulopathy and longer operating times[10].

Table 9. Contingency Table 2x2: Prolonged Intraoperative Hypotension - AKI 3

Prolonged intraoperative hypotension	Postoperative AKI 3 Number of patients (%)		Total Number of patients (%)
	Present	Absent	
Present	7	4	11
Absent	2	15	17
Total	**9**	**19**	**28**

Table 10. Contingency Table 2x2: Prolonged Intraoperative Hypotension (present/absent) - Postoperative Neurological Complications - number of patients (%)

Prolonged intraoperative hypotension	Postoperative neurological complications Number of patients		Total Number of patients
	Present	Absent	
Present	6	5	11
Absent	1	16	17
Total	**7**	**21**	**28**

The complexity of the diagnostic and surgery treatment in these cases was discussed in the Romanian medical literature by Sinescu et al.[11], emphasizing the importance of haemodinamic monitoring, without showing the impact of prolong intraoperative hypotension on postoperative outcome.

The radical nephrectomy with thrombectomy has been shown to be associated with major perioperative morbidity (up to 70%) and mortality (3-16%)[12]. The review of Gaudani et al. in 2016 finds surgical risk to be substantial in these cases, with in-hospital mortality up to 40% and postoperative complications in up to 47% of cases[3]. International Renal Cell Carcinoma-Venous Thrombus Consortium identified the factors influencing perioperative mortality: patient comorbidities, performans status, distant metastatic spreading and the extent of the tumour thrombus above the diaphragm[12]. However, the impact of intraoperative haemodynamic changes or hypotension have not been studied in the medical literature regarding this kind of surgery.

This study showed the association of the intraoperative hypotension with the prognostic in the case of patients with radical nephrectomy with thrombectomy. The team work is important, but also the haemodynamic monitoring and the action aswell. The medical team's attention should be focused mainly on mitigating this risk factor by minimizing intraoperative blood loss, avoiding embolic phenomena, achieving adequate volume replacement, using vasopressor or inotropic medication as needed to avoid hypotension episodes as much as possible and limit their duration. Reducing intraoperative hypotension and limitation of exposure to nephrotoxic agents seems to be more cheap and effective in limiting AKI than any other method[13].

The use of the 5Ts in perioperative goal directed haemodynamic therapy was proposed by a recent editorial[14]: target population, timing of intervention, type of intervention, target variable, target value. Thus, high-risk patients have to be selected (target population)[14]. Haemodynamic optimization should start before induction of general anaesthesia (timing of intervention)[14]. The editorial proposes different types of interventions: volume replacement, vassopressors and inotrops and the target variables has to be personalized. The team should focus on the dynamic and static preload variables, but mainly on the variables reflecting blood flow[14]. The patients undergoing surgery to remove kidney tumour together with its high venous extension are high risk patients because of the significant blood loss, embolic events and comorbidities. Echocardiography provides also important diagnostic information and can modify surgical management, especially when an atrial thombus is identified[15].

The importance of intraoperative hypotension is highlighted in the literature. Althought intraoperative hypotension, a common occurrence in general anesthesia, is recognized to be involved in inadequate organ perfusion, the literature is not consistent in defining intraoperative arterial hypotension. In 2007, there were identified 140 different definitions from

130 studies[16]. Classically, it was defined as a function of the patient's preoperative blood pressure values, accepting an intraoperative blood pressure within a 20% margin from the preoperative blood pressure values of the patient[17]. However, more recent studies have discussed various definitions of intraoperative hypotension, in terms of mean or systolic blood pressure, absolute value or relative to baseline values. Intraoperative blood pressure as a risk factor is easy to measure and control[17]. The review of Wesselink et al. concludes that organ injury occurs when mean arterial pressure drops below 80 mm Hg for more than 10 minutes, and that this risk increases as blood pressure decreases[18]. Another study found that mean blood pressure below 60 mm Hg for more than 20 minutes and mean blood pressure below 55 mm Hg for more than 10 minutes are risk factors for postoperative acute kidney injury in noncardiac surgery[19]. Salmasi et al. analysed retrospectively a large cohort of pacients also in noncardiac surgery and concluded that mean blood pressure under 65 mm Hg or relative thresholds of 30% from the baseline were related to myocardial and kidney injury[20]. In cardiac surgery, postoperative acute kidney injury occurs in nearly 30% of interventions, severe acute kidney injuries occurring in about 2-5%, with an associated mortality of 50%[21]. Regarding the effect of intraoperative hypotension on neurological function, Drummond et al. showed that the mean of the lowest limit of arterial blood pressure at which cerebral flow autoregulation takes place in normotensive adults is no less than 70 mmHg[22]. The average of the mean blood pressure limit at which cerebral ischemic symptoms are established is 40-50 mmHg at Willis's polygon in normotensives in the vertical position and 45-55 mmHg with the patient in dorsal decubitus which corresponds to an mean blood pressure of 65-70 mmHg[22].

Hypotension is proved to be also associated with 30 day mortality[23]. Studies showed that maintaining the mean arterial pressure above 60-70 mm Hg is more important than avoiding blood pressure variability[23]. Moreover, the duration of hypotension is strongly envolved in organ-specific injury[24].

In 2019, the Perioperative Quality Initiative published a consensus statement on intraoperative blood pressure. This established that mean arterial pressure below 60-70 mm Hg during surgery is associated with myocardial injury, acute kidney injury and death, injury being a function of hypotension severity and duration[25].

Thus, the medical literature points to the fact that intraoperative hypotension is associated with postoperative complications, both in cardiac and noncardiac surgery. Our study refers to the patients who underwent a combined surgery: radical nephrectomy with thombectomy using extracorporeal circulation. We showed that prolong intraoperative hypotension is strongly associated with organ dysfunction, death, postoperative AKI 3 and postoperative neurological complications.

The limitations of the study are given by the fact that it is retrospective, with a relatively small number of patients included, operated in our center. This was, however, to be expected, given the low incidence of the diagnostic. Another limitation is represented by the intermitent manual intraoperative records of the mean arterial pressure, despite the continuously mean arterial pressure measurement via an arterial catheter. The proved association between prolong intraoperative hypotension and postoperative outcome is relevant only in our medical center and only for the type of surgery described, due to the limitations of the study. The results need to be validated in a multicenter prospective study.

CONCLUSION

Prolonged intraoperative hypotension, defined as mean blood pressure below 60 mm Hg for more than 20 minutes (calculated cumulatively pre-, intra- and post-extracorporeal circulation) was associated with the occurrence of severe postoperative complications (Clavien Dindo IV and V), neurological complications and severe postoperative acute kidney injury (AKI3). The medical team should work together to reduce the length of hypotension that is inherent to this surgery, in order to minimize its postoperative impact.

Conflict of interest: none declared.

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