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Open kidney cancer surgery and perioperative cardiac arrhythmias

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Introduction Although 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 undergoing urological surgery and furthermore to define whether combining general with epidural anesthesia prevents them.
Material and methods The study included 50 adults, without a prior cardiac or arrhythmia history, undergoing an open kidney cancer surgery, who were randomly allocated to receive either general or combined epidural/general anesthesia. A 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 gender, body mass index (BMI), laboratory tests and the intake of intravenous fluids did not influence the occurrence of arrhythmia.
Conclusions Perioperative cardiac arrhythmias (usually sinus arrhythmias) are common during an open kidney surgery and occur regardless of the anesthetic technique and usually do not require any treatment. Age, hypertension, long operation time or low body temperature predispose the patient to perioperative cardiac arrhythmias during surgery.

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INTRODUCTION

The incidence of cardiac arrhythmias during anesthesia can be high and depends on the type of 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 general surgery is concerned, it is sparse and obsolete.

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 beds elevated. Such a position may cause a hemodynamic instability and as a consequence a cardiac arrhythmia. Regrettably, there is no literature data on this subject.

The aim of this prospective, randomized study was to investigate 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.

MATERIAL AND METHODS

After local bioethical committee approval and written informed consent was obtained, 50 adult consecutive patients, with suspicion of renal cell carcinoma, 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 electrocardiogram (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 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 (7 p.m.–7 p.m.). 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 Group E, the epidural anesthesia was performed (usually L2–L3) with the catheter directed cephalad. Then 10 ml 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 succinylcholine 1–1.5 mg/kg (Chlorsuccillin, Jelfa) in case of difficult facemask ventilation. After an intubation for the conduction of anesthesia, a mixture of $O_2 \pm N_2O$ (FiO_2 >0.35) and sevoflurane (Sevoflurane Baxter, Baxter Polska) was used. The analgesia was maintained with fentanyl and muscle relaxation with cisatracurium. A drip infusion of crystalloids 3–5 ml/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. The non-invasive blood pressure was measured with a cuff placed on the dependent arm [3]. Before the end of surgery, paracetamol (Perfalgan Bristol-Myers Squibb) and ketoprofen (Ketonal, Sandoz) 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 the numerical rating scale (NRS). The blood laboratory tests (complete blood count, coagulation parameters, 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 (<50 bpm)
- Sinus tachycardia (>100 bpm)
- Sinus arrhythmia (variation in the P-P interval of more than 120 ms)
- Sinus arrest (pause >2 s)
- Ventricular events, VE (>50/24 h or >1000/24 h among patients older than 60 years)
- Supraventricular events, SVE (>100/24 h or >1000/24 h 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

The following were considered as QTc interval abnormalities:
- QTc shortening <0.36 s (women) and <0.35 s (men)
- QTc lengthening >0.46 s (women) and >0.45 s (men)

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

- The preoperative period – from 7 p.m. until the beginning of the anesthesia procedure
- The intraoperative period – from the beginning to the end of the anesthesia procedure
- The postoperative period – from the end of the anesthesia procedure until 7 p.m.

Data analysis was performed in Statistica 12.0 (Stat-Soft 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 registration artefacts, the ECG analysis was impossible to perform in two patients
and a further 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, 91.3% of patients had a 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 had entered the operation room therefore, it was not included in further arrhythmia analysis. Only one patient received succinylcholine, despite the bradycardia <50 bpm observed during surgery, he had no further arrhythmias.

Among 30 (65.21%) patients the following cardiac arrhythmias were observed and analyzed (Table 2):
- 27 – bradycardia (minimum 24 bpm)
- 4 – P-P interval >2 seconds (longest pause was 4.6 s)
- 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 periods analyzed.

Although all patients had no prior arrhythmia history, 7 of them presented with an arrhythmia in the preoperative period and in 6 of these patients (85.71%) the arrhythmia was observed later as well.

Table 1. *Patient characteristics*

	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			0.88	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. *Number of arrhythmias observed in the groups during Holter ECG analysis*

	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. *The sinus arrest incidence*

Group	Patient No.	No. of incidence	Maximum length	Preoperative period	Intraoperative period	Postoperative period
G	3	23	2.6 s	–	✓	✓
G	9	4	2.3 s	–	✓	✓
E	6	1	2.4 s	–	✓	–
E	42	1	4.6 s	–	✓	–

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

Table 4. *Prolonged QTc interval*

Group	Patient No.	Gender M (male)/F (female)	Preoperative period (maximum)	Intraoperative period (maximum)	Postoperative period (maximum)
G	41	F	–	–	0.495 s
E	1	M	–	0.456 s	–
E	4	M	–	0.460 s	–
E	6	F	–	–	0.511 s
E	20	M	–	–	0.459 s
E	24	F	–	–	0.461 s
E	25	F	–	–	0.482 s
E	28	F	–	–	0.470 s
E	42	F	–	–	0.635 s

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

Only one patient had an arrhythmia only 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 our assumptions, bradycardia was not observed among 19 patients (8 in Group G, 11 in Group E). This difference was 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 40 bpm was registered among 6/24 (25%) patients in Group G and 3/22 (13%) patients in Group E. The statistical analysis revealed that the difference was insignificant (p = 0.55, Yates' chi-square test).

Data concerning sinus arrest, the incidence of a P-P interval lasting longer than 2 s, is presented in Table 3. In Group E, sinus arrest was related to airway management/laryngeal manipulation (intubation or extubation). In Group G, it was observed during the surgery as well as in the postoperative period and appeared regardless of the doctor's or nurse's interventions.

Supraventricular events (SVE), single supraventricular extrasystoles, were registered in almost all patients (97.9%). This arrhythmia is common in healthy people and it intensifies with age. SVE >200/24 h, 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%). These are common in healthy people but should not exceed 50–200/24 h in young patients and 1000/24 h in patients older than 60 years; several contractions in a row are not normal either. Taking all of this 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 during the surgery as well as during the postoperative period. The difference is statistically significant (p = 0.017, chi-square test, Table 4). No correlation between prolonged QTc and ventricu-

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

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	

lar extrasystoles was observed (p = 0.72, chi-square test).

Identified factors influencing arrhythmia occurrence

Patients with arrhythmia were older (median: 61 years vs. 52.5 years; p = 0.03, Mann-Whitney test) and often with hypertension, which was diagnosed in 63% of participants. Among them, 79% 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 this data is presented in Table 5.

The drop of temperature during the surgery was similar regardless of 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-Spearman 0.14, t(N-2) 0.72; p = 0.48). The type of anesthesia performed (according to the randomization) did not significantly influence the temperature. The mean decrease of temperature was 0.32°C in Group G and 0,63 in Group E (p = 0.35, Mann-Whitney test).

Factors without proven influence on arrhythmia occurrence

The maximum observed blood loss during the surgery was 750 ml. None of the patients required blood transfusion during or after the surgery. The amount of blood loss did not significantly influence the heart

Table 6. *Factors without proven influence on arrhythmia occurrence*

	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	
min	1500.0	1500.0	p = 0.29
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

rhythm. The visual estimation of blood loss is subjective hence we compared the blood laboratory test results. The mean hemoglobin level decreased from 142 g/l to 117 g/l among patients with no cardiac arrhythmia and from 142 g/l to 115 g/l among those with observed arrhythmia. The difference is statistically insignificant. Moreover, no correlation was observed between other blood laboratory tests performed before and after the surgery and arrhythmia occurrence (morphology of blood cells, electrolytes – Ca, Mg, Na, K, renal function parameters – urea, creatine). The other unproven factors, like volume of fluids infused, are presented in 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 addition of epidural anesthesia to general anesthesia. Although some time has passed and medicine has changed, our results are similar to those presented in 1967 by Kuner et al. [4], who analyzed data collected by Holter ECGs from 154 patients during and after non-cardiac surgery, and who concluded that 61.7% of patients had a cardiac arrhyth-

mia (sinus tachycardia was excluded). In our study, after excluding tachycardia, 65.21% patients had a cardiac arrhythmia. Our results are also similar, to the one presented by Forest et al. [5], who concluded in a multicenter study of general anesthesia, a 70% incidence of tachycardia, bradycardia or arrhythmias in 17,201 patients with cardiac monitoring. Unfortunately, the trials on general surgery and arrhythmia are lacking and aged. To our knowledge, our findings represent the first analysis of cardiac arrhythmias during urological procedures.

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 <50 bpm in more than half of patients during surgery. Somewhat distinct results were presented by Fanelli et al. [6], who analyzed data obtained from cardiac monitoring of 1200 patients having combined general and epidural anesthesia for different general surgery procedures, and concluded that bradycardia <50 bpm 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. [7] observed no bradycardia <45 bpm at all in 210 patients undergoing epidural, general or combined anesthesia for hip endoprosthesis implantation. Mehta et al. [8] 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 extrasystoles were observed rarely (13% and 6.5%). They did not cause hemodynamic insufficiency. To our best knowledge there are no trials to compare these results with.

The literature, though scarce, focuses on the postoperative period [9]. The incidence of arrhythmia is 4–20% depending on surgery, monitoring and type of arrhythmia analyzed. A total of 7% are recognized as new and usually accompany various complications [10]. In this study, arrhythmia was observed postoperatively in 30.43% of patients.

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 the preoperative period. This was mainly bradycardia but also SVE or VE were observed. Considering that result, when facing arrhythmia in a potentially healthy patient undergoing surgery, we should consider whether it is really a new phenomenon.

In our study, we observed a sinus pause lasting 4.6 s during the laryngoscopy. That was probably a vagal reaction to the intubation tube being inserted too deeply. Mizuno et al. [11] and Cheong et al. [12] 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 were presented by Guven et al. [13] who performed 30 combined thoracic-epidural and general anesthesia procedures for lung resection surgery. In contrast, Deniz et al. [14] reported no QTC interval abnormalities after spinal anesthesia for caesarian section in 60 pregnant patients, but the observation lasted only 10 minutes.

Patient's physical condition and cardiac diseases can predispose to arrhythmia [15]. 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.

A total of 63% of patients had arterial hypertension, and statistically they had cardiac arrhythmia more frequently. Arterial hypertension is one of the most common factors predisposing to arrhythmias [16] and its association with kidney cancer is known [17]. Some authors emphasize that arterial hypertension predisposes to kidney cancer and normalization of blood pressure can decrease the risk [18] while others report that renal cancer can produce vasoactive peptides that induce hypertension and it can be suppressed after nephrectomy [19].

Kidney cancer can be a risk factor for arrhythmia. The tumor itself can extend into the inferior vena cava reaching even the right atrium. Extremely rare are intramyocardial metastasis without venous involvement. They may be asymptomatic but can manifest as a cardiac arrhythmia or longer QTc interval [20, 21].

In this study, a longer operation time predisposed the patient to arrhythmia. Similar results were presented by Zhang et al. [22], who assessed the complications after radical nephrectomy in a two-center 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 appeared to be a risk factor for arrhythmia. It is known that during the first two hours of the surgery the general anesthesia lowers the core body temperature more than the neuraxial anesthesia. Whether core hypothermia is worse with general or regional anesthesia is thus likely to depend largely on the duration and magnitude of surgery. The combined (epidural and general) anesthesia may be a greater risk factor of unintended hypothermia [23]. We took all the possible precautions during the surgery to prevent hypothermia and according to the randomization, the type of anesthesia performed did not significantly influence the patient's temperature. It is important to note that not only during surgery but also in the preoperative time, an unintended hypothermia can appear. That was also emphasized by Prado et al. [24] who had to exclude 10 patients out of 160 from the trial due to the tympanic membrane temperature measurements below 36°C. 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 if nephrectomy or nephron-sparing surgery (NSS) was performed. In our trial neither gender, BMI nor ASA status influenced the arrhythmia, but it is worth emphasizing 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 that 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, hypertension was prevalent, and an ultrasound examination 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 study groups were small. Therefore, it should be treated as a preliminary report.

CONCLUSIONS

We demonstrated that perioperative cardiac arrhythmias are common during open kidney cancer surgery and occur regardless of the anesthetic technique. Usually, 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, which is why there are considered as clinically insignificant. Age, hypertension, long operation time and low body temperature predispose the patient to perioperative cardiac arrhythmias.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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