Open kidney cancer surgery and perioperative cardiac arrhythmias

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Introduction Although the cardiac arrhythmias during anesthesia are often observed, the literature focuses mainly on cardio-thoracic surgery. We aimed to evaluate the incidence of arrhythmias appearing in the perioperative period in patients having a urological surgery and furthermore to define whether combining general with epidural anesthesia prevents them.

Materials and methods 50 adults, without a prior cardiac or arrhythmia history, undergoing an open kidney cancer surgery, were randomly allocated to receive either general or combined epidural/general anesthesia. The Holter monitor was applied the evening before the surgery, tracing continuously for a period of 24 hours (7PM-7PM). ClinicalTrials.gov NCT02988219

Results There was no statistical difference in the arrhythmia occurrence between the randomization groups. Among 65.21% the following arrhythmias were observed: 27 - bradycardia, 4 - sinus pause, 6 - ventricular extrasystoles (> 1000/ 24 hours), 3 - supraventricular extrasystoles (>200/24 hours). The patients with arrhythmia were older and often with hypertension ($p<0.01$). A longer surgery duration predisposed to arrhythmia appearance (122.5 vs 99 minutes), ($p<0.01$). The temperature measured at the beginning and at the end of the surgery was significantly lower among the participants with arrhythmia ($p=0.02$, $p=0.01$). The sex, BMI, laboratory tests and the intravenous fluids intake did not influence the occurrence of arrhythmia.

Conclusions 1. Perioperative cardiac arrhythmias (usually the sinus arrhythmias) are common during an open kidney surgery, occur regardless of the anesthetic technique and usually do not require any treatment
2. Age, hypertension, long operation time or low body temperature predispose to the perioperative cardiac arrhythmias during surgery

INTRODUCTION:
The incidence of cardiac arrhythmias during anesthesia can be high and depends on the type of the surgery applied. While they are a very common complication after cardiac surgery and a major source of

morbidity and mortality, after general surgery, they usually do not require clinically significant management.[1] Literature on arrhythmias during a cardio-thoracic surgery is abundant but as far as a general surgery is concerned, it is sparse and obsolete.

The kidney cancer surgery is performed under general anesthesia. It is recommended to combine it with regional anesthesia techniques as such a combination often reduces postoperative neurological, pulmonary, cardiac or endocrine complications, though regional analgesia has not been proven to improve the long-term morbidity statistics.[2]

A localized renal cancer is best managed by partial nephrectomy rather than by radical nephrectomy, irrespective of the surgical approach that can be open or laparoscopic, retro or trans-peritoneal. For the retroperitoneal approach the patient is usually placed in the lateral decubitus position. The operation table is scissored so the head and legs are low and the kidney rests elevated. Such position may cause a hemodynamic instability and as a consequence the cardiac arrhythmia. Regrettably, there is no literature data on that subject.

The aim of this prospective, randomized study was to investigate the cardiac arrhythmias in the perioperative period among patients undergoing open kidney cancer surgery in the lateral position. The type of arrhythmias, their incidence and necessity to treat among patients without arrhythmia history was assessed. Furthermore, it was evaluated whether combining general with epidural anesthesia prevents the arrhythmia.

METHODS:

After the local bioethical committee approval and the written informed consent obtaining, 50 adult, consecutive patients, with renal cell carcinoma suspicion, planned for the open, retroperitoneal, kidney cancer surgery, were randomly assigned (1:1), according to a computer-generated randomization list with permuted blocks to receive either general (group G) or epidural combined with general anesthesia (group E). The exclusion criteria were: contraindications for epidural anesthesia, pregnancy, prior arrhythmia history, irregular ECG or irrelevant blood electrolyte levels performed before the surgery, previous cardio-thoracic surgery, American Society of Anesthesiologist (ASA) physical status 4 and 5.

The day before the surgery a 12-lead ECG, a chest X-ray and the blood laboratory tests were performed. All patients went through an anesthetist evaluation and investigation. The 3-lead ECG Holter (Lifecard CF) monitor was applied in the evening, tracing continuously for a period of 24 hours (7PM-7PM). The CM5 lead configuration was obtained by keeping the right arm electrode at the manubrium sternum and the left arm electrode placed at V5 location.

The anesthetic technique was standardized. According to the randomization, in the group E, the epidural anesthesia was performed (usually L2-L3) with the catheter directed cephalad. Then 10ml of 0.25% bupivacaine with epinephrine (Marcaine – Adrenaline 0.5 %, Astra Zeneca) and 0.1 mg of Fentanyl (Fentanyl WZF, Polfa Warszawa) was administrated epidurally. The patient was subsequently placed in the supine position to let the level of regional anesthesia settle.

In both groups the general anesthesia was performed in the same way. All patients received intravenous Fentanyl 0.1 mg and Midazolam 2-3 mg (Midanium, Polfa Warszawa). The induction was preformed intravenously with Etomidate 0.2-0.3 mg/kg (Etomidate-lipuro, B.Brown Melsungen) and Cisatracurium 0.15 mg/kg (Nimbex, GlaxoSmithKline) or Succinylocholine 1-1.5 mg/kg (Chlorsuccillin, Jelfa) in case of difficult facemask ventilation. After an intubation for the conduction of anesthesia, a mixture of O2+/-N2O (FiO2 >0.35) and Sevoflurane was used. The analgesia was maintained with Fentanyl and muscle

relaxation with Cisatracurium. A drip infusion of crystalloids 3-5ml/kg/h was administrated intravenously. During general anesthesia a further monitoring of ventilation parameters, nasal temperature, bispectral index (BIS) and muscle relaxation (TOF-watch) was performed. The surgery was performed with patient placed in the lateral position with the scissored operation table.

Before the end of surgery Acetamiophen and Ketoprofen were administrated intravenously. Afterwards the pain therapy was conducted additionally with the continuous infusion either with 0.16% Bupivacaine epidurally (group E) or Fentanyl intravenously (group G). Pain treatment was monitored and corrected according to numerical rating scale (NRS). The blood laboratory tests (complete blood count, coagulation, basic metabolic panel) were performed two hours after the surgery.

The parameters evaluated in the study groups were: the type of cardiac arrhythmia, the incidence and necessity to treat.

The following were considered as arrhythmias:

• Sinus bradycardia (< 50bpm)
• Sinus tachycardia (> 100bpm)
• Sinus arrhythmia (variation in the P-P interval of more than 120 ms)
• Sinus arrest (pause >2s)
• Ventricular events, VE (>50/24h or >1000/24h among patients older than 60 years)
• Supraventricular events, SVE (>100/24h or >1000/24h among patients older than 60 years)
• Ventricular rhythms
• Ventricular tachyarrhythmia (ventricular tachycardia, flutter, fibrillation)
• Supraventricular tachyarrhythmia (supraventricular tachycardia, atrial flutter, atrial fibrillation)
• Pre-excitation syndromes

As a QTc interval abnormalities the above were considered

• QTc shorten <0.36s (women) and <0.35s (men)
• QTc lengthen >0.46s (women) and >0.45s (men)

A 24 hours of ECG Holter registration time was divided into three periods:

• A preoperative period – from 7 p.m. until the beginning of the anesthesia procedure
• An intraoperative period – from the beginning to the end of the anesthesia procedure
• A postoperative period – from the end of the anesthesia procedure till 7 p.m.

Data analysis was performed in Statistica 12.0 (StatSoft Poland Software). The results data in the quantitative scale were presented as mean +/- standard deviation (SD), those in the ordinal scale as median +/- interquartile range (upper and lower quartile) and categorical data as number of patients (percentage of sample). The Mann–Whitney test or t-Student test (normal distribution) were used to assess differences in continuous variables. The chi-squared test (for the count smaller than 5 with Yates correction) was used to evaluate the association between qualitative data (number of arrhythmias among groups). A statistically significant result is one in which the observed p-value is less than < 0.05.

RESULTS:

Due to the registration artefacts, the analysis of ECG was impossible in two patients, another two withdrew their consent. Data obtained from 46 patients were evaluated. The groups were similar. Patient characteristics are presented in Table 1.

During the whole observation period a 91.3% of patients had cardiac arrhythmia. Sinus tachycardia with a heart rhythm not exceeding 140 bpm was observed among 28 participants (excluding iatrogenic

tachycardia after atropine admission). It was mainly observed in the preoperative period just before the patient has entered the operation room therefore, it was not included in further arrhythmia analysis.
Among 30 (65.21%) of patients the following cardiac arrhythmias were observed and analyzed. (Table 2).
27 – bradycardia (min. 24 bpm)
4 - P-P interval > 2 seconds (longest pause was 4.6s)
6 – ventricular events (> 1000/ 24 hours)
3 – supraventricular events (>200/24 hours)
There was no statistically significant difference in the arrhythmia occurrence between the randomization groups in either of the period analyzed.
Although all patients had no prior arrhythmia history the 7 of them revealed the arrhythmia in the preoperative period and in 6 out of them (85.71%) the arrhythmia was observed later on as well. Only one patient had the arrhythmia just in the postoperative period. More than one type of cardiac arrhythmia was observed among 8 patients (3 in group G, 5 in group E), with bradycardia always being one of them.
Analysis of each type of arrhythmia observed:
Bradycardia - In accordance with assumptions, bradycardia was not observed among 19 patients. (8 in group G, 11 in group E) This difference is statistically insignificant (p=0.26, chi-square test). If bradycardia occurred in the preoperative period, it was always observed later. A heart rhythm slower than 40bpm was registered among 6/24 (25%) patients in the group G and 3/22 (13%) patients in the group E. The statistical analysis revealed that the difference is insignificant (p=0.55, Yates' chi-square test).
Sinus arrest - the incidence of a P-P interval lasting longer than 2s was presented in Table 3. In group E the sinus arrest was related to the airway management/laryngeal manipulation (intubation or extubation). In group G it was observed as well during the surgery as in the postoperative period and appeared regardless of the doctor or nurse's proceeding.
Supraventricular events (SVE) - single supraventricular extrasystolies were registered in almost all patients (97.9%). This arrhythmia is common in healthy people and it intensifies with age. SVE > 200/24h, were observed only in 3 patients (2 in group E, 1 in group G).
Ventricular events (VE) - single premature ventricular contractions were observed in 40 patients (83%). There are common in healthy person but then there are not exceeding 50-200/24h in young and 1000/24h among patients older than 60 years; several contractions in a row are not a norm either. Taking all that into account, 6 patients presented ventricular extrasystoles (3 in each group).
QTc interval abnormalities
The overall rate of patients who had QTc interval abnormalities was 12. A shortened QTc interval was observed only in the postoperative period (2 patients in each group). A prolonged QTc interval increases the risk of ventricular events; in group G it was observed in one patient only. In Group E, 8 patients had prolonged QTc as well during the surgery as in the postoperative period. The difference is statistically significant (p=0.017, chi-square test). Table 4
No correlation between prolonged QTc and ventricular extrasystolies was observed. (p=0.72, chi-square test).
Identified factors influencing arrhythmia occurrence.
Patients with arrhythmia were older (median: 61yrs vs 52.5yrs; p=0.03, Mann-Whitney test) and often with hypertension that was diagnosed in 63% of participants. 79% among them had cardiac arrhythmia during the study (p=0.01, chi-square test). Beta-adrenolytics neither prevent nor predispose them (p=

0.26, Yates' chi-square test).

There was a statistically significant difference between arrhythmia appearance and surgery duration. The mean surgery time for the patients with arrhythmia was 128.03 minutes (SD 29.39) and for those without arrhythmia it was 109.33 (SD 34.65), median 122.5 minutes vs. 99 minutes (p=0.036, Mann-Whitney test).

The nasal temperature measurement in the beginning and at the end of surgery was significantly lower among participants with arrhythmia and it is presented in Table 5.

The drop of temperature during the surgery was similar regardless the arrhythmia occurrence. The difference between the mean temperature at the beginning and at the end of surgery was 0.34°C among patients without arrhythmia and 0.57°C in those with arrhythmia (p = 0.2, Mann-Whitney test). There was also no correlation between surgery duration and temperature decrease (R-Speraman 0.14, t(N-2) 0.72; p=0.48). The type of anesthesia performed (according to the randomization) did not influence the temperature.

Factors without proven influence on arrhythmia occurrence

No correlation was observed between the blood laboratory tests performed before and after the surgery and arrhythmia occurrence. The other unproven factors are presented in the Table 6.

DISCUSSION:

The study has shown that during kidney cancer surgery in the lateral position, the incidence of cardiac arrhythmias in the perioperative period is very high (91,3 %). This complication may occur irrespectively of the epidural anesthesia addition to the general anesthesia. Although the time has passed and the medicine has changed, the results are similar to those presented in 1967 by Kuner et al.[3] who analyzed data collected by ECG Holter from 154 patients during and after non-cardiac surgery and who concluded that 61.7% of patients had cardiac arrhythmia (sinus tachycardia was excluded). In our study after excluding tachycardia - 65.21% patients had cardiac arrhythmia. Our results are also similar to the one presented by Forest et al.[4] who concluded in a multicenter study of general anesthesia the 70% incidence of tachycardia, bradycardia or arrhythmias in 17201 patients observed on cardiac monitor. Unfortunately the trials on general surgery and arrhythmia are lacking and aged. To our knowledge, these findings represent the first demonstration of the cardiac arrhythmia during urological procedure.

In our study, the type of arrhythmia mainly observed was a sinus rhythm abnormality – tachycardia or bradycardia, single patient's sinus pauses, ventricular or supraventricular extrasystoles.

We observed bradycardia <50bpm in more than half of patients during surgery. Somewhat distinct results were presented by Fanelli et al.[5] who analyzed data obtained from cardiac monitor on 1200 patients having combined general and epidural anesthesia for different general surgery procedures and concluded that bradycardia <50bpm was observed among 4.5% of patients just after the epidural anesthesia and among 12.7% during surgery. Other trials conducted on small groups of patients have different bradycardia criteria therefore it is hard to compare the results. Borghi et al.[6] observed no bradycardia <45bpm at all in 210 patients having epidural, general or combined anesthesia for hip endoprothesis. Mehta et al.[7] observed a 20% decrease of heart rate in 6 patients out of 30, who had combined spinal-epidural (CSE) anesthesia for cholecystectomy. Unfortunately, there are no trials considering bradycardia during kidney surgery.

In the present series of 46 patients the single VE and SVE were observed very often (83% and 97.9%) but pairs, several contractions in a row or a large number of extrasystolies were observed rare (13% and

6.5%). They did not cause hemodynamic insufficiency. To our best knowledge there are no trials to compare.

The literature, though scarce, focuses on postoperative period.[8] The incidence of arrhythmia is 4-20% depending on surgery, monitoring and type of arrhythmia analyzed. 7% are recognized as new ones and usually accompanies the complications.[9] In this study, arrhythmia was observed postoperatively in 30.43%.

It is important to note that cardiac arrhythmias occurring before surgery are a relevant factor of arrhythmia incidence during and after surgery. Although in our study all patients had normal ECG before the surgery and did not have arrhythmia history, 15.21% of them had arrhythmia registered by Holter ECG during preoperative period. It was mainly bradycardia but also SVE or VE were observed. Thanks to that result, when facing arrhythmia in potentially healthy patient while on surgery, we should consider whether it is really a new phenomenon.

In our study we observed a sinus pause lasting 4.6s during the laryngoscopy. That was probably a vagal reaction to the too deeply inserted intubation tube. Mizuno et al.[10] and Cheong et al.[11] have reported similar reactions to intubation or laryngoscope placement. Despite this sinus pause all the other arrhythmias observed by the authors in the present study had no hemodynamic or life-threatening consequences.

We showed that epidural anesthesia neither predisposed nor protected from arrhythmia incidence, however longer QTc interval was statistically more frequent in this group. Fortunately, it did not influence the VE occurrence. Similar results presented Guven et al.[12] who performed 30 combined thoracic-epidural and general anesthesia for lung resection surgery. In contrast, Deniz et al.[13] reported no QTC interval abnormalities after spinal anesthesia for caesarian section in 60 pregnant, but the observation lasted only 10 minutes.

Patient's physical condition and cardiac diseases can predispose to arrhythmia.[14] Age over 60 is a risk factor and that fact was confirmed in the present study. As the average age of people diagnosed with kidney cancer is also over 60, authors decided not to limit the age of enrolled patients.

63% of patients had arterial hypertension, and statistically they had cardiac arrhythmia more frequently. Arterial hypertension is one of the most common factors of arrhythmia[15] and its association with kidney cancer is known.[16] Some authors emphasize that atrial hypertension predispose to kidney cancer and normalization of blood pressure can decrease the risk[17] while others report that renal cancer can produce vasoactive peptides that induce hypertension and it can be suppress after nephrectomy.[18] Kidney cancer can be an arrhythmia risk factor. It can extend into vena cava inferior reaching event the right atrium. Extremely rare are intramyocardial metastasis without venous enrolment. They may be asymptomatic but can manifest as cardiac arrhythmia or longer QTc interval.[19],[20]

In this study, a longer operation time predisposed the patient to arrhythmia. The similar results were presented by Zhang et al.[21] who assessed the complications after radical nephrectomy in two-centers retrospective analysis conducted on 568 patients. They revealed that the factors predisposing to complications are: age, ASA status, blood loss and longer operation time. In 8 patients they observed the cardiac arrhythmia but there are no specific data on the type of arrhythmia and time of observation.

Lower body temperature at the beginning and at the end of surgery occurred to be an arrhythmia risk factor. It is important to notice that not only during surgery but also in the preoperative time, an unintended hypothermia can appear. That was also emphasized by Prado et al. [22] who had to exclude

10 patients out of 160 from the trial due to the tympanic membrane temperature measurements below 36 oC. Contrary to the outcomes presented in this study, he reported the correlation between epidural anesthesia and the decrease of temperature during surgery.

All the enrolled patients were operated with the same surgical access and arrhythmia occurred regardless the nephrectomy or NSS was performed. In our trial neither gender, BMI nor ASA status influenced the arrhythmia, but it is worth to emphasize that patient's maximum ASA status was 3. There was no need for blood transfusion and no change in the laboratory blood tests results after surgery required special treatment.

Findings of this study must be assessed within the context of its limitations. We observed the patients only for 24 hours and no further follow-up analysis was conducted. Its major limitation was no echocardiogram performed before surgery. Although the ECG made before the operation was normal, a hypertension was prevalent, and an ultrasound diagnostic should be taken under consideration as it can reveal the presence of the arrhythmia substrate.

The study was also limited by the fact that the groups were small. Therefore, it should be treated as a preliminary report.

Conclusions:

We demonstrated that the perioperative cardiac arrhythmias are common during open kidney cancer surgery and occur regardless of the anesthetic technique. Usually the sinus arrhythmias (tachycardia, bradycardia, sinus pause) and supraventricular or ventricular extrasystoles are observed. Such arrhythmias are mainly mild, do not require special treatment and do not cause serious cardiac events that is why there are considered as clinically insignificant. The age, hypertension, long operation time and low body temperature predispose the patient to the perioperative cardiac arrhythmias.

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Attached tables:

1. Table1.doc
2. Table2.doc
3. Table3.doc
4. Table4.docx
5. Table5.doc
6. Table6.doc
7. Tablelegend.doc

Table 1.

	No. of patients	Gender male/female	Age –yr (mean)	Age –yr (median)	BMI (mean)	ASA status (median)	NSS/ Nephrectomy
Group G	24	13/11	58.87 (SD 8.5)	61	28.14 (SD 4.84)	2	17/7
Group E	22	12/10	54.72 (SD 9.04)	57	30.04 (SD 7.01)	2	12/10
p-value		0.98		0.11	0.31	0.88	0.25

Group G – general anesthesia, Group E – combined general and epidural anesthesia

ASA, *American Society of Anesthesiologists;* BMI, *body mass index;* NSS – *nephron sparing surgery*

Table 2.

	preoperative period		intraoperative period		postoperative period	
	Group G	Group E	Group G	Group E	Group G	Group E
Bradycardia						
<50 bpm	3	3	10	7	4	4
<40 bpm	0	0	4	3	2	0
Pause	0	0	2	2	2	0
VE	1	1	3	1	3	2
SVE	1	0	1	1	1	2
No. of patients:	3 (12.5%)	4 (18.2%)	16 (66.7%)	12 (54.5%)	8 (33.3%)	6 (27.27%)
chi-square test	p=0.6		p=0.4		p=0.6	

Group G – general anesthesia, Group E – combined general and epidural anesthesia

SVE - *supraventricular events*; VE – *ventricular events*

Table 3.

Group	Patient Nō	No. of incidence	Maximum length	Preoperative period	Intraoperative period	Postoperative period
G	3	23	2.6s	-	✓	✓
G	9	4	2.3s	-	✓	✓
E	6	1	2.4s	-	✓	-
E	42	1	4.6s	-	✓	-
Group G – general anesthesia, Group E – combined general and epidural anesthesia						

Table 4.

Group	Patient Nō	Gender M (male)/ F (female)	Preoperative period (maximum)	Intraoperative period (maximum)	Postoperative period (maximum)
O	41	F	-	-	0.495s
K	1	M	-	0.456s	-
K	4	M	-	0.460s	-
K	6	F	-	-	0.511s
K	20	M	-	-	0.459s
K	24	F	-	-	0.461s
K	25	F	-	-	0.482s
K	28	F	-	-	0.470s
K	42	F	-	-	0.635s
Group G – general anesthesia, Group E – combined general and epidural anesthesia					

Table 5.

arrhythmia		Median	Min	Max	Lower quartile	Upper **quartile**	p-value
no	Beginning of the surgery	36.3	35.8	36.7	36.0	36.6	p=0.02
yes		35.9	34.5	36.7	35.6	36.1	
no	End of the surgery	36.1	35.0	36.6	35.5	36.3	p=0.01
yes		35.2	31.8	36.4	35.1	35.6	

Table 6.

	Arrhythmia	No arrhythmia	p-value
Gender male/female	17/13	8/8	p=0.66
BMI (mean)	29.53	28.92	p=0.74
ASA status (median)	2	2	p=0.44
Nephrectomy/NSS	10/18	7/11	p=0.83
Intravenous fluid intake – ml			
mean:	2304.4	2163.8	
median:	2100.0	2100.0	p=0.29
min	1500.0	1500.0	
max	4125.0	3400.0	
SD	535.06	469.60	
No. of patients	28	18	

ASA, *American Society of Anesthesiologists;* BMI, *body mass index; NSS – nephron sparing surgery*

Table legend:

Table 1. Patient characteristics.

Table 2. Number of arrhythmias observed in the groups during the Holter ECG analysis.

Table 3. The sinus arrest incidence.

Table 4. Prolonged QTc interval.

Table 5. Patients body temperature in °C at the beginning and at the end of a surgery and arrhythmia appearance.

Table 6. Factors without proven influence on arrhythmia occurrence.